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# Ophthalmology

**FIFTH EDITION**

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# Ophthalmology





# Ophthalmology

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## COLOR CODING

*Ophthalmology* is organized into 12 parts, which are color-coded as follows for quick and easy reference:

Part 1: Genetics
Part 2: Optics and Refraction
Part 3: Refractive Surgery
Part 4: Cornea and Ocular Surface Diseases
Part 5: The Lens
Part 6: Retina and Vitreous
Part 7: Uveitis and Other Intraocular Inflammations
Part 8: Intraocular Tumors
Part 9: Neuro-Ophthalmology
Part 10: Glaucoma
Part 11: Pediatric and Adult Strabismus
Part 12: Orbit and Oculoplastics

## EXPERTCONSULT WEBSITE

- Full searchable text and downloadable image gallery
- Full reference lists for each chapter
- Additional online content including text, figures, & video clips

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Total running time approximately 2 hours and 34 minutes



# Preface

It's been 20 years since the first edition of *Ophthalmology* was published. We are delighted that our textbook now has gone to a fifth edition. The longevity of this title reflects the uniqueness and utility of its format; the hard work of our authors, editors, and publishers; and the pressing need in our field for updated, clinically relevant information. We continue to recognize the advantage of a complete textbook of ophthalmology in a single volume rather than multiple volumes. The basic visual science is admixed with clinical information throughout, and we have maintained an entire separate section dedicated to genetics and the eye.

*Ophthalmology* was never intended to be encyclopedic, but with each edition we strived to make it quite comprehensive, readable, and easy to access. Like the fourth edition, this edition is thoroughly revised, with new section editors and many new authors. Chapters have been rewritten and restricted to reflect the new way diseases are diagnosed, categorized, and treated. We have discarded out-of-date material and have added numerous new items. Extra references and other material have been moved online to keep the book itself as one volume.

# Preface to First Edition

Over the past 30 years, enormous technologic advances have occurred in many different areas of medicine—lasers, molecular genetics, and immunology to name a few. This progress has fueled similar advances in almost every aspect of ophthalmic practice. The assimilation and integration of so much new information makes narrower and more focused ophthalmic practices a necessity. As a direct consequence, many subspecialty textbooks with extremely narrow focus are now available, covering every aspect of ophthalmic practice. Concurrently, several excellent multivolume textbooks detailing all aspects of ophthalmic practice have been developed. Yet there remains a need for a complete single-volume textbook of ophthalmology for trainees, nonophthalmologists, and those general ophthalmologists (and perhaps specialists) who need an update in specific areas in which they do not have expertise. *Ophthalmology* was created to fill this void between the multivolume and narrow subspecialty book.

This book is an entirely new, comprehensive, clinically relevant, single-volume textbook of ophthalmology, with a new approach to content and presentation that allows the reader to access key information quickly. Our approach, from the outset, has been to use templates to maintain a uniform chapter structure throughout the book so that the material is presented in a logical, consistent manner, without repetition. The majority of chapters in the book follow one of three templates: the disease-oriented template, the surgical procedure template, or the diagnostic testing template. Meticulous planning went into the content, sectioning, and chapter organization of the book, with the aim of presenting ophthalmology as it is practiced, rather than as a collection of artificially divided aspects. Thus, pediatric ophthalmology is not in a separate section but is integrated into relevant sections across the book. The basic visual science and clinical information, including systemic manifestations, is integrated throughout, with only two exceptions. We dedicated an entire section to genetics and the eye, in recognition of the increasing importance of genetics in ophthalmology. Optics and refraction are included in a single section as well because an understanding of these subjects is fundamental to all of ophthalmology.

To achieve the same continuity of presentation in the figures as well as in the text, all of the artworks have been redesigned from the authors' originals, maximizing their accessibility for the reader. Each section is color coded for easy cross-referencing and navigation through the book. Despite the extensive use of color in artworks and photographs throughout, the cost of this comprehensive book has been kept to a fraction of the multivolume sets. We hope to make this volume more accessible to more practitioners throughout the world.

Although comprehensive, *Ophthalmology* is not intended to be encyclopedic. In particular, in dealing with surgery, we do not stress specific techniques or describe rarer ones in meticulous detail. The rapidly changing nature of surgical aspects of ophthalmic practice is such that the reader will need to refer to one or more of the plethora of excellent books that cover specific current techniques in depth. We concentrate instead on the areas that are less volatile but, nevertheless, vital surgical indications, general principles of surgical technique, and complications. The approach to referencing is parallel to this: For every topic, all the key references are listed, but with the aim of avoiding pages of redundant references where a smaller number of recent classic reviews will suffice. The overall emphasis of *Ophthalmology* is current information that is relevant to clinical practice superimposed on the broad framework that comprises ophthalmology as a subspecialty.

Essential to the realization of this ambitious project is the team of Section Editors, each bringing unique insight and expertise to the book. They have coordinated their efforts in shaping the contents list, finding contributors, and editing chapters to produce a book that we hope will make a great contribution to ophthalmology.

We are grateful to the editors and authors who have contributed to *Ophthalmology* and to the superb, dedicated team at Mosby.

Myron Yanoff  
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# Dedication

We would like to dedicate this book to our wives, Karin Yanoff and Julie Starr-Duker, and to our children—Steven, David, and Alexis Leyva-Yanoff; Joanne Grune-Yanoff; and Jake, Claire, Bear, Becca, Sam, Colette, and Elly Duker—all of whom play such an important part in our lives and without whose help and understanding we would have never come this far.

# Fundamentals of Human Genetics

Janey L. Wiggs

## 1.1

**Definition:** The central principles of human genetics with relevance to eye disease.

### Key Features

- Gene structure and expression.
- Organization and inheritance of the human genome.
- Mutations and clinical phenotypes.
- Gene-based therapies.

## DNA AND THE CENTRAL DOGMA OF HUMAN GENETICS

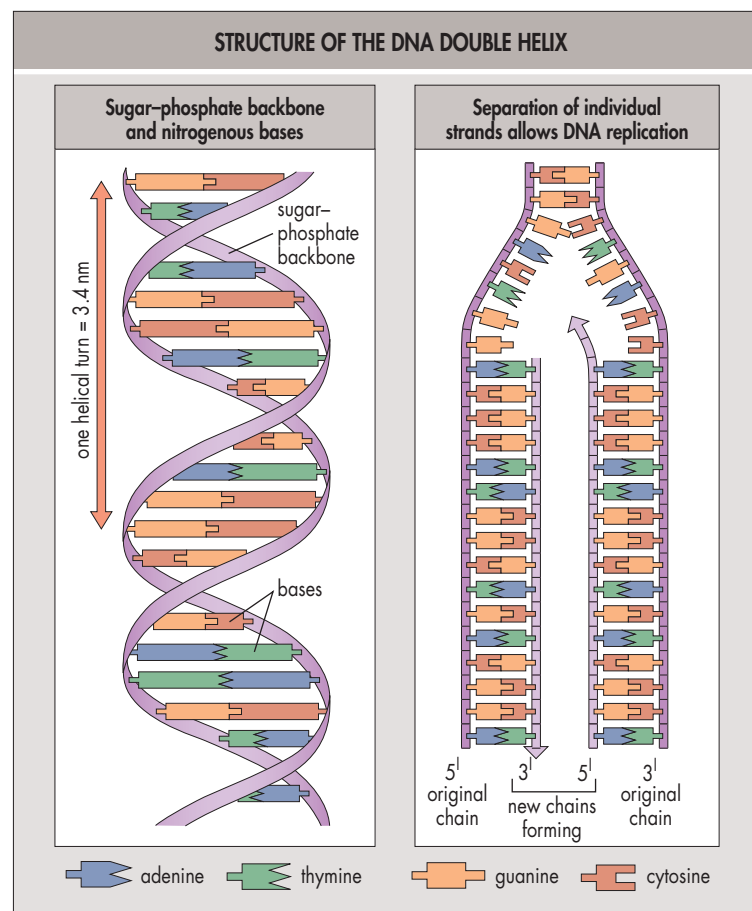
The regulation of cellular growth and function in all human tissue is dependent on the activities of specific protein molecules. In turn, protein activity is dependent on the expression of the genes that contain the correct DNA sequence for protein synthesis. The DNA molecule is a double-stranded helix. Each strand is composed of a sequence of four nucleotide bases—adenine (A), guanine (G), cytosine (C), and thymine (T)—joined to a sugar and a phosphate. The order of the bases in the DNA sequence forms the genetic code that directs the expression of genes. The double-stranded helix is formed as a result of hydrogen bonding between the nucleotide bases of opposite strands.<sup>1</sup> The bonding is specific, such that A always pairs with T, and G always pairs with C. The specificity of the hydrogen bonding is the molecular basis of the accurate copying of the DNA sequence that is required during the processes of DNA replication (necessary for cell division) and transcription of DNA into RNA (necessary for gene expression and protein synthesis; Fig. 1.1.1).

Gene expression begins with the recognition of a particular DNA sequence called the promoter sequence as the start site for RNA synthesis by the enzyme RNA polymerase. The RNA polymerase “reads” the DNA sequence and assembles a strand of RNA that is complementary to the DNA sequence. RNA is a single-stranded nucleic acid composed of the same nucleotide bases as DNA, except that uracil takes the place of thymine. Human genes (and genes found in other eukaryotic organisms) contain many DNA sequences that are not translated into polypeptides and proteins. These sequences are called intervening sequences or introns. Introns do not have any known specific function, and although they are transcribed into RNA by RNA polymerase, they are spliced out of the initial RNA product (termed heteronuclear RNA, or hnRNA) to form the completed messenger RNA (mRNA). Untranslated RNA may have specific functions. For example, antisense RNA and micro RNAs (miRNA) appear to regulate expression of genes.<sup>2</sup> The mRNA is the template for protein synthesis. Proteins consist of one or more polypeptide chains, which are sequences of specific amino acids. The sequence of bases in the mRNA directs the order of amino acids that make up the polypeptide chain. Individual amino acids are encoded by units of three mRNA bases, termed codons. Transfer RNA (tRNA) molecules bind specific amino acids and recognize the corresponding three-base codon in the mRNA. Cellular organelles called ribosomes bind the mRNA in such a configuration that the RNA sequence is accessible to tRNA molecules and the amino acids are aligned to form the polypeptide. The polypeptide chain may be processed by a number of other chemical reactions to form the mature protein (Fig. 1.1.2).

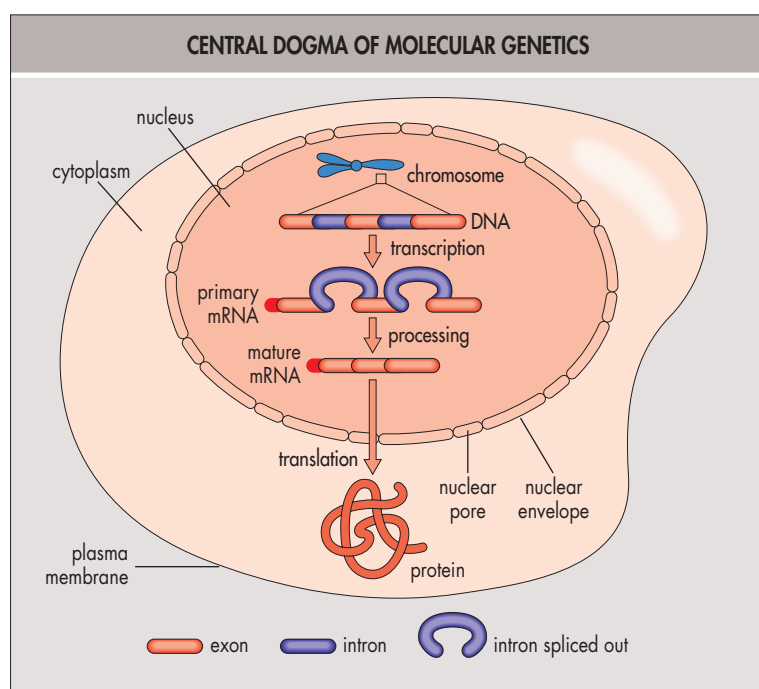
## HUMAN GENOME

Human DNA is packaged as chromosomes located in the nuclei of cells. Chromosomes are composed of individual strands of DNA wound about proteins called histones. The complex winding and coiling process culminates in the formation of a chromosome. The entire collection of human chromosomes includes 22 paired autosomes and two sex chromosomes. Women have two copies of the X chromosome, and men have one X and one Y chromosome (Fig. 1.1.3).

The set consisting of one of each autosome as well as both sex chromosomes is called the *human genome*. The chromosomal molecules of DNA from one human genome, if arranged in tandem end to end, contain approximately 3.2 billion base pairs (bp). The Human Genome Project was formally begun in 1990 with the defined goals to: identify all the approximately 20,000–25,000 genes in human DNA; determine the sequences of the 3 billion chemical base pairs that make up human DNA; store this information in publicly available databases; improve tools for data analysis; transfer related technologies to the private sector; and address the



**Fig. 1.1.1 Structure of the DNA Double Helix.** The sugar-phosphate backbone and nitrogenous bases of each individual strand are arranged as shown. The two strands of DNA pair by hydrogen bonding between the appropriate bases to form the double-helical structure. Separation of individual strands of the DNA molecule allows DNA replication, catalyzed by DNA polymerase. As the new complementary strands of DNA are synthesized, hydrogen bonds are formed between the appropriate nitrogenous bases.



**Fig. 1.12 The Central Dogma of Molecular Genetics.** Transcription of DNA into RNA occurs in the nucleus of the cell, catalyzed by the enzyme RNA polymerase. Mature mRNA is transported to the cytoplasm, where translation of the code produces amino acids linked to form a polypeptide chain, and ultimately a mature protein is produced.

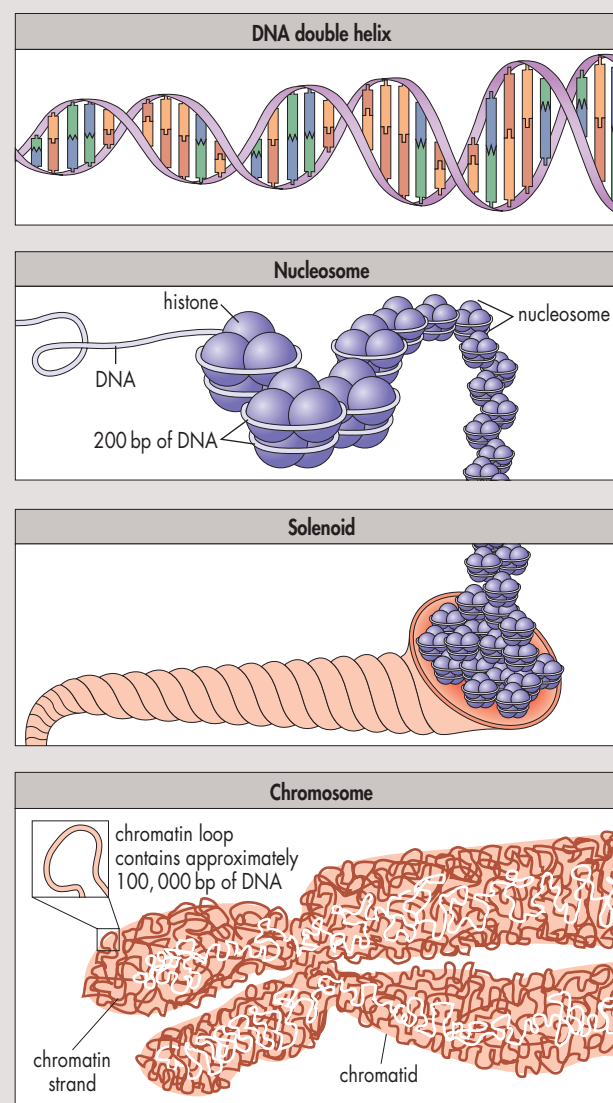
ethical, legal, and social issues that may arise from the project. One of the most important goals, the complete sequence of the human genome, was completed in draft form in 2001.<sup>3</sup> Catalogs of variation in the human genome sequence have also been completed, with the microsatellite repeat map in 1994,<sup>4</sup> the release of the HapMap from the International HapMap Consortium in 2004,<sup>5</sup> and more recently a catalog of variants from the 1000 genomes project.<sup>6</sup> dbSNP (<https://www.ncbi.nlm.nih.gov/projects/SNP/>) is a database listing single nucleotide polymorphisms (SNPs) that are single-letter variations in a DNA base sequence. SNPs are bound together to form haplotypes, which are blocks of SNPs that are commonly inherited together. This binding occurs through the phenomenon of linkage disequilibrium. Within a haplotype block, which may extend for 10,000–100,000 bases of DNA, the analysis of only a subset of all SNPs may “tag” the entire haplotype. The International HapMap project has performed an initial characterization of the linkage disequilibrium patterns between SNPs in multiple different populations. The SNP haplotype blocks identified can be examined for association with human disease, especially common disorders with complex inheritance. Knowledge about the effects of DNA variations among individuals can lead to new ways to diagnose, treat, and prevent human disease. This approach has been used successfully to identify the risk loci for age-related macular degeneration,<sup>7–9</sup> myopia,<sup>10,11</sup> primary open-angle glaucoma,<sup>12–14</sup> and Fuchs’ endothelial dystrophy.<sup>15</sup>

## Mitosis and Meiosis

In order for cells to divide, the entire DNA sequence must be copied so that each daughter cell can receive a complete complement of DNA. The growth phase of the cell cycle terminates with the separation of the two sister chromatids of each chromosome, and the cell divides during mitosis. Before cell division, the complete DNA sequence is copied by the enzyme DNA polymerase in a process called DNA replication. DNA polymerase is an enzyme capable of the synthesis of new strands of DNA using the exact sequence of the original DNA as a template. Once the DNA is copied, the old and new copies of the chromosomes form their respective pairs, and the cell divides such that one copy of each chromosome pair belongs to each cell (Fig. 1.14). Mitotic cell division produces a daughter cell that is an exact replica of the dividing cell.

Meiotic cell division is a special type of cell division that results in a reduction of the genetic material in the daughter cells, which become the reproductive cells—eggs (women) and sperm (men). Meiosis begins with DNA replication, followed by a pairing of the maternal and paternal chromosomes (homologous pairing) and an exchange of genetic material

## PACKAGING OF DNA INTO CHROMOSOMES



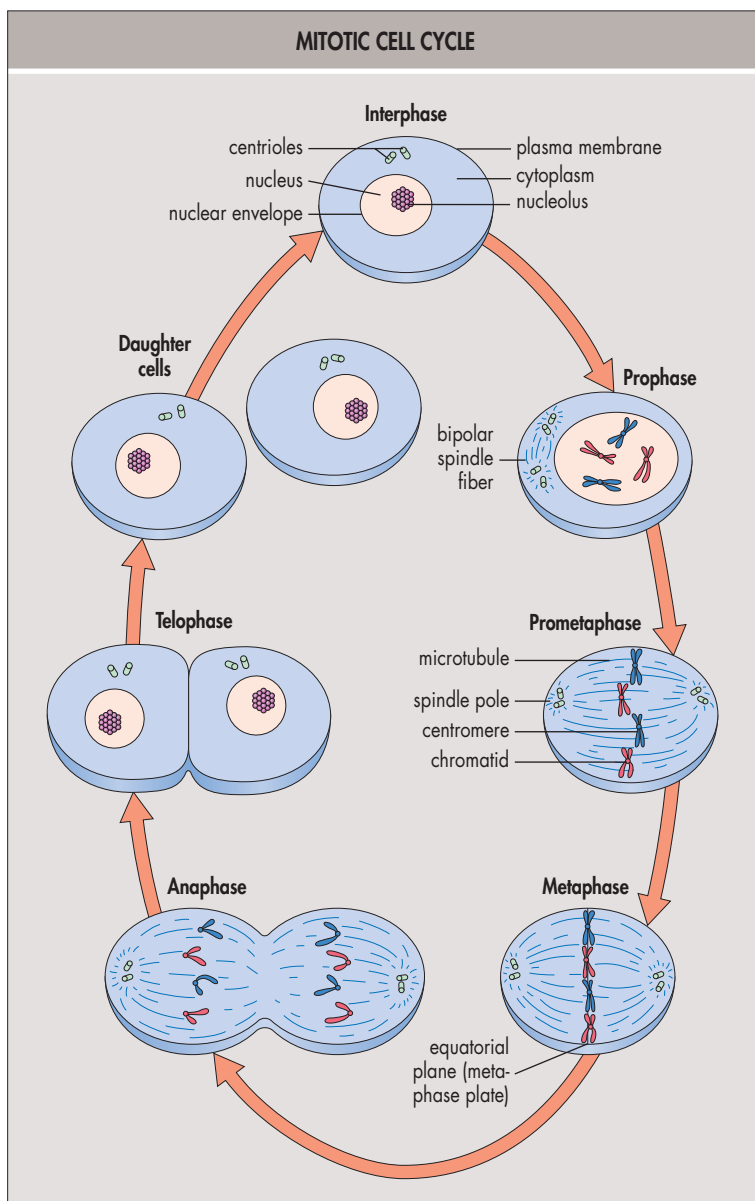
**Fig. 1.13 The Packaging of DNA Into Chromosomes.** Strands of DNA are wound tightly around proteins called histones. The DNA–histone complex becomes further coiled to form a nucleosome, which in turn coils to form a solenoid. Solenoids then form complexes with additional proteins to become the chromatin that ultimately forms the chromosome.

between chromosomes by recombination (Fig. 1.15). The homologous chromosome pairs line up on the microtubule spindle and divide such that the maternal and paternal copies of the doubled chromosomes are distributed to separate daughter cells. A second cell division occurs, and the doubled chromosomes divide, which results in daughter cells that have half the genetic material of somatic (tissue) cells.

## BASIC MENDELIAN PRINCIPLES

Two important rules central to human genetics emerged from the work of Gregor Mendel, a nineteenth century Austrian monk. The first is the principle of segregation, which states that genes exist in pairs and that only one member of each pair is transmitted to the offspring of a mating couple. The principle of segregation describes the behavior of chromosomes in meiosis. Mendel’s second rule is the law of independent assortment, which states that genes at different loci are transmitted independently. This work also demonstrated the concepts of dominant and recessive traits. Mendel found that certain traits were dominant and could mask the presence of a recessive gene.

At the same time that Mendel observed that most traits segregate independently, according to the law of independent assortment, he unexpectedly found that some traits frequently segregate together. The physical arrangement of genes in a linear array along a chromosome is the

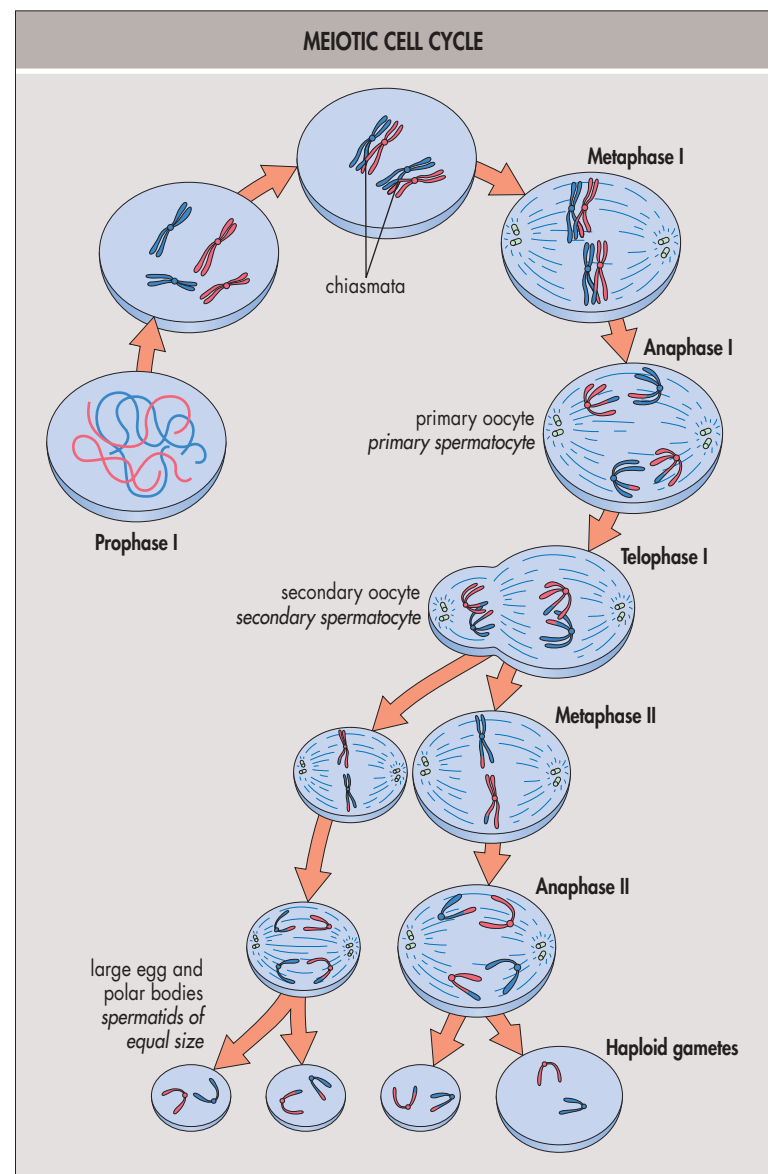


**Fig. 1.1.4 The Mitotic Cell Cycle.** During mitosis, the DNA of a diploid cell is replicated, which results in the formation of a tetraploid cell that divides to form two identical diploid daughter cells.

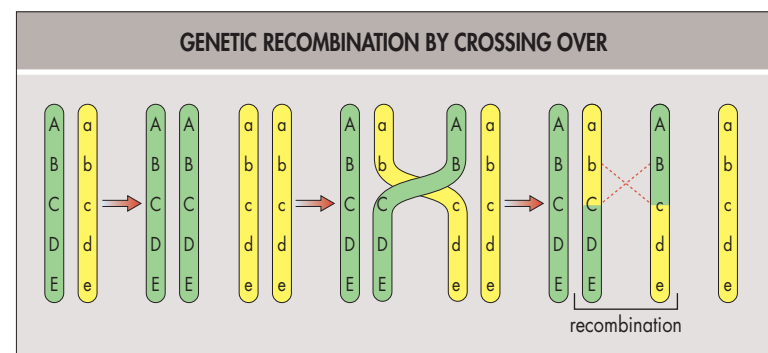
explanation for this surprising observation. On average, a recombination event occurs once or twice between two paired homologous chromosomes during meiosis (Fig. 1.1.6). Most observable traits, by chance, are located far away from one another on a chromosome, such that recombination is likely to occur between them, or they are located on entirely different chromosomes. If two traits are on separate chromosomes, or a recombination event is likely to occur between them on the same chromosome, the resultant gamete formed during meiosis has a 50% chance of inheriting different alleles from each loci, and the two traits respect the law of independent assortment. If, however, the loci for these two traits are close together on a chromosome, with the result that a recombination event occurs between them only rarely, the alleles at each loci are passed to descendent gametes “in phase.” This means that the particular alleles present at each loci in the offspring reflect the orientation in the parent, and the traits appear to be “linked.” For example, in Mendel’s study of pea plants, curly leaves were always found with pink flowers, even though the genes for curly leaves and pink flowers are located at distinct loci. These traits are linked, because the curly leaf gene and the pink-flower gene are located close to each other on a chromosome, and a recombination event only rarely occurs between them. Recombination and linkage are the fundamental concepts behind genetic linkage analysis.

## MUTATIONS

Mutations are changes in the gene DNA sequence that result in a biologically significant change in the function of the encoded protein. If a



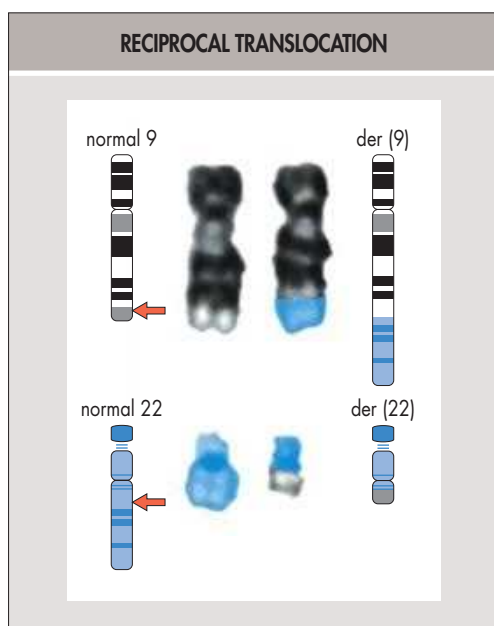
**Fig. 1.1.5 The Meiotic Cell Cycle.** During meiosis, the DNA of a diploid cell is replicated, which results in the formation of a tetraploid cell that divides twice to form four haploid cells (gametes). As a consequence of the crossing over and recombination events that occur during the pairing of homologous chromosomes before the first division, the four haploid cells may contain different segments of the original parental chromosomes. For brevity, prophase II and telophase II are not shown.



**Fig. 1.1.6 Genetic Recombination by Crossing Over.** Two copies of a chromosome are copied by DNA replication. During meiosis, pairing of homologous chromosomes occurs, which enables a crossover between chromosomes to take place. During cell division, the recombined chromosomes separate into individual daughter cells.

particular gene is mutated, the protein product might not be produced, or it might be produced but function poorly or even pathologically (dominant negative effect). *Point mutations* (the substitution of a single base pair) are the most common mutations encountered in human genetics. *Missense mutations* are point mutations that cause a change in the amino





**Fig. 1.1.7 Reciprocal Translocation Between Two Chromosomes.** The Philadelphia chromosome (responsible for chronic myelogenous leukemia) is shown as an example of a reciprocal chromosomal translocation that results in an abnormal gene product responsible for a clinical disorder. In this case an exchange occurs between the long arm of chromosome 9 and the long arm of chromosome 22.

acid sequence of the polypeptide chain. The severity of the missense mutation is dependent on the chemical properties of the switched amino acids and on the importance of a particular amino acid in the function of the mature protein. Point mutations also may decrease the level of polypeptide production because they interrupt the promoter sequence, splice site sequences, or create a premature stop codon.

Gene expression can be affected by the insertion or deletion of large blocks of DNA sequence. These types of mutations are less common than point mutations but may result in a more severe change in the activity of the protein product. A specific category of *insertion mutations* is the expansion of trinucleotide repeats found in patients affected by certain neurodegenerative disorders. An interesting clinical phenomenon, “anticipation,” was understood on a molecular level with the discovery of trinucleotide repeats as the cause of myotonic dystrophy.<sup>16</sup> Frequently, offspring with myotonic dystrophy were affected more severely and at an earlier age than their affected parents and grandparents. Examination of the disease-causing trinucleotide repeat in affected pedigrees demonstrated that the severity of the disease correlated with the number of repeats found in the myotonic dystrophy gene in affected individuals. This phenomenon has been observed in a number of other diseases, including Huntington’s disease.<sup>17</sup>

*Chromosomal rearrangements* may result in breaks in specific genes that cause an interruption in the DNA sequence. Usually, the break in DNA sequence results in a truncated, unstable, dysfunctional protein product. Occasionally, the broken gene fuses with another gene to cause a “fusion polypeptide product,” which may have a novel activity in the cell. Often, such a novel activity results in an abnormality in the function of the cell. An example of such a fusion protein is the product of the chromosome 9;22 translocation that is associated with many cases of leukemia (Fig. 1.1.7).<sup>18,19</sup>

A set consisting of one of each autosome as well as an X or a Y chromosome is called a haploid set of chromosomes. The normal complement of two copies of each gene (or two copies of each chromosome) is called diploidy. Rarely, as a result of abnormal chromosome separation during cell division, a cell or organism may have three copies of each chromosome, which is called *triploidy*. A triploid human is not viable, but some patients have an extra chromosome or an extra segment of a chromosome. In such a situation, the abnormality is called *trisomy* for the chromosome involved. For example, patients with Down syndrome have three copies of chromosome 21, also referred to as trisomy 21.<sup>20</sup>

If one copy of a pair of chromosomes is absent, the defect is called *haploidy*. Deletions of the X chromosome are frequently the cause of Duchenne’s muscular dystrophy.<sup>21</sup>

*Polymorphisms* are changes in DNA sequence that don’t have a significant biological effect. These DNA sequence variants may modify disease processes, but alone are not sufficient to cause disease. Human DNA sequence is highly variable and includes single nucleotide polymorphisms (SNPs), microsatellite repeat polymorphisms (20–50 bp repeats of CA or GT sequence), variable number of tandem repeat polymorphisms (VNTR, repeats of 50–100 bp of DNA), or larger insertion deletions.<sup>22</sup>

## GENES AND PHENOTYPES

The relationship between genes and phenotypes is complex. More than one genetic defect can lead to the same clinical phenotype (genetic heterogeneity), and different phenotypes can result from the same genetic defect (variable expressivity). Retinitis pigmentosa is an excellent example of genetic heterogeneity, as it may be inherited as an X-linked, autosomal dominant, autosomal recessive, or digenic trait, and more than 200 causative genes have been identified.<sup>23</sup> Other ocular disorders that are genetically heterogeneous include congenital cataract, glaucoma, and age-related macular degeneration. Different genes may contribute to a common phenotype because they affect different steps in a common pathway. Understanding the role of each gene in the disease process can help define the cellular mechanisms that are responsible for the disease.

For many genes, a single mutation that alters a critical site in the protein results in an abnormal phenotype. For some diseases, the resulting phenotypes are remarkably similar regardless of the nature of the mutation. For example, a wide variety of mutations in *RB1* cause retinoblastoma. Other diseases, however, exhibit variable expressivity, in which an individual’s mutation may be responsible for severe disease, mild disease, or disease that is not clinically detectable (incomplete penetrance). There are many examples of ocular disease demonstrating variable expressivity, including Kjer’s autosomal dominant optic atrophy,<sup>24</sup> Axenfeld–Rieger syndrome,<sup>25</sup> and aniridia.<sup>26</sup>

Different mutations in the same gene can also result in different phenotypes (allelic heterogeneity). Allelic heterogeneity accounts for the different phenotypes of dominant corneal stromal dystrophies caused by mutations in the *TGFBI/BIGH3*.<sup>27</sup> The phenotypic expression of a mutation may depend on its location within a gene. Such variable expressivity based on the location of the mutation is exemplified by mutations in the *rds* gene, which may cause typical autosomal dominant retinitis pigmentosa or macular dystrophy depending on the position of the genetic defect.<sup>28</sup>

## PATTERNS OF HUMAN INHERITANCE

The most common patterns of human inheritance are autosomal dominant, autosomal recessive, X-linked recessive, and mitochondrial. Fig. 1.1.8 shows examples of these four inheritance patterns. Other inheritance patterns less commonly encountered in human disease include X-linked dominant, digenic inheritance (polygenic), pseudodominance, and imprinting. Fig. 1.1.9 defines the notation and symbols used in pedigree construction.

### Autosomal Dominant

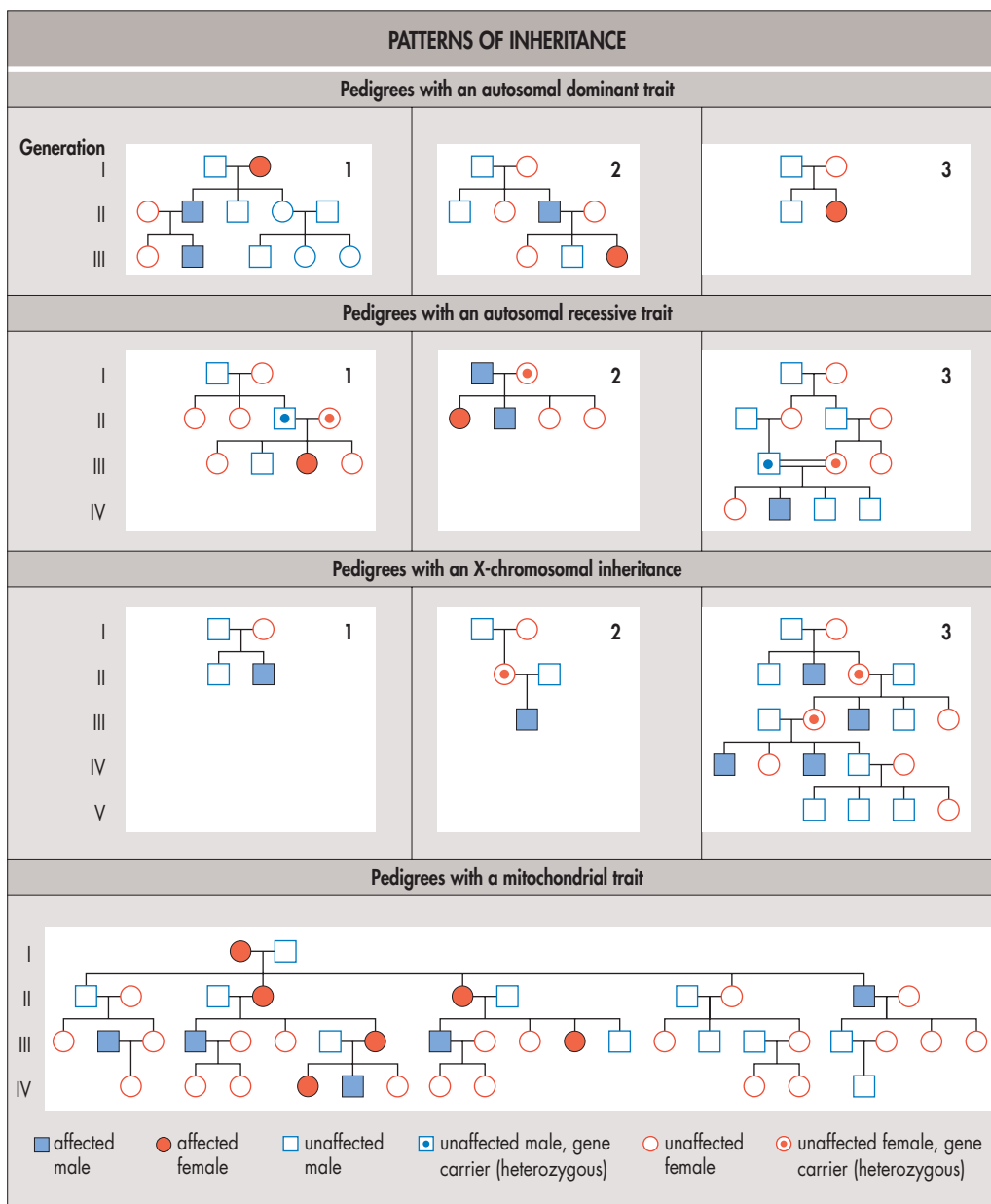
A disease-causing mutation that is present in only one of the two gene copies at an autosomal locus (heterozygous) is a dominant mutation. For example, a patient with dominant retinitis pigmentosa will have a defect in one copy of one retinitis pigmentosa gene inherited from one parent who, in most cases, is also affected by retinitis pigmentosa. The other copy of that gene, the one inherited from the unaffected parent, is normal (wild type). Affected individuals have a 50% chance of having affected siblings and a 50% chance of passing the abnormal gene to their offspring; 50% of children of an affected individual will be affected. For a dominant disease, males and females transmit the disease equally and are affected equally.

True dominant alleles produce the same phenotype in the heterozygous and homozygous states. In humans, most individuals affected by a disease caused by a dominant allele are heterozygous, but occasionally homozygous mutations have been described. In cases where the homozygous individual is more severely affected than the heterozygous individual, the disease is more appropriately noted to be inherited as a semidominant trait. For example, alleles in the *PAX3* gene, causing Waardenburg’s syndrome, are semidominant, because a homozygote with more severe disease compared with their heterozygote relatives has been described.<sup>29</sup>

In some pedigrees with an autosomal dominant disease, some individuals who carry the defective gene do not have the affected phenotype. However, these individuals can still transmit the disease gene to offspring and have affected children. This phenomenon is called reduced penetrance. The gene responsible for retinoblastoma (*RB1*) is only 90% penetrant, which means that 10% of the individuals who inherit a mutant copy of the gene do not develop the tumor.<sup>30</sup>

### Autosomal Recessive

Diseases that require both copies of a gene to be abnormal for development are inherited as recessive traits. Heterozygous carriers of mutant genes are



**Fig. 1.1.8 Patterns of Inheritance.** For pedigrees with an autosomal dominant trait, panel 1 shows inheritance that originates from a previous generation, panel 2 shows segregation that originates in the second generation of this pedigree, and panel 3 shows an apparent “sporadic” case, which is actually a new mutation that arises in the most recent generation. This mutation has a 50% chance of being passed to offspring of the affected individual. For pedigrees with an autosomal recessive trait, panel 1 shows an isolated affected individual in the most recent generation (whose parents are obligate carriers of the mutant gene responsible for the condition), panel 2 shows a pair of affected siblings whose father is also affected (for the siblings to be affected, the mother must be an obligate carrier of the mutant gene), and panel 3 shows an isolated affected individual in the most recent generation who is a product of a consanguineous marriage between two obligate carriers of the mutant gene. For pedigrees with an X-chromosomal trait, panel 1 shows an isolated affected individual whose disease is caused by a new mutation in the gene responsible for this condition, panel 2 shows an isolated individual who inherited a mutant copy of the gene from the mother (who is an obligate carrier), and panel 3 shows segregation of an X-linked trait through a multigeneration pedigree (50% of the male offspring are affected, and their mothers are obligate carriers of the disease). For pedigrees with a mitochondrial trait, the panel shows a large, multigeneration pedigree—men and women are affected, but only women have affected offspring.

usually clinically normal. The same recessive defect might affect both gene copies, in which case the patient is said to be a *homozygote*. Different recessive defects might affect the two gene copies, in which case the patient is a *compound heterozygote*. In a family with recessive disease, both parents are unaffected carriers, each having one wild-type gene (allele) and one mutant gene (allele). Each parent has a 50% chance of transmitting the defective allele to a child. Because a child must receive a defective allele from both parents to be affected, each child has a 25% chance of being affected ( $50\% \times 50\% = 25\%$ ), and 50% of the offspring will be carriers of the disease. If the parents are related, they may be carriers of the same rare mutations, and there is a greater chance that a recessive disease can be transmitted to offspring. Males and females have an equal chance of transmitting and inheriting the disease alleles.

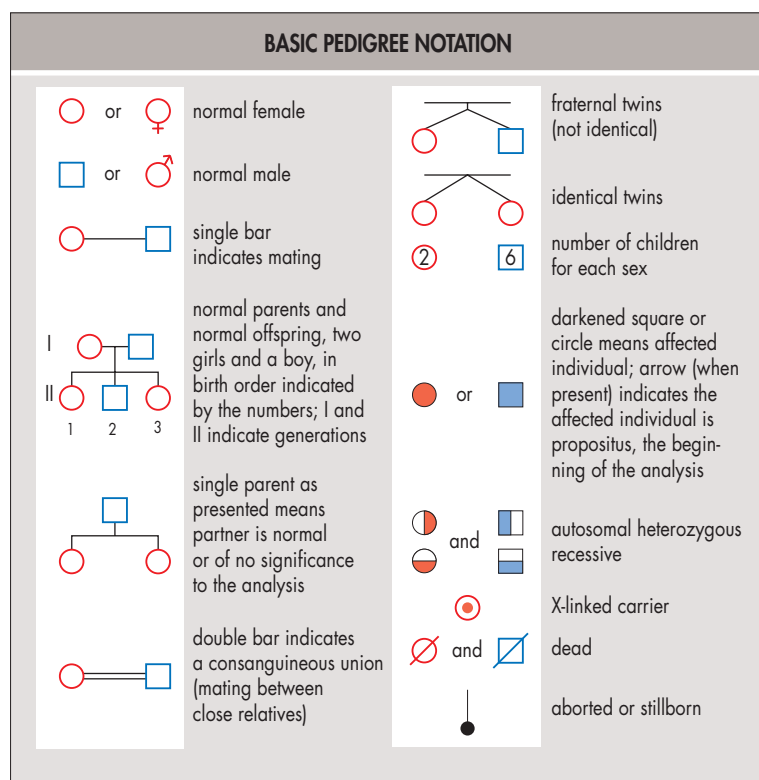
## X-Linked Recessive

Mutations of the X chromosome produce distinctive inheritance patterns, because males have only one copy of the X chromosome and females have two. Most X-linked gene defects are inherited as X-linked recessive traits. Carrier females are typically unaffected because they have both a normal copy and a defective copy of the disease-associated gene. Carrier males are affected because they only have one defective X chromosome and they do not have a normal gene copy to compensate for the defective copy. All of the daughters of an affected male will be carriers of the disease gene because they will inherit the defective X chromosome. None of the sons of an affected male will be affected or be carriers because they will inherit the Y chromosome. Each child of a carrier female has a 50% chance of inheriting the disease gene. If a son inherits the defective

gene, he will be affected. If a daughter inherits the defective gene, she will be a carrier. An important characteristic of X-linked recessive disorders is that males never transmit the disease to sons directly (male-to-male transmission).

Usually female carriers of an X-linked disease gene do not have any clinical evidence of the disease. However, for some X-linked diseases, mild clinical features can be found in female carriers. For example, in X-linked retinoschisis, affected males are severely affected, whereas carrier females have a visually insignificant but clinically detectable retinal abnormality.<sup>31</sup> Mild phenotypic expression of the disease gene can be caused by the process of *lyonization*. In order for males (with one X chromosome) and females (with two X chromosomes) to have equal levels of expression of X-linked genes, female cells express genes from only one of their two X chromosomes. The decision as to which X chromosome is expressed is made early in embryogenesis, and the line of descending cells faithfully adheres to the early choice. As a result, females are mosaics, with some cells in each tissue expressing the maternally derived X chromosome and the remainder expressing the paternally derived X chromosome. When one of the X chromosomes carries an abnormal gene, the proportion of cells that express the mutant versus the normal gene in each tissue can vary.

Females can also be affected by an X-linked recessive disease if the father is affected and the mother coincidentally is a carrier of a mutation in the disease gene. In this case, 50% of daughters would be affected, because 50% would inherit the X chromosome from the mother carrying the disease gene, and all the daughters would inherit the X chromosome from the father carrying the disease gene. Because most X-linked disorders are rare, the carrier frequency of disease genes in the general population is



**Fig. 1.1.9 Basic Pedigree Notation.** Typical symbols used in pedigree construction are defined.

low, and the chance that a carrier female would mate with a male affected by the same disease is quite low.

## Mitochondrial Inheritance

Mitochondria are small organelles located in the cytoplasm of cells. They function to generate ATP for the cell and are most abundant in cells that have high energy requirements, such as muscle and nerve cells. Mitochondria have their own small chromosome—16,569 bp of DNA encoding for 13 mitochondrial proteins, 2 ribosomal RNAs, and 22 tRNAs. Mutations occurring in genes located on the mitochondrial chromosome cause a number of diseases, including Leber's hereditary optic atrophy<sup>32</sup> and Kearns-Sayre syndrome.<sup>33</sup> Mutations occurring on the mitochondrial chromosome are inherited only from the mother because virtually all human mitochondria are derived from the maternal egg. Fathers do not transmit mitochondria to their offspring.

Cells vary in the number of mitochondria they contain, and when cells divide, the mitochondria are divided randomly. As a result, different cells can have varying numbers of mitochondria, and if a fraction of the mitochondria contain a mutated gene, different cells will have a varying proportion of healthy versus mutant mitochondria. The distribution of mutant mitochondria is called *heteroplasmy*, and the proportion of mutant mitochondria can vary from cell to cell and can also change with age. Differences in the relative proportions of mutant mitochondria can partly explain the observed variable severity of mitochondrial diseases and also the variable age of onset of mitochondrial diseases.

## Pseudodominance

This term describes an apparent dominant inheritance pattern due to recessive defects in a disease gene. This situation arises when a parent affected by a recessive disease (two abnormal copies of the disease gene) has a spouse who is a carrier of one abnormal copy of the disease gene. Children from this couple will always inherit a defective gene copy from the affected parent and will have a 50% chance of inheriting the defective gene copy from the unaffected carrier parent. On average, half of the children will inherit two defective gene copies and will be affected. The pedigree would mimic a dominant pedigree because of apparent direct transmission of the disease from the affected parent to affected children and because approximately 50% of the children will be affected. Pseudodominant transmission is uncommon, because few people are asymptomatic carriers for any particular recessive gene.

## X-Linked Dominant Inheritance

This inheritance pattern is similar to X-linked recessive inheritance, except that all females who are carriers of an abnormal gene on the X chromosome are affected rather than unaffected. All of the male offspring are also affected. Incontinentia pigmenti is probably inherited as an X-linked dominant trait. Affected females have irregularly pigmented atrophic scars on the trunk and the extremities and congenital avascularity in the peripheral retina with secondary retinal neovascularization.<sup>34</sup> This and other X-linked dominant disorders occur almost always in females, and it is likely that the X chromosome gene defects causing these diseases are embryonic lethals when present in males.

## Digenic Inheritance and Polygenic Inheritance

Digenic inheritance occurs when a patient has heterozygous defects in two different genes, and the combination of the two gene defects causes disease. Individuals who have a mutation in only one of the genes are normal. Digenic inheritance is different from recessive inheritance, because the two mutations involve different disease genes. In some retinitis pigmentosa families, mutation analysis of the peripherin gene and the *ROM1* gene showed that the affected individuals harbor specific mutations in both genes. Individuals with a mutation in only one copy of either gene were unaffected by the disease.<sup>35</sup> Triallelic inheritance has been described in some families affected by Bardet-Biedl syndrome (BBS). In these pedigrees, affected individuals carry three mutations in one or two BBS genes (12 BBS genes have been identified),<sup>36</sup> and unaffected individuals have only two abnormal alleles. In some families, it has been proposed that BBS may not be a single-gene recessive disease but a complex trait requiring at least three mutant alleles to manifest the phenotype. This would be an example of triallelic inheritance.<sup>37</sup>

If the expression of a heritable trait or predisposition is influenced by the combination of alleles at three or more loci, it is polygenic. Because of the complex inheritance, conditions caused by multiple alleles do not demonstrate a simple inheritance pattern. These complex traits may also be influenced by environmental conditions. Examples of phenotypes in ophthalmology that exhibit complex inheritance because of contributions of multiple genes and environmental factors are myopia,<sup>38</sup> age-related macular degeneration,<sup>39</sup> and adult-onset open-angle glaucoma.<sup>40</sup>

## Imprinting

Some mutations give rise to autosomal dominant traits that are transmitted by parents of either sex, but they are expressed only when inherited from a parent of one particular sex. In families affected with these disorders, they would appear to be transmitted in an autosomal dominant pattern from one parent (either the mother or the father) and would not be transmitted from the other parent. Occasionally, the same mutation gives rise to a different disorder depending on the sex of the parent transmitting the trait. These parental sex effects are evidence of a phenomenon called *imprinting*. Although the molecular mechanisms responsible for imprinting are not completely understood, it appears to be associated with DNA methylation patterns that can mark certain genes with their parental origin.<sup>41</sup>

## MOLECULAR MECHANISMS OF DISEASE

### Autosomal Dominant

Disorders inherited as autosomal dominant traits result from mutations that occur in only one copy of a gene (i.e., in heterozygous individuals). Usually, the parental origin of the mutation does not matter. However, if the gene is subject to imprinting, then mutations in the maternal or paternal copy of the gene may give rise to different phenotypes.

### Haploinsufficiency

Under normal circumstances, each copy of a gene produces a protein product. If a mutation occurs such that one copy of a gene no longer produces a protein product, then the amount of that protein in the cell has been reduced by half. Mutations that cause a reduction in the amount of protein or lead to inactivation of the protein are called *loss-of-function* mutations. For many cellular processes, this reduction in protein quantity does not have consequences, i.e., the heterozygous state is normal, and these mutations may be inherited as recessive traits (see later section). However, for some cellular processes there is an absolute requirement for the full dosage of protein product, which can only be furnished if both copies of

a particular gene are active. Diseases that are caused by inheritance of a single mutation reducing the protein level by half are inherited as dominant traits.

### Gain-of-Function Dominant Negative Effect

Autosomal dominant disorders can be caused by mutant proteins that have a detrimental effect on the normal tissue. Mutations in one copy of a gene may produce a mutant protein that can accumulate as a toxic product or in some other way interfere with the normal function of the cell. The mutant protein may also interfere with the function of the normal protein expressed by the remaining normal copy of the gene, thus eliminating any normal protein activity. It is possible to have gain-of-function mutations that can also be dominant negative because the new function of the protein also interferes with the function of the remaining normal copy of the gene.

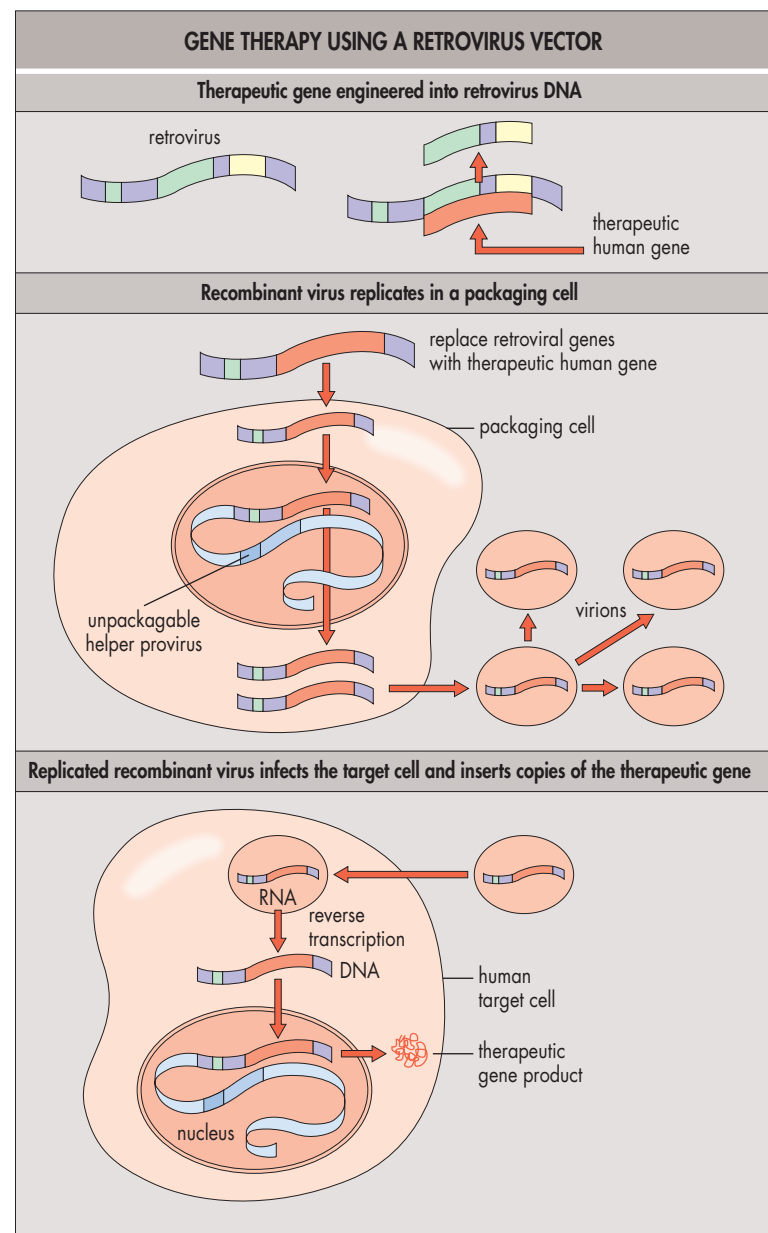
### Autosomal and X-Linked Recessive

Recessive disorders result from mutations present on both the maternal and paternal copies of a gene. Mutations responsible for recessive disease typically cause a loss of biological activity, either because they create a defective protein product that has little or no biological activity or because they interfere with the normal expression of the gene (regulatory mutations). Most individuals heterozygous for recessive disorders, both autosomal and X-linked, are clinically normal.

## GENE THERAPY

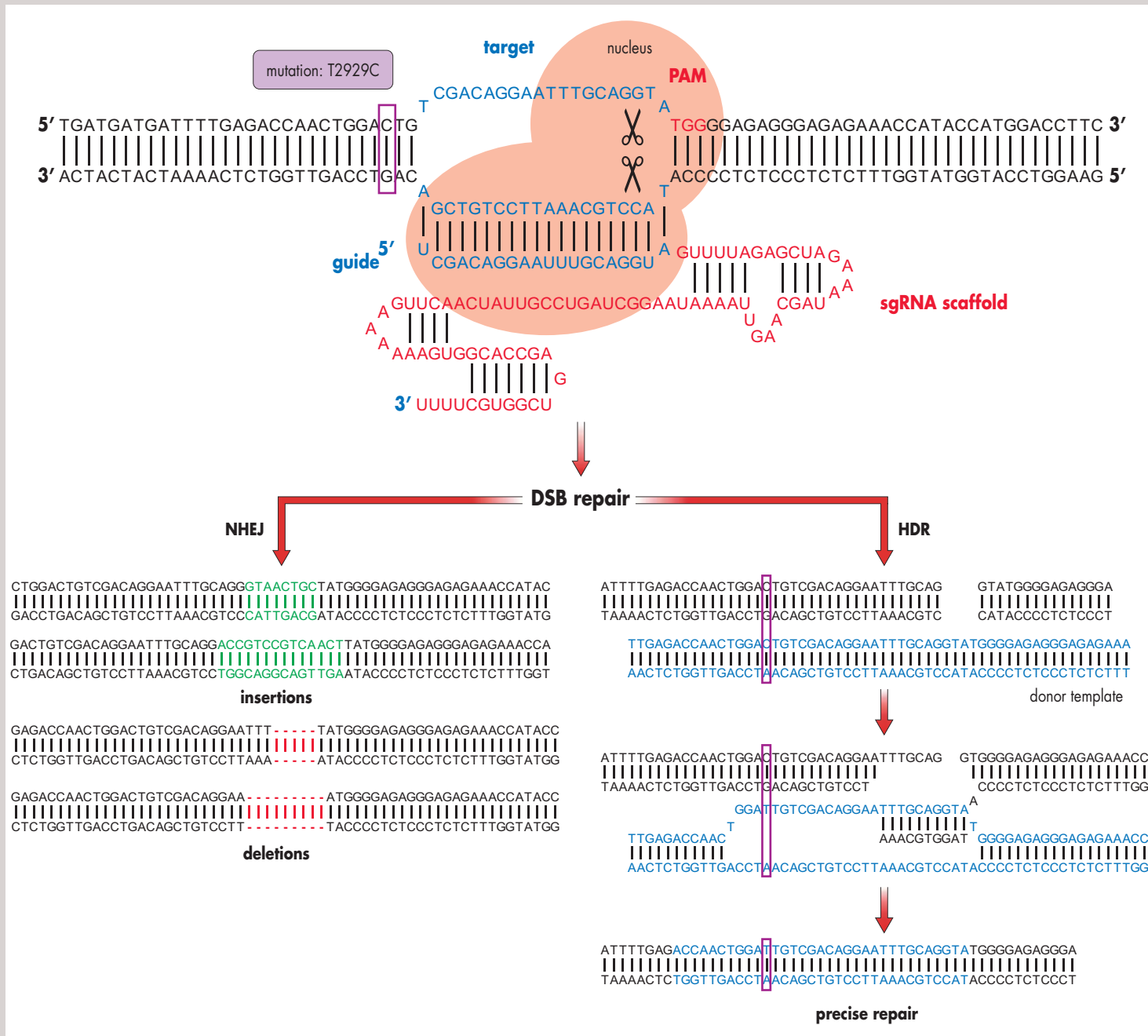
Mutations in the DNA sequence of a particular gene can result in a protein product that is not produced, works poorly, or has acquired a novel function that is detrimental to the cell. Gene-based therapies can involve delivery of a normal gene to disease tissue, replacing or augmenting protein activity with other proteins or small molecules, decreasing abnormal gene expression, or genome-editing techniques to repair the mutation. Therapeutic genes can be delivered to specific tissues using modified viruses as vectors<sup>42</sup> (Fig. 1.1.10). A successful example of this approach is the restoration of vision in a canine model of Leber's congenital amaurosis using a recombinant adeno-associated virus carrying the normal gene (*RPE65*).<sup>43</sup> Human trials using a similar approach also successfully restored vision in patients with *RPE65* mutations.<sup>44</sup>

Diseases caused by mutations that create a gene product that is destructive to the cell (dominant negative or gain of function mutations) need to be treated using a different approach. In these cases, genes or oligonucleotides—in particular antisense molecules—that can reduce expression of the mutated gene are introduced into the cell.<sup>45</sup> Gene editing using CRISPR/Cas9 (Fig. 1.1.11) is another potentially useful approach for gain of function or loss of function mutations.<sup>46</sup> Recent advances have produced highly potent in vivo gene therapy vectors for targeting retina.<sup>47</sup> In addition, new methods are emerging to introduce therapeutic genes into damaged tissue using nonviral mechanisms based on nanotechnology.<sup>48</sup>



**Fig. 1.1.10 Gene Therapy Using a Retrovirus Vector.** A therapeutic gene is engineered genetically into the retrovirus DNA and replaces most of the viral DNA sequences. The “recombinant virus” that carries the therapeutic gene is allowed to replicate in a special “packaging cell” that also contains normal virus that carries the genes required for viral replication. The replicated recombinant virus is allowed to infect the human diseased tissue, or “target cell.” The recombinant virus may invade the diseased tissue but cannot replicate or destroy the cell. The recombinant virus inserts copies of the normal therapeutic gene into the host genome and produces the normal protein product.





**Fig. 1.1.11 Gene Editing Using CRISPR/Cas9.** The CRISPR/Cas-DNA binding creates a double-stranded DNA break (DSB), which can be repaired through nonhomologous end joining (NHEJ) or homology directed repair (HDR) pathways. Here, the *Streptococcus pyogenes* Cas9 nuclease, with a “NGG” protospacer adjacent motif (PAM) sequence, has been directed to target the region containing the BEST1 c929T > C (Ile310Thr) mutation. The guide RNA is complementary to the non-PAM strand, and the DNA cut site is three nucleotides from the PAM sequence. Double strand DNA breaks typically undergo repair by NHEJ, which results in deletions and insertions of variable length. DNA nicks are generally repaired through HDR, where a donor template can be used to incorporate precise genomic modifications. (Adapted from Hung SS, McCaughey T, Swann O, et al. Genome engineering in ophthalmology: application of CRISPR/Cas to the treatment of eye disease. *Prog Retin Eye Res* 2016;53:1–20.)

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# Molecular Genetics of Selected Ocular Disorders

Janey L. Wiggs

# 1.2

**Definition:** The molecular mechanisms underlying selected inherited eye disorders as defined by the responsible genetic mutations.

## Key Features

- Inherited disorders affecting the ocular anterior segment.
- Genetic defects causing abnormal ocular development.
- Inherited retinal degenerations.
- Retinoblastoma.
- Disorders involving the optic nerve and extraocular muscles.

## INTRODUCTION

Tremendous advances in the molecular genetics of human disease have been made in the past 20 years. Many genes responsible for inherited eye diseases have been isolated and characterized, and the chromosomal location of a number of additional genes has been determined. Identifying and characterizing genes responsible for human disease has led to DNA-based methods of diagnosis; novel therapeutic approaches, including gene therapy; and improved knowledge about the molecular events that underlie the disease processes. The disorders discussed in this chapter represent important examples of major advances in human ocular molecular genetics.

Although all inherited disorders are the result of gene mutations, the molecular consequences of a mutation are quite variable. The type of mutation responsible for a disease usually defines the inheritance pattern. For example, mutations that create an abnormal protein detrimental to the cell are typically autosomal dominant, because only one mutant gene is required to disrupt normal cell function. Mutations that result in proteins that have reduced biological activity (loss of function) may be inherited as autosomal dominant or autosomal recessive conditions, depending on the number of copies of normal genes (and the amount of normal protein) required. Disorders may be caused by mutations in mitochondrial DNA that result in a characteristic maternal inheritance pattern. Also, mutations in genes carried on the X chromosome result in characteristic inheritance patterns.

## DOMINANT CORNEAL DYSTROPHIES

The autosomal dominant corneal dystrophies are an excellent example of dominant negative mutations that result in the formation of a toxic protein. Four types of autosomal dominant dystrophies that affect the stroma of the cornea are well characterized<sup>1</sup>:

- Groenouw (granular) type I.
- Lattice type I.
- Avellino (combined granular-lattice).
- Reis-Bücklers.

Although all four corneal dystrophies affect the anterior stroma, the clinical and pathological features differ. The granular dystrophies typically form discrete, white, localized deposits that may obscure vision progressively. Histopathologically, these deposits stain bright red with Masson

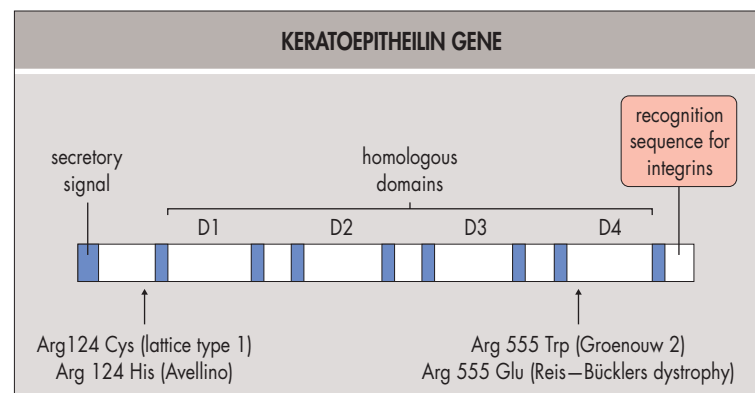
trichrome and have been termed “hyalin.” In lattice dystrophy, branching amyloid deposits gradually opacify the visual axis. These deposits exhibit a characteristic birefringence under polarized light after staining with Congo red. Avellino dystrophy includes features of both granular and lattice dystrophies. Reis-Bücklers dystrophy appears to involve primarily Bowman’s layer and the superficial stroma.

All four dystrophies were mapped genetically to a common interval on chromosome 5q31, and mutations in a single gene, *TGFB1* (also known as *BIGH3*), located in this region were found in affected individuals.<sup>2</sup> The product of this gene, keratoepithelin, is probably an extracellular matrix protein that modulates cell adhesion. Four different missense mutations, which occur at two arginine codons in the gene, have been found (Fig. 1.2.1). Interestingly, mutations at one of these arginine codons cause lattice dystrophy type I or Avellino dystrophy, the two dystrophies characterized by amyloid deposits. Mutations at the other arginine codon appear to result in either granular dystrophy or Reis-Bücklers dystrophy. The mutation analysis of this gene demonstrates that different mutations within a single gene can result in different phenotypes.

The mutation that causes Avellino and lattice dystrophies abolishes a putative phosphorylation site, which probably is required for the normal structure of keratoepithelin. Destruction of this aspect of the protein structure leads to formation of the amyloid deposits that are responsible for opacification of the cornea. Consequently, the mutant protein is destructive to the normal tissue. Mutations at the R555 (arginine at amino acid position 555) appear to result in either granular dystrophy or Reis-Bücklers dystrophy. These phenotype-genotype correlations demonstrate the variable expressivity of mutations in this gene and the significance of alteration of the arginine residues 124 and 555.

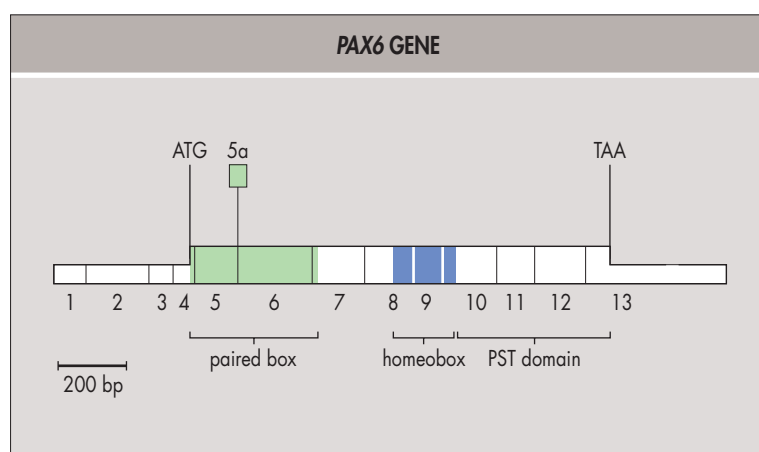
## ANIRIDIA, PETER’S ANOMALY, AUTOSOMAL DOMINANT KERATITIS

Some cellular processes require a level of protein production that results from the expression of both copies of a particular gene. Such proteins may be involved in a variety of biological processes. Certain disorders are caused by the disruption of one copy of a gene that reduces the protein level by half. Such a reduction is also called “haploinsufficiency.”



**Fig. 1.2.1 Keratoepithelin Gene.** Arrows point to the location of the reported mutations.





**Fig. 1.2.2 The *PAX6* Gene.** (Data with permission from Glaser T, et al. *PAX6* gene mutations in aniridia. In: Wiggs JL, editor. *Molecular genetics of ocular disease*. New York: Wiley-Liss; 1995. p. 51–82.)

Mutations in the *PAX6* gene are responsible for aniridia, Peter's anomaly, and autosomal dominant keratitis.<sup>3</sup> Most of the mutations responsible for these disorders alter the paired-box sequence within the gene (Fig. 1.2.2) and result in inactivation of one copy of the *PAX6* gene. The paired-box sequence is an important element that is necessary for the regulatory function of the protein. Losing half the normal paired-box sequence, and probably other regulatory elements within the gene, appears to be the critical event that results in the associated ocular disorders. The protein plays an important role in ocular development, presumably by regulating the expression of genes that are involved in embryogenesis of the eye. A reduction in the amount of active gene product alters the expression of these genes, which results in abnormal development. The genes that code for the lens crystallin proteins are one class of genes developmentally regulated by the *PAX6* protein.

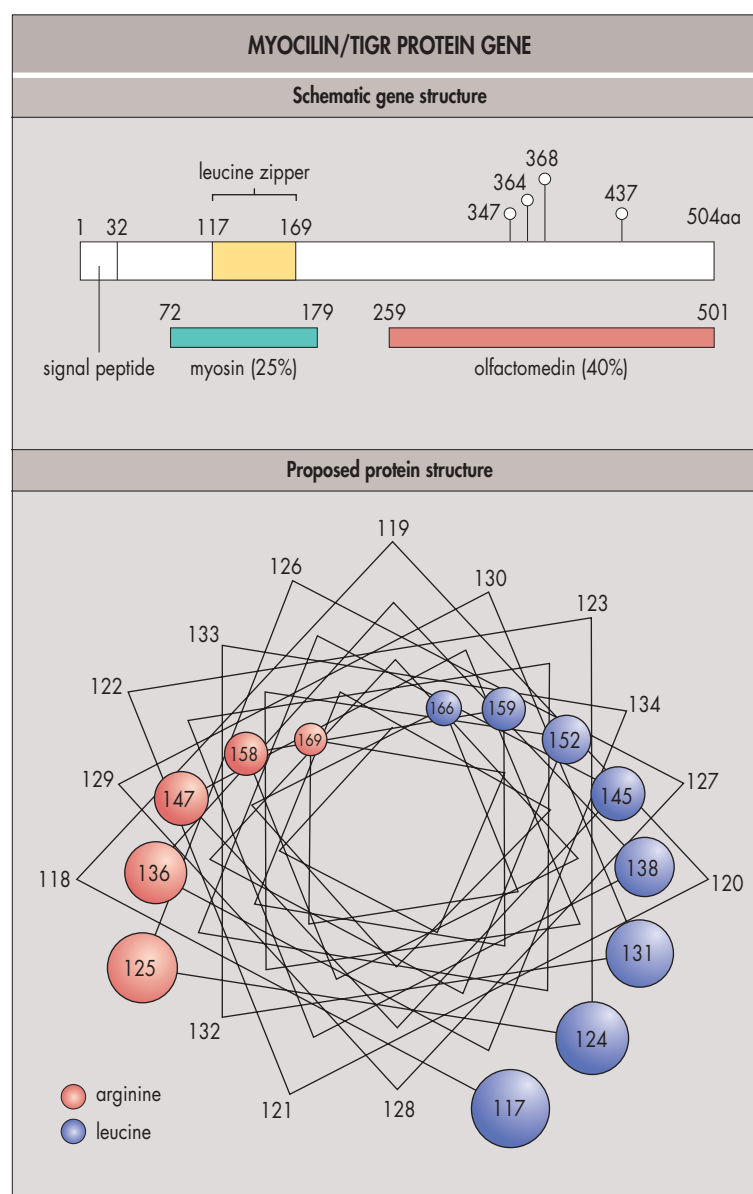
The clinical disorders caused by mutations in *PAX6* exhibit extensive phenotypic variability. Similar mutations may give rise to aniridia, Peter's anomaly, or autosomal dominant keratitis. Variation in the phenotype associated with a mutation is termed "variable expressivity" and is a common feature of disorders that arise from haploinsufficiency. It is possible that the variability of the mutant phenotype results from the random activation of downstream genes that occurs when only half the required gene product is available.

## RIEGER'S SYNDROME

Rieger's syndrome is an autosomal dominant disorder of morphogenesis that results in abnormal development of the anterior segment of the eye. Typical clinical findings may include posterior embryotoxon, iris hypoplasia, iridocorneal adhesions, and corectopia. Approximately 50% of affected individuals develop a high-pressure glaucoma associated with severe optic nerve disease. The cause of the glaucoma associated with this syndrome is not known, although anomalous development of the anterior chamber angle structures is usually found.

Genetic heterogeneity of Rieger's syndrome is indicated by the variety of chromosomal abnormalities that have been associated with the condition, including deletions of chromosome 4 and chromosome 13. Genes for Rieger's syndrome are located on chromosomes 4q25, 13q14, and 6p25. Iris hypoplasia is the dominant clinical feature of pedigrees linked to the 6p25 locus, whereas pedigrees linked to 4q25 and 13q14 demonstrate the full range of ocular and systemic abnormalities found in these patients.

The genes located on chromosomes 4q25 and 6p25 have been identified.<sup>4</sup> The chromosome 4q25 gene (*PITX2*) codes for a bicoid homeobox transcription factor. Like *PAX6*, this gene is expressed during eye development and is probably involved in the ocular developmental processes. The chromosome 6p25 gene *FOXC1* (also called *FKHL7*) is a member of a forkhead family of regulatory proteins. *FOXC1* is expressed during ocular development, and mutations alter the dosage of the gene product. There is some indication that the *FOXC1* protein and the *PITX2* protein interact during ocular development. The identification of other genes responsible for Rieger's syndrome and anterior segment dysgenesis is necessary to determine whether these genes are part of a common developmental pathway or represent redundant functions necessary for eye development.



**Fig. 1.2.3 *MYOC* (Myocilin).** The myosin-like domain, the olfactomedin-like domain, and the leucine zipper are indicated. Amino acids altered in patients with juvenile- or adult-onset glaucoma are shown. (Reprinted by permission of Federation of the European Biochemical Societies from Orteto J, Escibano J, Coca-Prados M. Cloning and characterization of subtracted cDNAs from a human ciliary body library encoding TIGR, a protein involved in juvenile open angle glaucoma with homology to myosin and olfactomedin. *FEBS Lett* 1997;413:349–53.)

## JUVENILE GLAUCOMA

Primary juvenile open-angle glaucoma is a rare disorder that develops during the first two decades of life. Affected patients typically present with a high intraocular pressure (IOP), which ultimately requires surgical therapy. Juvenile glaucoma may be inherited as an autosomal dominant trait, and large pedigrees have been identified and used for genetic linkage analysis. One gene responsible for this condition, *MYOC*, codes for the myocilin protein and is located on chromosome 1q23 (*GLC1A*).

Myocilin has been shown to be expressed in the human retina, ciliary body, and trabecular meshwork. The protein has several functional domains, including a region homologous to a family of proteins called olfactomedins. Although the function of the protein and the olfactomedin domain is not known, nearly all the mutations associated with glaucoma have been found in the olfactomedin portion of the protein (Fig. 1.2.3).<sup>5</sup> Mutations in myocilin also have been associated with some cases of adult-onset primary open-angle glaucoma. Patients with only one copy of the myocilin gene (because of chromosomal deletion removing the second copy of the gene) or without any functional myocilin (caused by homozygosity of a stop-codon polymorphism in the first part of the gene) do not develop glaucoma. Collectively these results suggest that mutations in myocilin cause a gain-of-function or dominant negative effect rather than a loss-of-function or haploinsufficiency. The role of myocilin in IOP

elevation is not completely known, but in vitro studies show that myocilin mutants are misfolded and detergent resistant. Myocilin mutations may be secretion incompetent and accumulate in the endoplasmic reticulum (ER) inducing ER stress. Recent studies using a transgenic mouse model indicate that compounds that relieve ER stress can also reduce the mutation-associated elevation of IOP.<sup>6</sup>

CONGENITAL GLAUCOMA

Congenital glaucoma is a genetically heterogeneous condition, with both autosomal recessive and autosomal dominant forms reported. Two genes responsible for autosomal recessive congenital glaucoma have been identified, *CYP11B1*, a member of the cytochrome P-450 family of proteins (cytochrome P-45011B1)<sup>7</sup> and *LTBP2* (latent transforming growth factor beta binding protein 2).<sup>8</sup> Mutations in *CYP11B1* have been identified in patients with autosomal recessive congenital glaucoma from all over the world but especially in areas where consanguinity is a custom.<sup>9</sup> Responsible mutations disrupt the function of the protein, implying that a loss of function of the protein results in the phenotype.<sup>9</sup> Recurrent mutations are likely to be the result of founder chromosomes that have been distributed to populations throughout the world.<sup>10,11</sup> Because the defects responsible for congenital glaucoma are predominantly developmental, cytochrome P-45011B1 and latent transforming growth factor beta binding protein 2 must play a direct or indirect role in the development of the anterior segment of the eye.

NONSyndromic Congenital Cataract

At least one-third of all congenital cataracts are familial and are not associated with other abnormalities of the eye or with systemic abnormalities. A number of different genes can contribute to congenital cataract, including some that code for the crystallin proteins.<sup>12</sup> The human  $\gamma$ -crystallin genes constitute a multigene family that contains at least seven highly related members. All seven of the  $\gamma$ -crystallin genes have been assigned to chromosome 2q34-q35. Of the genes mapped to this region, only two of them,  $\gamma$ -C and  $\gamma$ -D, encode abundant proteins. Two of the genes,  $\gamma$ -E and  $\gamma$ -F, are pseudogenes, which means they are not expressed in the normal lens. A pedigree affected by the Coppock cataract, a congenital cataract that involves primarily the embryonic lens, was shown to be linked genetically to the region that contains the  $\gamma$ -crystallin genes. In individuals affected by the Coppock cataract, additional regulatory sequences have been found in the promoter region of the  $\gamma$ -E pseudogene.<sup>13</sup> This result implies that the  $\gamma$ -E pseudogene is expressed in affected individuals and that expression of the pseudogene is the event that leads to cataract formation. A number of other genes have been associated with hereditary cataract. A useful collection of mutations and phenotypes can be found at the OMIM website (Table 1.2.1).

RETINITIS PIGMENTOSA

The molecular genetics of retinitis pigmentosa (RP) is exceedingly complex. The disease can exhibit sporadic, autosomal dominant, autosomal recessive, X-linked, or digenic inheritance. At least 200 genes are known to be associated with RP, and a number of genes have been mapped but not yet found. Most of these genes are expressed preferentially in the retina, but some are expressed systemically. A useful resource listing genes responsible for various forms of retinal diseases, including retinitis pigmentosa, can be found at the RetNet website (<http://www.sph.uth.tmc.edu/Retnet/>).

Mutations in rhodopsin can cause an autosomal dominant form of RP that provides an interesting example of how mutant proteins can interfere with normal cellular processes. Initially, one form of autosomal dominant RP was mapped to chromosome 3q24. With a candidate gene approach, the rhodopsin gene was identified as the cause of the disease in affected families.<sup>14</sup> Many of the first mutations detected in the rhodopsin protein were missense mutations located in the C-terminus of the gene (Fig. 1.2.4). To explore the pathogenical mechanisms of these mutations, transgenic mice were created that carried mutant copies of the gene.<sup>15</sup> Histopathological studies of these mice showed an accumulation of vesicles that contained rhodopsin at the junction between the inner and outer segments of the photoreceptors. The vesicles probably interfere with the normal regeneration of the photoreceptors, thus causing photoreceptor degeneration. Because the C-terminus of the nascent polypeptide is involved in the transport of the maturing protein, the accumulation of rhodopsin-filled vesicles is likely to result from abnormal transport of the mutant rhodopsin to the membranes of the outer segments.

Null mutations (mutations that cause a prematurely shortened or truncated protein) also have been found in the rhodopsin gene in patients who have autosomal recessive retinitis pigmentosa (see Fig. 1.2.4).<sup>16</sup> Mutations responsible for recessive disease typically cause a loss of biological activity,

TABLE 1.2.1 Web-Based Resources for Inherited Human Ocular Disorders

NCBI	National Center for Biotechnology Information	<a href="http://www.ncbi.nlm.nih.gov/">http://www.ncbi.nlm.nih.gov/</a>
OMIM	Online Mendelian Inheritance in Man	<a href="http://www.ncbi.nlm.nih.gov/omim">http://www.ncbi.nlm.nih.gov/omim</a>
RetNet	Retinal disease genes	<a href="http://www.sph.uth.tmc.edu/Retnet/">http://www.sph.uth.tmc.edu/Retnet/</a>
Genes and Disease (NCBI Bookshelf)	Systemic inherited disorders	<a href="http://www.ncbi.nlm.nih.gov/books/NBK22183/">http://www.ncbi.nlm.nih.gov/books/NBK22183/</a>
UCSC	Human genome sequence browser	<a href="http://www.genome.ucsc.edu">http://www.genome.ucsc.edu</a>

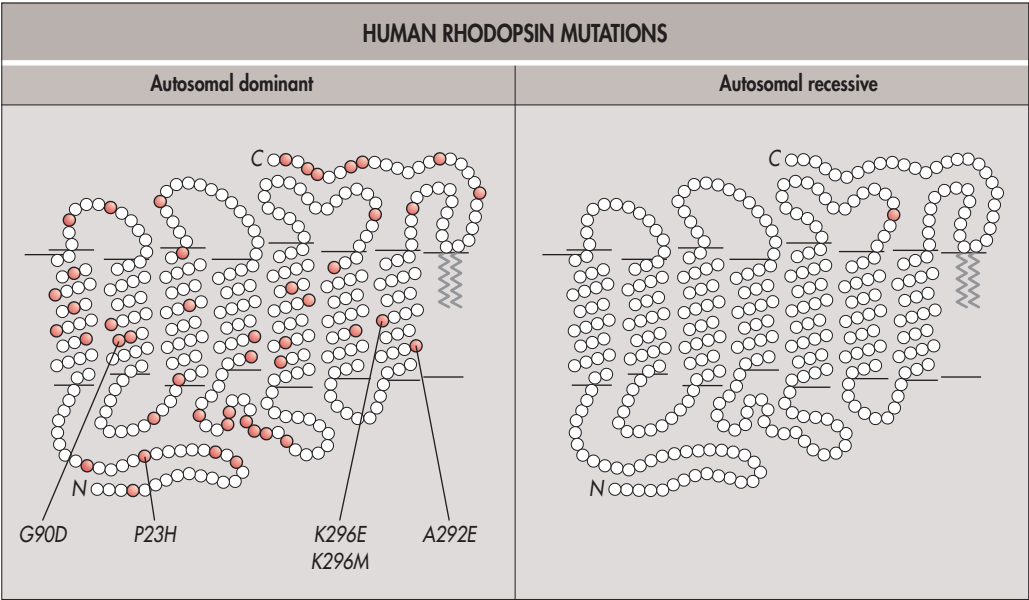


Fig. 1.2.4 Human Rhodopsin Mutations. The red circles indicate the amino acids altered by mutations in the gene in patients who have autosomal dominant retinitis pigmentosa. The translational stop site that results from a nonsense mutation is indicated as a red circle in a patient who has autosomal recessive retinitis pigmentosa.

either because they create a defective protein product that has little or no biological activity or because they interfere with the normal expression of the gene (regulatory mutations). Most individuals heterozygous for autosomal recessive disorders are clinically normal. Unlike the missense mutations responsible for the dominant form of the disease, the null mutations in rhodopsin produce an inactive protein that is not destructive to the cell. Null mutations result in retinitis pigmentosa only when they are present in both copies of the gene. Mutations in just one copy of the gene (heterozygous individuals) do not have a clinically detectable phenotype.

## STARGARDT DISEASE

Stargardt disease is characterized by progressive bilateral atrophy of the macular retinal pigment epithelium (RPE) and neuroepithelium, with the frequent appearance of orange–yellow flecks distributed around the macula. The choroid is characteristically dark on fluorescein angiography in about 80% of cases. The disease results in a loss of central acuity that may have a juvenile to adult onset and is inherited as an autosomal recessive trait. Inactivation of both copies of the responsible gene is necessary to cause the disease. Mutations in a photoreceptor cell-specific ATP-binding transporter gene (*ABCA4* or *ABCR*) have been found in affected patients.<sup>17,18</sup> Most disease-related mutations are missense mutations in conserved amino acid positions. The retina-specific ABC transporter (*ABCA4*) responsible for Stargardt disease is a member of a family of transporter proteins and is expressed in rod photoreceptors, which indicates that this protein mediates the transport of an essential molecule either into or out of photoreceptor cells. Accumulation of a lipofuscin-like substance in *ABCA4*-related disease may result from inactivation of this transporter protein.

## X-LINKED JUVENILE RETINOSCHISIS

Retinoschisis is a maculopathy caused by intraretinal splitting; the defect most likely involves retinal Müller cells. Retinoschisis is inherited as an X-linked recessive trait. X-linked recessive disorders, like autosomal recessive disorders, are caused by inactivating mutations. Because men have only one X chromosome, one mutant copy of a gene responsible for an X-linked trait results in the disease. Usually women are heterozygous carriers of recessive X-linked traits and do not demonstrate any clinical abnormalities. Mutations in the gene coding for retinoschisin have been shown to be the cause of the disease.<sup>19</sup> The protein is involved in cell–cell interaction and may be active in cell adhesion processes during retinal development. Most retinoschisis gene (*XLR51*) mutations cause a loss of protein function.

## NORRIE'S DISEASE

Norrie's disease is an X-linked disorder characterized by progressive, bilateral, congenital blindness associated with retinal dysplasia that has been referred to as a “pseudoglioma.” The disease can include mental retardation and hearing defects. Norrie's disease is inherited as an X-linked recessive trait, and a causative gene has been identified on the X chromosome that has a tertiary structure similar to transforming growth factor- $\beta$ .<sup>20</sup> Norrie's disease is a member of the familial exudative vitreoretinopathy (FEVR) syndromes, which are genetically heterogeneous inherited blinding disorders of the retinal vascular system, and to date three other loci have been mapped.<sup>21</sup> Mutations in the Norrie's disease gene have been found in a small subset of patients with severe retinopathy of prematurity (ROP), although defects in this gene do not appear to be a major factor in ROP.<sup>22</sup>

## SORSBY'S MACULAR DYSTROPHY

Sorsby's macular dystrophy is an autosomal dominant disorder characterized by early onset bilateral and multifocal choroidal neovascularization resulting in macular edema, hemorrhage, and exudation. The disease typically begins at about 40 years of age. Missense mutations in the gene that codes for tissue inhibitor metalloproteinase-3 (TIMP-3) have been found in affected individuals.<sup>23</sup> This protein is involved in remodeling of the extracellular matrix. Inactivation of the protein may lead to an increase in activity of the metalloproteinase, which may contribute to the pathogenesis of the disease.<sup>23</sup>

## GYRATE ATROPHY

Hyperornithinemia results from deficiency of the enzyme ornithine ketoacid aminotransferase and has been shown to be the cause of gyrate

atrophy, an autosomal recessive condition characterized by circular areas of chorioretinal atrophy. Mutations in the gene for ornithine ketoacid aminotransferase mapped to chromosome 10q26 have been associated with the disease in affected individuals.<sup>24</sup> Most of the responsible mutations are missense mutations, which presumably result in an inactive enzyme. One mutation has been found in homozygous form in the vast majority of apparently unrelated cases of gyrate atrophy in Finland, an example of a founder effect that produces a common mutation in an isolated population.

Identification of the enzyme defect responsible for this disease makes it an interesting candidate for gene therapy. Previous studies indicated that a lower ornithine level, achieved through a strict low-arginine diet, may retard the progression of the disease.<sup>25</sup> Replacement of the abnormal gene—or genetic engineering to produce a supply of normal enzyme—may result in a reduction of ornithine levels without dietary restrictions.

## COLOR VISION

Defective red–green color vision affects 2%–6% of men and results from a variety of defects that involve the color vision genes. In humans, the three cone pigments—blue, green, and red—mediate color vision. Each visual pigment consists of an integral membrane apoprotein bound to the chromophore 11-*cis* retinal. The genes for the red and green pigments are located on the X chromosome, and the gene for the blue pigment is located on chromosome 7. The X chromosome location of the red and green pigment genes accounts for the X-linked inheritance pattern observed in red or green color vision defects.

The common variations in red or green color vision are caused by the loss of either the red or the green cone pigment (dichromasy) or by the production of a visual pigment with a shifted absorption spectrum (anomalous trichromasy). A single amino acid change (serine to alanine) in the red photopigment gene is the most common color vision variation. Among Caucasian men, 62% have serine at position 180 in the red pigment protein, and 38% have alanine in this position. Men who carry the red pigment with serine at position 180 have a greater sensitivity to long-wavelength radiation than do men who carry alanine at this position.<sup>26</sup> Recent work suggests that gene therapy could correct color vision defects.<sup>27</sup>

## RETINOBLASTOMA

A gene responsible for the childhood eye tumor retinoblastoma was identified in 1986 on chromosome 13q14.<sup>28</sup> The gene product is involved in regulation of the cell cycle. Absence of this protein in an embryonic retinal cell results in the uncontrolled cell growth that eventually produces a tumor.<sup>29</sup> Susceptibility to hereditary retinoblastoma is inherited as an autosomal dominant trait. Mutations in the retinoblastoma gene result in underproduction of the protein product or production of an inactive protein product. A retinal cell that has only one mutant copy of the retinoblastoma gene does not become a tumor. However, inactivation of the remaining normal copy of the retinoblastoma gene is very likely in at least one retinal cell out of the millions present in each retina. Among individuals who inherit a mutant copy of the retinoblastoma gene, 90% sustain a second hit to the remaining normal copy of the gene and develop a tumor (Fig. 1.2.5).<sup>30</sup> Fifty percent of the offspring of individuals affected by hereditary retinoblastoma will inherit the mutant copy of the gene and are predisposed to develop the tumor. Approximately 10% of individuals who inherit a mutation do not sustain a second mutation and do not develop a tumor. The offspring of these “carrier” individuals also have a 50% chance of inheriting the mutant copy of the retinoblastoma gene (see Fig. 1.2.5).

## ALBINISM

Autosomal recessive diseases often result from defects in enzymatic proteins. Albinism is the result of a series of defects in the synthesis of melanin pigment.<sup>31</sup> Melanin is synthesized from the amino acid tyrosine, which is first converted into dihydroxyphenylalanine through the action of the copper-containing enzyme tyrosinase. An absence of tyrosinase results in one form of albinism. Mutations in the gene that codes for tyrosinase are responsible for tyrosinase-negative ocular cutaneous albinism. Most of the mutations responsible for this disease cluster in the binding sites for copper and disrupt the metal ion–protein interaction necessary for enzyme function.<sup>32</sup> Both copies of the gene for tyrosinase must be mutated before a significant interruption of melanin production occurs. Heterozygous individuals do not have a clinically apparent phenotype, which suggests that one functional copy of the gene produces sufficient active enzyme for the melanin level to be phenotypically normal (Fig. 1.2.6).

## LEBER'S OPTIC NEUROPATHY

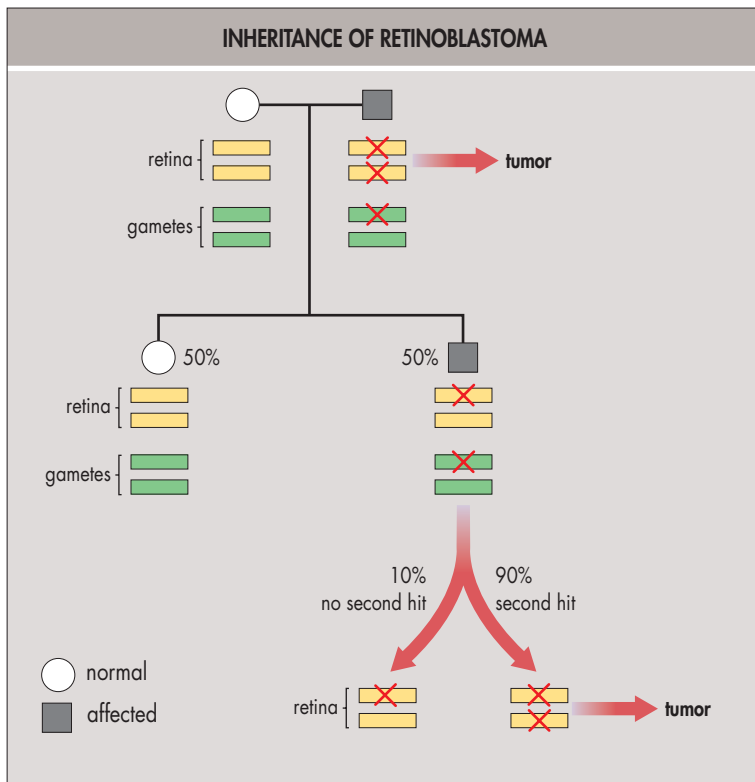
Mutations in mitochondrial DNA are an important cause of human disease. Disorders that result from mutations in mitochondrial DNA demonstrate a maternal inheritance pattern. Maternal inheritance differs from mendelian inheritance, in that men and women are affected equally, but only affected females transmit the disease to their offspring. The characteristic segregation and assortment of mendelian disorders depend on the meiotic division of maternal and paternal chromosomes found in the nucleus of cells. In contrast, mitochondrial DNA is derived from the maternal egg and replicates and divides with the cell cytoplasm by simple fission. A mutation that occurs in mitochondrial DNA is present in all cells of the organism, which includes the gametes. Female eggs have abnormal mitochondria that may be passed to offspring. Sperm contain mitochondria but do not transmit mitochondria to the fertilized egg. A man who carries a mitochondrial DNA mutation may be affected by the disease, but he cannot transmit the disease to his offspring.

Leber's hereditary optic neuropathy (LHON) was one of the first diseases to be recognized as a mitochondrial DNA disorder.<sup>33</sup> In familial cases

of the disease, all affected individuals were related through the maternal lineage, consistent with inheritance of human mitochondrial DNA.

Patients affected by LHON typically present in midlife with acute or subacute, painless, central vision loss that results in a permanent central scotoma and loss of sight. The manifestation of the disease varies tremendously, especially with respect to onset of visual loss and severity of the outcome. The eyes may be affected simultaneously or sequentially; the disease may progress rapidly over a period of weeks to months or slowly over several years. Within a family, the disease may also vary among affected members.

Several factors contribute to the variable phenotype of this condition. Certain mutations are associated with more severe disease, and some mitochondrial DNA haplotypes appear to be associated with more severe disease.<sup>34</sup> Another important factor that affects the severity of the disease is the heteroplasmic distribution of mutant and normal mitochondria. Not all mitochondria present in diseased tissue carry DNA mutations. During cell division, mitochondria and other cytoplasmic organelles are distributed arbitrarily to the daughter cells. Consequently, the daughter cells are likely to have unequal numbers of mutant and normal mitochondria (Fig. 1.2.7). Because the diseased mitochondria are distributed to developing tissues, some tissues accumulate more abnormal mitochondria than others. Hence, some individuals have more abnormal mitochondria in the optic nerve and develop a more severe optic neuropathy.



**Fig. 1.2.5 Inheritance of Retinoblastoma.** Individuals who inherit a mutation in the retinoblastoma gene are heterozygous for the mutation in all cells of the body. The “second hit” to the remaining normal copy of the gene occurs in a developing retinal cell and leads to tumor formation (see text for explanation).

## CONGENITAL FIBROSIS SYNDROMES AND DISORDERS OF AXON GUIDANCE

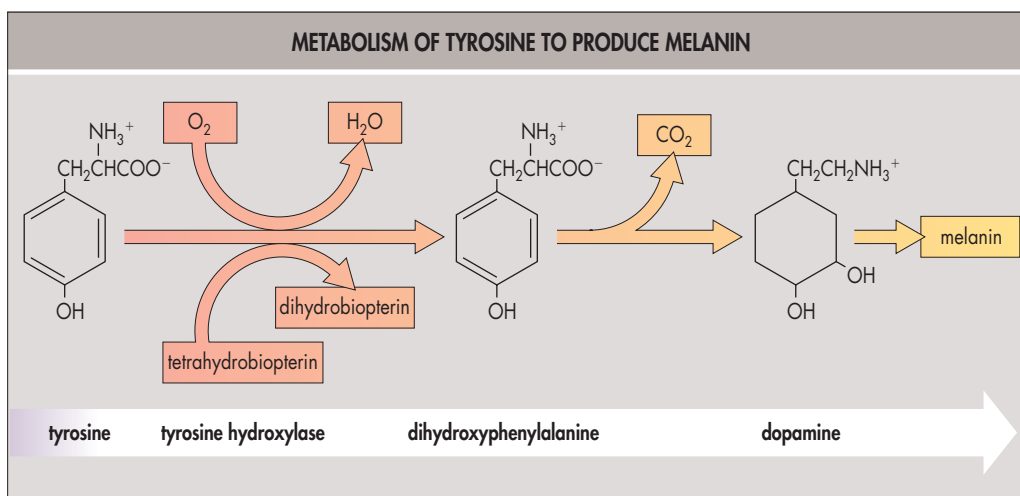
Congenital fibrosis of the extraocular muscles and Duane's syndrome are inherited forms of congenital fibrosis and strabismus. At least 20 genes contribute to these conditions and other disorders of axon guidance,<sup>35</sup> with the *ARIX/PHOX2A* genes causing congenital fibrosis of extraocular muscles type 2<sup>36</sup> and the *SALL4* gene causing Duane's radial ray syndrome.<sup>37</sup>

## AUTOSOMAL DOMINANT OPTIC ATROPHY

Of the inherited optic atrophies, autosomal dominant Kjer optic atrophy is the most common. This disease results in a progressive loss of visual acuity, centrocecal scotoma, and bilateral temporal atrophy of the optic nerve. The onset is typically in the first two decades of life. The condition is inherited as an autosomal dominant trait with variable expressivity, and mutations in *OPA1* have been found in a number of affected families.<sup>38,39</sup> *OPA1* codes for a dynamin-related GTPase that is targeted to mitochondria and may function to stabilize mitochondrial membrane integrity. It is interesting that this gene and the gene responsible for another optic atrophy, Leber's hereditary optic atrophy (see earlier), both function in the mitochondria, emphasizing the critical role of mitochondria in optic nerve function.

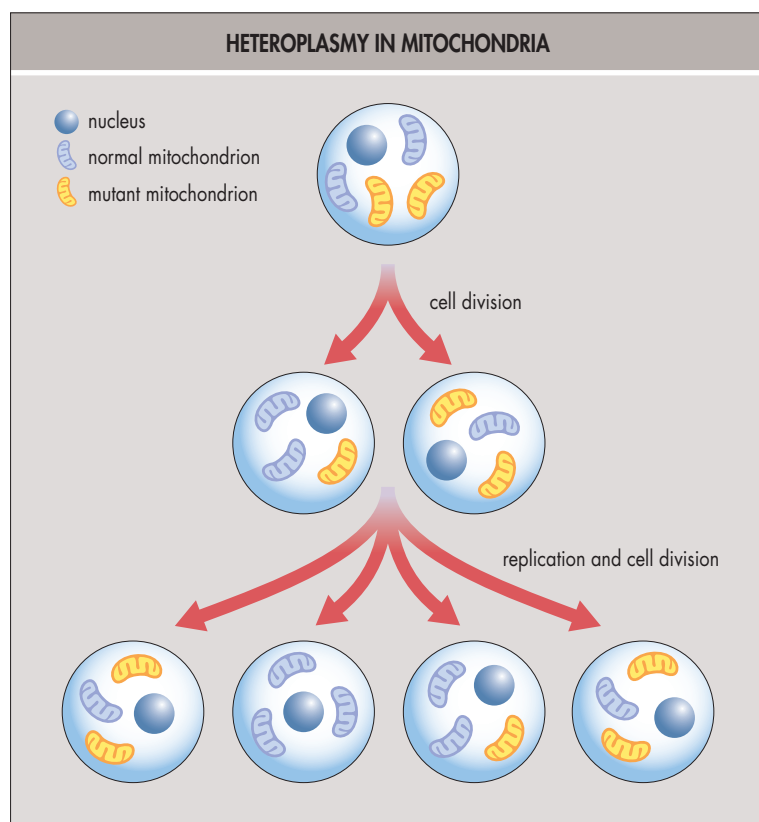
## COMPLEX TRAITS

Human phenotypes inherited as polygenic or “complex” traits do not follow the typical patterns of mendelian inheritance. Complex traits are relatively



**Fig. 1.2.6 Metabolism of Tyrosine to Produce Melanin.** In the final step, dopamine is converted into an indole derivative that condenses to form the high-molecular-weight pigment melanin.





**Fig. 1.2.7 Heteroplasmy in Mitochondria.** Daughter cells that result from the division of a cell that contains mitochondria with mutant DNA may contain unequal numbers of mutant mitochondria. Subsequent divisions lead to a population of cells with different numbers of normal and abnormal mitochondria.

common disorders. Generally, DNA variants associated with these disorders are not causal but influence disease susceptibility.<sup>40</sup> Environmental factors may also contribute to complex disease risk. For example, genetic variants in complement factor H (CFH) and *LOC37718* are known to be major genetic risk factors for age-related macular degeneration,<sup>41–44</sup> and combined with smoking the risk is increased.<sup>45</sup> The genome-wide association study (GWAS) approach has also successfully identified genes contributing to other common complex ocular conditions and traits,<sup>40</sup> including primary open-angle glaucoma,<sup>46,47</sup> primary angle-closure glaucoma,<sup>48</sup> exfoliation syndrome and glaucoma,<sup>49,50</sup> myopia,<sup>51,52</sup> and Fuchs' endothelial dystrophy.<sup>53</sup>

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# Genetic Testing and Genetic Counseling

# 1.3

Janey L. Wiggs

**Definition:** A genetic test is any clinical or laboratory investigation that provides information about the likelihood that an individual is affected with a heritable disease. The majority of genetic tests are based on molecular evaluations of genomic DNA designed to identify the DNA mutations responsible for the disease.

**Key Features**

- Indications and methods for genetic testing for ocular disorders.
- Genetic counseling and ethical issues.

GENETIC TESTING

Role of Genetic Testing in the Clinic

DNA-based genetic tests can identify individuals at risk for disease before any clinical evidence is present (presymptomatic testing).<sup>1</sup> This information coupled with effective genetic counseling and clinical screening can be useful. An effective presymptomatic test needs to meet the specificity and sensitivity expectations for any clinical test. Sensitivity is the number of affected individuals that are positive for a test compared with the total number of affected individuals (including those that tested negative for the test). Specificity is the number of unaffected individuals that are negative for the test compared with the total number of unaffected individuals tested (including those that tested positive for the test) (Fig. 1.3.1).

The identification of a mutation responsible for a disease through DNA-based genetic testing can establish a molecular diagnosis. For some disorders, such as juvenile open-angle glaucoma caused by mutations in *MYOC*,<sup>2</sup> specific mutations have been correlated with severity of disease or other clinical features that are useful prognostically. A molecular diagnosis may also help guide therapy and is required before gene-based therapies can be utilized. For example, mutations in a number of different genes can cause Leber’s hereditary amaurosis, but only those patients with disease due to mutations in *RPE65* will benefit from novel *RPE65*-based therapies using gene replacement.<sup>3</sup>

SPECIFICITY AND SENSITIVITY		
	Affected individuals	Unaffected individuals
Individuals positive for test	A	B
Individuals negative for test	C	D
Sensitivity $\frac{A}{A+C}$ Specificity $\frac{D}{B+D}$		

**Fig. 1.3.1 Definition of Sensitivity and Specificity for a Laboratory Test.** Sensitivity is defined as the number of affected individuals positive for the test (A) divided by the total number of affected individuals tested (A + C). Specificity is defined as the number of unaffected individuals negative for the test (D) divided by the total number of unaffected individuals tested (B + D).

Methods for DNA-Based Genetic Testing

Although genetic testing can be performed using DNA, RNA, or protein, DNA is the easiest to work with, and most genetic tests use this as the starting material. A biological sample from the patient is needed before genetic testing can be performed. The inclusion of family members may help the evaluation, but they are not absolutely required. DNA for testing can be obtained from a number of sources, including blood samples, mouthwash samples or buccal swabs, archived pathology specimens, or from hair.<sup>4-6</sup>

Genomic DNA sequencing is the most commonly used method to detect mutations. For many disorders, sequencing the entire responsible gene is necessary, including all exons, immediate flanking intron sequences with splice signals and 5’ and 3’ flanking regulatory regions. Some disorders are caused by a specific mutation in a gene, and genetic testing can be limited to an evaluation of a single gene. For other diseases, however, such as the inherited retinal degenerations, sequencing multiple genes may be required before a causative mutation is identified. For diseases with many causative genes, a panel test that allows for sequencing all genes at once is both more effective and more efficient.<sup>7</sup> Alternatively, whole exome sequencing (WES) that captures and sequences all coding regions of the genome can also be a preferred approach for disorders with many possible genetic mutations.<sup>8</sup> Genomic DNA sequencing will not usually identify large chromosomal abnormalities, including large copy number variations (deletions or insertions) or chromosomal translocations. Other techniques are necessary to detect large chromosomal abnormalities, including karyotyping and multiplex ligation-dependent probe amplification (MLPA).<sup>9,10</sup> For diseases that are caused primarily by a limited set of mutations (for example, the three mutations that commonly cause Leber’s hereditary optic neuropathy (LHON),<sup>11</sup> specific tests such as allele-specific polymerase chain reaction (PCR) amplification or TaqMan assays can be used and can be more efficient than sequencing the entire gene (Table 1.3.1).

Current Recommendations for Genetic Testing for Ophthalmic Diseases

Currently, genetic testing is indicated for patients with clinical evidence of a disorder whose causative genes have been identified and for which

TABLE 1.3.1 Common Types of Genetic Tests

Method	Indication	Example
Single gene DNA sequencing	Different mutations distributed throughout a single gene are known to cause the inherited condition	Sequencing <i>OPA1</i> in patients with autosomal dominant optic neuropathy
Multiple gene DNA sequencing	Mutations in multiple genes are known to cause the condition	Inherited retinal degenerations
Multiplex ligation-dependent probe amplification (MLPA)	Detects deletions and duplications in genes known to cause the condition and that may be missed by sequence-based approaches	MLPA testing for <i>PAX6</i> deletions in patients with aniridia
TaqMan assay or allele-specific assay	Detects a single DNA base pair change and is used if a small set of mutations are primarily the cause of the condition	Three mutations commonly cause Leber’s hereditary optic neuropathy (LHON)
Karyotype	Detects large chromosomal rearrangements including deletions, duplications, and translocations	Down syndrome

the identification of the genetic mutation contributing to the disease has sufficient specificity and sensitivity that testing will be clinically useful. Serious failures of a diagnostic test are false positives (individuals without the disease who test positively) and false negatives (individuals with the disease who test negatively). Although genes have been identified for some common complex disorders such as age-related macular degeneration, primary open-angle glaucoma, and exfoliation syndrome, in general, testing for these mutations is not sufficiently sensitive and specific that the test results are clinically meaningful. For example, over 90% of patients with exfoliation syndrome carry one of two missense changes in *LOXL1*; however, up to 80% of normal individuals also carry these same DNA sequence variants.<sup>12</sup> Clearly the identification of these missense mutations alone is not clinically useful. Examples of genetic tests that are useful include *RPE65* for Leber's hereditary amaurosis,<sup>13</sup> *PAX6* for aniridia,<sup>14</sup> *MYOC* for early onset primary open-angle glaucoma,<sup>15</sup> and *OPA1* for optic neuropathy,<sup>16</sup> as well as many other genes that are known to cause inherited ocular conditions.<sup>17</sup>

## CLIA Laboratories

Laboratories in the United States offering genetic testing must comply with regulations under the Clinical Laboratory Improvement Amendments of 1988 (CLIA). The Centers for Medicare and Medicaid Services administers CLIA and requires that laboratories meet certain standards related to personnel qualifications, quality control procedures, and proficiency testing programs in order to receive certification. This regulatory system was put in place to encourage safe, accurate, and accessible genetic tests. In addition to ensuring that consumers have access to genetic tests that are safe, accurate, and informative, these policies encourage the development of genetic tests, genetic technologies, and the industry that produces these products. A number of CLIA-certified laboratories performing genetic testing for eye diseases exist in the United States. For a list of CLIA-certified laboratories participating in the National Eye Institute (NEI)-sponsored eyeGENE network, see the NEI website at <http://www.nei.nih.gov>. CLIA-certified laboratories offering genetic testing can also be found at GeneTests: <https://www.genetests.org/>.

## Genetic Reports

A genetic test report is a sensitive document that is the main form of communication between the CLIA laboratory and the physician requesting the genetic test. Genetic test reports may be shared with the patient and with genetic counselors. The report should include (1) the type of genetic test performed (i.e., sequencing or other methodology), (2) the gene or genes that were evaluated, (3) the results of the testing, (4) information about the pathogenicity of the sequence variants, (5) recommendations for clinical follow-up based on the results of testing, and (6) literature references providing additional information about the genes and mutations responsible for the disease. The report should be written clearly and have appropriate contact information.

Novel DNA sequence changes are frequently found as a result of genomic DNA sequencing. New DNA sequence changes (variants) may be benign polymorphisms or causative mutations. Additional studies must be done before the sequence change can be designated as disease causing. Demonstrating that the mutant protein has an abnormal function or evaluation of the mutant gene in an animal model would be an ideal test of pathogenicity, but these approaches are time consuming and may not be possible. Current approaches to evaluate the pathogenicity of a novel DNA sequence variant are based on (1) population data, (2) computational and predictive data from *in silico* estimates for pathogenicity such as SIFT<sup>18</sup> and PolyPhen-2,<sup>19</sup> (3) functional data, and (4) segregation data for families.<sup>20</sup>

## GENETIC COUNSELING

Genetic counseling has become an important part of any clinical medicine practice. In 1975 the American Society of Human Genetics adopted this descriptive definition of genetic counseling<sup>21</sup>:

Genetic counseling is a communication process which deals with the human problems associated with the occurrence or risk of occurrence of a genetic disorder in a family. This process involves an attempt by one or more appropriately trained persons to help the individual or family to (1) comprehend the medical facts including the diagnosis, probable course of the disorder, and the available management, (2) appreciate the way heredity contributes to the disorder and the risk of recurrence in specified relatives,

(3) understand the alternatives for dealing with the risk of recurrence, (4) choose a course of action that seems to them appropriate in their view of their risk, their family goals, and their ethical and religious standards and act in accordance with that decision, and (5) to make the best possible adjustment to the disorder in an affected family member and/or to the risk of recurrence of that disorder.

## Clinical Evaluation and Family History

An accurate diagnosis is the first step in productive genetic counseling. The patient-physician discussion of the natural history of the disease and of its prognosis and management is entirely dependent on the correct identification of the disorder that affects the patient. Risk assessment for other family members and options for prenatal diagnosis also depend on an accurate diagnosis. In some cases, appropriate genetic testing may help establish the diagnosis. Examination of other family members may be indicated to determine whether a particular finding is hereditary.

A complete family history of the incidence of the disorder is necessary to determine the pattern of inheritance of the condition. The mode of inheritance (i.e., autosomal dominant, autosomal recessive, X-linked, or maternal) must be known to calculate the recurrence risk to additional family members, and it helps confirm the original diagnosis. For the record of family information, the gender and birth date of each individual and his or her relationship to other family members are indicated using the standard pedigree symbols. It is also helpful to record the age of onset of the disorder in question (as accurately as this can be determined). The pedigree diagram must include as many family members as possible. Miscarriages, stillbirths, and consanguineous parents are indicated.

Occasionally a patient may appear to be affected by a condition that is known to be inherited, but the patient is unable to provide a family history of the disease. Several important explanations for a negative family history must be considered before the conclusion is made that the patient does not have a heritable condition. First, the patient may not be aware that other family members are affected by the disease. Individuals frequently are reluctant to share information about medical problems, even with close family members. Second, many disorders exhibit variable expressivity or reduced penetrance, which means that other family members may carry a defective gene that is not expressed or results in only a mild form of the disease that is not readily observed. Third, false paternity may produce an individual affected by a disease that is not found in anyone else belonging to the acknowledged pedigree. Genetic testing can easily determine the paternity (and maternity) of any individual if blood samples are obtained from relevant family members. Fourth, a new mutation may arise that affects an individual and may be passed to offspring, even though existing family members show no evidence of the disease.

## Risk Prediction Based on Inheritance

Once the diagnosis and family history of the disorder are established, risk prediction in other family members (existing and unborn) may be calculated. The chance that an individual known to be affected by an autosomal dominant disorder will transmit the disease to his or her offspring is 50%. This figure may be modified depending on the penetrance of the condition. For example, retinoblastoma is inherited as an autosomal dominant trait, and 50% of the children of an affected parent should be affected. However, usually only 40%–45% of the children at risk are affected, because the penetrance of the retinoblastoma trait is only 80%–90%, which means that 5%–10% of children who have inherited an abnormal copy of the retinoblastoma gene do not develop ocular tumors.

An individual affected by an autosomal recessive trait will have unaffected children unless he or she partners with another individual affected by the disease or with an individual who is a carrier of the disease. Two individuals affected by an autosomal recessive disease produce only affected offspring. (There are some rare exceptions to this rule. If the disease is the result of mutations in two different genes, it is possible for two individuals affected by an autosomal recessive trait to produce normal children. Also, in rare cases, different mutations in the same gene may compensate for each other, and the resultant offspring will be normal.) If an individual affected by an autosomal recessive disease partners with a heterozygous carrier of a gene defect responsible for that disorder, the chance of producing an affected child is 50%. Among the offspring of an individual affected by an autosomal recessive disease, 50% will be carriers of the disorder. If one of these offspring partners with another carrier of the disease, the chance of producing an affected child is 25%.



**BOX 1.3.1 Types of Clinical Genetics Services and Programs****Center-Based Genetics Clinic**

- Outreach clinics
- Inpatient consultations

**Specialty Clinics**

- Metabolic clinic
- Spina bifida clinic
- Hemophilia clinic
- Craniofacial clinic
- Other single-disorder clinics (e.g., neurofibromatosis type 1 clinic)

**Prenatal Diagnosis Program: Perinatal Genetics**

- Amniocentesis/chorionic villus sampling clinics
- Ultrasound program
- Maternal serum  $\alpha$ -fetoprotein program

**Genetic Screening**

- Newborn screening program/follow-up clinic
- Other population-screening programs (e.g., for Tay–Sachs disease)

**Education/Training**

- Healthcare professional
- General public
- School system
- Teratology information services

X-linked disorders are always passed from a female carrier who has inherited a copy of an abnormal gene on the X chromosome received from either her mother (who was a carrier) or her father (who was affected by the disease). Man-to-man transmission is not seen in diseases caused by defects in genes located on the X chromosome. Among sons born to female carriers of X-linked disorders, 50% are affected by the disease, and 50% of daughters born to female carriers of X-linked disorders are carriers of the disease. All the daughters of men affected by X-linked disorders are carriers of the disease.

Mitochondrial disorders are inherited by sons and daughters from the mother. The frequency of affected offspring and the severity of the disease in affected offspring depend on the number of abnormal mitochondria present in the egg that gives rise to the affected child. Diseased and normal mitochondria are distributed randomly in all cells of the body, including the female gametes. As a result, not all the eggs present in a woman affected by a mitochondrial disorder have the same number of affected mitochondria (heteroplasmy). Men affected by mitochondrial disorders only rarely have affected children, because very few mitochondria in the developing embryo are derived from the sperm used to fertilize the egg.<sup>22</sup>

With careful diagnosis and family history assessment, even sporadic cases of heritable disorders are identifiable. In such cases, an estimate of recurrence risk can be calculated using the available pedigree and clinical information and the statistical principle called Bayes' theorem. These individuals should be referred to clinical genetics services such as those commonly found in hospital settings (Box 1.3.1).

**Indications to Refer for Genetic Counseling****Known Inherited Condition**

Genetic counseling can be useful for a family with a member affected by an established diagnosis. In this case the goal of the counseling is to describe recurrence risks for other family members. For example, if a child has retinoblastoma and a positive family history, the family may be referred for genetic counseling to review recurrence risks. If diagnostic testing has been performed, that can also be discussed and will aid in the presentation of the recurrence risks, especially if other family members have been tested.

**Ocular and Systemic Congenital Anomalies**

Individuals with multiple ocular and systemic anomalies may or may not fit into a particular syndrome. In these situations, the experience of a geneticist in recognizing malformation patterns and understanding the variability of genetic conditions can aid diagnosis. If an underlying cause is identified, relatives can then undergo genetic counseling.

**Specific Eye Diseases**

A genetic evaluation is important for families with inherited eye diseases. Many ophthalmological diseases have a well-documented inheritance pattern, and describing the inheritance to family members may help identify affected relatives who could be diagnosed and treated early in the course of the disease. This is especially important in families with conditions such as dominantly inherited juvenile glaucoma.

**Ocular Defects Associated With Genetic Diseases**

Many genetic diseases have associated ocular defects. For example, a diagnosis of neurofibromatosis type 1 may be made in a child because Lisch nodules were detected on a clinical examination.<sup>23</sup> The child and family should be referred for genetic counseling to help define the recurrence risks for other family members.

**Confidentiality**

Confidentiality is an important issue in genetic testing and genetic counseling. Confidentiality issues should be discussed before the initiation of testing so there is consensus on how results are reported, who receives results, and where the information is documented.

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# Light

Scott E. Brodie

## 2.1

**Definitions:**

Light – Electromagnetic energy detectable by the eye.  
Geometrical Optics – The properties of light governed by propagation in straight lines, refraction, and reflection.  
Physical Optics – The properties of light described by wave phenomena such as interference, diffraction, and polarization.  
Quantum Optics – The properties of light described by absorption and emission of energy in discrete quanta, proportional to frequency.

**Key Features**

- Specular Reflection – Light reflects off smooth surfaces so that the angle of incidence equals the angle of reflection.
- Snell’s Law – The relationship between the bending of light at an interface surface to the speed of light on either side of the interface.
- Vergence Equation – The relationship between the power of a lens and the location of the images it forms.

**INTRODUCTION**

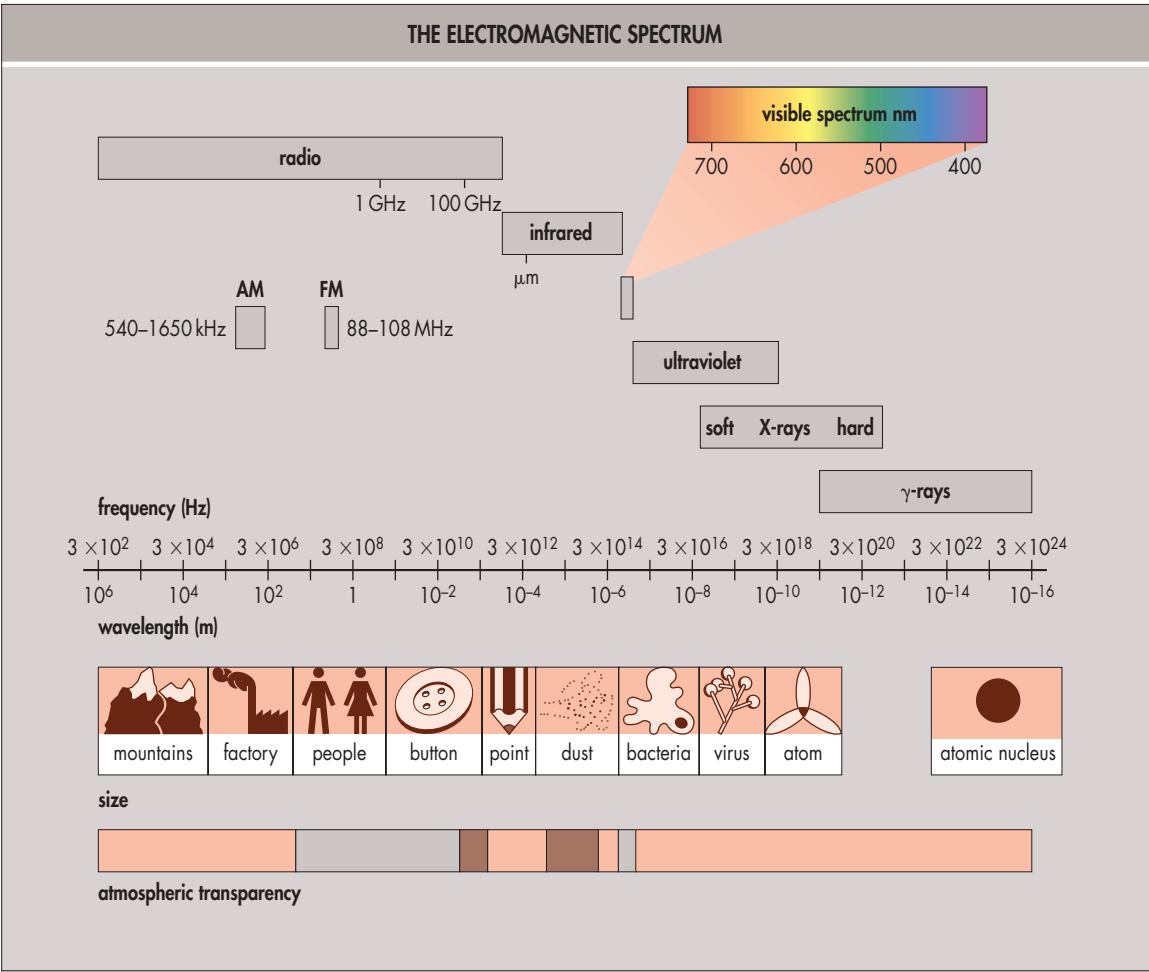
Visible light is the portion of the electromagnetic spectrum that can be detected by the eye. In practice, this ranges from wavelengths of about

750 nm (red) to about 440 nm (violet). Longer wavelengths may be discernable as heat (“infrared”) and can be detected by suitable photographic emulsions and electronic camera chips. Shorter wavelengths (“ultraviolet”) are sometimes visible in eyes after removal of the crystalline lens and can be seen by some insects (Fig. 2.1.1).

The behavior of light under ordinary circumstances is very familiar, but careful observations reveal important subtleties that have fascinated scientists for hundreds of years. In general, the behavior of light in detail depends on the scale of the objects with which it interacts.

Interactions between light and large objects (relative to the wavelength of the light) generally follow simple geometrical rules and come under the heading of “geometrical optics.” This is the regime of typical human experience—light rays travel in straight lines through homogeneous media but may be reflected by polished smooth surfaces or may be refracted (bent) as they pass from one medium to another. These interactions of light with matter are governed by the law of (specular) reflection and Snell’s law, respectively. Geometrical optics is the appropriate tool for understanding the use of lenses for the formation of images—as in the human eye—or as modified by lenses such as spectacles, contact lenses, or intraocular lens implants.

When the dimensions of optical systems are comparable to the wavelength of the light passing through them, the effects of interference become evident, demonstrating the “wave-like” properties of light. Perhaps the most common example is the diffraction of light as it passes through



**Fig. 2.1.1 The Electromagnetic Spectrum.** The pictures of mountains, people, buttons, viruses, etc., are used to produce a real (i.e., visceral) feeling of the size of some of the wavelengths. In the bar at the bottom of the figure, gray portions of the bar indicate regions of the spectrum to which the atmosphere is transparent. (Adapted from Zeilik M. *Astronomy: the evolving universe*. 3rd ed. New York: Harper & Row; 1982.)

finite apertures, such as the pupil of the human eye. Because the light bends slightly under these circumstances, diffraction limits the sharpness of images formed through small apertures. Wave properties of light also are seen in the phenomena of polarization and are exploited in such optical instruments as interferometers (which accurately measure very small distances) and clinical devices such as the optical coherence tomographer, which exploits interference between beams of light that have scattered from various surfaces within the eye to provide high-resolution images of ocular tissues. These phenomena are discussed later under the heading of “Wave Properties of Light.”

At the smallest scales and energies, the quantum behavior of light becomes evident. Quantum effects are responsible for the operation of lasers, the characteristic absorption and emission spectra of various materials, and the phenomena of fluorescence and phosphorescence.

## GEOMETRICAL OPTICS

Under ordinary conditions, light travels through homogeneous media in straight lines. This can be exploited by simple devices such as the “camera obscura” or pinhole camera, which forms images of bright objects by selecting a single ray of light from each point in the source object that threads through a small aperture to form an inverted image on a convenient surface beyond the pinhole. Although these images enjoy an excellent depth of field, bringing objects both near and far into sharp focus, the small aperture limits the amount of light available to form the image (Fig. 2.1.2).

On the other hand, the paths of light rays can be altered by reflection or refraction. In reflection, the incoming ray of light reverses direction to create equal angles between the incoming ray and the exiting ray, as measured from a line through the point of contact perpendicular to the reflecting surface (the “surface normal”). This is the “law of (specular) reflection.” Specular (mirror-like) reflection is seen as light encounters smoothly polished surfaces, such as mirrors, and still pools of liquids, such as water or mercury. Flat reflecting surfaces recreate accurate reproductions of the source objects (with, of course, the left–right direction reversed). Curved reflecting surfaces can be used to magnify or minify the source objects, as used for special purposes such as telescopes, shaving mirrors, or the minifying mirrors rearview mirrors used in automobiles (Fig. 2.1.3).

When light traverses a boundary between two transparent media where the speed of light differs between the two materials, the path of the light may be deflected from a straight line by the process of refraction.<sup>1</sup>

The deviation is described by “Snell’s law” as follows. First, compute the “refractive index” of each material as the ratio of the speed of light in a

vacuum divided by the speed of light in the medium—the refractive index is often denoted by the letter  $n$ , and is always greater than 1.0 for material media, as light will always travel through a material medium more slowly than through a vacuum. If we measure the angle between the incoming light ray and the surface normal at the point of contact (the “angle of incidence”) and compare it with the angle between the surface normal and the outgoing ray that emerges from the point of contact as the light moves away from the interface in the second medium, we have

$$n_1 \sin \theta_1 = n_2 \sin \theta_2$$

where  $n_1$  and  $n_2$  are the refractive index of the first and second material, respectively, and  $\theta_1$  and  $\theta_2$  are the angles made by the incident and emerging rays with the surface normal (Fig. 2.1.4).

In practice, if the light goes from a “rarer” medium, such as air (with a greater velocity of light and thus a smaller refractive index), to a “denser” medium (with a slower velocity of light and thus a greater refractive index), such as water or glass, the light will bend *toward* the surface normal. (Of course, this use of the word “dense” has nothing to do with the specific gravity of the materials.) Light that travels from a “slow” medium to a medium with a greater velocity of light will bend *away* from the surface normal.

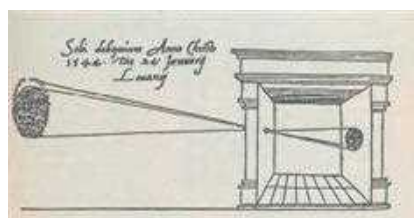
The bending of light across such an interface is readily appreciated when looking at objects in a pool of water from the air above, where objects are typically seen as farther away than they really are because the light from the objects bends toward the observer as it passes from the water to the air (Fig. 2.1.5).

Ordinary prisms work the same way. Light passing through a prism is bent toward the base of the prism. Objects viewed through a prism are seen displaced toward the apex. The strength of a prism is usually given in terms of “prism diopters”—a prism that deflects a beam of light by  $d$  cm at a distance 1.0 m from the prism is said to have a strength of  $d$  prism diopters, usually abbreviated “Δ.”

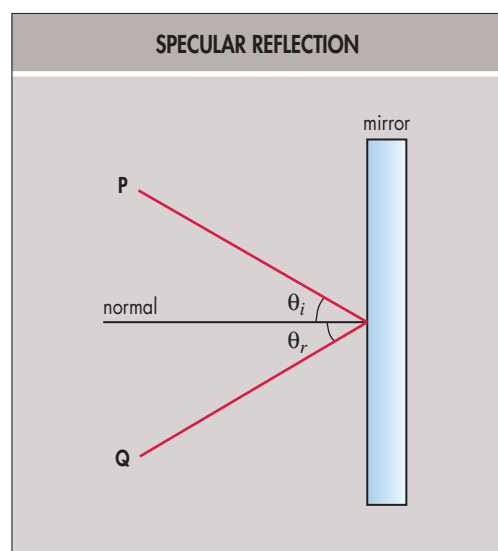
If the angle of incidence for light going from a “slow” to a “fast” medium exceeds the “critical angle” where  $\sin \theta = n_2/n_1$ , then Snell’s law cannot be satisfied, and the light ray is reflected at the interface rather than refracted across it. This “total internal reflection” is employed by prisms in high-quality binoculars, for example (Fig. 2.1.6).

When light passes through a curved surface such as the surface of a lens, the deflection depends in detail on the shape of the surface. For lenses with spherical surfaces, for which one can determine a geometrical center of curvature, and for light rays that closely approximate the line between the source objects and the center of curvature (the “optic axis”), one can use Snell’s law to show that the lens will form a pointlike image of a point source and derive simple rules relating the location of the source objects, the curvature (or power) of the lens, and the location of the image formed by the lens. This is referred to as “stigmatic imagery” (Fig. 2.1.7).

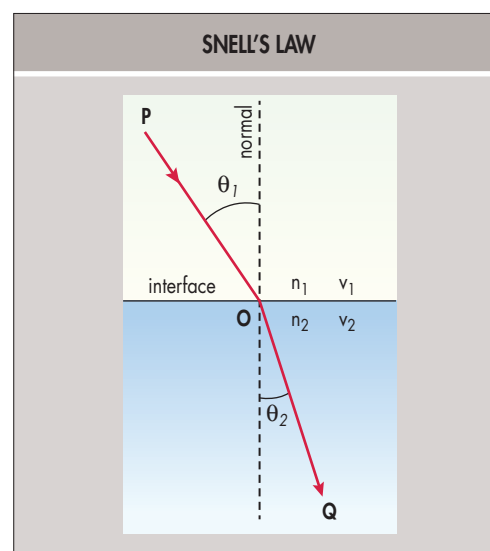
Stigmatic imagery is strictly possible only for “paraxial” rays and lenses with relatively small apertures (though larger than the pinhole apertures described earlier). Nevertheless, this formulation of geometrical optics is very useful in a wide variety of settings, even when the strict assumptions are not met. For example, in the human eye, strict stigmatic imaging is



**Fig. 2.1.2 The Camera Obscura.** (From Wikipedia “Camera Obscura”; public domain.)



**Fig. 2.1.3 Specular Reflection.** (From Wikipedia, “Specular Reflection”; available for unrestricted use from Creative Commons.)



**Fig. 2.1.4 Snell’s Law.** (From Wikipedia, “Snell’s Law”; public domain.)



possible only when the pupil is fairly small, but because awareness of the sharpness of the image formed on the retina by the optics of the eye is dominated by the image presented to the fovea, the paraxial regime remains an adequate description and is routinely used to guide the prescription of spectacle lenses and contact lenses.

## BASIC STIGMATIC OPTICS

A convex lens will image the light from an infinitely distant object (such as a star) at a finite distance, say  $f$ , from the lens on the side opposite from the source. This distance is referred to as the focal length of the lens and is measured in meters. The “power” of the lens,  $P$ , is given by the equation  $P = 1/f$ . In this context, the units for lens power are referred to as “diopters” and abbreviated “D.” For objects closer than infinity, the image location is determined by the relation

$$1/u + P = 1/v, (*)$$

where  $u$  is the distance in meters from the lens to the source object (objects to the left of the lens are considered to be at distances less than 0); and  $v$  is the distance from the lens to the image. This formula is referred to as the vergence equation. In practice, if an image is formed to the right of such a lens, increasing the power  $P$  will pull the image closer to the lens; reducing the power  $P$  will push it farther away.<sup>2</sup>



**Fig. 2.1.5 Refraction at an Air–Water Interface.** The portion of the soda straw seen through the surface of the water is closer than it appears. (After Wikipedia, “Refraction”; available for unrestricted use from Creative Commons; original figure has been truncated.)

For thin lenses, the power of two lenses placed in contact with each other and used as a single lens system is approximately additive:  $P = P_1 + P_2$ .

Lenses can also be fabricated with concave surfaces. These lenses, which are assigned powers less than 0, do not form images by themselves but can be used to adjust the power of convex lenses by means of the addition formula above. Placing such a lens adjacent to an existing lens system can reduce the effective power, for example, pushing an image farther to the right, as described earlier.

If light approaches or leaves a lens through a medium other than air or a vacuum (with  $n = 1.0$ ), the equation (\*) must be modified as follows:

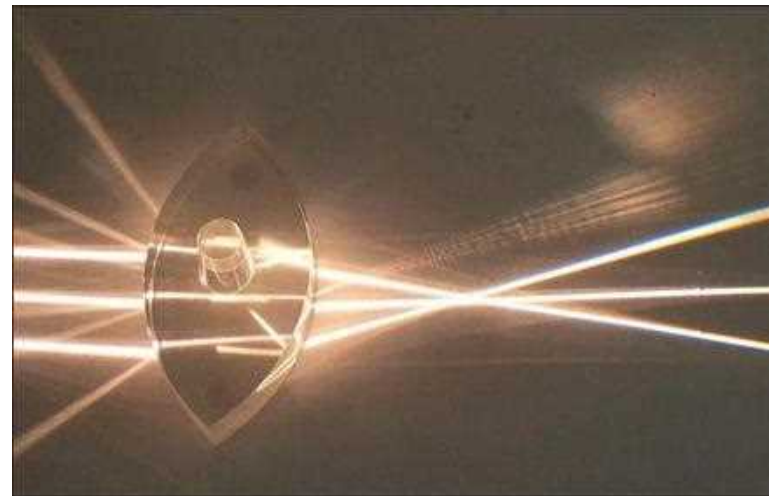
$$n_1/u + P = n_2/v$$

where  $n_1$  and  $n_2$  are the refractive indices of the media to the left and right of the lens, respectively.

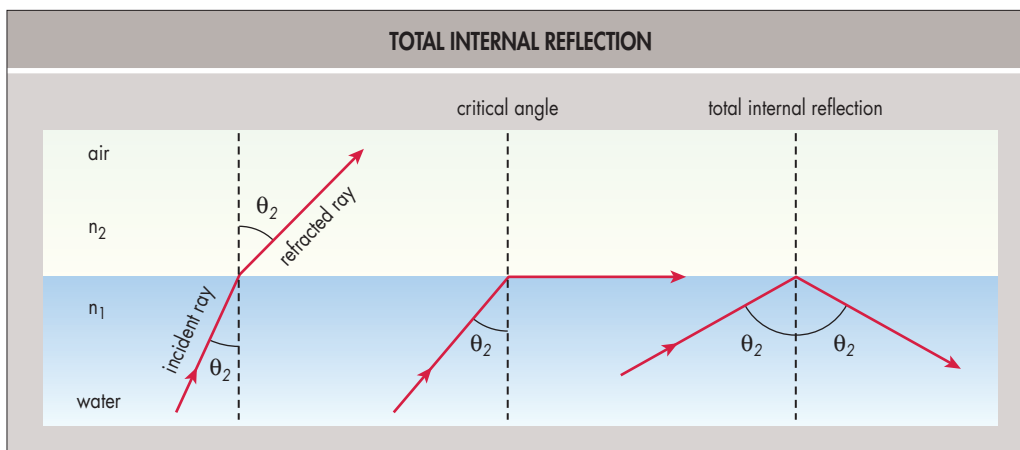
If lenses are used in combination but spaced apart, the image formed by the first lens encountered by the light becomes the source for the next lens in sequence, and the effect of each lens in the sequence is thus analyzed in turn.

For example, in a myopic eye, the optical power of the cornea and lens system is too great for the axial length of the eye, and images of distant objects are formed in front of the retina. A correcting concave (minus-power) lens placed in front of the eye will move the image farther away from the anterior segment, placing it on the fovea, allowing for clear vision and normal acuity. In a hyperopic eye, the optical power of the anterior segment is too little for the axial length of the eye, and so additional plus-lens power is placed in front of the eye to pull the image forward and clarify the vision. See Section 2.4 for further details.

If light passes through the periphery of a thin lens, it encounters inclined surfaces resembling those of a prism, oriented base-inward for a convex lens or base-outward for a concave lens. In general the deflection is proportional to the power of the lens and the distance of the incident ray from the optical center.



**Fig. 2.1.7 Image Formation by a Biconvex Lens.** (After Wikipedia, “Lens [Optics]”; available through Creative Commons; original figure has been truncated.)



**Fig. 2.1.6 Total Internal Reflection.** (From Wikipedia, “Refraction”; available for unrestricted use from Creative Commons.)

Comparison between the definition of the prism diopter and the definition of dioptric power for lenses yields the “Prentice rule”: The prismatic effect of lens decentration is given by the formula  $d(\Delta) = P \cdot r$ , where  $d$  is the prismatic effect in prism diopters,  $P$  is the power of the lens in diopters, and  $r$  is the distance from the optical axis of the lens to the incident ray of light in centimeters.

## ASTIGMATIC OPTICS

Lens surfaces with more complex shapes than the spherical surfaces discussed earlier cannot form simple point images. The simplest case is that of “toric surfaces” resembling the surface of the side of a rugby ball, an American football, or the outer rim of an automobile tire inner tube (Fig. 2.1.8).

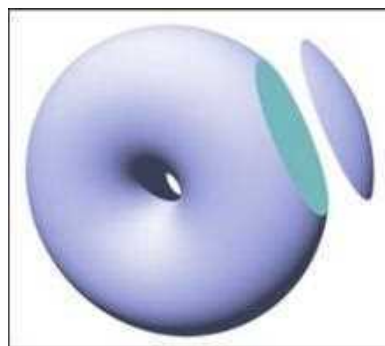
Such a surface has different degrees of curvature in different directions at each point. Typically, the maximal and minimal curvatures occur in perpendicular directions at each location. If the surface is sufficiently regular, it can be characterized as equivalent to a spherical refracting surface taken together with a cylindrical surface, with maximal refracting power in one direction and no power in the perpendicular direction. Such lenses form a complex image of a source object point consisting of two perpendicular “focal lines” at the two distances corresponding to the optical powers of the steepest and flattest meridians of the surface (Fig. 2.1.9).

In practice, such a lens can produce stigmatic imagery with the addition of a correcting cylinder oriented to compensate for the variation in power of the original lens.

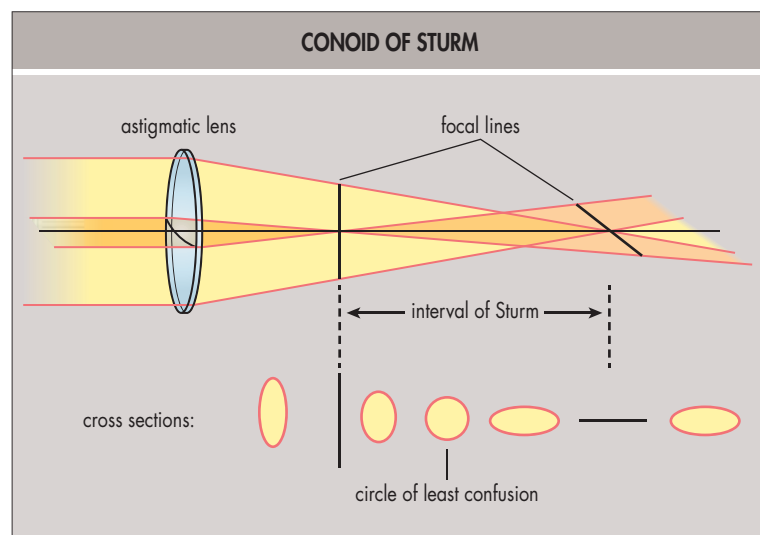
More complex surfaces and their optical effects are discussed in Section 2.6 on Wavefront Optics and Optical Aberrations of the Eye.<sup>3</sup>

## WAVE PROPERTIES OF LIGHT

In the nineteenth century, it was realized that light exhibits behaviors suggestive of wave propagation, which cannot be incorporated into the simple geometrical framework described earlier. These include interference,



**Fig. 2.1.8 Toric Surface.** (From Wikipedia, “Toric Lens”; available under GNU Free documentation license.)

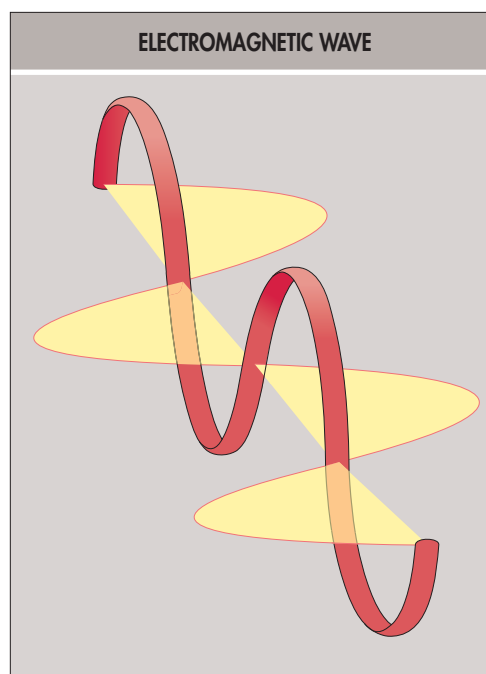


**Fig. 2.1.9 Conoid of Sturm.** Astigmatic imaging of a point source by a toric lens forming a complex figure between two perpendicular focal lines. ([From AccessLange: General Ophthalmology / Printed from AccessLange ([accessmedicine.com](http://accessmedicine.com)). Chapter 20, Optics and refraction, Paul Riordan-Eva] Copyright ©2002–2003 The McGraw-Hill Companies. All rights reserved.)

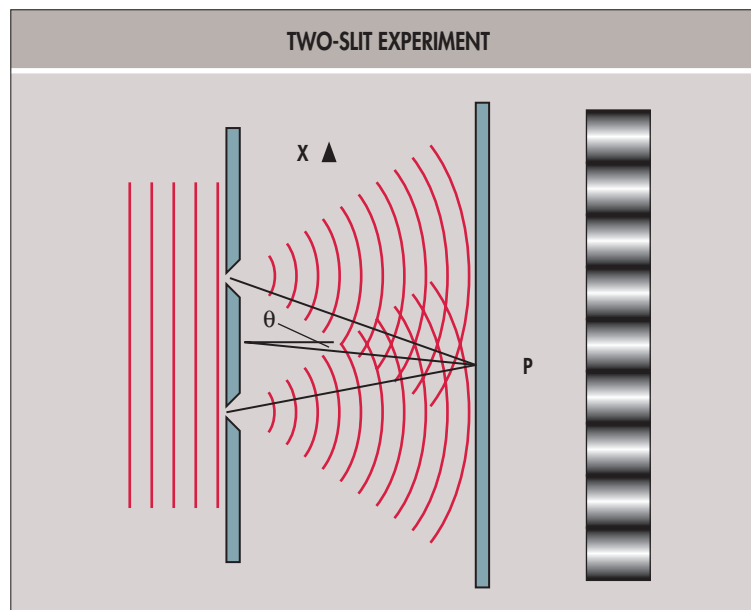
diffraction, polarization, and dispersion. These phenomena are readily understood in terms of the classical Maxwell equations of electricity and magnetism but are reasonably appreciated with less detailed descriptions, which simply identify light with a single transverse wave (that is, a wave that oscillates in a direction perpendicular to the propagation of the light)<sup>4</sup> (Fig. 2.1.10).

## Interference

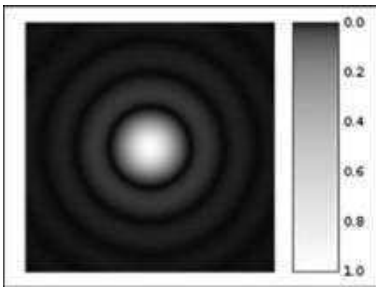
Suppose monochromatic light passes through a narrow slit and then in turn through one of two narrow slits separated by a small distance and is then allowed to land on a screen. Instead of two stripes, one for each of the final slits, the light creates a pattern of alternating bright and dark stripes. This is apparently due to the variation in the path length from the two slits to each image point on the screen, so that the waves emanating from each slit alternately reach the image screen so that the peaks coincide (producing a bright stripe—“constructive interference”) or so that a peak from one slit coincides with a trough from the other slit (producing a dark stripe—“destructive interference”). As the observation point on the screen moves to one side, the relative distance from each of the final slits varies. When the distances differ by exactly one wavelength, the pattern repeats (Fig. 2.1.11).



**Fig. 2.1.10 Electromagnetic Wave.** An electromagnetic wave consists of an oscillating electric field perpendicular to an oscillating magnetic field. Both fields are perpendicular to the direction of propagation.



**Fig. 2.1.11 The “two-slit experiment.”** (From Wikipedia “Double-slit experiment”; licensed under the Creative Commons Attribution-Share Alike 3.0 Unported license.)



**Fig. 2.1.12** The Airy disc. (From Wikipedia, “Airy disk”; public domain.)

Similar patterns can be seen with light passing through a single slit or round aperture, as the light coming from the edge of the aperture interferes with the light coming from the opposite edge, as if the edges were the “slits” in a two-slit experiment. In the case of a circular aperture, the stripes take the form of concentric rings. The central spot in the pattern is known as the “Airy disc” (Fig. 2.1.12).

In general, the spacing between interference fringes will vary with the wavelength of the source illumination—shorter wavelengths give rise to more narrowly spaced fringes. Narrow slits or spacing between the slits leads to wider spacing between fringes, as greater angles are needed to create path length differences of a half wavelength.

Nearly monochromatic light is needed to observe these effects, so as to produce consistent patterns of peaks and troughs.

## Diffraction

As described earlier, interference of portions of a light beam passing near the opposite edges of a small aperture creates a pattern of fringes that extends beyond the geometrical shadow of the aperture on the screen. In this context, the apparent “spreading out” of the light beyond the geometrical limits of the expected image is referred to as “diffraction.” In most contexts, it is sufficient to consider the diameter of the Airy disc as a useful description of the magnitude of this effect. For monochromatic light of wavelength  $\lambda$ , the angular extent of the Airy disc is given by

$$\sin \theta = 1.22 \lambda / d,$$

where  $d$  is the diameter of the aperture. For the human eye, this is comparable to the diameter of a single foveal cone, suggesting that the optics of the eye have evolved to approach “diffracted limited” resolution (Fig. 2.1.13).

## Polarization

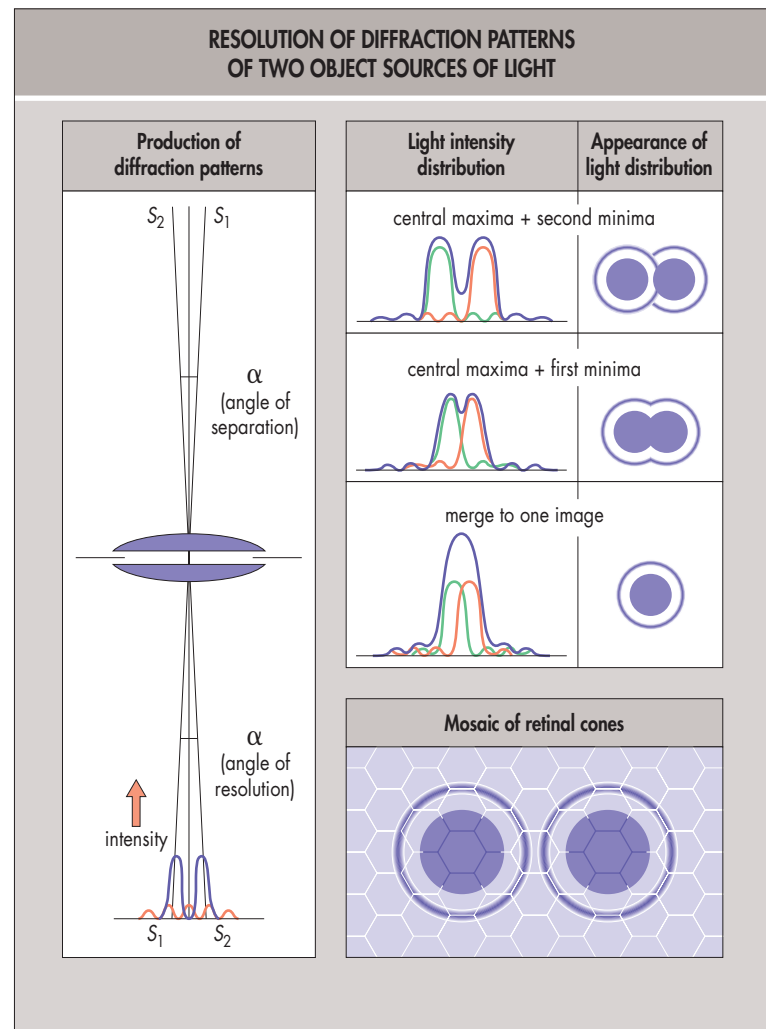
The association of an oscillation perpendicular to the direction of propagation of a light beam endows it with a specific orientation. If this orientation is consistent across the beam of light, it is said to exhibit “polarization.” In practice, polarization is demonstrated by the interactions of light with materials that exhibit a particular, consistent molecular organization, such as certain (“birefringent”) crystals or manufactured materials (Polaroid filters) (Fig. 2.1.14).

Polarized light can also occur in nature when light is reflected from a suitable surface, such as a flat pool of water. The preferred direction of polarization is parallel to the reflecting surface, in this case horizontal. Sunglasses containing filters that preferentially transmit vertically polarized light will selectively block these reflections, which make up the bulk of the annoying stray light seen when driving or boating.

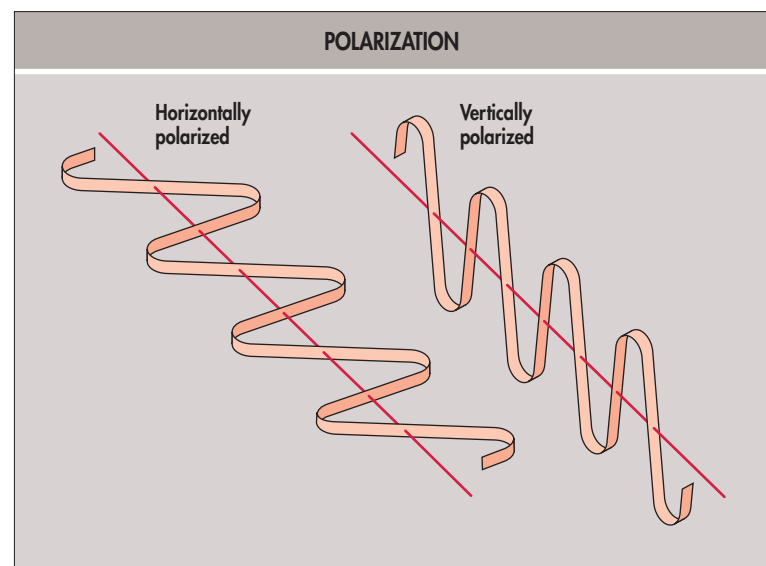
Polarized light filters also are useful in certain eye examinations. Stereoscopic depth perception tests are designed to create separate images for the two eyes, each polarized in one of two perpendicular directions. When viewed through glasses with polarized filters placed perpendicular to each other, each eye can see only one of the test targets, creating a stereoscopic 3-D image. Similar strategies can be used to control which eye sees particular acuity targets to reveal possible malingering.

## Dispersion

Visible light varies in wavelength from red (with the longest wavelengths) to blue and violet (with the shortest wavelengths). All wavelengths travel through a vacuum or through air at the same velocity. However, material media may transmit light at different velocities depending on its wavelength. This phenomenon is referred to as “dispersion,” and it accounts for the ability of prisms to break up white light into its constituent colors,



**Fig. 2.1.13 Resolution of Diffraction Patterns of Two Object Sources of Light.** Two object sources of light ( $S_1$  and  $S_2$ ) cannot be resolved if their diffraction patterns (Airy discs) overlap substantially. Two refraction patterns are produced by a circular aperture placed between two lenses, and resultant patterns of the light intensity distribution and appearance are shown. The central maxima of one diffraction pattern falls on the second minima of the diffraction pattern from the second source; the central maxima of one diffraction pattern falls on the first minima of the diffraction pattern from the second source, and the two images can just be resolved (Rayleigh criterion); the two images merge as one. Bottom right, mosaic of retinal cones with the diffraction pattern superimposed. (Adapted from Jenkins FA, White HE. *Fundamentals of optics*. New York: McGraw-Hill; 1950. p. 290–3; and Emsley HH. *Visual optics*. London: Hatton Press; 1950. p. 47.)



**Fig. 2.1.14 Polarization.** Both transverse waves propagate in the same direction but oscillate in different planes. Here, only the scalar wave approximation is adopted, and only the electric field is shown.



**Fig. 2.1.15 Dispersion of White Light by a Prism.** (From Wikipedia “Prism”; licensed under the Creative Commons Attribution-Share Alike 3.0 Austria license.)

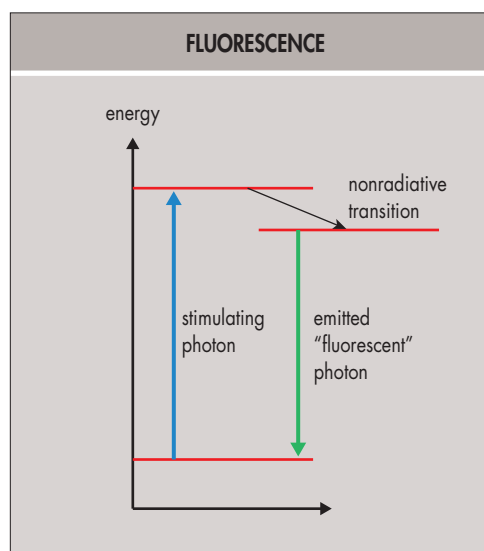
as light of each color is refracted by a prism to slightly different degree (Fig. 2.1.15).

In most optical devices, this effect is something of a nuisance, producing colored fringes at the edge of images. In practice this is corrected in high-quality optics by using lenses of different types of glass in such a way as to cause their dispersion effects to cancel out. In the human eye, this effect is referred to as “chromatic aberration,” which is the basis of the “duochrome” test used to refine measurements of refractive error.

## Quantum Effects

At the smallest scales, the quantum-mechanical nature of the interactions between light and matter become evident. These effects reflect the observation that an energy transfer between light and matter occurs only in fixed amounts (“quanta”) with energy proportional to the frequency of the light, according to Planck’s equation:  $E = h\nu$ , where  $h$  is Planck’s constant.<sup>5</sup>

For example, the electrons in a molecule transition between various energy states by exchanging light energy (“photons”) with the environment. As the various available energy states form a series of discrete values, the energy of the various possible transitions can take only certain discrete values. These are appreciated as the emission lines seen in the spectrum when such a material is heated to incandescence, which are characteristic of the material, or as absorption lines seen when broadband light passes through a gaseous medium, absorbing only light of the frequencies (colors) corresponding to permissible transitions of electrons between allowed energy levels.



**Fig. 2.1.16 Energy Levels in a Hypothetical Fluorescent Molecule.** A relatively high-energy photon raises an electron to the highest level. The electron drops to a nearby level by nonradiative means and then drops to its original low level emitting a lower energy photon than the one originally absorbed.

## Fluorescence and Phosphorescence

In some cases, the energy absorbed by a molecule will be dispersed in stages, initially dropping from one state to a nearby state (the energy released in the form of thermal energy of the molecule, rather than released as a photon), and subsequently the remaining energy released as a photon as the electron returns to its initial base level. In such an event, the energy of the photon that is emitted will be less than that of the photon that was initially absorbed, and so will necessarily be seen as a photon of a different wavelength, shifted toward the red end of the spectrum (Fig. 2.1.16).

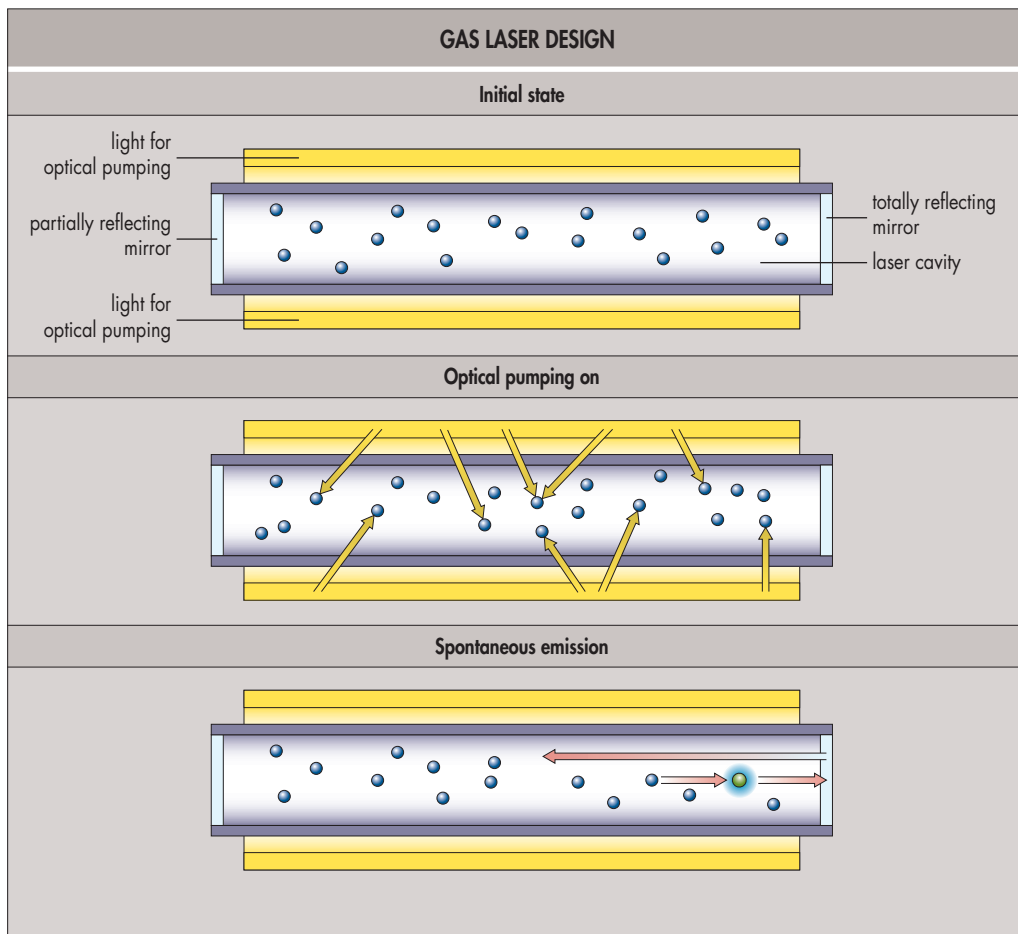
If this transition occurs promptly, the effect is referred to as fluorescence. For example, the dye molecule fluorescein, frequently used as a disclosing agent in ophthalmology, absorbs photons in the blue portion of the spectrum but fluoresces a yellow–green color. If the intermediate level is more stable, the intermediate energy state can persist for many hours, resulting in a prolonged release of the light energy as the final energy transition occurs over an extended period. In this case the process is known as phosphorescence.

## Lasers

The operation of laser devices is another important manifestation of a quantum effect. In this case a working medium is “pumped” into a metastable state by absorbing energy from an external source, often a flash of light from an ordinary source.<sup>6</sup> This produces an “inversion,” with an excess of electrons at an elevated energy state. The probability of such electrons dropping to their base energy level is enhanced by interaction with another photon of the same energy as the latent transition—this is referred to as “stimulated emission of radiation.”

In practice, the working medium is contained in a cylindrical cavity with a reflecting mirror at one end and a partially reflecting mirror at the other. After creation of the inversion, as electrons revert to their base level, photons of an energy corresponding to this transition start to bounce back and forth between the two mirrors, stimulating more photon emissions of precisely the same energy. The corresponding light beams accumulate homogeneously in the laser cavity, and eventually the excess energy emerges through the partially silvered mirror as a highly monochromatic beam of light with a very high degree of coherence (all waves with peaks and troughs aligned parallel to the laser cavity mirrors). The resulting laser light can be very accurately collimated into a beam with little angular divergence, suitable for applications from photocoagulation of retinal lesions to serving as a lecture pointing device (Fig. 2.1.17).





**Fig. 2.1.17 Gas Laser.** A typical design consists of a gas-filled cavity, external optical pumping lights, and a resonator that comprises partially and totally reflecting mirrors. Without optical pumping, most of the gas atoms are in lower energy states and incapable of undergoing either spontaneous or stimulated emission. With optical pumping, photons from the external lights are absorbed by the gas atoms, which raises the energy of the atoms and makes them capable of undergoing spontaneous or stimulated emission. Ultimately, the majority of atoms are in excited states—a population inversion. One of the higher energy atoms spontaneously emits a photon that produces stimulated emissions as it passes by other high-energy atoms. As the photons are reflected back and forth across the cavity multiple times, a chain reaction of stimulated emissions is produced.

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# Optics of the Human Eye

*Daniel Diniz, Francisco Irochima, Paulo Schor*

## 2.2

**Definition:** The classic optics of the eye are best understood in terms of the optical characteristics of its components—the cornea, pupil, crystalline lens, and retina—and how they function in combination.

### Key Features

The quality and characteristics of the different optical components and the combination are described in these terms:

- Cornea.
- Pupil.
- Lens.
- Accommodation.
- Scattering.
- Aberrations.
- Retina.
- Resolution and focal length.
- Depth of focus.
- Refractive errors.

### INTRODUCTION

Each optical component of the eye contributes to image formation on the retina and its brain interpretation. In order to discuss these components, we must first define the limits of normality considering the best image quality that can be produced by an emmetropic eye (an eye without refractive error). The determination of these limits is important, as they serve as guides for intervention on clinical practice. This chapter discusses individual optical variables that characterize the normal human eye as well as abnormal conditions of the refracting apparatus of the eye, also called ametropia.

### CORNEA

The cornea's anterior surface is approximately spherical, with a radius of curvature that is typically a bit less than 8 mm. This surface is responsible for about two-thirds of the eye's refractive power. Technology based in the Scheimpflug principle allows for the detailed analysis of each interface together with the local thickness in estimating the total corneal power for an individual eye before and after corneal surgery.<sup>1</sup> The corneal stroma must be transparent for high-quality image formation on the retina, yet the normal human cornea scatters 10% of the incident light.<sup>2</sup> By comparison, the corneal stroma of the eagle is almost as transparent as glass.<sup>3</sup> This factor (along with the larger pupil size and finer cone diameter) is why the resolution of the eagle eye is better than 120 cycles per degree, which is equivalent to a Snellen acuity of 20/5 (6/1.5).<sup>4</sup>

The aspherical shape of the cornea's anterior surface affects the quality of the retinal image. Normal corneas have a flatter periphery and steeper center, counteracting the effect of paraxial light that tends to bend more at peripheral areas. The "Q" factor, also named asphericity or eccentricity factor, quantifies this central-periphery flattening and averages  $-0.25$  in normal eyes. A more negative number means that this cornea is steeper than normal (i.e., central keratoconus), and less negative "Qs" are seen, for example, in postrefractive myopic procedures. Such knowledge was built into equipment for new refractive surgeries that allows for the control of final "Q" factor, aiming for better contrast definition after surgery.<sup>5</sup>

Corneal astigmatism is caused by this surface having different radii of curvature along different meridians (directions in the coronal plane). A

survey of normal eyes shows that almost every human eye has a baseline corneal astigmatism of at least  $0.25$ – $0.50$  D.<sup>6</sup> Spherical aberration is caused by the radius of curvature of the corneal surface changing (generally increasing) with distance from the center of the pupil to the pupillary margin. Several devices based on Placido's ring principle provide quantitative data on corneal aberrations.<sup>7</sup> The amount of spherical aberration contributed by the cornea varies with pupillary aperture and individual corneal shape. For a pupil 4 mm in diameter, spherical aberration varies from  $+0.21$  D to  $+1.62$  D, depending on the specific corneal form.<sup>8</sup>

### PUPIL

The iris expands or contracts to control the amount of light admitted to the eye. The pupil can range in diameter from 8 mm in very dim light down to about 1.5 mm under very bright conditions.<sup>9</sup> A strong association exists between visual acuity and pupillary diameter. For example, visual acuity has been shown to improve steadily as background illumination increases up to a value of  $3400$  cd/m<sup>2</sup>.<sup>10</sup> This improvement is due to blockage of paraxial aberrant rays and brain compensation for the resulting dimming of retinal illumination. To deliver more light (larger pupil) without aberration it is necessary to control the peripheral shape of the cornea.

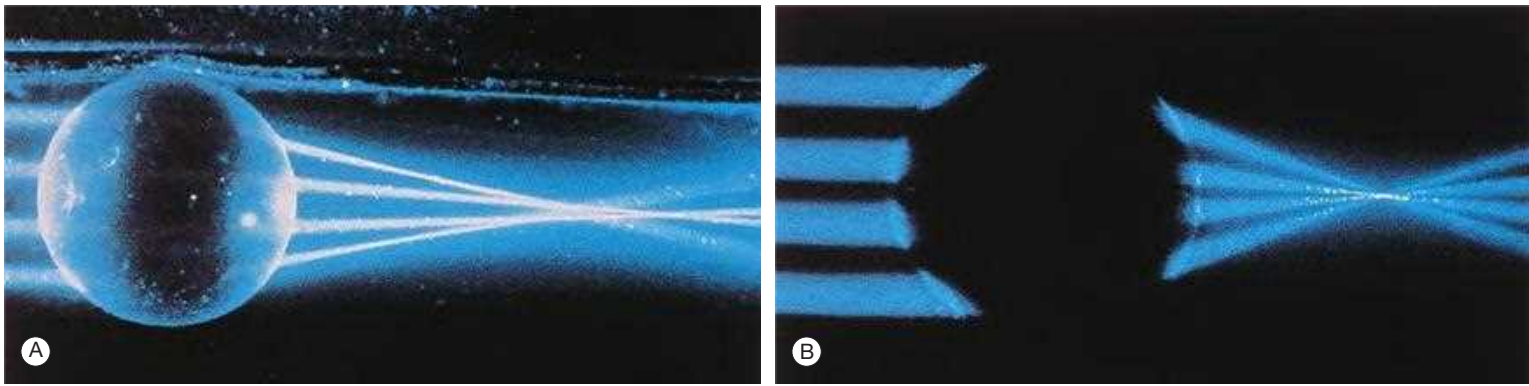
Retinal image quality, as determined by optical aberrations such as spherical aberration, tends to improve with decreasing pupil diameter, because peripheral optical aberrations decrease with decreasing pupil size. On the other hand, retinal image quality is limited by diffraction, which tends to improve with increasing pupil diameter. For most eyes the best retinal images are obtained when the pupil diameter is about 2.4 mm, which is the diameter at which the effects of aberration and diffraction are balanced optimally. Thus the optimal pupillary size seems to be determined by several influences. In fact, Campbell and Gregory have shown that pupil size tends to be adjusted automatically to give optimal visual acuity over a wide range of luminance.<sup>11</sup>

### LENS

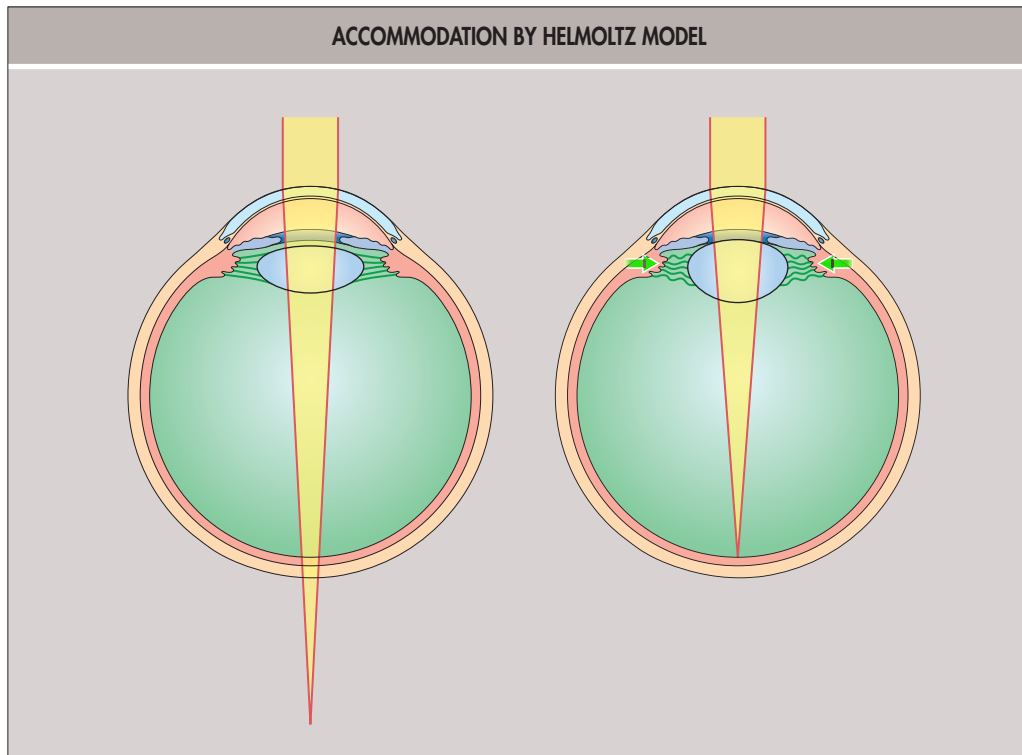
The crystalline lens, which has about one-third of the eye's refractive power, enables the eye to change focus. When the eye views nearby objects, the ciliary muscle changes the shape of the crystalline lens by making it more bulbous and, consequently, optically more powerful. The lens of a young adult can focus over a range greater than 10 D. Presbyopia, which begins at about 40 years of age (depending on the environmental factors such as temperature),<sup>12</sup> is the inability of the eye to focus (accommodate) due to hardening of the crystalline lens with age. Experiments that disrupt the hard collagen within the lens are ongoing and may provide new insights in presbyopia correction.<sup>13</sup> When the eye can no longer accommodate at the reading distance, positive spectacle lenses of about 1.5–3 D are prescribed to correct the difficulty.

The normal 20-year-old crystalline lens scatters about 20% of the incident light. The amount of scatter is more than double this in the normal 60-year-old lens.<sup>14</sup> Such scatter significantly diminishes contrast sensitivity.<sup>15</sup> Also, the normal 20-year-old lens absorbs about 30% of incident blue light. At age 60, this absorption increases to about 60% of the incident blue light.<sup>16</sup> The increase of blue light absorption with age results in subtly decreased color discrimination and decreased chromatic aberration. It is possible that this increased absorption helps to reduce the amount of UV light reaching the older retina, protecting it from oxidative damage, which is seen in age-related macular degeneration.

The variation in index of refraction of the crystalline lens (higher index in the nucleus, lower index in the cortex) is responsible for neutralization of a good part of the spherical aberration caused by the human cornea. A progression toward positive spherical aberration throughout life due to the



**Fig. 2.2.1 Spherical Aberrations Produced by Lenses of the Same Shape.** (A) A glass lens. (B) A fish lens. The variation in index of refraction is responsible for the elimination of spherical aberration in the fish lens. (Reproduced from Fernald RD. Vision and behavior in an African Cichlid fish. *Am Sci* 1984;72:58–65.)



**Fig. 2.2.2 Accommodation by von Helmholtz Model.** (Courtesy Francisco Irochima, MD.)

crystalline lens has been described.<sup>17</sup> Fig. 2.2.1 shows how this variation of index of refraction in the spherical fish lens almost eliminates its spherical aberration compared with a spherical glass lens.<sup>18</sup>

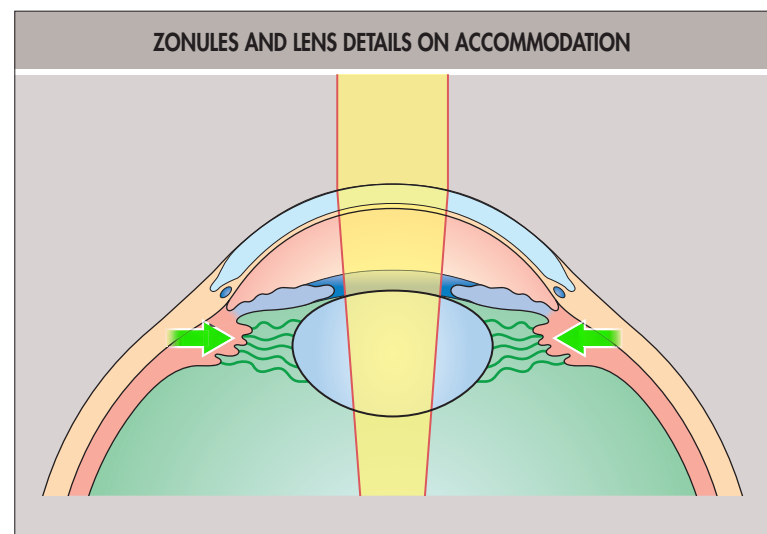
## ACCOMMODATION

In a convergent optical system, as an object approaches, its formed image moves away from its original position, that is, farther away from the lens. Accommodation is a complex mechanism involving sensory and neuromuscular phenomena by which the human eye, through contraction of the ciliary muscle, changes the optical power of the lens to assist the convergence of the image to the retina, adjusting the focus to different distances between the object of regard and the eye.

According to the von Helmholtz model (the most widely held theory), when the visual target approaches nearer to the eye, there is a stimulus to the contraction of the ciliary muscle that leads to a relaxation of the suspensory ligaments of the lens, increasing its anterior–posterior diameter, and a forward shift of the lens, and, consequently, its dioptric power<sup>19,20</sup> (Figs. 2.2.2 and 2.2.3). The opposite occurs when relaxation of this musculature occurs.

The precise details of the mechanism of accommodation remain unclear to this day. Discussion of the various hypotheses currently under investigation is beyond the scope of this chapter.

The ability of the lens to change its shape is called physical accommodation, whereas the contraction capacity of the ciliary muscle is called



**Fig. 2.2.3 Zonules and Lens Details as Described by von Helmholtz.** Contraction of ciliary muscle leading to relaxation of the zonules and accommodation. (Courtesy Francisco Irochima, MD.)



physiological accommodation. Both alter the refractive power of the system and can be measured. If the lens becomes stiffer and unsightly, unable to alter its shape, physical accommodation is impaired even with the strength of the preserved ciliary muscle. A similar process may occur with physiological accommodation if weakness of the ciliary muscle<sup>21</sup> exists.

## Range and Amplitude

The greatest distance an object can be clearly seen by the eye with relaxed accommodation is called the “far point.” The nearest point at which an object can be clearly seen is called the “near point,” which is the location of the focus obtained with maximum accommodation. The range of accommodation, by definition, is the distance between these two points. The amplitude, measured in diopters, refers to the refractometric difference between the eye in maximum relaxation and maximum accommodation.

- **Far point:** The greatest distance at which an object can be seen clearly in the absence of accommodation.
- **Near point:** The closest distance at which an object can be seen clearly when maximum accommodation is used.
- **Range of accommodation:** Distance between the far point and the near point.
- **Amplitude of accommodation:** Difference in dioptric power between the eye at rest and the fully accommodated eye.

The amplitude of accommodation can be measured directly by the method of spheres. In this method, we ask the patient to look at an object 40 cm away and change his/her need for accommodation with the addition of lenses. By adding negative lenses, the accommodation is stimulated until the image begins to blur. For example, suppose the patient accepts  $-2$  D with clear vision. As we add positive lenses, the accommodation will relax until the image begins to blur again. Suppose in this situation, the lens used was  $+3$  D. In this case the patient has a 5 D amplitude of accommodation.

Further information can be obtained with simple examination. Placing an object at the nearest point where the patient can obtain sharp vision will determine the near point. Moving away the object, we define the far point. In the case of a patient with 3 D of amplitude: If he or she is emmetropic, the far point will be in infinity and the near point will be to 33 cm. If the patient is a 3 D hyperope, the near point will be at infinity, because all the accommodation must be used to clarify the acuity at distance. If the patient has a myopia of 3 D, the near point will be 16.7 cm because the accommodation together with the refractive error amounts to a total of 6 D of refractive power.

In a hyperope, the accommodation necessary to see clearly at a distance is the same diopters of the magnitude of their hypermetropia. However, to see a near object 10 cm from the eye, as we saw before, 10 diopters (D) should be added to this value.

In hyperopia, there is *no* object distance for which a clear retinal image can be obtained without accommodation (or optical correction)—the optical apparatus of the eye has too little dioptric power at rest to focus an object on the retina. In this case we may define the far point of the eye as the (virtual) point, located *behind* the eye, which is imaged by the relaxed optics of the eye on the retina. Additional plus lens power, either from accommodation or supplied by a spectacle lens, is necessary to obtain a clear image.

For example, assuming a 4 D hyperope with amplitude of accommodation of 8 D, the (virtual) far point is at 25 cm behind the eye. With an accommodating effort of 4 D, the parallel rays from an object at infinity converge to the retina. Note that with an 8 D effort, this hyperope can converge divergent rays from a point 25 cm away from the eye. Assuming that this is the maximum available accommodation, by definition this is the near point (Fig. 2.2.4). It is important to note that this hyperope needs to accommodate between 4 D and 8 D to see objects ranging from infinitely distant to the near point. In other words, in some situations, the hyperope can have the same range as an emmetrope but the required amplitude of accommodation is necessarily greater, that is, the hyperope needs a greater accommodative effort. The prescription of lenses for this patient should take into account maintaining a more physiological accommodative effort. This process is discussed in the next chapter.

In myopes, the far point is at a finite distance in front of the eye. In a myopic eye that sees objects at most up to 20 cm distant from the eye, a myopia of  $1/0.2 = 5$  D exists. Remember that the accommodation of an eye when viewing an object at the far point is fully relaxed. If the near point is at 10 cm, the accommodation range will be  $\alpha = 20 - 10 = 10$  cm. As at this

point, as we saw before, the added refractive power of the system is 10 D. The amplitude of accommodation will be the difference of the power in the two points, that is,  $A = P - R = 10 - 5 = 5$  D. Notice that a 5 D myopic eye accommodates 5 D to focus an image at 10 cm. Therefore, although myopes cannot see objects at distance clearly, they have the advantage of being able to see objects at closer range with a smaller effort of accommodation (Fig. 2.2.5).

## SCATTERING

Another significant optical factor that degrades vision is intraocular light scatter. The mechanism of light scatter is different from the aberrations discussed earlier, each of which deviates the direction of light rays coming from points in object space to predictable and definite directions in image space. With light scattering, incoming light rays are deflected from their initial (i.e., prescattered) direction into random (postscattered) directions, which generally lie somewhere within a cone angle of approximately a degree or so. Therefore a dioptric value cannot be placed on the blur caused by light scatter. A glaring light worsens the effect of light scatter on vision. Thus a young, healthy tennis player may not see the ball when it is nearly in line with the sun. Light scattering is the mechanism associated with most cataracts and causes significant degradation of vision due to image blur, loss of contrast sensitivity, and veiling glare.

## ABERRATIONS

Aberrations are changes in image formation that do not occur in a classically paraxial system.<sup>22</sup> In other words, in specific situations, such as when light incidence occurs at an angle far above the reference axis of the system, no formation of an image exists at a single point. In practice, an optical system never makes a perfect point image and this does not depend only on the regularity of the surface. With the advent of wavefront aberrometry, several new types of aberrations—especially those of high orders—can be classified and today become major challenges for optical system manufacturers and refractive surgeons.

The aberrations are divided into monochromatic and chromatic. The monochromatic aberrations can be further subdivided into several types: astigmatism, defocus, tilt, spherical aberration, among others.

### Monochromatic Aberrations

Monochromatic aberrations of a geometrical nature are also called figure aberrations. In spherical aberration, for example, light rays that refract at the extreme periphery of a convergent lens have a different focus from those that enter the eye more centrally, better aligned with the optical axis. Thus between them, many of the rays will cross at intermediate points, degrading the nominal point image (see Fig. 2.2.1). A comet-like tail or directional flare appearing in the retinal image is a manifestation of another aberration called coma. This occurs due to the obliquity of the system, resulting from misalignment of the various refracting surfaces in the eye. A large amount of coma ( $0.3 \mu\text{m}$  of coma alone) may point to specific corneal diseases such as keratoconus or a decentered intraocular lens. Several other forms of monochromatic aberrations are induced by differences in the axial curvature of the lens and inclination of the light beams, among others.

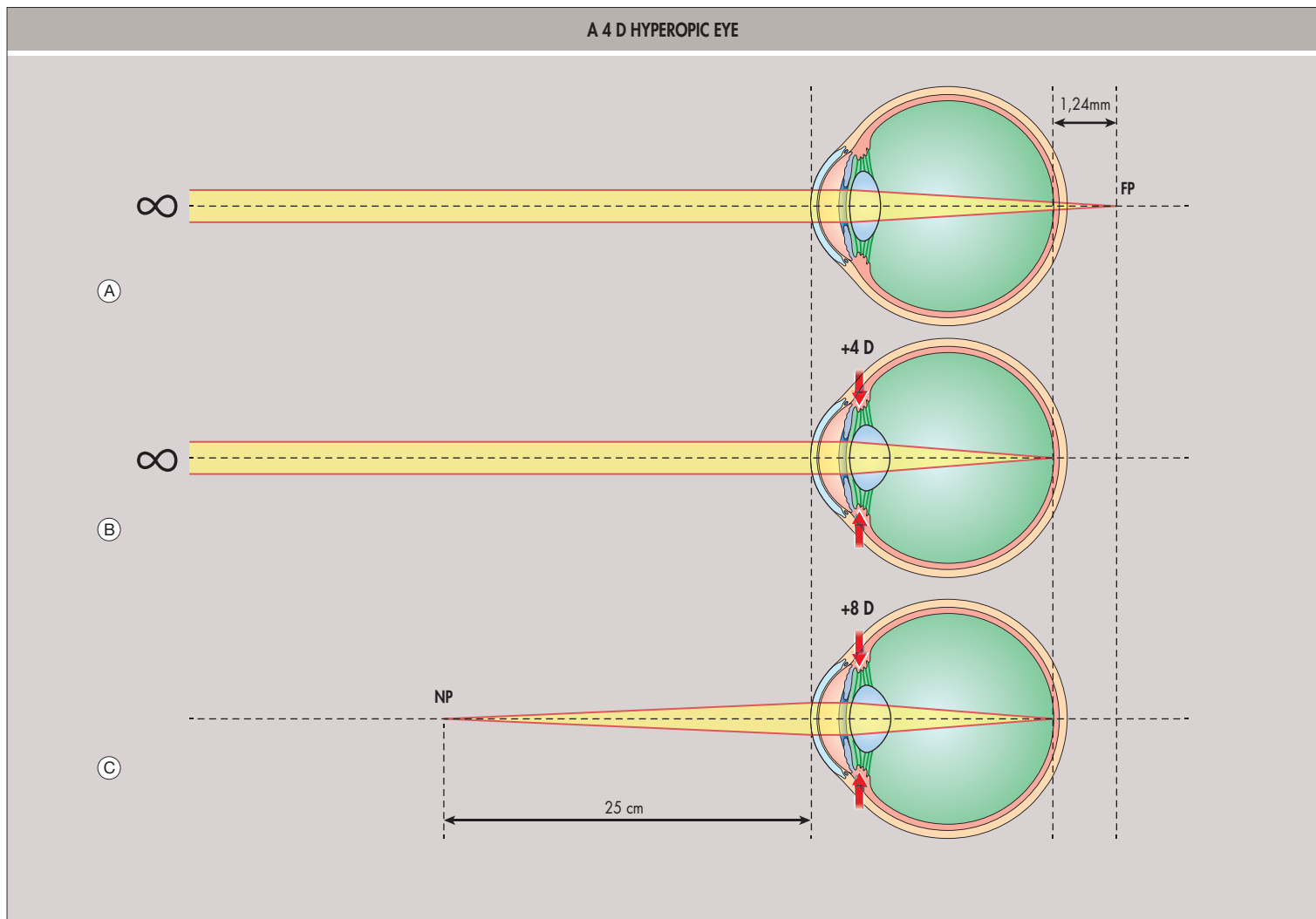
### Chromatic Aberrations

Because the index of refraction of the ocular components of the eye varies with wavelength, colored objects located at the same distance from the eye are imaged at different distances with respect to the retina. This phenomenon is called axial chromatic aberration. In the human eye the magnitude of chromatic aberration is approximately 3 D.<sup>23</sup> However, significant colored fringes around objects generally are not seen because of the preferential spectral sensitivity of human photoreceptors. Studies have shown that humans are many times more sensitive to yellow-green light with a central wavelength at 560 nm than to red or blue light.<sup>8</sup> Amber spectacles used to enhance night vision partially block the blue light, lowering the effect of chromatic aberration.

The specific types of each monochromatic and chromatic aberration are discussed in Chapter 2.6.

## RETINA

An image may be considered as made up of an array of pointlike regions. When a picture on the video screen is viewed with a magnifying glass, these small regions, called *pixels*, are seen clearly. Technological evolution



**Fig. 2.2.4 A 4 D Hyperope Eye.** (A) The far point (FP) is at 1.24 mm behind the retina. (B) The image focus on retina after 4 D of accommodation. (C) The near point (25 cm) after maximum accommodation of 8 D. (Courtesy Francisco Irochima, MD.)

has produced screen resolution above the human vision threshold in the new generation of smartphones or monitors with so-called retina display. Likewise, the pixel elements comprising a retinal image are the cone and rod photoreceptors. It is the finite size of these photoreceptors that ultimately determines the eye's ability to resolve fine details.

The finest details in a retinal image can be resolved only within the foveal macular area. This elliptical zone of about 0.1 mm in maximal width (Fig. 2.2.6)<sup>24</sup> has an angular size of approximately  $0.3^\circ$  about the eye's visual axis. It contains about 30,000 tightly packed light-sensitive cones. The cones themselves have diameters of 1–2  $\mu\text{m}$  (a dimension comparable to 3–4 wavelengths of green light) and are separated by about 0.5  $\mu\text{m}$ .<sup>25</sup> Cone size is an important factor in determining the ultimate resolution of the human eye. No nerve fiber layer, ganglion cell layer, inner plexiform layer, or inner nuclear layer is present in much of the fovea, and in the very center of the fovea no outer nuclear layer is present. Only the so-called Henle's fiber layer, consisting of the axons between the cones and their synaptic pedicles, and the cones themselves are found.

Another important aspect of the cone receptors is their orientation. Each cone functions as a "light pipe" or a fiber optic that is directed to the second nodal point of the eye (Fig. 2.2.7). This orientation optimally receives the light that forms an image and, together with the black pigment epithelium of the retina, partially prevents this light from scattering to neighboring cones.<sup>26</sup> Müller cells may also be considered living optic fibers in the retina,<sup>27</sup> preventing light scatter.

Another retinal factor that helps to improve vision is the configuration of the foveal pit, which is a small concavity in the retina. This recessed shape acts as an antiglare device in which the walls of the depression prevent stray light within the internal globe of the eye from striking the cones at the center of the depression. Finally, the yellow macular pigment may be considered to act as a blue filter that limits chromatic aberration

and absorbs scattered light, which is predominantly of shorter wavelength (i.e., the blue end of the spectrum).

## RESOLUTION AND FOCAL LENGTH

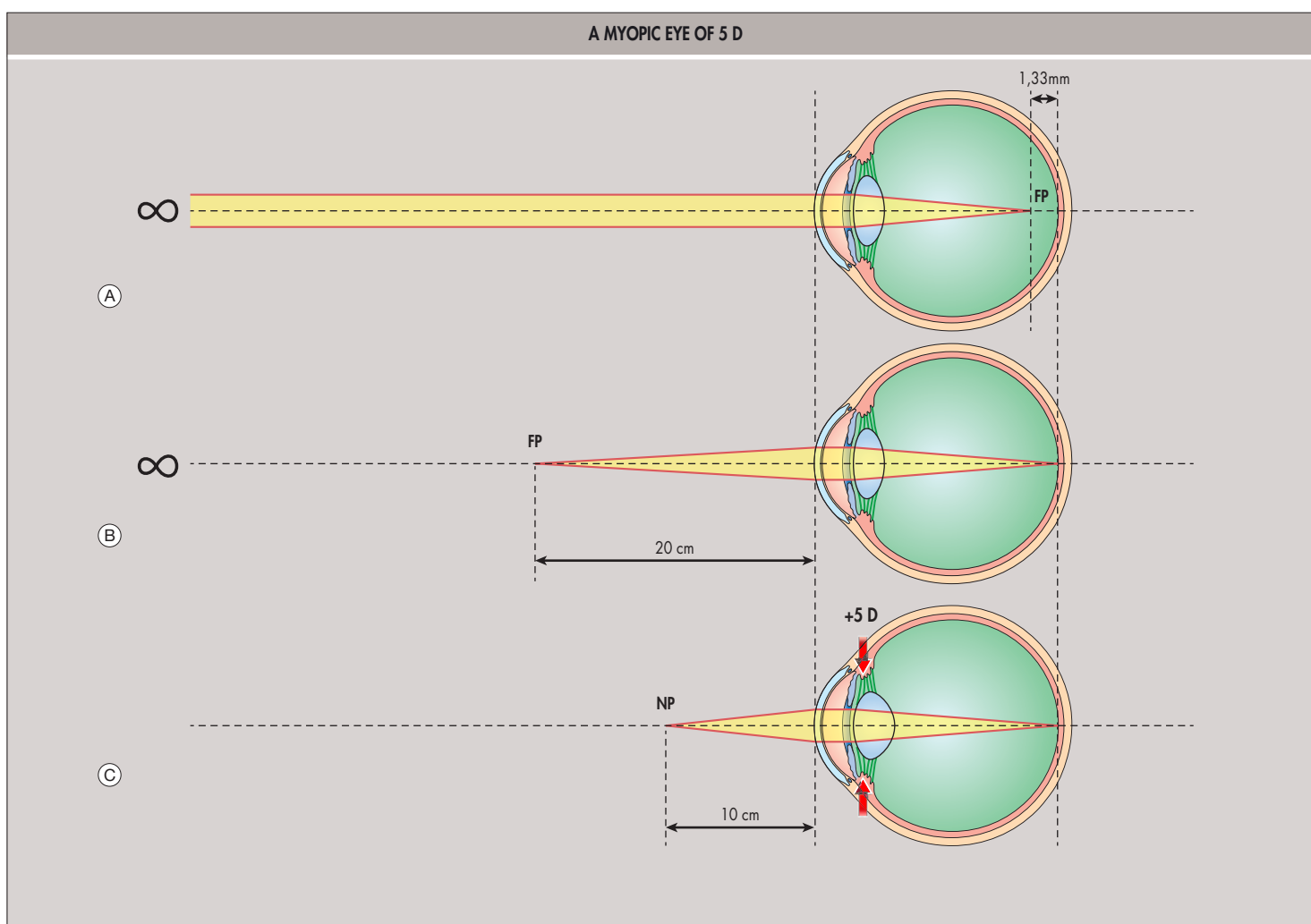
A derivation of the theoretical diffraction-limited resolution of a normal emmetropic human eye must consider the eye's optimal pupil diameter, its focal length, which is associated with its axial length, and the anatomical size of the photoreceptors. A point object imaged by a diffraction-limited optical system has an angular diameter in radians (diameter at one-half the peak intensity of the Airy disc) given by Eq. 2.2.1.

$$\text{Angular diameter} = \frac{1.22 (\text{wavelength})}{\text{pupil diameter}} \quad \text{Equation 2.2.1}$$

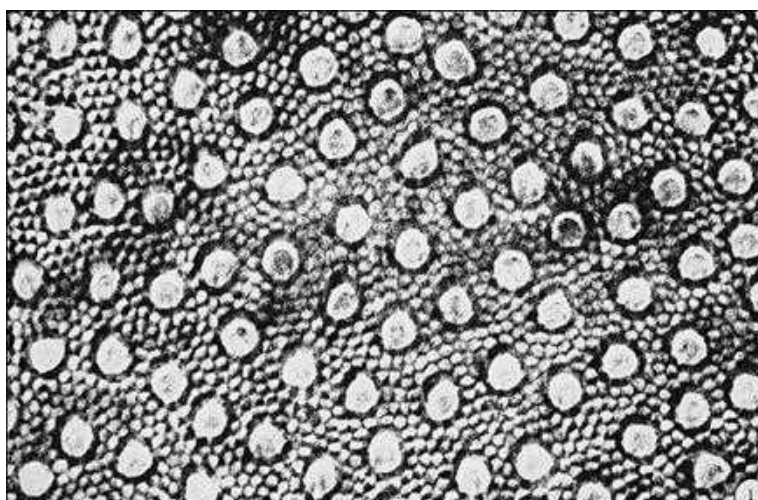
In Eq. 2.2.1, let pupil diameter be 2.4 mm, which for a normal eye is the largest pupil diameter for which spherical aberration is insignificant, and let the wavelength be 0.00056 mm (yellow-green light) to find the diffraction-limited angular diameter = 0.00028 radians (or, equivalently, 0.98 minutes of arc). Note that this angular diameter matches the angular resolution of an eye with 20/20 Snellen acuity, because the black-on-white bands of the letter E on the 20/20 line of the Snellen chart are spaced 1 minute of arc apart.

The spatial diameter in millimeters of the diffraction-limited Airy disc on the retina is found by multiplying the angular diameter, given by Eq. 2.2.1, by the effective focal length of the eye.

$$\text{Spatial diameter} = (\text{angular diameter}) \times (\text{effective focal length}) \quad \text{Equation 2.2.2}$$



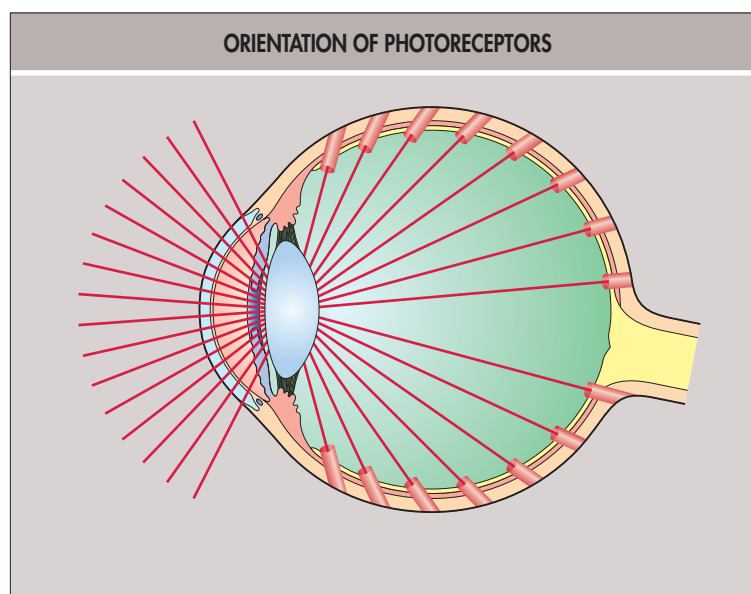
**Fig. 2.2.5 A Myopic Eye of 5 D.** (A) Far point is situated at 1.33 m in front of the retina. (B) At 20 cm distance, the image focus on retina without accommodation. (C) Maximum accommodation of 5 D and the near point at 10 cm. (Courtesy Francisco Irochima, MD.)



**Fig. 2.2.6 Retinal Mosaic (Rhesus Monkey) in an Area Adjacent to the Fovea.** The large circles are rods and the clusters of small circles are cones. This section gives a perspective of the different receptor sizes. (From Wassle H, Reiman HJ. The mosaic of nerve cells in mammalian retina. *Proc R Soc Lond B* 1978;200:441–61.)

Using the angular diameter found from Eq. 2.2.1 and a value of 17 mm for the eye's effective focal length (i.e., second nodal point to retina distance) in Eq. 2.2.2 results in the diffraction-limited spatial diameter = 0.0048 mm (i.e., 4.8  $\mu\text{m}$ ).

It is interesting to use our results to make a comparison with Kirschfield's estimate that about five receptors are needed to scan the Airy disc to obtain the maximal visual information available.<sup>28</sup> If we assume



**Fig. 2.2.7 Orientation of the Photoreceptors.** They all point toward the second nodal point of the eye. (Courtesy Francisco Irochima, MD.)

that the foveal cones are approximately 1.5  $\mu\text{m}$  in diameter and are separated by about 0.5  $\mu\text{m}$  of space, then the distance between neighboring cones is 2.0  $\mu\text{m}$ . We estimate the number of receptors covered by the Airy disc by calculating in Eq. 2.2.3 the ratio of the area of the Airy disc to the area occupied by a single cone.



$$\text{Number of cones covered by Airy disc} = \frac{(\text{spatial diameter of disc})^2}{(\text{distance between cones})^2}$$

**Equation 2.2.3**

Using Eq. 2.2.3 we find that approximately six receptors are covered by the Airy disc in close accord with Kirschfield's estimate of five. Thus given an eye with maximal sensitivity to yellow light and an optimal pupil size of 2.4 mm, we find that the human eye's 17 mm effective focal length and, correspondingly, its 24 mm axial length are properly sized to achieve optimal resolution for the cone sizes present. The higher resolution of the eagle's eye compared with the human's eye probably results from a larger pupil size-to-focal-length ratio, cones of smaller diameter, and a clearer cornea and lens.<sup>3</sup>

## REFRACTIVE ERRORS

In an emmetropic eye, parallel light rays that come from infinity, after refracting on the cornea and lens of an eye at rest, converge on the retina. Refractive errors, or ametropias, are anomalies of the optical state of the eye that cause imperfect focus on the retina, leading to a poor quality of the final image.

Refractive errors can occur for several reasons:

### *Change in Size or Position or Absence of Optical Elements*

A major cause of ametropia is a mismatch between the axial length and the refractive power of the optical elements of the eye, for example in an enlarged eye the image is formed in front of the retina—this is referred to as axial myopia. Similarly, on an eye with reduced anterior–posterior diameter, the image is formed behind the retina, referred to as axial hypermetropia (Figs. 2.2.8 and 2.2.9).

If the lens is positioned more anterior or posterior than the normal range, similar refractive errors occur. If the lens is displaced anteriorly, myopia results. Conversely, if the lens is displaced posteriorly, this causes hypermetropia. The lens may also be subluxated or tilted, causing astigmatism.

The absence of the lens, or aphakia, reduces the high power of convergence of the optical system, producing high hypermetropia.

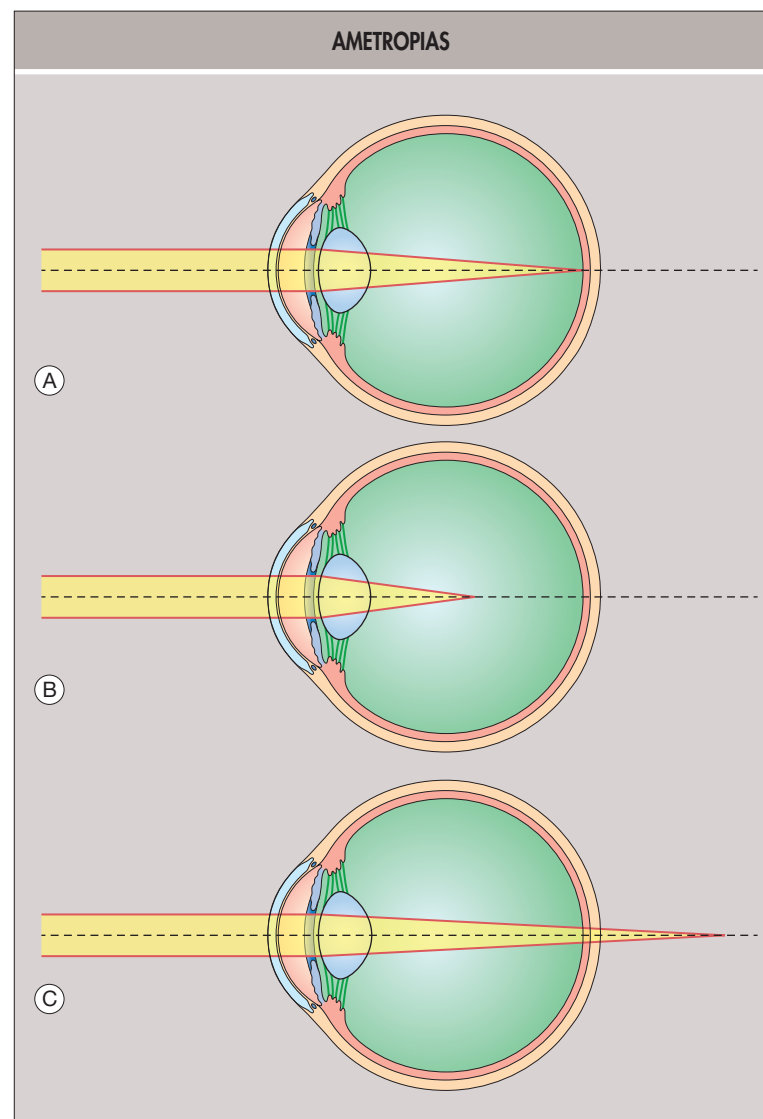
### *Change in the Shape of Optical Elements*

Irregularities on the surface of the cornea can occur with the formation of images in two different planes, instead of a single point, causing astigmatism. If the curvature is regular but steep, it causes refractive myopia. If it's more flat, it causes refractive hyperopia. These types of ametropia are widely seen in clinical practice in various corneal diseases, such as keratoconus, marginal pellucid degeneration, and keratoglobus.

### *Change in Refractive Indexes*

The refractive power created at a tissue interface is proportional to the difference in the refractive indices of the two tissues. If, as a consequence of some pathology, the index of refraction of the aqueous humor increases, the negative power of the interface between the cornea and aqueous humor will be decreased, causing index myopia. Index hyperopia occurs if it is decreased. The opposite occurs with changes in the refractive index of the vitreous body. If the refractive index of the vitreous increases, becoming closer to that of the lens, light will be refracted less at the lens–vitreous interface, causing index hyperopia. Index myopia occurs if the refractive index of the vitreous is decreased. Such changes in the index of aqueous and vitreous are seldom observed (except following surgical procedures, which may temporarily replace these tissues with air or silicone oil). It is believed that during aging, with the formation of nuclear cataract, the lens nucleus increases its refractive index, producing mild myopia. Something similar happens with cortical cataract, which with aging approaches the index of refraction of the nucleus, causing mild hypermetropia. Such ametropic effects of lens aging are often the presenting signs of cataract formation and may be mistaken for “improvement” of presbyopia (“second sight”). Frequently, further lens changes eventually degrade image quality, necessitating cataract extraction surgery.

It is important to note that there often appears to be a coordination between the axial growth of the eye and the evolving refractive power of the anterior segment, so that the net refractive error is typically less severe than might be expected if these structures developed independently—a phenomenon referred to as “emmetropization.” Thus one cannot accurately predict the refractive error simply knowing only the axial length or refractive power of the eye in isolation.<sup>21</sup>



**Fig. 2.2.8 Ametropias.** (A) Emmetropic eye. (B) Myopic eye. (C) Hyperopic eye. (Courtesy Francisco Irochima, MD.)

## Myopia

Myopia is the condition in which parallel light rays from infinity, as they refract on cornea and lens, converge at a focus in front of the retina. There the light rays cross, forming a “blur circle” for each point of the source object. The image that projects itself into the retina thus corresponds to the sum of the blur circles, causing poor image quality.

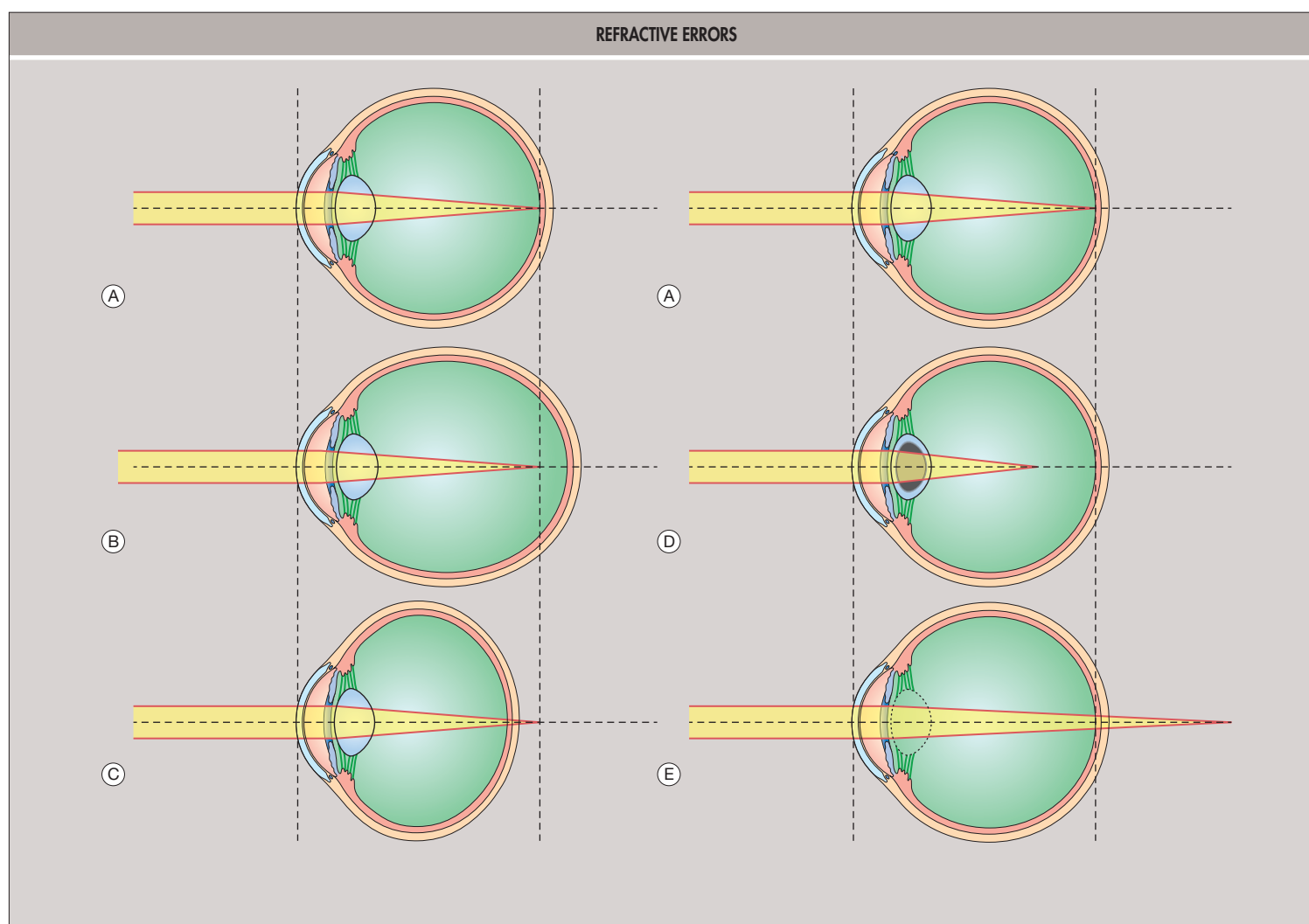
Only diverging rays from nearby objects naturally converge to a sharp focus on a myopic eye's retina. Due to the high positive power, parallel rays from infinity or convergent rays tend to converge until they reach a focus in front of a retinal point. Therefore it is common to see a myopic person bringing objects near the eye to improve the quality of the image, so that the rays of light leaving the object diverge. Another method of correction is the prescription of negative lenses, which cause the parallel rays from an object at infinity to diverge as they enter the eye, allowing a sharp focus on the retina.

In myopia the distance from the nodal point (optic center) to the retina is greater than is found in a typical “normal” eye, and, therefore, the projected image will be larger than normal, unlike hyperopes, in whom the optics project a smaller image.

The far point in myopia is at a finite distance in front of the eye. As seen previously, the emmetropic eye has the far point at infinity. In myopes, the distance to the far point is inversely proportional to the ametropia. For example, a myope of 0.25 D has its far point in  $1/0.25 = 4$  m.

On the other hand, the myope needs less accommodative effort for near vision. Thus the accommodation, if used in its entirety, can maintain an object in good definition even at small distances, smaller than those accepted by the emmetrope. For example, a 4 D myopic patient who





**Fig. 2.2.9 Refractive Errors.** (A) Emmetropic eye. (B) Axial myopia. (C) Axial hyperopia. (D) Index myopia (nuclear cataract). (E) Aphakia. (Courtesy Francisco Irochima, MD.)

accommodates up to 8 D will have its far point at 25 cm, that is, without accommodation, he or she will see an object clearly at this distance, acting like an emmetropic accommodating 4 D. His or her near point will be  $100 / (4 + 8) = 8.3$  cm, because at this distance the eye resembles that of an emmetropic accommodating 12 D but with less effort.

## Hypermetropia

Hypermetropia, or hyperopia, is the condition in which parallel light rays from infinity converge on a focus behind the retina after refracting on the cornea and lens. What is projected into the retina thus corresponds to blur circles formed before the light rays converge to a point, causing poor image quality.

Contrary to common belief, there are more hyperopes in the world population than myopes. However, many do not manifest it until the age of 40, as their refractive errors are typically neutralized by accommodation without spectacle correction. After age 40 years, the amplitude of accommodation decreases, generating presbyopia, which will be further discussed later.

At birth the human eye usually has a hyperopia of + 2.25 D that increases and peaks at approximately 8 years of age. After this age, the eye will progressively become more myopic, reaching emmetropia in adulthood.<sup>29</sup> Growth of the eye during development is a complex process, usually accompanied by changes in corneal curvature and in the dioptric power of the lens. Hyperopia occurs when there is an imbalance between these mechanisms, such as the axial diameter decreasing relative to the refractive power of the other elements of the eye, as discussed previously. Generally the shortening of the eye does not exceed 2 mm. Each millimeter of shortening of the diameter corresponds to about 3 D of refractive error. Therefore, excluding pathological abnormalities such as microphthalmia, few hyperopic eyes exceed a refractive error of 6 D.<sup>21</sup>

In hyperopia the far point is a virtual point located behind the retina, because only converging rays can focus on the retina of an uncorrected

hyperope (Fig. 2.2.10). Because not enough convergence exists to see objects at a distance, positive dioptric power must be added, which is usually done through prescription of converging lenses, artificial corneal steeping by refractive surgery, or by the physiological mechanism of accommodation itself. For eyes with the same amplitude of accommodation, the hyperope has its near point at a greater distance, because part of its accommodation is already used to converge parallel rays from infinitely distant sources, unlike in myopia (Fig. 2.2.11).

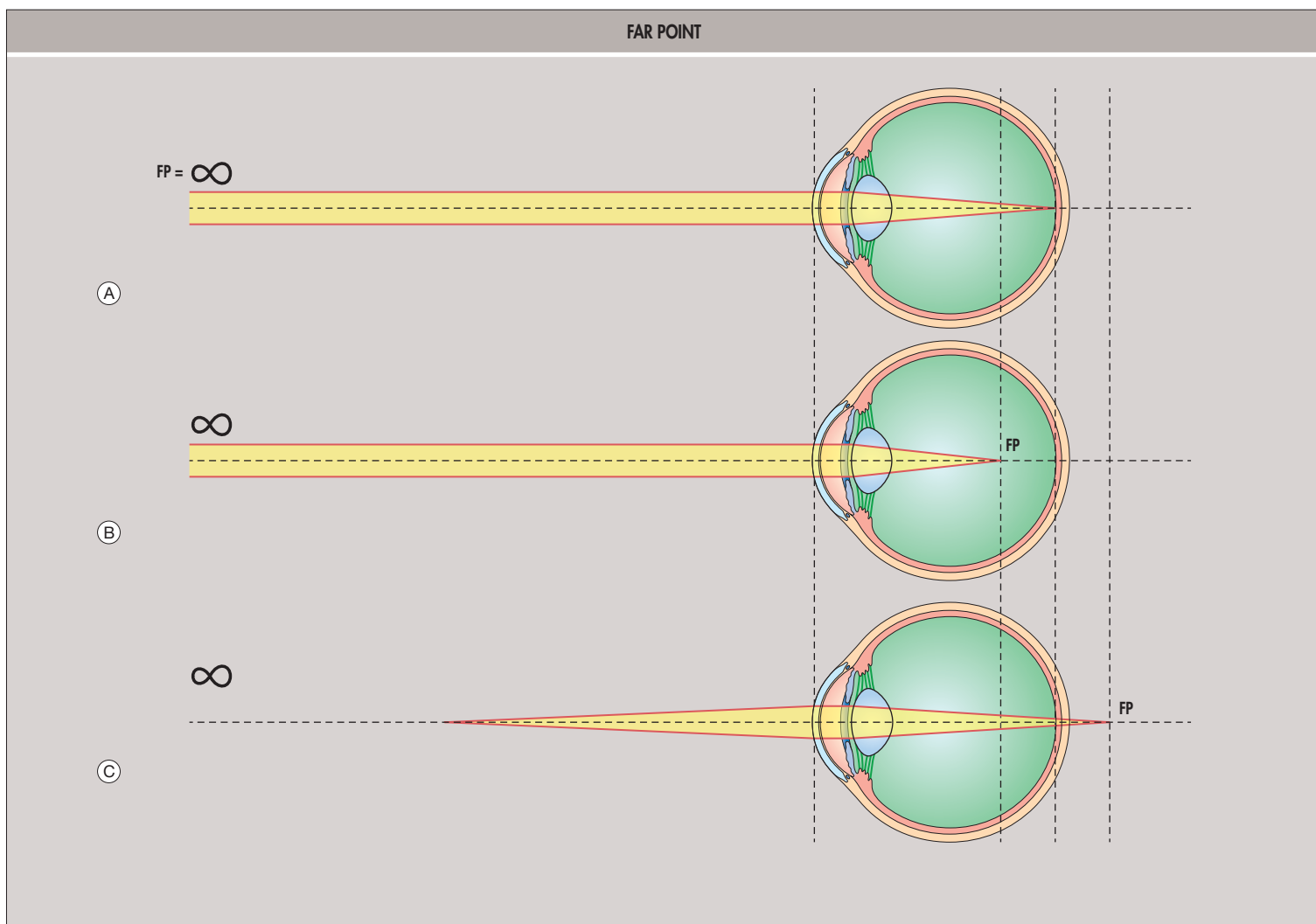
Hyperopia can be divided into latent and manifest hyperopia. Ideally, a clinical refraction is performed with the eye in a state of complete relaxation of accommodation. Such a state is artificially induced by cycloplegic eyedrops and does not occur in an eye in its natural state. Thus, if the ametropia measured during cycloplegia were used as the prescribed correction, this would likely be uncomfortable and not generate the best quality of vision for the patient, who would probably continue to exhibit some degree of accommodative tone after the cycloplegia wears off.

Indeed, the normal tonus of the ciliary body obscures a latent hyperopia, that is, an accommodation that is present even with the eye adjusted to fix a distant image, using the least possible accommodative effort. Latent hyperopia usually is around 1 D, and its understanding is important in daily practice for prescribing a more physiological refraction to the patient.<sup>30</sup>

The manifest hyperopia is the amount of diopter power required to reach emmetropia after minimal (latent) accommodation. Taking into account that in that state, there is still available some power of accommodation, one may subdivide the manifest hyperopia in two facultative and absolute hypermetropia. The facultative is that part of manifest hyperopia that can be overcome by accommodation. Thus the absolute is the remaining refraction error after maximum accommodative effort (Fig. 2.2.12).

## Astigmatism

Astigmatism is a condition in which the light rays, after refracting, do not converge to a single point. Due to variations in the curvatures of the cornea



**Fig. 2.2.10** Far point on (A) emmetropic eye, (B) myopic eye, (C) hyperopic eye. (FP) Far point. (Courtesy Francisco Irochima, MD.)

or the lens in different axes, instead of focusing the light from a point source to a single point, the image consists of two lines, separated from each other.

When the light from the main meridians that focus on the system in this optical condition are at right angles to each other, this is referred to as regular astigmatism. If, however, these principal meridians form a right angle but not oriented horizontally and vertically (at  $90^\circ$  and  $180^\circ$ ), the condition is described as oblique astigmatism. If the cornea or lens are so irregular that they do not form well-defined meridians, the condition is described as irregular astigmatism.

In regular astigmatism, depending on where the two lines focus, one may specify further subtypes. If both are in front of the retina, the refractive state is compound myopic astigmatism. Similarly, if both are behind, a compound hypermetropic astigmatism results. If one line focuses on the retina but the other line is in front or behind, one obtains a simple myopic or simple hypermetropic astigmatism, respectively. If one line focuses in front and the other behind the retina, the condition is called mixed astigmatism (Fig. 2.2.13).

In the space between the two focal lines, the light rays determine a characteristic geometrical figure called the conoid of Sturm (Fig. 2.2.14). The spacing of these focal lines (i.e., the size of the conoid) is a measure of astigmatism, and its correction is based on merging the focal lines into one, collapsing the conoid of Sturm to a single point. If the error is not corrected, the projected image on the retina within this space will form circles, ellipses, or lines, but never a single point, causing a blurred image. Note, however, that cylindrical lenses apply their power under the rays to  $90^\circ$  from the plane of their axis, not altering the rays on their own axis. Thus correction with cylindrical lenses can only be done in regular astigmatism.

In the center of the conoid, there is a region where the image is closest to forming a point, a circular region (due to the pupil shape) called the circle of least confusion. The circle of least confusion is the “best” image after light passes through an optical system with spherocylindrical power

(an eye with astigmatism). Thus with the spherical equivalent of optical correction, which places this circle on the retina, we will have the best image that can be obtained by correcting an astigmatism with only spherical lenses.

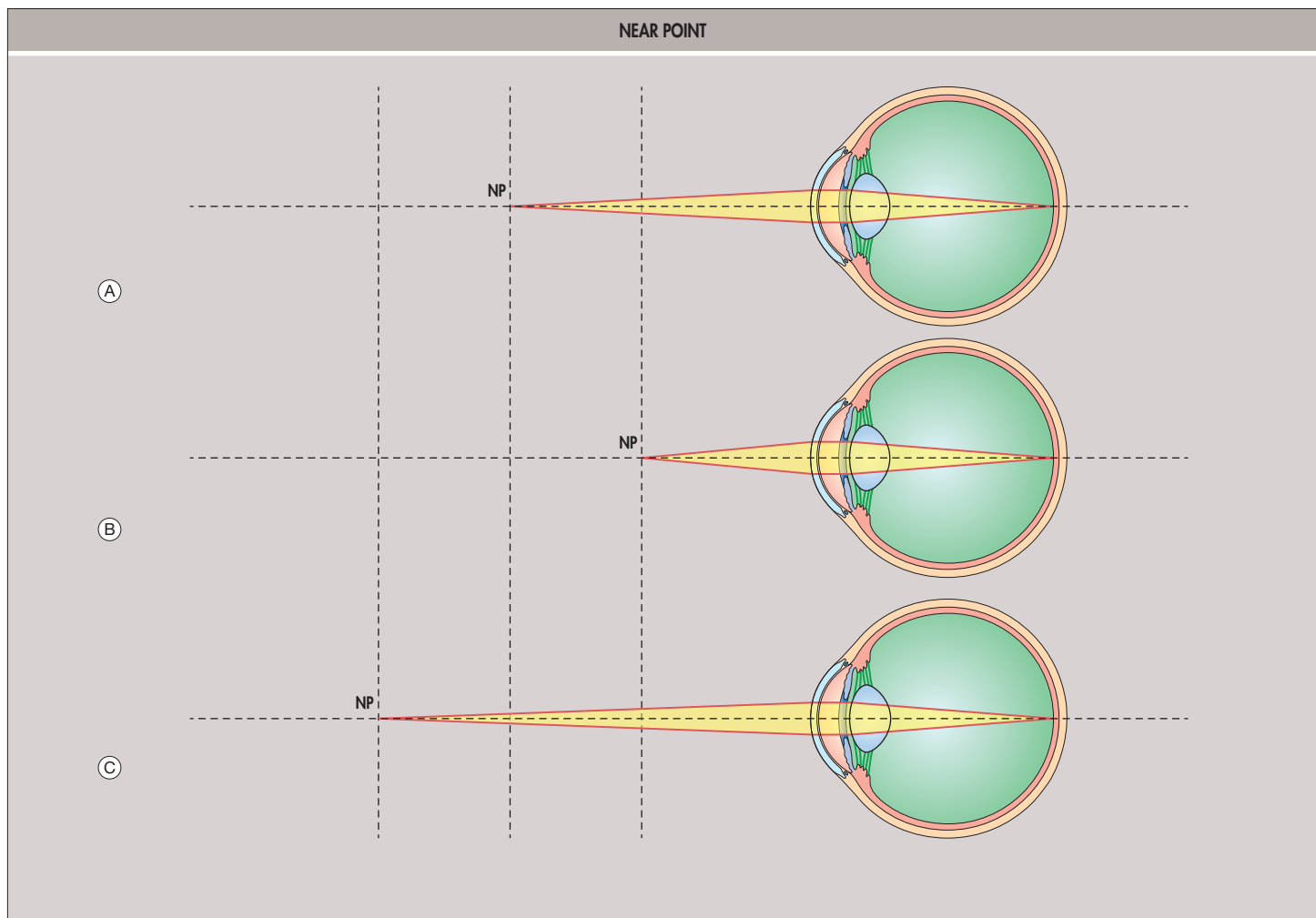
Although no eye is perfectly free from astigmatism, in practice it is necessary to correct astigmatic refractive errors only when patients experience symptoms such as decreased visual acuity or eye fatigue from constantly adjusting accommodation to optimize the seeing between the two focal lines.

## Presbyopia

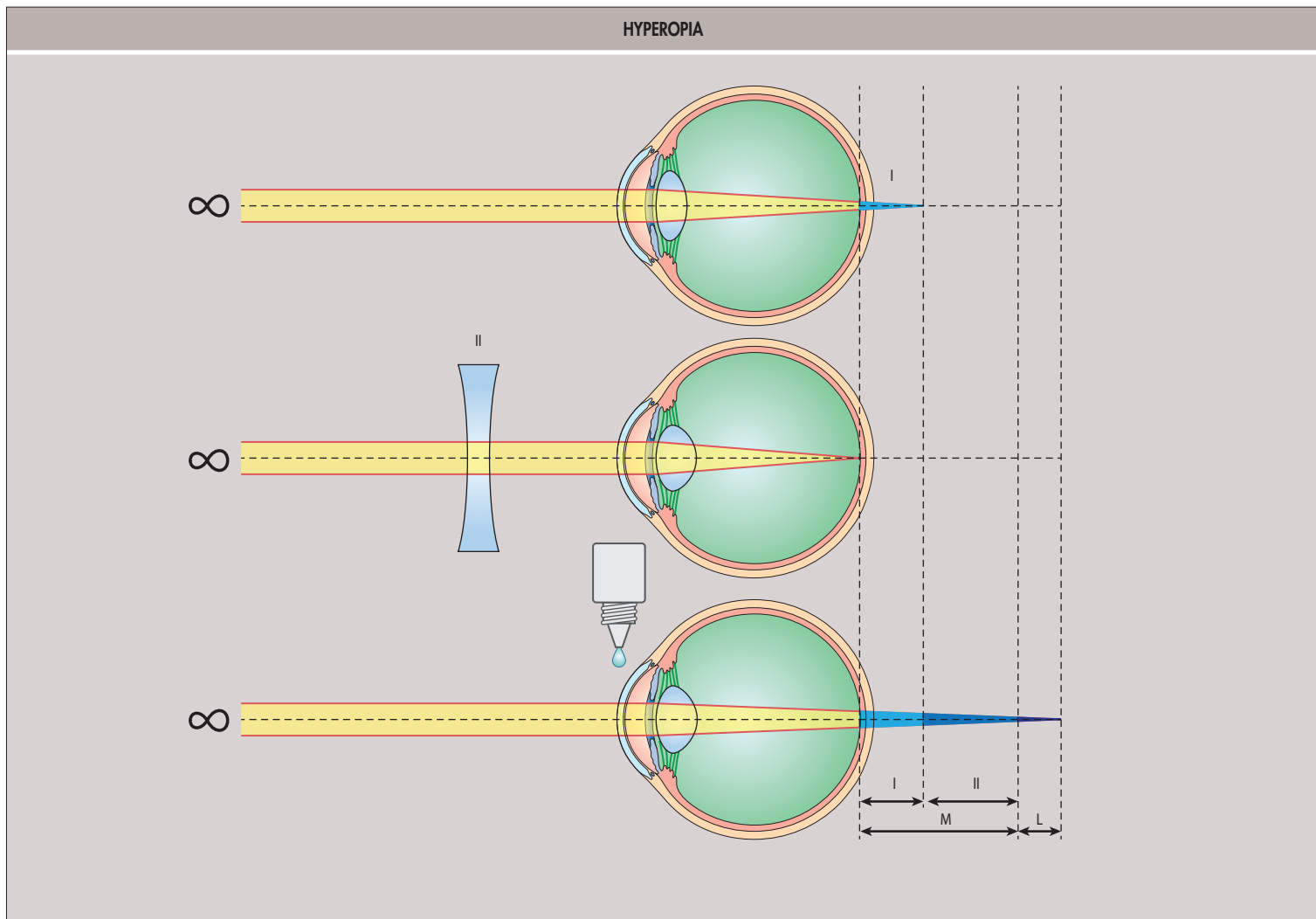
As seen earlier, manifest hyperopia has its facultative and absolute component. The facultative component, which can be compensated by accommodation, decreases progressively with age, so the absolute hyperopia will eventually become evident in those hyperopes that did not exhibit this component earlier in life (when hyperopia is totally neutralized by accommodation). In such symptomatic patients, absolute hyperopia increases and symptoms become more evident around the age of 40, requiring greater optical correction. Myopes, as they have the near point at a shorter distance, usually have a “natural protection” against presbyopia. Myopes with small refractive errors, however, will also require positive diopter power for near objects after a more significant progression of presbyopia.

Fisher<sup>31</sup> published an important paper in 1988 breaking previous paradigms, such as those published by von Helmholtz<sup>32</sup> that presbyopia was due to lenticular sclerosis and by Donders,<sup>33</sup> who argued that the loss of strength of the contraction of the ciliary muscle was the main cause.

In his article, Fisher states that at the beginning of presbyopia, there is in fact hypertrophy of the ciliary muscle as a compensatory form to the greater difficulty of lenticular diameter alteration. This difficulty, however, was not due to sclerosis but rather to the stiffening of the lens capsule associated with changes in the zonule structure, which became more compact.<sup>31</sup>

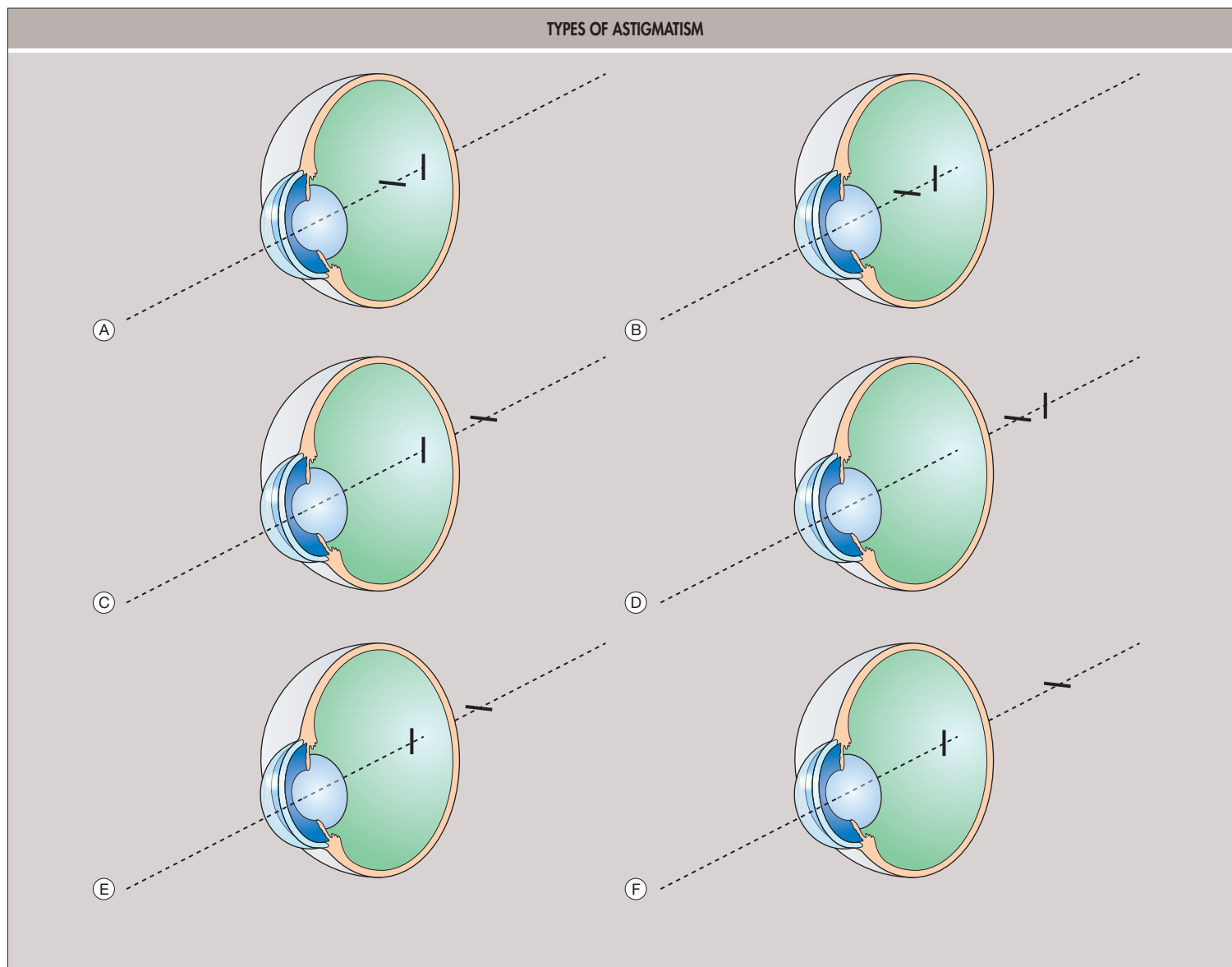


**Fig. 2.2.11** Near point on (A) emmetropic eye, (B) myopic eye, (C) hyperopic eye. (NP) Near point. (Courtesy Francisco Irochima, MD.)

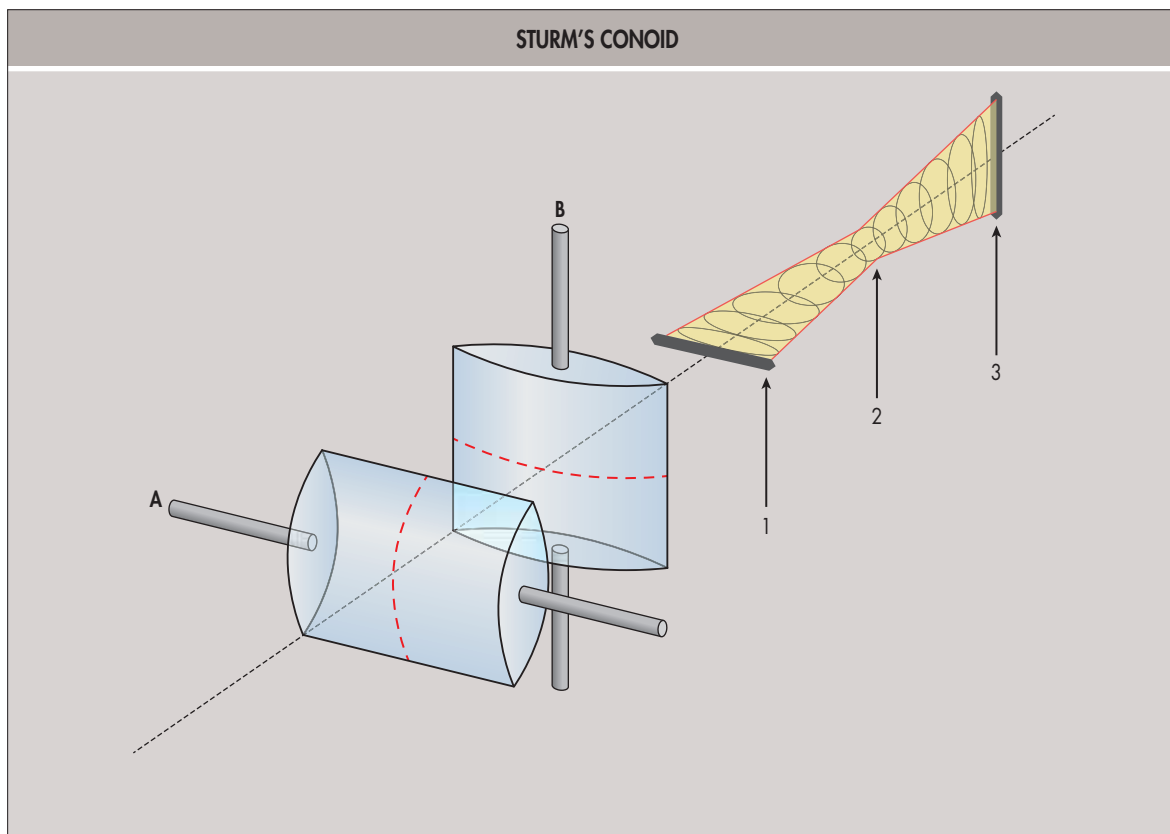


**Fig. 2.2.12 Hyperopia.** (I) Absolute hyperopia—fraction of the hyperopia that cannot be corrected by accommodation. (II) Facultative hyperopia—can be measured by divergent lenses. M—Manifest hyperopia. L—Latent hyperopia, detected with cycloplegic eyedrops. ( $\infty$  - infinite). (Courtesy Francisco Irochima, MD.)

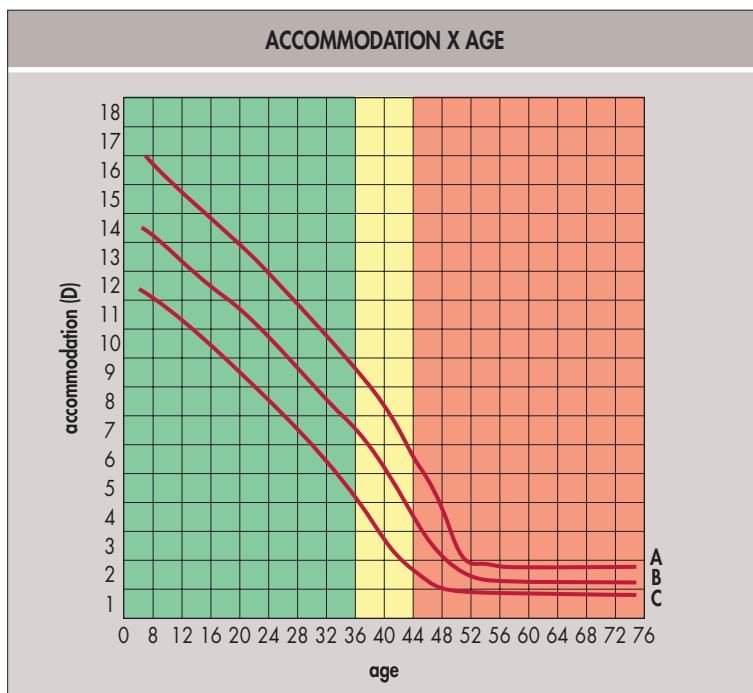




**Fig. 2.2.13 Types of Astigmatism.** (A) Simple myopic astigmatism. (B) Compound myopic astigmatism (notice that both of lines are in front of the retina). (C) Simple hypermetropic astigmatism. (D) Compound hypermetropic astigmatism. (E) Equidistant mixed astigmatism. (F) Nonequidistant mixed astigmatism. (Courtesy Francisco Irochima, MD.)



**Fig. 2.2.14** Sturm's Conoid Formed by Two Perpendicular Cylinders (A and B). (A) 180° axis cylinder. (B) 90° axis cylinder. (1) Focal line from cylinder A. (2) Less confusion circle. (3) Focal line from cylinder B. (Courtesy Francisco Irochima, MD.)



**Fig. 2.2.15** Accommodation (D – diopters) X Age (years), according to Duane.<sup>34</sup> (A) Minimum values, (B) medium values, (C) maximum values. (Courtesy Francisco Irochima, MD.)

Later, it was proved that the role of the stiffening of the crystalline nucleus itself would also play a part in the phenomenon. Thus aging would be associated with complex physical and optical changes in the crystalline structure responsible for changes not only limited to loss of accommodation and cataract.<sup>30</sup>

With the loss of amplitude of accommodation during aging, therefore, the near point gradually recedes, making it harder to see near objects with clarity. This phenomenon should not be seen as pathological, but rather as a normal—indeed inevitable—consequence of aging.

Note that at age 45 the range of accommodation is around 2 D. In practice, this does not mean that the patient will be able to routinely exert this

entire accommodative power, because maximal prolonged accommodative effort is usually only one-third to one-half the total amplitude. Thus in a comfortable and tolerable way, the routinely available accommodation at that age usually is less than 1 D, which means that optical corrections will usually be necessary for near vision in a previously emmetropic patient (Fig. 2.2.15).

The treatment of presbyopia is performed with the use of convex lenses, bringing the near point to a region of comfortable working distance that is compatible with the patient's needs. With advancing age, the depth of focus through a presbyopic correction will decrease, potentially creating a gap between the closest focus with the distance correction, and the most distant focus available through the reading correction. If this is bothersome, the patient may be helped by a prescription for trifocals, with an intermediate presbyopic correction zone, or progressive lenses, which provide a continuous transition between distance and near corrections.

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# Clinical Refraction

Albert Wu

## 2.3

**Definition:** The neutralization of an individual's refractive error using a variety of tests in which the patient's responses determine the lens power that best produces a sharply focused image on the retina.

### Key Features

- The selection of a prescription for corrective lenses that balances optical clarity with other important physical and psychological factors, such as equality of magnification, single vision, and comfort.
- The determination of the most appropriate form of optical correction based on the patient's visual needs and on environmental factors.

### INTRODUCTION

Many people equate an eye examination with a refraction test for glasses. The confusion is understandable because for the vast majority, especially those in the preretirement age group, eyeglasses or contact lenses resolve the main complaints they have about their eyes. Also, refraction is almost always part of a comprehensive eye examination, not only to provide a prescription for corrective lenses but also to determine the best acuity that an eye can achieve.

Refraction is only one of the many methods used to determine the function and health of the visual system. Because of the value of the results, it is important to develop an efficient and accurate basic refractive technique that can be modified when unusual variations present themselves.

Although often relegated as a purely technical task in the spectrum of high-technology examination and treatment procedures that characterize contemporary ophthalmic practice, refraction provides relief for one of the world's most common physical defects. An understanding of the concepts used to identify and measure refractive errors is the basis for prescribing individual corrections that offer patients improved quality of life.

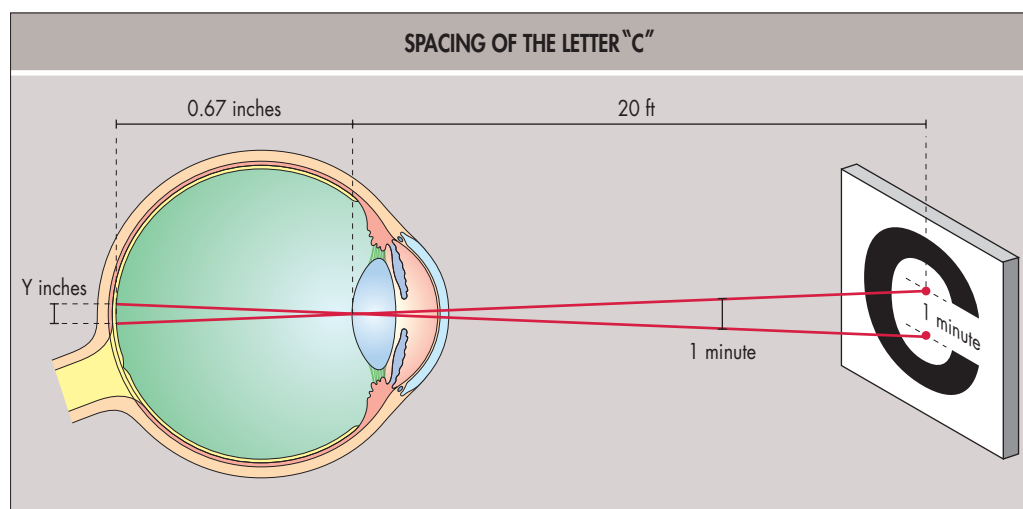
### HISTORY

Spectacles were first described during the Middle Ages. In 1266 Roger Bacon magnified print in a book using a segment of a glass sphere. A painting completed in 1352 shows a prelate wearing lenses in a mounting. In the late fifteenth century, merchants sold spectacles to buyers who chose them on the basis of their own judgment of how vision improved. As the trade of lens-making proliferated throughout Europe, it became organized into a guild. Although cylindrical lenses had been manufactured since 1827, it was not until Donders published his methods of refraction that correcting astigmatism became an exact science. In 1893 when American Optical developed the trial case of lenses, opticians—rather than spectacle peddlers—became the primary providers of eye examinations.<sup>1</sup> Although instrument-makers have dramatically improved the ability of examiners to provide accurate and repeatable lens prescriptions, most subjective techniques still rely on a comparison of views through different lenses.

### VISUAL ACUITY

The idea that the minimal separation between two point sources of light was a measure of vision dates back to Hooke in 1679, when he noted, "tis hardly possible for any animal eye well to distinguish an angle much smaller than that of a minute: and where two objects are not farther distant than a minute, if they are bright objects, they coalesce and appear as one."<sup>2</sup> In the early nineteenth century, Purkinje and Young used letters of various sizes for "judging the extent of the power of distinguishing objects too near or too remote for perfect vision." Finally, in 1863, Professor Hermann Snellen of Utrecht developed his classic test letters. He quantitated the lines by comparison of the visual acuity of a patient with that of his assistant, who had perfect vision. Thus 20/200 (6/60) vision meant that the patient could see at 20 ft (6 m) what Snellen's assistant could see at 200 ft (60 m).<sup>3</sup>

The essence of correct identification of the letters on the Snellen chart is to see the clear spaces between the black elements of the letter. Thus in Fig. 2.3.1, the angular spacing between the bars of the C is 1 minute for the



**Fig. 2.3.1 Spacing of Gap in the Letter "C."** This letter is used to determine the minimal separable spacing or resolution of the eye at the retina. The gap in the letter C subtending 1 minute, when imaged on the retina, has a dimension (Y) representing the resolution of the eye where  $\tan(1 \text{ minute}) = Y/0.67$  (with Y in inches); therefore,  $Y = 0.00019$  inches (or 4.8 m). The overall size of the letter is  $X = 0.349$  inches, and the gap dimension is 0.070 inches (see text).



20/20 (6/6) letter. The entire letter has an angular height of 5 minutes. To calculate the height,  $x$ , of a 20/20 (6/6) letter, use Eq. 2.3.1.

$$\tan(5 \text{ minutes}) = \frac{x \text{ feet}}{20}$$

Equation 2.3.1

From Eq. 2.3.1,  $x = 0.0291 \text{ ft}$  (0.349 in). In like manner, the 20/200 (6/60) letter is 10 times taller, or 3.49 in (8.87 cm) high.

Testing Distance

The Snellen acuity test traditionally is done at a distance of 20 feet (6 m). At this distance, very little accommodation is required by the patient. For hospital patients, testing must often be carried out in a smaller room. If the doctor stands at the foot of the bed and the patient sits propped up at the head of the bed, the distance between them is about 5 feet (1.5 m). Thus the classic Snellen chart, with its conventional notations, may be used if the chart is reduced to one-fourth its original size. Admittedly, a test at 5 ft (1.5 m) requires the emmetropic patient to accommodate 0.67 diopters (D).

Other Considerations

Over the years, it has become apparent that projection of the Snellen chart onto a screen in a darkened examination room does not give an accurate replication of “everyday” visual function. For example, the high contrast black-on-white letters do not represent the contrast of most objects seen in everyday life. The dark examination room, which is devoid of glare sources, also is not representative of most daytime visual tasks.

As the projector bulb ages or collects dirt, and as the projection lens becomes dusty, the contrast of the letters projected on the chart decreases. Thus a change in readings between patient visits may not always arise from a significant change in the visual status of the patient. At present, British standards require 480 to 600 lux to illuminate distant wall charts and 1200 lux to illuminate projected charts.<sup>4</sup>

As the letters become smaller on the Snellen chart, the number of letters per line increases. Thus one error per line means a different degree of impairment for each line. It is necessary, therefore, to establish criteria by which it can be agreed that a patient has seen the line. Some clinicians credit a patient if more than one-half the letters are identified correctly. Others require identification of all the letters before credit is given. Also remember that no orderly progression of size change exists from line to line. Thus a two-line change on the Snellen chart going from the 20/200 (6/60) line to the 20/80 (6/24) line represents an improvement of visual acuity by a factor of 2.5, whereas a two-line change going from the 20/30 (6/9) line to the 20/20 (6/6) line represents an improvement by only a factor of 1.5.

Another problem is that the identification of different letters of the same size has been shown to vary in difficulty. Thus A and L are easier to identify than E. The Bailey–Lovie chart (Fig. 2.3.2), designed by two Australian optometrists<sup>5</sup> and modified by Ferris et al.<sup>6</sup> in 1982, uses 10 letters of similar difficulty with five different letters per line and has uniform proportional size change between neighboring lines. Another approach is

to use the Landolt ring test in which circles of decreasing size, each with an open gap, are used in successive lines, with the orientation of the gaps in the circles randomly changing.

The 20/20 (6/6) Snellen line represents the ability to resolve 1 minute of arc, which is close to the theoretical diffraction limit, but the occasional patient can see the 20/15 (6/4.5) or, rarely, 20/10 (6/3) line. Four explanations suggest themselves. First, some individuals may have cone outer segment diameters of less than 1.5  $\mu\text{m}$ , which would give a finer-grain mosaic having cone separations of less than 1 minute of arc. Second, longer eyes provide slightly magnified retinal images, thereby tending to yield better acuities. Third, some eyes may have less aberration than others, which would allow them to function optimally with larger pupils having, consequently, better diffraction-limited performance. Finally, our experience with a small aperture corneal inlay has taught us that brain processing cancels much of the diffraction noise for apertures between 1.5 mm to 2.0 mm (US PATENT # 4955904, Atebara, Miller. US PATENT #5245367, Miller/Meshel. US PATENT #6899424, Miller, Blanco).

Contrast Sensitivity

Visual acuity testing is relatively inexpensive, takes little time to perform, and describes visual function with one notation, such as 20/40 (6/12). Best of all, for more than 150 years it has provided an end point for the correction of a patient’s refractive error. Yet contrast sensitivity testing, a time-consuming test born in the laboratory of the visual physiologist and described by a graph rather than a simple notation, has become a popular clinical test recently. It describes a number of subtle alterations of vision not accounted for by the visual acuity test. Thus it more accurately quantifies the loss of vision in cataracts, corneal edema, neuro-ophthalmic diseases, and certain retinal diseases. Although these advantages have been known for a long time, the recent enhanced popularity has arisen because of patients with cataracts. As lifespan increases, more patients who have cataracts request medical help. Very often, their complaints of objects that appear faded or objects that are more difficult to see in bright light are not described accurately by their Snellen acuity scores. Contrast sensitivity tests and glare sensitivity tests do quantitate many of these complaints.

Contrast sensitivity testing is similar to Snellen visual acuity testing in that it tests using several different sized letters or grid patterns. However, it is different from visual acuity testing because the letters (or grid patterns) are displayed in six or more shades of gray instead of the standard black letters of the Snellen chart. Thus contrast sensitivity testing reports show a contrast threshold (i.e., lightest shade of gray just perceived) for each of several letter (or grid pattern) sizes.

Contrast

The components of a conventional newspaper photo consist of various regions associated with the scene where each region is filled in with a definite density of black dots depicting that region’s contrast or level of gray. Such newspaper photos may have over 100 half-tone levels (i.e., densities of black dots) to represent the different contrast levels in the scene.

Whereas a black letter on a white background is a scene of high contrast, a child crossing the road at dusk and a car looming in a fog are scenes of low contrast. The contrast of a target on a background is defined by Eq. 2.3.2.

$$\text{contrast} = \frac{\text{target luminance} - \text{background luminance}}{\text{target luminance} + \text{background luminance}}$$

Equation 2.3.2

As an example, suppose a photometer measures the luminance of a target at 100 units of light and the luminance of the background at 50 units of light. Substitution into Eq. 2.3.2 gives Eq. 2.3.3.

$$\text{contrast} = \frac{100 - 50}{100 + 50} = 0.33 \text{ (or 33\%)}$$

Equation 2.3.3

Suppose the contrast of a target of a certain size is 0.33, which also may represent a particular older patient’s threshold, which means that this patient cannot detect similar-sized targets of lower contrast. The older patient’s contrast sensitivity (CS) is the reciprocal of the contrast, namely  $CS = 3.0$ . On the other hand, a young, healthy subject viewing a target of the same size may have a contrast threshold of 0.01 with a corresponding  $CS = 100$ . Occasionally subjects (for certain-size targets) have even better contrast thresholds. A subject could have a contrast threshold of 0.003, which converts into a CS of 333. In the visual psychology literature, CS often is described in logarithmic terms. For example, associated with CS

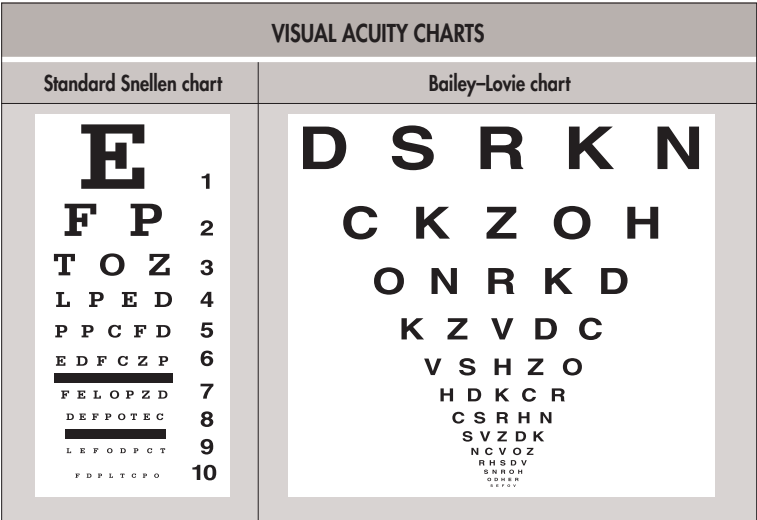


Fig. 2.3.2 Visual Acuity Charts. Standard Snellen and Bailey–Lovie charts.

= 10 is  $\log(\text{CS}) = 1$ , with  $\text{CS} = 100$  is  $\log(\text{CS}) = 2$ , and with  $\text{CS} = 1000$  is  $\log(\text{CS}) = 3$ , and so on.

### Targets

Both the visual scientist and the optical engineer use a series of alternating black and white bars as targets. The optical engineer describes the fineness of a target by the number of line pairs per millimeter (a line pair consists of a dark bar with a white space next to it). The higher the number of line pairs per millimeter, the finer is the target. For example, about 82 line pairs per millimeter imaged on the retina of an eye with a focal length of 21 mm is equivalent to a periodic black–white target in object space, where the white space between two black spaces subtends approximately a minute of arc (like the letter E of the Snellen chart viewed at 20 ft). Equivalently, with a Snellen chart viewed at 20 ft, 109 line pairs per millimeter on the retina is equivalent to the 20/15 (6/4.5) letters.

The vision scientist generally describes a periodic bar pattern in terms of its spatial frequency as perceived at the test distance—the units are cycles per degree (cpd). A cycle is a black bar and a white space. To convert Snellen units into cpd at the 20 ft (6 m) testing distance, the Snellen denominator is divided into 600 (180). For example, 20/20 (6/6) converts into 30 cpd. Likewise, 20/200 (6/60) converts into 3 cpd.

### Sine Waves

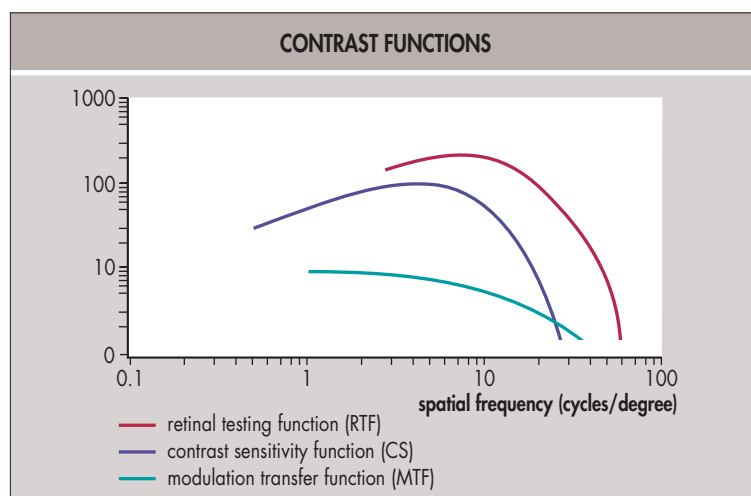
So far, targets have been described as high-contrast dark bars of different spatial frequency against a white background. These also are known as square waves or Foucault gratings. However, in optics very few images can be described as perfect square waves with perfectly sharp edges. Diffraction tends to make most edges slightly fuzzy, as do spherical aberration and oblique astigmatism, particularly in the case of the optics of the eye. If the light intensity is plotted across a strongly blurred image of a Foucault grating, a sine wave pattern results. Sine wave patterns have great appeal because they can be considered the essential elements from which any pattern can be constructed. The mathematician can break down any alternating pattern, be it an electrocardiogram or a trumpet's sound wave, into a unique sum of sine waves. This mathematical decomposition of patterns into sinusoidal components is known as a Fourier transformation. Fourier's theorem describes the way that any pattern may be written as a sum of sine waves that have various spatial frequencies, amplitudes, and phases.

Also, it is thought that the visual system of the brain may operate by breaking down observed patterns and scenes into sine waves of different frequencies. The brain then adds them up again to produce the mental impression of a complete picture. Fourier transformations may be the method the visual system uses to encode and record retinal images. It has been shown that different cells or “channels” occur in the retina, lateral geniculate body, and cortex that selectively carry different spatial frequencies.<sup>7</sup> So far, six to eight channels have been identified. It also has been shown that all channels respond to contrast—the cortex shows a linear relationship between the amplitude of the neuronal discharge and the logarithm of the grating contrast. Consequently, many contrast sensitivity tests are based on sine wave patterns rather than square wave patterns.

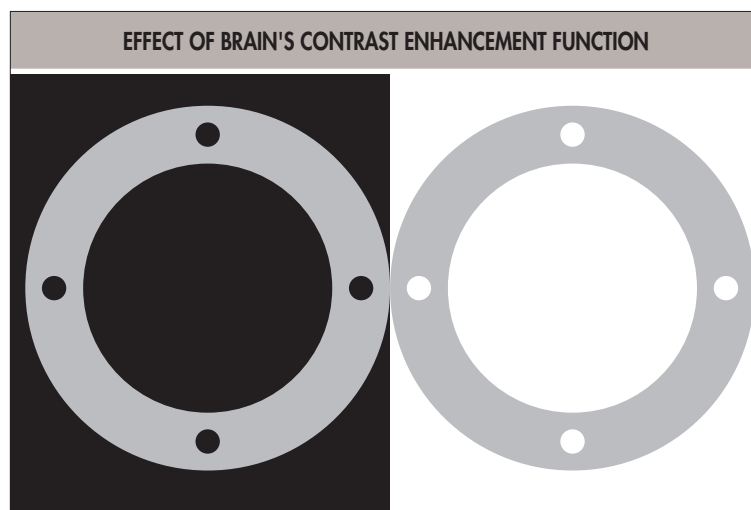
### Recording Contrast Sensitivity

Fig. 2.3.3 shows a number of functions, including the contrast sensitivity testing function for a normal subject. The shape of the human eye's contrast sensitivity function is different from that of an inanimate optical imaging systems in which the function generally decreases continuously from very low to very high spatial frequencies. For the normal human eye, the contrast sensitivity generally increases from very low frequencies to about 6 cpd and then decreases with increasing frequency beyond 6 cpd. The decrease of the contrast sensitivity with frequency above 6 cpd is due to the influence of diffraction and aberrations, which make the detection of finer details more difficult. The increase of the contrast sensitivity with frequency up to 6 cpd is due to the retina–brain processing system, which is programmed to enhance our contrast sensitivity in the range of 2 to 6 cpd. Receptor fields, on–off systems, and lateral inhibition are the well-known physiological mechanisms that influence the different spatial frequency channels and are responsible for such enhancement. In Fig. 2.3.3, the plot labeled retinal testing function (RTF) represents the retinal–neural system's contrast sensitivity performance.<sup>8–10</sup> A striking proof of brain enhancement of contrast is given in Fig. 2.3.4.

Also shown in Fig. 2.3.3 is the plot labeled modulation transfer function (MTF), which represents the sinusoidal components of the object-to-image transfer function for the purely optical portion of the visual system (cornea, lens).<sup>11</sup> The MTF is described more completely in the next section. A significant mathematical relationship exists among the three functions,



**Fig. 2.3.3 Contrast Functions.** The human eye's contrast sensitivity (CS) function is the product of the contrast transfer function of the purely optical contribution, called the modulation transfer function (MTF), and the contrast sensitivity function of the purely neuroretinal contribution, called the retinal testing function (RTF). The MTF is magnified 10× in the graph. (Redrawn from Mainster MA. Contemporary optics and ocular pathology. Surv Ophthalmol 1978;23:135–42.)



**Fig. 2.3.4 Effect of Brain's Contrast Enhancement Function.** One gray circle is seen against a black background and one against a white background. The brain's contrast enhancement function makes the gray look lighter against the dark background and darker against the light background.

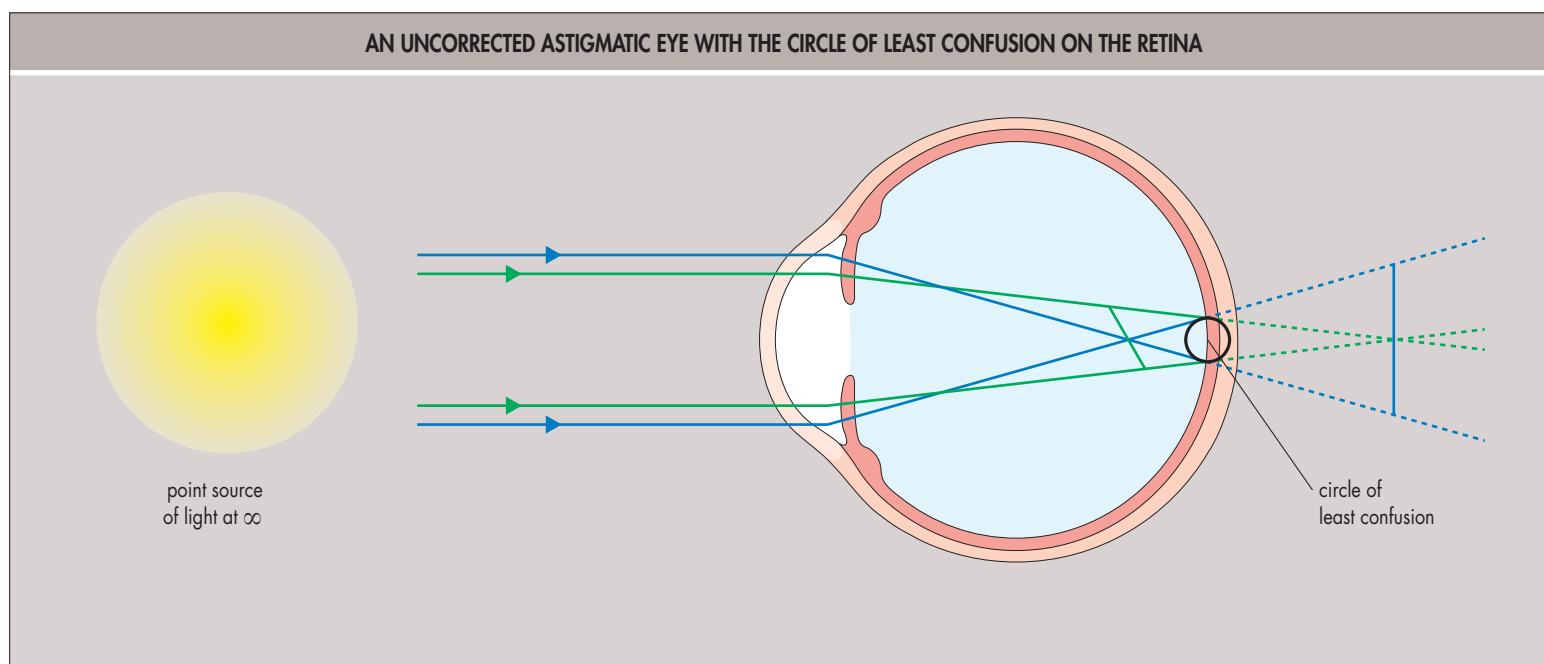
which is expressed by Eq. 2.3.4, the so-called Campbell–Green relation,<sup>11</sup> and is illustrated in Fig. 2.3.3. The Campbell–Green relation has been demonstrated in clinical studies.<sup>12</sup>

$$\text{CS} = \text{RTF} \times \text{MTF} \text{ for all frequencies} \quad \text{Equation 2.3.4}$$

Differences in the contrast sensitivity function are expected among different subject groups. For example, contrast sensitivity decreases with age, for which two factors appear to be responsible. First, the normal crystalline lens scatters more light with increasing age,<sup>13</sup> which thus blurs the edges of targets and degrades the contrast. Second, the retina–brain processing system itself loses its ability to enhance contrast with increasing age.

The contrast sensitivity function also is an accurate method by which to follow certain disease states. For example, the contrast sensitivity function of a patient who has a cataract is diminished, as it is in another light-scattering lesion, corneal edema. Because the contrast sensitivity function is dependent on central nervous system processing, it is not surprising that conditions such as optic neuritis and pituitary tumors also characteristically have diminished contrast sensitivity functions.

The contrast sensitivity of patients also decreases as the illumination decreases.<sup>14</sup> Thus contrast sensitivity for a spatial frequency of 3 cpd typically drops from 300 to 150 to 10 as the retinal luminance drops from 9 trolands to 0.09 trolands to 0.0009 trolands. (The troland is a psychophysical unit. One troland is the retinal luminance produced by the image of an object, the luminance of which is 1 lumen/m<sup>2</sup> (1 lux) for an area of



**Fig. 2.3.5 An Uncorrected Astigmatic Eye With the Circle of Least Confusion on the Retina.** The horizontal and vertical focal lines are dioptrically equal in front of and behind the retina.

the entrance pupil of 1 mm<sup>2</sup>.) Therefore, when careful contrast sensitivity function comparisons are made, the illuminance of the test targets must be kept at the recommended value.

## SPHERICAL EQUIVALENT

There are three basic components in the specification of a spectacle lens: the spherical power, the astigmatic cylinder axis, and the cylinder power. An accurate determination of the spherical component is predicated on having fully corrected the astigmatic error to ensure that a point focus is obtained with the final correcting lens. Therefore subjective examinations proceed in that order. In eyes with astigmatism, each of the principal meridians produces a linear image at its focal distance. In the space between foci—the interval of Sturm—the image has a progressive change in its elliptic profile. At the focal distance of the dioptric average of the two principal powers, the image is round and is called the circle of least confusion. In an eye uncorrected for astigmatism, the best acuity occurs when the circle of least confusion falls on the retina (Fig. 2.3.5). At all other points within the astigmatic pencil, the image is distorted along the principal meridians whereby each point source produces an oval image.<sup>3</sup> The oval images of two or more adjacent point objects overlap along one of the principal meridians and appear darker along their long axes. Some refractive techniques use this effect to neutralize the astigmatic focus subjectively.

Spherical equivalent is an important optical concept that is applicable in the dispensing of contact lenses and glasses. It is defined as the spherical power whose focal point coincides with the circle of least confusion, where one would see minimal blurring in their vision. To calculate the spherical equivalent, disregard the axis and add half the cylinder power to the sphere power. This is the algebraic sum of the value sphere and half the cylinder value, representing the average of the two powers that make up spherocylinder.

A plus cylinder example:

$$+2.00 + 3.00 \times 120$$

The spherical equivalent is:

$$+2.00 + (+3.00/2) = +3.50$$

A minus cylinder example:

$$+2.00 - 3.00 \times 120$$

The spherical equivalent is:

$$+2.00 + (-3.00/2) = +0.50$$

Practically speaking, the spherical equivalent is useful for prescribing a spherical contact lens to a patient with a low level of astigmatism. It also is useful when prescribing astigmatic contact lens to an individual with high astigmatism beyond the maximum cylinder correction of  $-2.75$  commonly offered by many contact lens companies. As a result, one might prescribe the lesser amount of astigmatism and correct the spherical power based on the spherical equivalent. Another similar use of spherical equivalent would be when prescribing glasses to a patient with high astigmatism and reducing the full cylinder correction to help the patient adjust to their prescription.

## DETECTING ASTIGMATISM

One of the most common reasons that patients seek eye care is to obtain correction of their refractive error. However, refraction is also a diagnostic tool used to differentiate decreased acuity caused by uncorrected or incompletely corrected refractive error from blurred vision related to eye disease.

In most cases the final determination of the refractive correction is based on the patient's appreciation of the lens power that provides the clearest vision at the desired viewing distance. This procedure, subjective refraction, is a time-honored combination of the technical skill required to select a lens that produces a sharply focused image on the retina tempered with the fine art of determining the best overall correction incorporating other factors such as the balance between the two eyes, the patient's visual needs, the patient's age, and the rate of change of the refractive error. The concepts and procedures described here refer to neutralization of the refractive error with spectacles, but most of these principles and techniques also apply to correction using contact lenses.

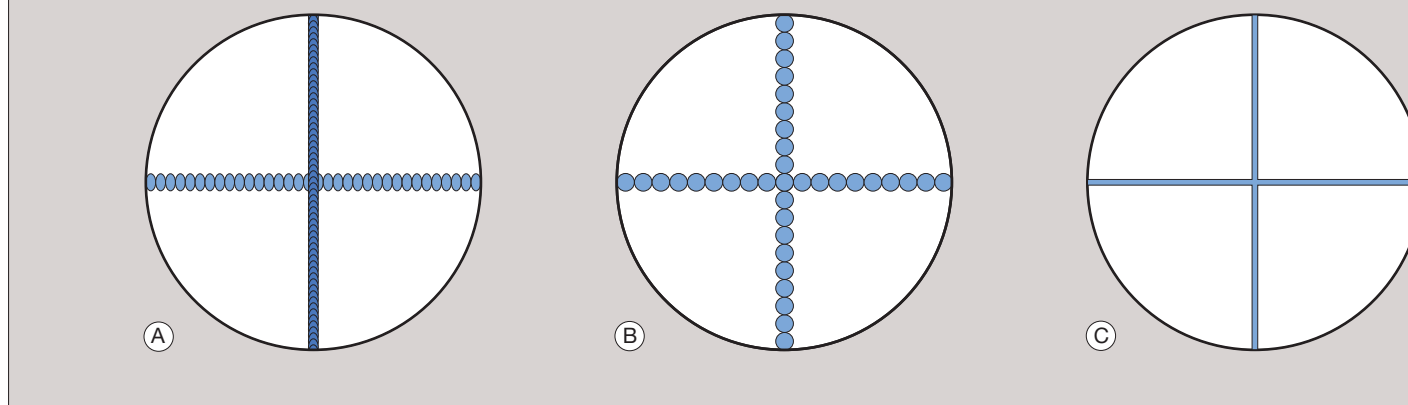
## Utility of the Test

Subjective refraction is usually performed after an in-depth history has been obtained, which includes ascertaining that clear vision has been achieved previously in both eyes, describing visual symptoms and any relief provided with the current correction, and specific visual requirements related to work and avocations. It should be performed before any other test that might alter the patient's responses because of physical changes to the eye, such as Goldmann tonometry and gonioscopy. Any examination procedure that uses bright lights, such as ophthalmoscopy or slit-lamp evaluation, can produce a photostress response. Refraction should be done either before these tests are performed or after an appropriate recovery period.

## Procedure

Although a totally subjective test is possible, most examiners use a baseline starting point, such as an evaluation of the patient's previous

## THE PRINCIPAL MERIDIANS OF THE CLOCK CHART



**Fig. 2.3.6 The Principal Meridians of the Clock Chart.** (A) As seen by an eye with uncorrected astigmatism in which each image appears as a vertical oval. The overlapping ovals make the vertical line darker. (B) The same eye when the correct amount of cylinder is in place and the fogging lens has not been removed. Each image appears as a blurred circle so that all the lines appear equally dark. (C) The same eye with the full spherocylindrical correction in place. Each image appears as a sharp point, giving an even, well-focused appearance to the chart.

eyeglasses, retinoscopy, or the results of an automated refraction, which they then refine to meet the patient's requirements. In general, the goal is to determine the maximum plus-lens (or minimal minus-lens) power correction that provides clear far vision while minimally exerting accommodation, and a near correction that provides clear vision at the desired distances. Many methods have been developed to determine the "best" correction, any of which an adept refractionist can call on to resolve a specific refractive quandary. For the purposes of this chapter, only the most widely accepted methods are described.

## Instrumentation

As with most healthcare procedures, many levels of sophistication in the instruments are available to perform this technique. They range from highly automated scanners and analyzers that provide an objective measure of the eye's refractive error in seconds to the centuries-old method of placing loose lenses by hand into a trial frame worn by the patient. Each method has its proponents and in particular situations, each method has its advantages.

Automated refractors analyze the focal power of emitted light from the eye and convert it into a dioptric correction. They are very fast, require minimum skill levels to operate, and are fairly accurate. They also are very expensive. Certain high-end models have subjective refraction capability so that the correction can be refined in the instrument. Portable and hand-held automated refractors now are available.

Most practitioners rely on the manually operated refractor or phoropter that contains a battery of lenses arranged in geared wheels that can be positioned in front of the patient's eyes. The lenses can be changed quickly to provide a wide array of plus and minus spherical lenses as well as a range of cylindrical lenses, available in either minus cylinder and plus cylinder configurations, that can be rotated to the appropriate axis.

A trial frame can be used to mount loose trial lenses in front of the patient's eyes. Trial frame refraction is a time-consuming procedure, and because of the thickness of individual lenses, especially at stronger powers, a power shift is induced when several lenses are stacked together. This error can be minimized by placing the strongest spherical lens in the rear well closest to the patient's eye. A variation of this technique is to use a clip-on trial lens holder, which can be mounted on the patient's current glasses or on a "loaner" pair of glasses made up in a spherical power close to the patient's required correction. This works exceptionally well when the existing eyeglasses contain a strong spherical or cylindrical component. The most practical use of a trial frame or clip-ons is to allow the patient to experience the change in correction before investing in a new pair of glasses.

## Determination of the Cylinder Axis

The "clock dial," a standard target in most ophthalmic projector systems, is a circular chart with radii drawn at 30° intervals. When the correct power

toric lens is interposed along the appropriate axis, each image is circular and all of the radii appear equally dark (Fig. 2.3.6). The starting point of the test is to have sufficient plus lens power in the tentative correction so that the focal points of both principal meridians are anterior to the retina yet are recognizable. This "fogging" technique serves to inhibit the natural accommodative response to blur; any focusing effort only further blurs the image. In practice, the initial starting sphere (obtained by omitting the minus cylinder from the net retinoscopy result, the previous spectacle correction, or the autorefraction result) is placed before the eye under test. For an eye correctable to 20/20 (6/6), sufficient plus lens power is added to blur the 20/40 (6/12) line of letters, usually at least 1.00 D.

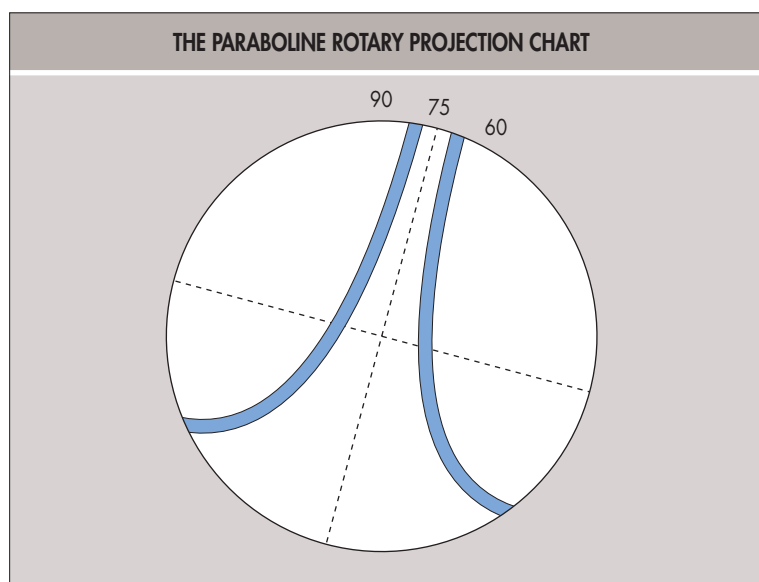
In eyes with more astigmatism, enough plus power must be added to fog the least myopic or the most hyperopic meridian. The clock chart is projected and the patient is asked, "Which, if any, spokes on the wheel are darker?" Because the details of the chart are standardized at the 20/30 level, incremental reductions in plus power are required until some of the lines are clear. If no astigmatism is present, all of the spokes remain equally blurred as plus power is reduced. In astigmatic eyes, the focal line produced by the flatter principal meridian is closer to the retina and appears darker or bolder. With high values of astigmatism, one or two lines are prominent, whereas at lower values several lines may initially appear equally dark. The center of the group is identified by the patient. A direct method of communicating the correct axis is to have the patient point out the darkest meridian with a laser pointer.<sup>15</sup> The axis of the correcting minus cylinder is placed at 90° to this line.

Another simple method is to use the lowest "clock time" of the darkest line and multiply by 30. For example, if the vertical line were darkest, the patient would respond, "The 6 o'clock/12 o'clock line." The correcting cylinder should be placed at axis 180° (6×30). Minus cylinder lenses are then added in 0.25 D increments until all the spokes are equally dark. To maintain the refractive fog, a +0.25 D sphere is added for each -0.50 D of cylinder that is added. When equality of the spokes is reported, the process should be continued until reversal occurs to ensure that the full cylinder power has actually been identified.

Because the meridians on the clock chart are 30° apart, the true axis may lie between them. There are several other commonly used charts that can refine the axis more precisely. The sunburst chart has radial lines that are only 15° apart, but it is often difficult to communicate the precise axis to the examiner because of fluctuations in response related to minor head movements. The Paraboline rotary slide (Fig. 2.3.7) has two symmetrical parabolic arcs whose asymptotic ends approximate the image of an arrowhead.<sup>16</sup> With the eye in a "fogged" state, the slide is rotated until both halves of the arrowhead appear equally dark. The axis can be read from a protractor projected onto the screen. Along the principal axes of the pattern is a cross of dotted lines, which is then used as described before to determine the correct cylinder power.

The Jackson cross-cylinder (JCC) test is perhaps the most commonly used method for subjectively determining the presence of astigmatism and for refining the power and axis of a refractive cylinder. It relies on the

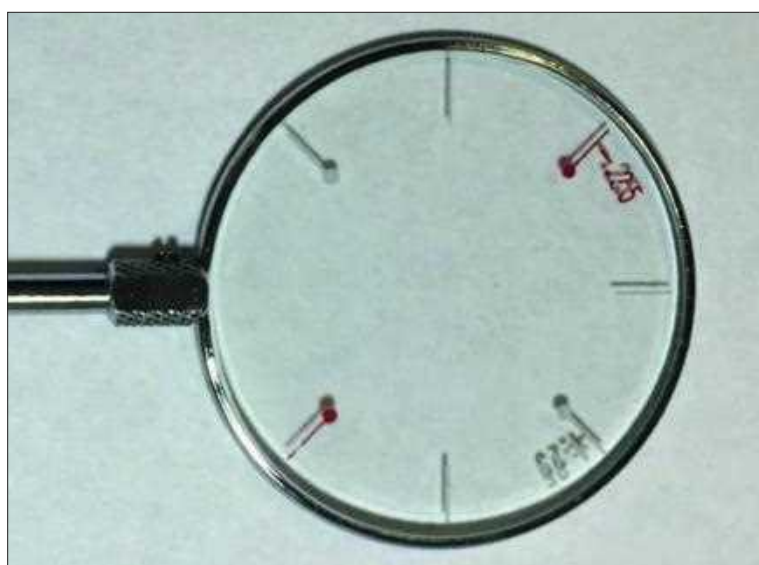




**Fig. 2.3.7 The Paraboline Rotary Projection Chart.** The axis of the correcting lens is determined by rotating the slide until both arms of the pattern appear equally dark.



**Fig. 2.3.9** The refractor-mounted Jackson cross-cylinder is in place to check for axis orientation of a cylinder of axis 90°.



**Fig. 2.3.8 The Handheld Jackson Cross-Cylinder.** Note the red circles at the ends of the minus axis. (Courtesy Scott Brodie.)

principle of placing the circle of least confusion on the retina. A crossed cylinder is a lens whose principal powers are equal and opposite in sign. Each end of the minus axis is marked with a red dot, whereas the plus axis has white dots. The rotating handle in the manual lens and the pivot axis in the refractor-mounted JCC is 45° away from the principal meridians to allow the lens to be flipped quickly into two primary positions. When the circle of least confusion lies on the retina, meridians are equally out of focus (see Figs. 2.3.8, 2.3.9).

A cylindrical lens whose minus axis is lined up exactly along the astigmatic plus axis of the eye produces a resultant spherocylinder whose axis is also coincident. However, if the correcting lens axis is not aligned with the astigmatic axis of the eye, the resultant cylinder's axis lies oblique to the other two axes. The power of the resultant cylinder varies in proportion to the amount of axial rotation between the axis of the eye and the axis of the lens. The JCC is used to determine the correct axis and power of the correcting lens by producing larger or smaller circles of least confusion on the retina in each of its flipped positions. The correcting cylinder can be changed until the sizes of the blur circles are equal. As in all astigmatic correction techniques, the cylinder axis needs to be established before the power can be determined.

When the JCC is used to locate the correcting axis, the images are equally blurred when the principal meridians of the JCC are equally misaligned with the true correcting axis of the eye. To refine the astigmatic correction, the starting point correction is placed before the eye. The handle of the

JCC is aligned along the minus axis of the spectacle lens, placing the JCC's principal meridians each 45° away. Using a target one line larger than the best acuity obtained through the tentative correction, the examiner flips the JCC and asks the patient the famous question, "Which is better—one or two?" The endpoint is the answer, "They are equally blurred." If one position of the JCC produces a better image, the axes of both the tentative correcting lens and the JCC are moved 5° in the direction of the red dots on the JCC (if using minus-cylinder trial lenses—if using plus-cylinder trial lenses, rotate the tentative correcting lens toward the preferred orientation of the white dots). In most refractor models, the cylinder axis and the JCC rotate together. The lens is flipped again and the patient is given the opportunity to compare the image through each lens. At the axis at which equality of blur is located, the lenses should be rotated another 5° in the same direction. If the previous response was accurate, the new position should produce a reversal in direction.

## Determination of Cylinder Power

To determine the correct minus cylinder power, the JCC is rotated until one set of principal meridians overlies the minus axis of the correcting lens. The handle of the manual JCC is now 45° away. On the refractor units, the position is marked by a click-stop detent. Using the same line of letters, the JCC is flipped and again the patient is asked to choose the better of the two images. If the JCC's minus axis, marked by the red dots, is aligned with the cylinder axis, a cylinder of 0.25 D more minus power is added to the correction. If the better image is produced when the plus axis, marked by the white dots, is aligned, the cylinder power is adjusted by adding +0.25 D. To ensure that the circle of confusion remains on the retina, for each 0.50 D of cylinder that is added, a 0.25 D sphere of the opposite power should be added. The procedure is repeated until the two images are equally blurred. Going one lens past to reversal ensures that the correct lens is selected.

## Rechecking the Sphere

Once the proper cylindrical correction has been established, the final sphere needs to be determined. One simple technique is to "refog" the eye using plus lenses to minimize the effects of uncontrolled accommodation. Obviously, this is more of an issue in younger individuals who have a large accommodative reserve. Using the line of expected best acuity, the power is reduced by 0.25 D at a time with a sufficient intervening pause to allow the patient to attempt to interpret the letters. Once the letters are identified, the next smaller line is presented. If these letters are not clearly recognized, power is reduced by another 0.25 D. If the letters are still not clear, the previous lens probably produces the sharpest unaccommodated focus. If the letters are seen, the process is repeated with the next smaller line. Many individuals have the capability to see details smaller than those on the 20/20 line. It is important to record the best acuity to establish a baseline for future comparisons.



**Fig. 2.3.10** When letters on the green side of the chart are clearer, more spherical plus power needs to be added.

Another technique commonly used to refine the final sphere is the duochrome test, which makes use of the chromatic aberration of the eye.<sup>17</sup> White light entering the eye is refracted according to its component wavelengths. In an emmetropic eye, blue light focuses about 1 D myopic, whereas red light focuses about 0.5 D hyperopic but equidistant from the retina. The duochrome test uses a pair of colored filters built into the projector chart, the peak transmission of one at 530 nm (green) and of the other at 670 nm (red) (Fig. 2.3.10). In corrected emmetropia, a matched presentation of letters is equally blurred on each side of the chart. With the best spherocylindrical correction, the patient is asked to look at the letters on the green side. They remain in focus only when accommodation is relaxed. Because the letters on the red side can be made clearer by accommodating for them, the patient is asked to look quickly at the letters on the red side and then back at the green and compare their clarity. If the letters on the green side are clearer, the correcting sphere is changed by 0.25 D in the plus direction. If the letters on the red side are clearer, 0.25 D is added in the minus direction. This test is sensitive enough for 0.25 D to cause a reversal in clarity.

## Final Checks

### Accommodation

Cycloplegic eyedrops can be used to eliminate accommodation during the examination. In most cases, the results of a cycloplegic refraction are not prescribed as a correction. Rather, this type of examination is used in selected circumstances to determine the baseline refractive status of the eye. There are two common situations in which this is valuable:

- In young individuals who are suspected of accommodative spasm, especially when it is accompanied by esophoria or esotropia, it is important to prescribe the strongest plus power correction in order to relax accommodation. A follow-up examination not under cycloplegia is usually required to determine the maximum amount of lens power that can be tolerated in the natural state.
- Protocols for refractive surgery usually dictate that the cycloplegic refractive power of the eyes be determined before the procedure.<sup>18</sup>

### Binocular Balance

The entire procedure is repeated for each eye to produce two monocular subjective prescriptions. Assuming that the patient has clear, single binocular vision, the effects of compensating for an existing heterophoria or the effects of summation of vision from both eyes may alter the lens powers chosen for the binocular subjective prescription.<sup>19</sup> The process is usually accomplished in two steps.

The first is to ensure that equal accommodative effort is present between the two eyes. If the best-corrected vision is approximately the same in each eye, vision is fogged with +0.75 D lenses. Sufficient vertical prism is placed in front of each eye to produce two separate images of the isolated 20/40 (6/12) line. The patient is asked to compare the clarities of the upper line and the lower line. If they appear equally blurred, +0.25 D is added to one eye and they are compared again. The other eye should now see slightly

more clearly. The lens is removed and the process repeated for the other eye. Adjustments are made until the images are as equally blurred as possible. If there is no pair of lenses that produces an equality of blur between the two eyes, the pair that gives the slightly better image in front of the dominant eye is often preferred.

The best acuity line is then isolated on the chart. The fogging lenses are reduced from both eyes by 0.25 D at a time, allowing sufficient time between stages for the patient to adjust to the lens change. In the same way as with the monocular subjective test, the lens power that gives best acuity without inducing accommodation is usually the final choice. The duochrome test offers an alternative method of determining the lens powers that produce a sharp unaccommodated retinal image.

The same technique can be employed with eyes that have a moderate discrepancy in best-corrected vision, either from amblyopia or from some other abnormality. The lens powers can be balanced using a larger line of letters, for example the 20/80 (6/24) line, and then reduced to the best binocular acuity, which is that of the better eye. This solves the dilemma of trying to determine the best monocular subjective correction in an eye with poor visual discrimination.

Binocular refraction is an infrequently used technique in which both eyes are fixating while the monocular refraction is measured. Most contemporary devices use some form of vectographic separation in which a polarized target is presented to each eye through interposing polarized analyzers with a different axis in front of each eye. This has the advantage of mimicking the normal form of seeing, incorporating all of the patient's binocular efforts including horizontal and vertical phorias. In addition, this method offers the only way to identify a cyclophoria in which the astigmatic axes of the eyes are different under binocular conditions from when observed monocularly.<sup>20</sup>

Trial frame confirmation of the final prescription is often overlooked but is an extremely valuable verification of the comfort and acuity of the new lens power. Although an examination room of length 20 ft (6 m) is considered to be the equivalent of optical infinity, 0.17 D of accommodation is still required at that distance. It is psychologically reassuring for the patient to step out of the examination room and view the end of the hallway or, better still, the other side of the street, through the new lenses. This small investment of time may save lengthy follow-up visits that could result from miscommunication in the examination room.

If the cylinder correction is similar to that of the patient's old glasses, it is relatively straightforward to have the patient hand-hold spherical trial lenses in front of the glasses and compare vision with and without the change in prescription. This is a simple way to determine which is the more satisfactory lens correction when a discrepancy exists between the monocular subjective and the binocular subjective tests. As the monocular subjective test's endpoint is best acuity and the binocular subjective test's endpoint is equality of accommodation, some patients may have a slight difference in right and left eye acuities through the binocular prescription. This refinement offers them the opportunity to observe the difference between the two corrections and to make a practical choice between them.

If there is some doubt about the visual comfort of the change, the lenses can be held in position with a clip-on lens holder while the patient takes the opportunity to walk around and adjust to the difference. In some cases, it may be beneficial to allow patients to borrow the lenses and holders overnight to evaluate the lens changes in their own environment. It is important to mark the right and left lenses and, if cylinders are required, to provide a sketch to help align the axis marks.

A similar procedure can be used when the change in correction is a spherocylinder. It is unwieldy to place and remove more than one lens in front of the patient's glasses. If the new cylinder axis is different from that of the old eyeglasses, a calculation of resultant cylinder axis and power is required to determine the appropriate lens to hold in front of the glasses. In such a situation, it is more practical to place the new correction in a trial frame and to let the patient alternately view at a distance through the trial frame and the old glasses. The trial frame interpupillary distance, the vertical lens position, and the pantoscopic angle should be adjusted correctly, especially with strong lens powers.

## REFRACTING AT NEAR

The near correction is the distance correction with sufficient plus additional power (the "add") to satisfy individual needs for clear, comfortable single vision at a desired near point. Although there are normative tables for determining an add according to the patient's age, these simply function as benchmarks to help the examiner recognize a potential overcorrected or undercorrected condition. This is an important time to listen to



your patient. Although patients are notoriously inaccurate when estimating their working distances, the description of how they use their eyes at near helps to determine not only the strength of the lens power required for tasks at near, but also the form in which the correction will be most effective. For example, a presbyope who requires a +2.00 D add for reading may be very satisfied with a bifocal correction for most activities but may require a +1.25 D add in single vision lenses to work at a computer terminal.

One rule of thumb that has gained wide acceptance is that the near add at a given distance should allow half of the patient's accommodative amplitude to remain in reserve. The amplitude is determined by measuring the closest point at which an individual can maintain focus through the distance correction. For a prepresbyope, this simply means measuring the distance at which a fine line of print can no longer be focused. This distance, measured in centimeters, is divided into 100 to convert it into amplitude of accommodation. A presbyope needs to place a plus lens over the distance correction to be able to see the fine print. The closest distance to which the print can be moved before blurring is again converted into diopters and the power of the interposed lens subtracted to give the amplitude (Box 2.3.1, Fig. 2.3.11).

A clinical method commonly used to measure the near add is the fused cross-cylinder test. A cross made up of multiple horizontal and vertical lines is presented to the patient at a distance of 40 cm. A JCC with its minus axis vertical is placed in front of the distance correction. The patient is asked to compare the boldness of the horizontal and vertical lines of the cross. If no add is required, the lines are equally dark. If the horizontal lines are darker, plus power is added binocularly in 0.25 D increments until the lines are equally black or until the vertical lines become more prominent. This lens power becomes the tentative add.<sup>21</sup>

The final add is determined by verifying that the add is appropriate for the patient's visual needs. The range of clear near vision is the linear distance between the far point of the near lens (usually the reciprocal of the add power) and the near point of accommodation through the add. Because the range of vision is inversely proportional to the power of the lens, many experienced refractionists prescribe the weakest add that meets the patient's demands.<sup>22</sup> For most individuals, having a larger range in which objects are clear overrides the desire to see extremely fine print at a close distance. It is often helpful to patients who are receiving their first

presbyopic correction to have lenses held in place to demonstrate that their near correction will, of necessity, blur their distance vision.

In situations where an anisometropic distance correction is required, it is wise to measure the ranges monocularly to account for any optical effects related to the unequal strength of the lenses.<sup>23</sup> Unequal adds may be prescribed in certain other situations to keep the near and far points of the ranges at similar distances. As with any significant change, a trial frame evaluation of the new correction may help to identify any potential difficulties before glasses are fabricated. In some cases of anisometropia, bifocals may produce reading discomfort because of an induced vertical prismatic effect in the reading position of gaze. Specially designed slab-off lenses or single-vision reading glasses may be required.

Patients who require higher bifocal adds may not have sufficient accommodation to overlap their distance and near ranges of vision. This "dead zone" is problematic in certain jobs and avocations. An accountant may not be able to see a calculator clearly in its normal desktop position, and a violinist may have difficulty reading from a music stand. Although trifocals or progressive lenses may be satisfactory, special use lenses may be required, such as low-add bifocals with a high segment line.

Computer users who must also read place a unique set of demands on their glasses. The video screen is usually just below eye level at arm's length or slightly closer, whereas reading material and the keyboard are positioned lower and somewhat closer. It is often worthwhile to have patients adjust one of the computer terminals in the examiner's office to simulate their workstation conditions.<sup>24</sup> Eye-to-screen and eye-to-keyboard measurements can be used to determine the necessary add powers. Many presbyopic computer operators have occupational bifocals in which the top section of the lenses has the intermediate correction and the lower portion is set for the keyboard distance. When the operator leaves the workstation, these glasses are left at the terminal and a conventional correction is used. Progressive lenses often work very well at the computer, though the patient should be warned that the greater magnification at the bottom of the lenses will make the computer screen appear trapezoidal in shape.

The vast majority of presbyopic refractive errors are now corrected using multifocal progressive lenses. The continuity of focus that can be achieved by slight shifts in vertical head position combined with the lack of a visible line in the lens identifying the wearer as "older" has made this the default presbyopic lens design in affluent countries. In recent years, special use lenses have proliferated offering even more comfort and functionality for those who spend considerable time in activities with a high visual demand at near or intermediate distances.

### BOX 2.3.1 Calculated Near "Add" at Any Distance Should Keep Half of the Patient's Accommodative Amplitude in Reserve

With an extra +1.50 D lens the near point of accommodation is 40 cm (2.50 D).

The patient's amplitude is 1.00 D (2.50 D – 1.50 D).

For a working distance of 50 cm, 2.00 D of accommodation is required.

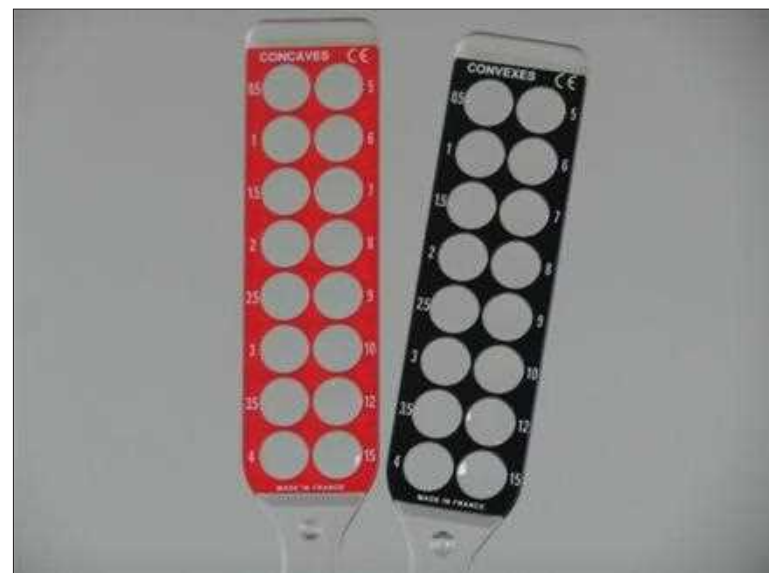
Therefore the patient's "add" for that distance is +1.50 D [2.00 D – ½ (1.00) D].



**Fig. 2.3.11** A near card is placed in front of the phoropter and slid back and forth to determine the closest distance at which the print can be seen before blurring takes place.

### ADDITIONAL SUBJECTIVE TECHNIQUES

Bedside examinations, nursing home visits, and equipment failure are examples of situations that require skill in trial frame refraction. When poorly controlled ambient lighting exists, retinoscopy is often an estimate at best. A retinoscopy rack made up of a battery of spherical lenses (Fig. 2.3.12) arranged in ascending order of power can be used to determine the



**Fig. 2.3.12** Plus and minus racks of spherical lenses, normally used for retinoscopy screening, are also useful to determine an approximate subjective spherical equivalent lens.

subjective spherical equivalent. Using this power as the initial trial frame starting lens, a handheld JCC can be used to determine the presence of any astigmatism. The handle is positioned along a true oblique meridian ( $45^\circ$  or  $135^\circ$ ) so that the principal powers are along the horizontal and vertical meridians. The lens is flipped and the patient is asked whether either position is better. If not, the handle is repositioned horizontally so that the principal powers now lie along the  $45^\circ$  and  $135^\circ$  meridians and the procedure is repeated. If again there is no preference, there is no clinically significant astigmatism in that eye. If the patient indicates a preference in any of those positions, the JCC tests proceed as described earlier.

Some examiners locate the axis of a tentative cylinder by rotating the lens and asking the patient to indicate the position where vision is the clearest. For strong cylinders, this is an accurate and repeatable technique. However, for low-power cylinders a range of axis positions exists that produce clear vision for most observers.<sup>25</sup> A modification of this test to increase its accuracy is to rotate the lens until a small line of letters first blurs noticeably then rotate the lens back in the opposite direction to first blur. The midposition is the correcting axis. This test is highly dependent on an acutely observant patient.

One drawback of the JCC is its reliance on the patient's visual memory to determine preferences. Modifications of the refractor-mounted versions exist that use split prisms to produce a simultaneous presentation of both positions of the JCC. The lens and device can be rotated together until the images are equally blurred to locate the cylinder axis. In the same way, the power can be determined by changing the correcting cylinder power until both images appear equal.

In situations where vision in an eye is very poor and no other instruments are available, the stenopeic slit can be used to screen for a high degree of astigmatism. It functions as a series of pinholes along a meridian. A trial frame or clip-on device is used to place the trial lens stenopeic slit in the lens cell and rotate it slowly. If there is a position that produces improved vision, it is treated as a principal meridian of the eye. With the slit still in place, spherical plus and minus lenses are positioned in front of it. A convenient method is to use the retinoscopy rack. When the lens power that gives the most improvement has been established, the stenopeic slit is rotated  $90^\circ$  and the procedure repeated. The two spherical lens powers are considered to be the correcting lens powers for each of the principal meridians. The powers are combined in a spherocylinder lens that is placed in the trial lens cell. If vision is improved sufficiently, it may be possible to refine the correction using conventional methods (Fig. 2.3.13).

## RETINOSCOPY

### Retinoscope

Every time a close-up photograph is taken of the face of a subject and a vivid red pupil (called *red eye*) seen instead of the usual black pupil, the



**Fig. 2.3.13** A Stenopeic Slit Is in Place to Check Along the 135th Meridian. Once the spherical power has been determined, the lens should be rotated  $90^\circ$  and the spherical power measured along the 45th meridian. The two powers can be combined into a spherocylindrical lens.

essence of retinoscopy is captured. The red reflex is produced when the flash lamp is positioned close to the optical axis of the camera.

The source of the red reflex is the aerial image of the blood-filled choroid superimposed on the pupil. Because the image is very small, it is seen only if the optical systems of the subject's eye and the camera, respectively, are close to alignment. Because the aerial image cannot be in the plane of the pupil, it must always be out of focus when the plane of the face or eye is in sharp focus. Von Helmholtz realized that the origin of the reflex must be the fundus itself and developed the ophthalmoscope to focus on the details of the fundus.<sup>26,27</sup> Thus the position of the aerial image of the fundus is determined by the optical components of the eye. Therefore determination of the position of the image can lead to determination of the refractive error of the eye. Cuignet, a French army ophthalmologist who measured the refractions of a large number of army recruits, must be credited with the development of a better way to define the position of the aerial image.<sup>28</sup> His method always brought the aerial image to the same location in space, at the examiner's eye, a principle employed by most contemporary retinoscopists. Subtraction of the dioptric-value equivalent of the "working distance" determined the power of the lens required to correct the refractive error.

### Optics of Retinoscopy

The essence of retinoscopy is to illuminate the retina and then locate the image of the retina in space. Thus the retinoscope combines a light source with an observation aperture (i.e., peephole). The position of the retinal image is called the *far point*. Its position in dioptric units is equal to the refractive error. Thus the eye may be considered as an element in an optical bench. When the light rays that leave the eye are made visible, the far point can be located and the refractive error calculated. Unfortunately, a side-view analysis of the human eye as though it is on an optical bench cannot be done. However, with this side-view analysis in mind, the mechanism of retinoscopy can be understood.

For the purposes of this description, it is assumed that a side-view analysis is possible. The retinoscopist places lenses in front of the patient's eye so that the patient's far point is focused at the peephole of the retinoscope. For example, the emmetrope's far point is at infinity. If the retinoscopist works at a distance of 25 inches (66 cm) from the patient (called the working distance), a  $+1.50$  D lens brings parallel light to a focus at 25 inches (66 cm) from the patient's eye. The far point of the myope lies between the examiner and the patient (Fig. 2.3.14). A minus lens of the appropriate power brings the image to the peephole of the retinoscope. The refractive error equals the dioptric power of the minus lens needed less that of the working-distance lens ( $+1.50$  D). Thus, if a  $-5.00$  D lens is needed to bring the far point to the examiner, then the refractive error is  $-5.00$  D  $+ 1.50$  D  $= -3.50$  D. The far point of the hyperope is theoretically behind the head of the patient. A plus lens of the appropriate power brings the far point to the peephole of the examiner. Thus, if a  $+5.00$  D lens is needed to bring the far point to the examiner, then the refractive error is  $5.00 + 1.50$  D  $= +6.50$  D.

### Neutrality

Cuignet found the position of the far point by using a version of the Foucault knife-edge test. Imagine a thin, sharp knife that moves across the beam of light that leaves the patient's eye. If the knife edge passes across the point of focus, then the knife edge blocks all the light for an instant, after which all the light reappears; the edge of the peephole of the retinoscope may



**Fig. 2.3.14** The Far Point of the Myopic Eye Lies Between the Patient and the Retinoscopist.



be considered such a knife edge. If the far point is brought to a focus at the peephole, then the focused light appears to vanish and reappear with a slight side-to-side motion of the peephole. This situation is called neutrality and represents the endpoint of retinoscopy. It is at this endpoint that the power of the lens in front of the patient's eye minus the +1.50 D working lens yields the value of the refractive error.

### With and Against Motion

The image that emerges from the patient's eye before neutrality is reached is significant. In a myopic eye, as the examiner moves the illumination light upward, the retina is illuminated in an upward direction. The real, inverted image of the retina is focused between the patient and examiner, and the retinal image appears to move downward in a direction opposite to the movement of the retinoscope. This is called *against* motion. Minus lenses are placed in front of the patient's eye until the focus is brought to the plane of the peephole, at which point neutrality is seen. In a hyperopic eye, as the beam from the retinoscope moves upward, the retina is illuminated in an upward direction. The virtual, upright image of the retina appears illuminated in an upward direction. Because the image moves in the same direction as the retinoscope, the motion is called a *with* motion. Plus lenses are placed in front of the patient's eye, the image is moved to the plane of the retinoscopic pinhole, and neutrality is seen.

### Other Clues

The retinoscopist must be aware of other subtle clues that differentiate fine with and against motions from neutrality. For example, the aerial image becomes larger the closer it is to the examiner's eye. A closer aerial image also appears to move faster because more of the closer image fills the peephole than does a smaller, more distant aerial image. A small movement of the peephole crosses a larger percentage of the aerial image and gives the appearance of a faster movement. The closer to neutrality, the faster is the movement of the reflex. In a similar vein, the brighter the reflex, the closer it is to neutrality. Here again, the closer the aerial image is to the retinoscopist (Newton's law), the brighter it is.

### Myopia Estimation

If the initial retinoscopic movement is slow and dull, with movement, then high myopia is present. To estimate quickly the amount of myopia without using trial lenses, simply move toward the patient and simultaneously move the retinoscope slowly from side to side. As the far point is reached, the endpoint of neutrality is given. The distance from the patient is the far point and must be converted into diopters. Thus, if neutrality takes place

at 75 inches (20 cm), the amount of myopia is 5.00 D (no working distance compensation is needed).

### Astigmatism

To determine the presence of astigmatism, simply sharpen the streak and slowly rotate it to 360°. If little or no astigmatism exists, the retinoscopic streak reflex always is parallel to the intercept. A break phenomenon occurs when the reflex is not in perfect alignment with the intercept as the streak is rotated. The orientation of the streak reflex when it lies parallel to the intercept indicates the direction of one of the major meridians of the astigmatism. The examiner must find the lens of neutrality for a side-to-side movement along that meridian and establish neutrality for the meridian 90° away. For example, assume that the maximum break phenomenon is along the 90° meridian. Rotate the streak into a horizontal position and move the retinoscope up and down (along the 90° meridian). Imagine that a +4.50 D sphere neutralizes the vertical movement. Now rotate the streak vertically and move it side to side along the 180° meridian. With the +4.50 D sphere in place, a -2.00 D cylinder of axis 90° neutralizes the side-to-side movement. Subtraction of the +1.50 D power of the working distance lens from the dioptric power of the sphere yields a +2.00 D sphere with a -2.00 D cylinder of axis 90°.

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# Correction of Refractive Errors

Bing Chiu, Joshua A. Young

## 2.4

**Definition:** Refractive errors may be corrected by means of spectacles, contact lenses, orthokeratology, intraocular lens implants, and keratorefractive surgery.

### Key Features

- Spectacle lens advantages: inexpensive; suitable to correct myopia, hyperopia, astigmatic refractive errors, and presbyopia; no permanent ocular alterations. Drawbacks: some patients may reject for cosmetic reasons; may cause image jump, object displacement, and alter retinal image size.
- Contact lens advantages: excellent cosmetic appearance, free from prismatic effects, minimize astigmatic distortions and problems with alterations in retinal image size. Drawbacks: correction of astigmatic errors and presbyopia may be difficult; expose patients to risk of corneal oxygen deprivation and corneal infections.
- Orthokeratology advantages: patients may be able to function without glasses or contact lenses during daytime. Drawbacks: require nighttime contact lens wear; correction may wane during daytime hours.
- Intraocular lens implant advantages: preferred correction for aphakia; may allow for correction of extreme myopia in phakic patients. Drawbacks: limited correction of presbyopia, astigmatism; phakic intraocular lenses may induce cataract formation.
- Keratorefractive surgery advantages: may eliminate need for glasses. Drawbacks: less predictable for correction of larger refractive errors; may destabilize cornea; risk of complications (small).

### INTRODUCTION

In an ideal eye, the combined optical contribution of the front of the eye focuses incoming rays of light onto the retina to produce a clear image. If this optically ideal eye requires no aid or accommodation to focus distant objects onto the retina, the eye is said to be emmetropic. Conversely, if an eye in its relaxed, nonaccommodating state and devoid of other pathology fails to produce a clear image on the retina from rays of light of a distant object, the eye is said to be ametropic. Ametropia encompasses a wide range of optical imperfections including myopia (nearsightedness or shortsightedness), hyperopia (farsightedness or long-sightedness), and astigmatism, itself a collection of different optical imperfections. Indeed, an almost limitless number of optical abnormalities exist beyond these, but such optical aberrations are not amenable to correction by spectacles, and discussion of these will be limited in this chapter.

In addition to the very obvious disadvantage of reducing visual clarity, ametropia may be an indicator of more serious ophthalmic disease. An adult whose previously stable refraction has begun to demonstrate increasing myopia may be demonstrating the refractive effect of a maturing nuclear cataract. A 20-year-old whose astigmatism has begun to worsen may be suffering from progressive keratoconus, a disease of ectasia of the most refractively important part of the eye, the cornea. The highly hyperopic middle-aged woman is at substantial risk of angle-closure glaucoma for precisely the same reason for which she is hyperopic, a small and therefore crowded eye.

A number of clinical modalities exist to correct ametropia. Each of these has limitations, and different types of correction are advantageous for different clinical settings. The simplest of these and the only method without medical risk is spectacle correction.

### SPECTACLE CORRECTION

Evidence of spectacle use dates to at least the late thirteenth century. Although this certainly implies that people with refractive errors could seek no remedy for the countless millennia that preceded the invention of spectacles, it has been suggested that ametropia, particularly myopia, was far less common in the ancient world than it is at present.

### Spectacle Material

Whether a person wears glasses for correction of refractive error, protection of eyes, or for cosmetic reasons, the materials of the lenses can play a significant role. For the patient who desires the best optical quality throughout her or his visual field, a thin lens with significant peripheral blurring might be a poor choice. Likewise, for the patient for whom impact protection is paramount, a glass lens that can easily break and shatter would be unsuitable.

Spectacle lenses are manufactured from a variety of materials<sup>1</sup> with characteristics that can be condensed into a few properties that describe the optical quality, strength, and density. The ideal material would be thin, lightweight, impact and scratch resistant, inexpensive, and devoid of optical distortion. The variety of available materials may be seen as a demonstration that no single optimal material exists. One unwanted property of lens material is the tendency to disperse white light into its component wavelengths. Rainbows are pretty in the sky but the color fringing that results from wavelength dispersion in spectacles is distracting and degrades image quality. This wavelength dispersion is referred to as chromatic aberration, and the degree to which materials disperse wavelengths is quantified as the Abbe number or V-number. Materials that minimize chromatic dispersion—those with higher Abbe numbers—are generally more desirable.

Of course, the primary reason for which lenses are designed is to bend or refract light. The degree to which a spectacle lens bends light is a function of its curvature and of the material from which it is made. For any given shape, certain materials will bend light more than others. The degree to which a material can bend or refract light is a function of the speed of light through that material. We generally think of the speed of light as the immutable value  $c$  or 299,792,458 m/s, but of course this is the speed of light through a vacuum. Through any other medium, light propagates at a velocity lower than  $c$ . Media through which light moves especially slowly have the greatest ability to refract. The degree to which a material is capable of refracting light is given by the ratio of  $c$  over the speed of light through the material. This ratio is called the index of refraction, and higher values indicate a greater ability of a material to refract light. Because a lens with greater intrinsic ability to refract light requires a less curved surface to achieve the desired refraction, high refractive index lenses can be made thinner than low refractive index lenses. For this reason, patients with high degrees of ametropia often opt for high index lenses.

Spectacles also serve as a barrier between the environment and the eyes. For some patients—those who are monocular or amblyopic and those who are engaged in work in which ocular trauma is possible—the strength of the lens material may be its most important property.<sup>2</sup> Standards are set by the US Food and Drug Administration (FDA) and American National Standards Institute (ANSI) for resistance of a material to penetration or shattering. Although glass lenses offer excellent optical quality and scratch resistance at a low cost, glass has fallen out of favor because of its poor impact resistance and high specific gravity, making it a heavy material. Plastic, also known as hard resin or Columbia resin (CR-39), has become the most common material for spectacles. It is light, impact resistant, and versatile, naturally UV blocking, and can be easily tinted or treated to be scratch resistant. However, plastic has a low index of refraction and

a thicker lens is therefore required. A stronger material, polycarbonate, is commonly used in protective wear. Originally made for aerospace and used in helmet visors and space shuttle windshields, this petroleum derivative plastic polymer has a high refractive index and low specific gravity with very high impact resistance. Although these lenses are thin and lightweight, polycarbonate has a relatively low Abbe number, and so high chromatic dispersion results. Polycarbonate is also prone to scratches, making scratch-resistant coating essential.

For high refractive errors, high refractive index materials can be beneficial, although not without costs—both optical and financial. Plastic or glass materials that are made with higher index of refraction (i.e., over 1.6) are lighter and thinner but are also prone to more chromatic aberration and distortion at the periphery of the lens. They also tend to be less impact and scratch resistant.

## Monofocal Spectacles

Monofocal spectacles correct for spherical refractive errors such as myopia and hyperopia, astigmatic refractive errors, and for combinations of spherical and astigmatic errors. For patients incapable of any degree of accommodation, for example patients who have undergone cataract extraction, these spectacles bring clear focus to objects at only a defined distance from the eye. For example, monofocal distance spectacles would not bring near objects into clear focus for such a patient. In clinical practice, monofocal lenses are prescribed to young, nonpresbyopic patients for all tasks and for presbyopic patients for limited tasks. For emmetropic presbyopic patients, those with naturally good distance vision but for whom accommodation is inadequate, monofocal reading glasses often are prescribed.

Clinicians prescribing monofocal spectacles specify only three parameters for each eye: the power of the spherical correction, the power of the astigmatic correction, and the orientation (axis) of the astigmatic correction. Although this prescription may compensate for the patient's refractive error, a number of factors other than these determine whether the patient will tolerate the prescribed lenses. These factors have in common the drawback that image distortion is intrinsic to spectacle correction. Most important, distortions arise from asymmetrical image magnification and may be illustrated in this thought experiment: Imagine an emmetropic patient looking through a telescope at a distant object. The telescope, a Galilean telescope in this case, consists of a plus-power or converging objective (the lens at the large end of the telescope) and a minus-power or diverging eyepiece. For this experiment, let's imagine that the minus-power eyepiece is a contact lens. Indeed, the telescope would exhibit the same degree of magnification if the eyepiece were a conventional lens or a contact lens. If we further imagine that our patient, rather than being emmetropic, has instead a refractive error equivalent to the contact-lens eyepiece, she or he would experience the same degree of magnification as our original emmetrope. Our ametropic patient is hyperopic. We know this because the correcting lens (i.e., the objective of the telescope) is plus powered and thus we see that hyperopes corrected with plus spectacles experience a degree of image magnification. The case of the myope is identical in every regard except that the "telescope" is now oriented backward and produces object minification.

The magnification produced by spectacles is generally tolerated well by patients as long as its magnitude is similar in each eye. However, asymmetrical magnification of only a few percent can produce symptoms sufficient to make spectacle correction intolerable. The degree of magnification is a function of two variables: the dioptric power of the spectacle lens (equivalent to the telescope's object lens) and the distance between the spectacle lens and the eye, known as the vertex distance (and equivalent to the length of the telescope's tube).

The condition of perceived difference in image size between right and left eyes is called aniseikonia. As a general rule, adults who are unaccustomed to large differences in prescriptions between right and left eyes will tolerate no more than 3 or 4 diopters of asymmetry in spectacles. This challenge arises clinically in the case of patients who are developing an asymmetrical increase in myopia from a maturing nuclear cataract (so-called myopic shift) or after cataract surgery if the refractive errors are substantially asymmetrical postoperatively.

Symptoms attributable to asymmetrical magnification are not limited to aniseikonia from asymmetrical spectacles. Asymmetrical magnification also can produce symptoms monocularly. Because the degree of magnification produced by a spectacle lens is dependent partly on the distance between the lens and the eye, the degree of magnification or minification is least at the center of the spectacle lens where the lens is closest to the cornea and increases farther away from the center of the

spectacle lens. This produces a type of distortion characteristic to each type of lens.

Spectacles to correct myopia employ minus-powered lenses. These lenses produce minification and, because the periphery of the image is minified to a greater extent, produce a sort of distortion in which the periphery of the image is rendered at a smaller scale than the center. This is referred to as "barrel distortion." Such distortion is readily observed when looking into a convenience store mirror, when looking at one's self in a mirrored sphere like a ball bearing, or viewing a scene through a fisheye lens.

Similarly, plus-powered spectacles for the correction of hyperopia produce distorted images in which the periphery is more magnified than the center. This "pin-cushion distortion" also may be observed when using a magnifying glass<sup>3</sup> (Fig. 2.4.1).

Perhaps the most disturbing sort of asymmetrical magnification induced by spectacle lenses is the meridional magnification intrinsic to astigmatic lenses. In this case the meridian of highest plus power produces relative magnification compared with the meridian of highest minus power. The net result is to produce images that are short and fat, tall and skinny, or magnified obliquely. This is especially disturbing when, as is often the case, astigmatic axes are oblique and at mirror-image orientations in the two eyes. Oppositely oriented meridional magnification may be misinterpreted as distortion in depth perception and can make spectacles intolerable even if the right and left lenses are of equal dioptric power.

## Bifocals

Traditional bifocal and trifocal lenses have been largely displaced by progressive lenses. Still, these older forms remain in wide use and in some clinical settings have advantages over the newer progressive designs. Bifocal lenses are distinguished by discrete segments for distance and for near with an abrupt transition between the two<sup>4</sup> (Fig. 2.4.2). Unlike monofocal

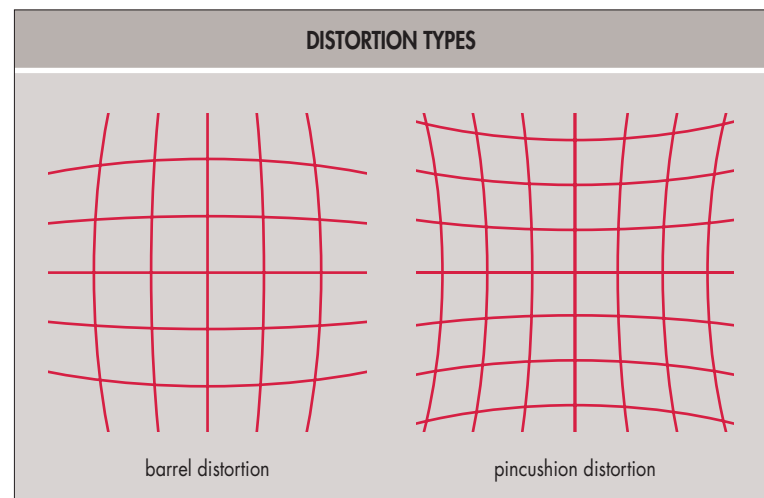


Fig. 2.4.1 Types of Distortion Induced by Spectacle Lenses. (Courtesy Joshua Young and Wikipedia, "Barrel distortion"; public domain.)

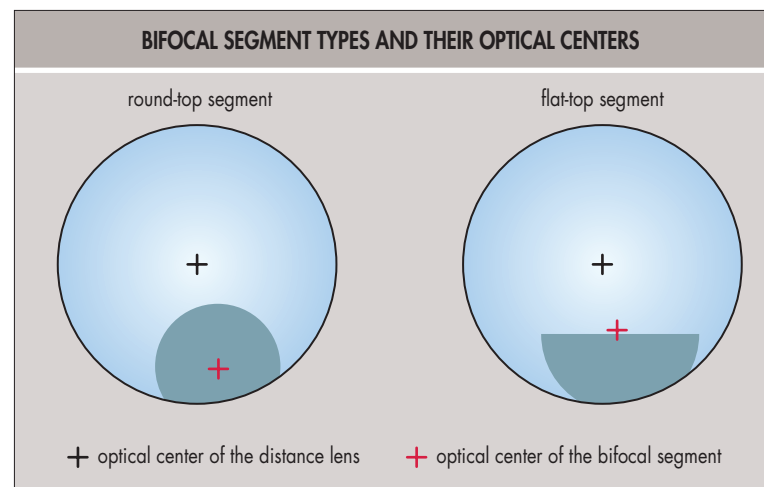


Fig. 2.4.2 Bifocal Segment Types and Their Optical Centers. (Courtesy Joshua Young.)



lenses, the prescriptions for which are ground into the back surface of the lens, bifocal segments are applied to the front surface. Bifocal designs take a number of forms, and the appropriate choice of bifocal segment is a function of the lens to which it is applied.

All bifocal segments are plus-dioptic powers. As such, they may be thought of as portions of a larger plus-powered lens. The round-type bifocal would then derive from the top of a plus-powered lens and the flat-top from the bottom of a plus-powered lens. This is highly significant because each type of bifocal adds a certain degree of prism to the bottom of the spectacles and produces a certain amount of discontinuity at the line of transition between the distance and near portions of the lens. The discontinuity of the image produced at the line between the distance and the near portion of the lens is called “image jump.” The degree of image jump is a function of the power of the reading add and of the distance between the optical center of the reading add and the top of the reading segment. By Prentice rule, discussed earlier in this volume, the amount of prism induced at the top of the bifocal segment is proportional to the distance between the optical center of the segment and the top of the segment. Round-top bifocals have the largest distance between these two points and therefore will produce the largest image jump for any given bifocal power. Traditional flat-top bifocals have only a small distance between the optical center and the top of the bifocal segment and produce only a very small amount of image jump.

Although image jump may be annoying to patients, it is not the chief determinant in choosing the appropriate bifocal segment design. Rather, the bifocal design is chosen in an effort to minimize the total amount of prismatic power induced at the bottom of the patient’s spectacle. All spectacles, even those without bifocal segments, demonstrate prismatic power for all locations away from the optical center. The amount of prismatic power at the bottom of the spectacle lens is important because the shift in the image induced by this prism may cause patients to miss obstacles on the ground or misjudge the location of curbs or steps. It is advantageous to choose a bifocal design that will incorporate a prism of opposite orientation to that already existing in the patient’s spectacles. In the case of hyperopic patients who are wearing spectacles that already incorporate a base up prism in the bottom portion of the lens, the appropriate bifocal choice would be one that demonstrates a base down prism (Figs. 2.4.3 and 2.4.4). This is necessarily a round-top bifocal segment. Such a choice will minimize the total prismatic power at the bottom of the patient’s spectacles and make it less likely that the patient will miss obstacles in his path. Keep in mind that this is the appropriate choice despite the fact that round-top bifocals produce more substantial image jump than flat-top type bifocals.

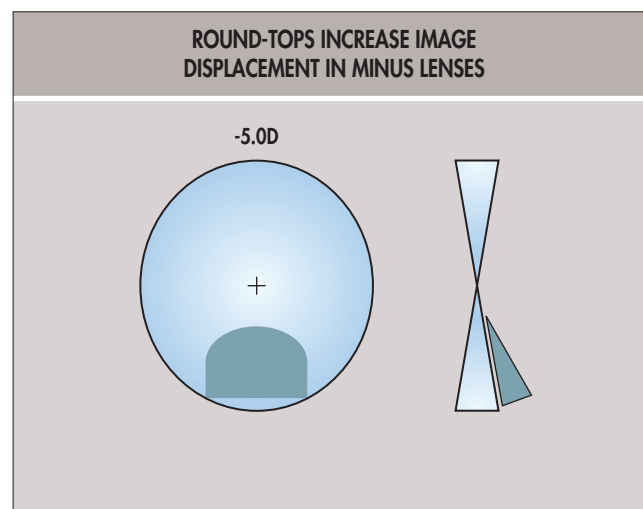
In the case of the myope who demonstrates a base down prism in the bottom portion of her or his spectacle lens, a base up bifocal design will prove complementary, and therefore a flat-top bifocal is the appropriate choice for this patient (Figs. 2.4.5 and 2.4.6).

Currently, choices exist beyond simple round-top and flat-top designs. Some flat-top shaped bifocals known as C-designs and D-designs actually extend above the optical centers of the reading segment. This results in only a small amount of induced prism over much of the area of the bifocal segment. Therefore this may be an acceptable design even in the case of hyperopic patients. It must be remembered that although this design does not make the image displacement produced by the total prism materially

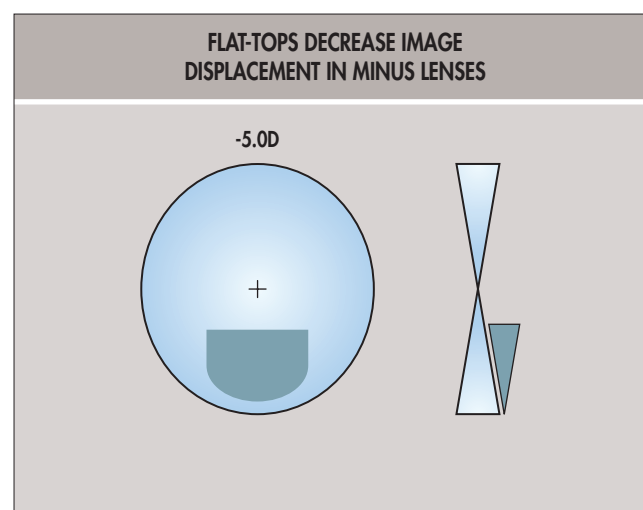
worse, the choice of this type of bifocal represents a missed opportunity to make the image displacement better.

## Progressive Spectacles

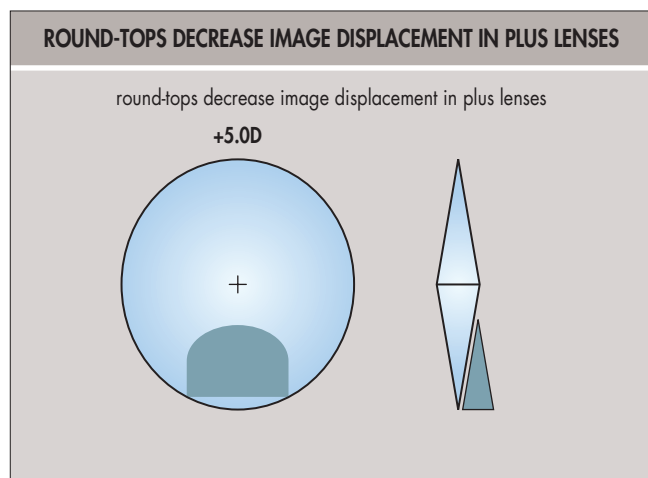
Progressive spectacles or progressive-addition lenses (PAL) hold a number of advantages over traditional bifocal and trifocal lenses. PAL spectacles appeal to patients because they are without visible lines and so do not



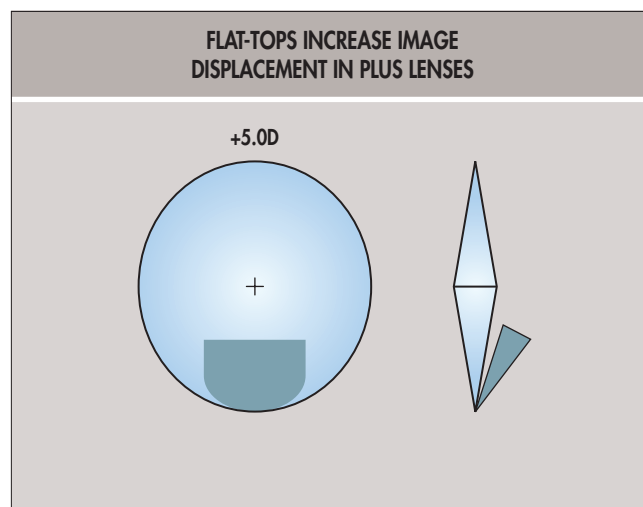
**Fig. 2.4.4 The Round-Top Bifocal Segment Increases Image Displacement in Myopic Spectacles.** (Courtesy Joshua Young.)



**Fig. 2.4.5 The Flat-Top Bifocal Segment Decreases Image Displacement in Myopic Spectacles.** (Courtesy Joshua Young.)



**Fig. 2.4.3 The Round-Top Bifocal Segment Decreases Image Displacement in Hyperopic Spectacles.** (Courtesy Joshua Young.)



**Fig. 2.4.6 The Flat-Top Bifocal Segment Increases Image Displacement in Hyperopic Spectacles.** (Courtesy Joshua Young.)

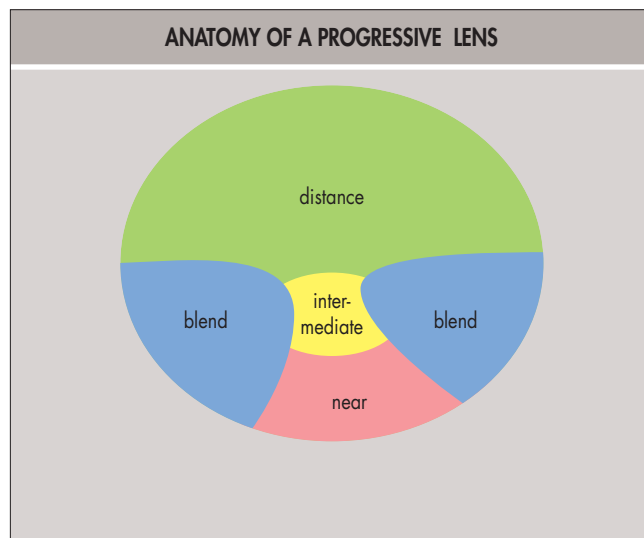


Fig. 2.4.7 Parts of a Progressive Addition Lens (PAL). (Courtesy Joshua Young.)

reveal that the patient is of presbyopic age. The lenses have several functional advantages as well. Because no discrete interface exists between the distance and near portions, no image jump occurs. Image displacement is not an independent variable in this type of lens design, and so no choices need be made by the prescribing physician to minimize image displacement either. Progressive lenses incorporate variable dioptric power between the distance portion in primary and upgaze and the reading portion at the bottom of the lens. Because the lens powers are graduated, there is at least some portion of the spectacle lens that will bring objects at intermediate distance into focus.<sup>5</sup>

Progressive lenses vary substantially in design, but all share a number of features. From primary gaze through the center of the lens to the top of the frame, progressive lenses provide a single correction for distance vision. The bottom of the lens contains a region of single power for reading. These two regions are connected in a narrow-waist corridor. The regions to the right and left of the corridor (looking down and to either side) do not provide clear focus at any distance because of the aberrations necessary to produce the graduated power along the centerline of the lens. These afocal areas are called blend zones and are the source of complaints from patients who find it difficult to adapt to progressive lenses (Fig. 2.4.7).

The width of the corridor and the amount of the lens devoted to intermediate vision vary by the particular lens design and manufacturer. Because sufficient room in the spectacle frame must exist beneath primary gaze for the graduation to incorporate an adequate reading portion, some frames are unacceptably short for the incorporation of a progressive lens.

## Occupational Bifocals

Before the advent of desktop computers, bifocal spectacles were probably adequate to most patients' needs. The distinguishing feature of desktop computers is that their screens represent an intermediate distance task that is performed in primary (i.e., straight-ahead) gaze or slightly below primary gaze. Because it is impossible to prescribe spectacles that have two different prescriptions in primary gaze, dedicated computer glasses are often warranted. Progressive spectacles may provide a useful solution if the computer screen can be placed so as to intercept the zone of intermediate-add correction. If the screen is placed too high for the patient to view the computer screen, he must adopt a chin-up position. This is inadvisable for lengthy computer use.

Another solution is to prescribe either single-vision spectacles for the computer distance—often 21 or 22 inches from the patient's eyes—or to prescribe glasses that are indeed bifocal but incorporate only the computer distance and reading distance without having any portion dedicated to far distance vision. These are called occupational bifocals and allow the patient to see the computer screen in primary gaze and to bring printed copy to the closer reading position in downgaze.

## Pantoscopic Tilt and Wrap Angle

In the course of normal activities, people tend to employ either primary gaze or downgaze. Few of our tasks require substantial upgaze. If spectacle

lenses were oriented in the horizontal or coronal plane, the spectacle lens would be farther from the eye in downgaze than in primary gaze. To compensate for this, spectacles incorporate a tilt to the lens about the horizontal axis. This pantoscopic tilt keeps the vertex distance (the distance between the cornea and the lens) more consistent in primary and downgaze. An additional benefit is that the patient gains a larger field of vision in the reading portion of the lens because it is closer to the eye. A similar tilt may be incorporated along the vertical axis. This is referred to as Z-tilt or as the wrap angle of the lens.

## Base Curve and Center Thickness

A number of other variables influence the degree of magnification produced by spectacle lenses. Because myopic spectacles induce a degree of minification, parameters such as base curve (or back curve) and center lens thickness may be altered to reduce this minification. Increasing the convexity of the back surface of the lens and increasing the thickness of the center of the lens will produce a small degree of magnification. In practice, these may be difficult to implement because increasing the thickness of the already thick lens of a high myope will make the spectacle heavy and less attractive and because increasing the back curve tends to increase the vertex distance of the lens.<sup>6a</sup>

## CONTACT LENSES

Although the idea of contact lenses dates at least to a sixteenth-century suggestion by Leonardo da Vinci, it was not until 1887 that a wearable contact lens was developed. This lens, made of blown glass, was much larger than the majority of modern contact lenses and was tolerated for no more than a couple of hours at a time.

Contact lenses of a modern design were introduced in the late 1940s and were made of polymethyl methacrylate (PMMA). These hard contact lenses are still encountered in clinical practice, but the majority of patients who report wearing "hard contact lenses" are not wearing these oxygen impermeable plexiglass lenses but rather lenses of rigid gas permeable material. Beginning in the 1970s, rigid gas permeable lenses were introduced. Soft hydrogel contact lenses were developed in the 1960s and newer silicone hydrogel contact lenses in the late 1990s.

Contact lens wear is associated with a number of risks and hygiene requirements that are more burdensome than simple spectacle wear.<sup>6b</sup> These risks will be discussed later in this chapter, but it bears discussing the advantages to contact lenses that offset these risks and cleaning requirements. The cosmetic advantage of forgoing spectacles is the most obvious benefit to contact lens wear, but several optical benefits also accrue. The pincushion and barrel distortions as well as the astigmatic distortions induced by meridional magnification are greatly minimized by the use of contact lenses. Additionally, much more substantial anisometropia is tolerated with contact lens wear than with spectacles. Indeed, aniseikonia that would otherwise prohibit the correction of monocular aphakia is generally tolerated in contact lenses. Symptoms of anisometropic anisophoria resulting from asymmetrical prismatic power induced by Prentice rule are completely negated with contact lens wear because the optical center of the contact lens moves with the patient's eye. Different types of contact lenses hold different advantages, and each major type of contact lens will be discussed in the section that follows.

## Vertex Correction

Because patients are aware that their prescriptions for spectacles do not vary with the type of frame they choose, it is not unreasonable for them to assume that the prescriptions are also identical for contact lenses. This is not the case, primarily because contact lenses are positioned at a different distance from the eye from spectacles. The distance between the correcting lens and the cornea is referred to as the vertex distance, and this distance must be accounted for when the contact lens prescription is given.

As the vertex distance decreases, the myopic correction must decrease as well. In the case of hyperopic patients, the hyperopic correction is higher in contact lenses than in spectacles. Similarly, myopic patients generally will have a contact lens prescription with a lower number than their prescription for spectacles. The difference produced by the change in vertex distance is small for low-to-moderate myopes and at least in theory should yield no difference for myopic or for hyperopic corrections with an absolute value of less than four diopters. In practice, it is generally beneficial to refract the patient with contact lenses on the eye and to adjust the contact lens by the power of this "overrefraction." A number of other parameters

must be considered when prescribing rigid gas permeable contact lenses to account for the effect of the tear lens, the shape of the tear film between the posterior surface of the contact lens, and the anterior surface of the patient's cornea.

## Rigid Contact Lenses

Rigid contact lenses are made from a number of materials, the salient features of which can be distilled into a few characteristics.<sup>7,8</sup> The rigidity of the material plays a major role in the function of the lenses and determines their flexibility and durability. The oxygen permeability or  $Dk$ , where  $D$  is the diffusion coefficient and  $k$  the solubility constant of oxygen in the material, describes the amount of oxygen that can penetrate through the lens to reach the corneal surface. Wetting angle is the angle created by placing a bead of water against a flat surface of the material and measuring the tangential surface of the bead of water to the horizontal surface, describing the tendency for water to spread on the lens surface.<sup>9</sup> A lower wetting angle indicates more spread of water and suggests the lens material will be more comfortable and offer better optics.

Historically, contact lenses were made from PMMA, a hard and durable material that had very low oxygen permeability but offered sharp optics. Beginning in the late 1970s, silicone has been incorporated into contact lens material to increase oxygen permeability through its bulky molecular structure. As such, most rigid gas permeable (RGP) lenses today are made from silicone acrylate, which allows for the required rigidity and durability while facilitating good oxygen permeability. Silicone does have a tendency to be more bioreactive, binding other hydrophobic substances on its surface, including lipid-containing mucus. The addition of fluorine may counteract this tendency and increase biocompatibility while also increasing the gas solubility.

RGP lenses, unlike most soft contact lenses, must be fit to the individual patient's eye, making this a more laborious process. The fit is first optimized with a set of trial lenses and then the power of the lens is further refined. The base curve of the lens retains its shape, and the space between the cornea and back surface of the lens is filled in with tears, creating a tear lens (Fig. 2.4.8). This tear lens can add plus power (when base curve is steeper than cornea curvature) or minus power (when base curve is flatter than cornea curvature). Because the tear film fills in any corneal surface irregularities, rigid contacts correct irregular corneal astigmatism better than soft lenses.

The most common placement position for RGP is apical alignment, in which the upper edge of the lens fits under upper eyelid, allowing lens to move with each blink, minimizing discomfort and circulating tears. Another position, the central fit, may be used instead, where the lens rests at the center of the cornea between upper and lower lids. With this fit, the eyelids strike the lens with each blink, resulting in increased lens sensation. This position is useful for patients who have large interpalpebral openings, astigmatism greater than 1.75 D, and corneas steep in the horizontal meridian.

A few other parameters can affect the fit of RGP lenses. Thickness and peripheral curves are typically standardized by the manufacturer. The edge thickness of the lens can affect positioning. A thicker edge maintains the lens position under the lid in apical alignment, whereas a thinner edge

maintains centration and comfort for central fit. The diameter of the RGP lens is fit usually to 2 mm less than the corneal diameter. Similar to steepening the base curve, increasing the diameter of a lens also will increase the central vault or sagittal depth of the lens. If the lens is fit too tightly, insufficient lens movement will be observed with each blink. The base curve then may be flattened or sagittal depth may be decreased by decreasing the diameter of the lens. Likewise, increasing the diameter or steepening base curve can tighten the fit of a lens that demonstrates excessive movement on blink.

## Special Purpose Contact Lenses

A number of conditions exist for which rigid gas permeable contact lenses may be of benefit and also for which standard rigid gas permeable contact lenses cannot be fit. The most important pathology that presents this clinical scenario is a condition of corneal ectasia called keratoconus. Patients with keratoconus experience thinning and steepening of the cornea with the apex of the steepness often outside of the geometrical center of the cornea. This steepness and asymmetry often make conventional rigid gas permeable contact lenses inappropriate. Special rigid contact lenses are designed to accommodate the conical shape of the pathological cornea. These contact lenses generally are smaller and steeper and more expensive than conventional rigid gas permeable contact lenses.

Patients who have undergone corneal transplantation may have irregular corneas that warrant rigid contact lens correction. These postoperative corneas are sufficiently different in shape from the surgically naïve cornea that conventional rigid contact lenses cannot be fit. Special contact lens fitting techniques are often warranted in this setting.

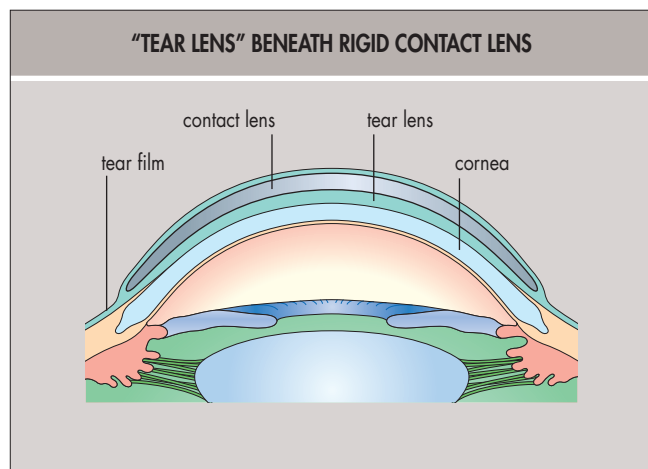
Although the intention of keratorefractive surgery is to reduce dependence upon external refractive correction, some patients still require spectacles or contact lenses. In the case of myopic keratorefractive surgery, the most common sort, the postoperative cornea is flatter centrally than it is in the midperiphery. This is exactly opposite to the case of the surgically naïve cornea and often requires contact lenses that are flat centrally as well. Such unconventional contact lenses are available and require special fitting techniques.

## Contact Lens Complications

Contact lens wear generally is a safe option but it is not without risk. Corneal pathology is dealt with elsewhere in this volume, but a brief review of contact lens-associated complications is worthwhile. Adverse events associated with contact lenses can be divided into contact lens intolerance and true contact lens complications. Intolerance to contact lenses may be the result of ocular surface disease as is often observed in patients with dry eyes. Patients with substantial atopy are often poor contact lens candidates and can exhibit both exaggeration of pre-existing ocular allergies and *de novo* reactions such as giant papillary conjunctivitis.<sup>3,4,10</sup> Patients with hypoesthesia either from previous injury or insult or as a result of herpetic infection are often poor contact lens candidates.

Genuine complications arising from contact lens wear may be sterile or infectious. Sterile infiltrates of the cornea may arise from hypoxia or immunological reactions to bacterial endotoxins.<sup>11</sup> These sterile ulcers are often difficult to distinguish from true infectious ulcers, and prudence dictates the treatment with antibiotic therapy even if the chief suspicion is that the ulcer is noninfectious. Bacterial keratitis is the most common serious complication arising from contact lens wear.<sup>12</sup> Even though the ulcer may be small, the development of a central corneal scar can produce a debilitating effect on the patient's vision, and the irregular topography that may result after healing of an ulcer may preclude successful spectacle wear. The risk of recalcitrant amoebic keratitis has prompted clinicians to insist that patients avoid exposing contact lenses and contact lens cases to tap water and to avoid at all costs exposure to outside bodies of water such as lakes, streams, and swimming pools.

Contact lenses may also produce transient effects on the cornea. Cornea molding, the deformation of the topography of the cornea, is a transient feature that may be observed in soft contact lens wear and is almost ubiquitous in rigid contact lens wear.<sup>13,14</sup> Patients with underlying corneal disease may experience corneal edema with contact lens wear, and even patients with otherwise healthy corneas may exhibit edema in the context of corneal hypoxia.<sup>15</sup> Chronic corneal hypoxia may induce the formation of corneal neovascularization, a condition called pannus. Pannus and corneal limbal stem cell pathology may be signs that the patient is wearing the contact lens in a manner not tolerated by the eye and that modification or cessation of contact lens wear is indicated.



**Fig. 2.4.8** The Space Between the Cornea and Back Surface of the Lens Is Filled in With Tears, Creating a Tear Lens. (Courtesy Joshua Young.)



## Soft Contacts

Although the practice of contact lens fitting is beyond the scope of this chapter, the differences between fitting soft contact lenses and rigid contact lenses are worth mentioning. In contrast to case of rigid contact lenses, the tear film between the soft contact lens and the cornea is optically neutral. Therefore any astigmatic correction must occur in the contact lens itself. Because the orientation of astigmatism correction is of great importance, toric soft contact lenses are designed with a variety of mechanisms to sustain the correct orientation. These include ballast weighting and lens edge modulation that, in interaction with the lid margin, maintains the appropriate orientation of the lens.

The primary consideration when fitting soft contact lenses is to achieve good approximation to the anterior surface of the cornea while avoiding such tight adherence of the contact lens to the surface of the eye that the contact lens does not move on blink.<sup>16a</sup> Contact lens movement is important to circulate the tear film underneath the contact lens. On the other hand, a contact lens that is too loose is uncomfortable for the patient. A raised edge of such a lens may cause other wear complications.

The primary distinction between different sorts of soft contact lens materials is between hydrogel and silicone hydrogel. The former are older materials and are less oxygen permeable. Although the newer silicone hydrogel contact lenses enable the movement of oxygen through the contact lens, they generally exhibit poorer wetting than older hydrogel materials.

## Contact Lens Correction of Presbyopia

Presbyopia is the condition of loss of accommodation that arises with increasing age. Presbyopia is a result of increasing rigidity of the crystalline lens and of changes in the ciliary body musculature and as such is not directly correctable by any external optical device. Although contact lenses cannot increase the flexibility or the range of accommodation of the presbyopic eye, a number of strategies have been developed to alleviate some of the symptoms of presbyopia. Several multifocal soft contact lenses have been developed using refractive rather than diffractive optics in contrast to the optical strategies developed for intraocular lenses.

Although multifocal contact lenses may provide focus for both distance and near, they do so with compromise to visual function. Patient dissatisfaction with multifocal contact lenses arises chiefly from decrease in optical quality. These lenses necessarily produce stray rays of light as light from distant objects encounters the near portion of the contact lens and vice versa.

An alternative to multifocal contact lenses is to employ a monovision strategy whereby one eye is fit with a distance contact lens and the other eye with a near-focus contact lens. Each of these lenses is monofocal and may be spherical or astigmatic. Although this may seem to be a less physiological approach than multifocal contact lenses that allow for a degree of fine stereopsis, monovision contact lenses are generally tolerated very well. As a rule, the patient's dominant eye is chosen for distance vision and the nondominant eye is set for either an intermediate distance as would be appropriate for use with a computer or for a reading distance requiring more disparity between the eyes.

Ocular dominance may be assessed in a number of ways, but one of the easiest is to cut a small hole in a piece of cardboard and have the patient fixate at an object while holding the cardboard at arm's length. Having the patient bring the cardboard toward the face while maintaining fixation of the object forces the patient to choose one eye over the other, because the cardboard necessarily occludes the fellow eye. Patients perform this task without realizing that they are forced to make a choice between the eyes.

## Orthokeratology

Myopia, or nearsightedness, is the most common eye disorder in the world, affecting over 85% of young adults in some Asian countries, with a natural tendency to progress with rates of 12% in preschool children that increases to over 50% by preteenage years. With high degrees of myopia, there are increased risks of blinding complications including glaucoma, retinal detachment, and myopic degeneration. A variety of interventions have been studied to slow progression of myopia. Although interventions such as undercorrection, bifocals, progressive lenses, and contact lenses likely do not slow progression, several interventions, including atropine eyedrops and orthokeratology, do seem to have some effect in reducing myopic progression.<sup>16b</sup>

Orthokeratology is the use of purpose-made rigid gas permeable contact lenses to temporarily reshape the cornea to reduce refractive errors such as myopia, hyperopia, or astigmatism.<sup>17</sup> Typically worn overnight, these reverse geometry contact lenses temporarily flatten the cornea centrally for myopic patients, which leads to central corneal epithelial thinning and steepening of the midperiphery, which in turn leads to midperipheral epithelial and stromal thickening. This results in correction of central refractive error while leaving peripheral myopic blur that may act to drive slowing of myopic progression. Younger children are often treated with the intention of reducing the axial elongation, but the FDA has not approved its use for this purpose.

Because these lenses are worn at night and do not move on the cornea, most individuals report no significant discomfort while wearing the lenses. However, these same properties create increased susceptibility to infection of the cornea, an especially concerning condition in a young child in whom amblyopia may be induced. In an attempt to mitigate the risk of infection and decreased oxygen tension at night, these rigid contact lenses are made with high DK values close to 100 to allow for more oxygenation.

## INTRAOCULAR LENSES

Intraocular lenses (IOLs) are discussed in the context of cataract surgery elsewhere in this volume, but it is worthwhile to discuss here the role that IOLs play in the correction of refractive errors. IOLs are broadly separated into categories based on their materials and the refractive errors that they correct. IOL materials include PMMA, silicone, and hydrophilic and hydrophobic acrylic.<sup>18</sup> Even within each of these categories, the optical properties of materials produced by different manufacturers vary in important ways. The Abbe numbers, discussed in the section on spectacle materials, vary by material, and this is relevant in the chromatic aberration produced by different intraocular lenses. Similarly, different materials pose different biocompatibility challenges.

Functionally, IOLs can be divided into monofocal, toric, and a variety of presbyopia-correcting designs. In their surgical roles, IOLs are categorized as anterior chamber, iris plane, sulcus lenses, and posterior chamber “in-the-bag” lenses. IOLs are primarily employed in cataract surgery as replacement for the crystalline lens removed during surgery but may also be used in patients who remain phakic, purely for refractive correction. Additionally, more than one IOL may be inserted into a single eye to achieve a particular refractive affect. When a second IOL is placed on top of another IOL, this second lens is referred to as a “piggyback lens.”

## Monofocal Intraocular Lenses

Monofocal IOLs have the broadest range of designs, including lenses designed for anterior chamber placement, sulcus and iris plane placement, piggyback, phakic, and one-piece and three-piece posterior chamber IOLs designed for placement within the capsule bag. Monofocal lenses are also available in spherical and aspherical designs produced to decrease spherical aberration created by the optics of the front of the eye. Monofocal IOLs also hold the advantage of enhanced visual quality compared with the multifocal lenses described later. This is perceived by the patient as higher contrast sensitivity.

An important consideration in choosing the appropriate power of an IOL is its intended postoperative location within the eye. This is referred to as the effective lens position or ELP.<sup>19</sup> As is the case with contact lenses described earlier, the anteroposterior position of the IOL changes its refractive effect. To achieve the same refractive effect, lenses with a more posterior position require higher plus dioptric powers. This is important clinically not only in the context of preoperative IOL calculation but in the event that the surgeon chooses to place a lens in the ciliary sulcus that was originally intended for placement within the capsular bag. This contingency may arise in the context of certain surgical complications, most commonly rupture of the posterior lens capsule.<sup>20</sup>

## Toric IOLs

Pre-existing astigmatism may be addressed during cataract surgery by incisional keratotomies, described elsewhere in this chapter, and by employing an astigmatism-correcting IOL. These toric IOLs differ from astigmatism-correcting contact lenses in that they incorporate no special elements to establish the orientation of the lens. Therefore IOLs are produced in different spherical and astigmatic powers but not in different axes. The axis of orientation is of great import to achieve the desired refractive result,<sup>21</sup> and many methods—from marking the cornea with a pen to



automated computer-based corneal registration—have been employed to ensure the appropriate toric IOL orientation.

Although toric are of immense value in clinical practice, their benefit is contingent on a number of factors.<sup>22</sup> Typically, the astigmatism of a nonoperated eye is primarily of corneal origin. However, the crystalline lens may itself be tilted, and this lenticular astigmatism is not amenable to correction with a toric IOL. Irregular astigmatism also is not completely correctable with a toric IOL, and caution must be exerted when employing a toric IOL in the context of keratoconus.

Even small misorientations of a toric IOL can produce clinically significant diminutions of the ability of the IOL to correct the patient's astigmatism. Each degree of misorientation will produce a diminution of effect of 3.3% and a rotation of the patient's axis of astigmatism. A misorientation of 30° completely negates the reduction of absolute astigmatism while simultaneously rotating the astigmatic axis to an orientation to which the patient is unaccustomed.

## Presbyopia Correcting Intraocular Lenses

Because presbyopia is the result of loss of accommodation, the obvious surgical solution would be the implantation of an accommodating intraocular lens. Such accommodating intraocular lenses are in clinical trials, but no truly accommodating intraocular lens has been approved to date for clinical use in the United States.

A number of alternatives to this ideal are available. It must be remembered that in addition to the out-of-pocket cost associated with these premium lenses, there is an optical cost that must be paid to achieve both distance and near vision. The first and optically simplest manner in which to address presbyopia during cataract surgery is to employ monofocal IOLs in a monovision strategy as is discussed in the section on contact lens correction of presbyopia.<sup>23</sup> Of course, a risk of this strategy is that the patient may not tolerate monovision or may only tolerate the degree of monovision that allows for intermediate (e.g., computer) use and does not yield the ability for closer reading without spectacles. The advantage of this strategy is that contrast sensitivity and overall visual quality is not diminished in either eye individually.

Multifocal IOLs are designed to project both distance and near images onto the patient's retina.<sup>24</sup> This is generally done by employing a refractive lens for the distance focus and a diffractive lens for reading (Fig. 2.4.9). The combination of refractive and diffractive elements holds the advantage of decreasing the overall chromatic aberration because short wavelength light converges to a greater degree than long wavelength light in refractive lenses, and the opposite is true in diffractive lenses. However, the rings employed in diffractive designs cause visual symptoms that disturb some patients.<sup>25,26</sup> Also, visual quality is poorer in multifocal lenses than in monofocal spherical or toric lenses. The degree to which these visual degradations are tolerated is impossible to predict preoperatively with certainty, and a higher number of multifocal lenses require explantation for reason of bothersome visual symptoms than is the case with monofocal IOLs.



**Fig. 2.4.9** A Type of Multifocal Intraocular Lens (IOL) With Refractive and Diffractive Elements. (© 2017 Novartis.)

Lenses designed to demonstrate functional vision over a range of distances have been introduced recently. These are generally referred to as extended depth of focus (EDOF) lenses. Although these lenses may provide a more uniform visual quality between far and intermediate distances, the visual quality is diminished across all distances compared with monofocal IOLs.

An early attempt to design an accommodating IOL was approved for clinical use in the United States.<sup>27</sup> However, this design yields insufficient presbyopia correction to replace reading glasses and is often referred to as a “pseudoaccommodative intraocular” lens.

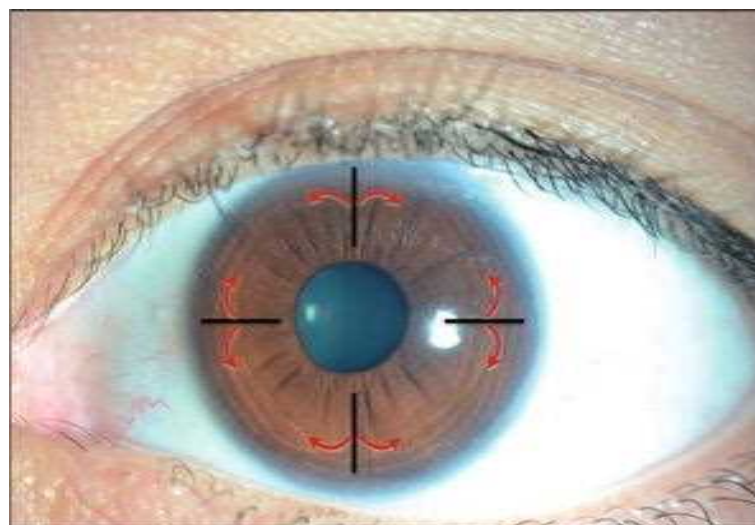
## KERATOREFRACTIVE SURGERY

The idea of refractive surgery is not a new one and dates to at least the late nineteenth century. Although refractive surgery may be undertaken to any of the optical surfaces of the front of the eye, the most fruitful approach has been the intentional modification of the shape of the cornea. The anterior surface of the cornea accounts for the great majority of the refractive power of the eye, and fractional modification of the surface curvature may produce tremendous refractive change.

Discussion in this section will center on corneal refractive surgery or keratorefractive surgery, but it bears mentioning that intraocular refractive surgery also is performed. Removal of the noncataractous crystalline lens and replacement with an IOL—so-called clear lens extraction—may be performed successfully for higher refractive errors at the expense of the loss of accommodation. This procedure is identical to conventional cataract surgery. Additionally, an IOL may be inserted into the eye without removal of the patient's own crystalline lens. This is referred to as phakic lens implantation or implantable collamer lens (ICL) surgery.<sup>28-31</sup>

The majority of patients who undergo refractive surgery are undergoing some modification of the shape of the anterior cornea. Initially, this was performed by making incisions in different patterns on the corneal surface. Radial incisions in the cornea cause circumferential flattening. Thereby myopic correction is achieved through the creation of a series of radial incisions centering about the central cornea but, of course, not passing through the corneal center. This is the basis of radial keratotomy, a procedure that can successfully correct substantial degrees of myopia<sup>32</sup> (Fig. 2.4.10). Although nomograms were developed for titratable correction of various degrees of myopia, radial keratotomy incisions proved to have an unstable effect for many patients over the long term. Patients who were initially corrected to emmetropia sometimes demonstrated a progressive increase in the degree of corneal flattening over many years postoperatively. These formerly myopic patients experience a trend toward increasing hyperopia over time.<sup>33</sup> Radial keratotomy also carries the additional concern of globe rupture with blunt trauma, even years after the surgery, because the structural integrity of the cornea has been violated and never completely recovers.

In a manner similar to the myopic correction achieved by radial keratotomy, astigmatic correction is achievable through tangential or arcuate incisions of the midperipheral or peripheral cornea. These incisions need



**Fig. 2.4.10** In Radial Keratotomy (RK) Surgery, Flattening Perpendicularly to the Radial Incisions Reduces the Average Refractive Power of the Cornea and Corrects for Myopia. (Courtesy Joshua Young.)

not be made as deep, and are generally fewer in number than those of radial keratotomy and so pose less of a structural risk to the eye. In the past, radial and arcuate incisions were combined to correct for myopic astigmatism.

Although radial incisions have largely been displaced by laser ablative surgery as discussed later, arcuate incisions continue to play a role for correction of low degrees of astigmatism during cataract surgery. Arcuate keratotomy has morphed into the limbal relaxing incisions (LRI) performed during cataract surgery.

Historically, myopic correction could be performed by the removal of a lenticule of corneal stromal tissue. This was performed using a motorized blade in a miniaturized device looking something like a wood plane. Automated lamellar keratectomy, ALK as it was called, formed the mechanical foundation of the microkeratome, the device created to produce corneal flaps for laser in situ keratomileusis (LASIK) surgery.

Incisional keratotomy may correct myopia and astigmatism, but the correction of hyperopia is not achievable in this manner. In order to steepen the central cornea, surgeons sought to create a zone of contraction of corneal tissue paracentrally. One approach to this was conductive keratoplasty (CK), in which heating was induced focally in a number of spots surrounding the center of the cornea.

In the mid-1990s, the excimer laser was introduced to clinical practice to perform athermal ablation of corneal tissue to reshape the cornea to produce the desired refractive effect. Excimer ablation holds the advantages of great precision without substantial compromise to the mechanical integrity of the cornea. However, ablation through the anterior layers of the corneal stroma, termed Bowman's layer, resulted in the creation of symptomatic corneal haze in some patients. Today this haze may be dealt with by using mitomycin C to modulate postoperative healing or may be avoided altogether through the creation of an anterior corneal flap under which the laser treatment is performed. The combination of ablation plus a flap is what it has been termed laser in situ keratomileusis. LASIK flaps may be produced by means of femtosecond laser rather than by mechanical microkeratome. The advantages of the flap are faster visual recovery, less corneal haze, and greater patient comfort. The disadvantage of the flap is that adhesion of the flap to the underlying cornea is not as strong as the shear resistance of the surgically naïve corneal tissue. Therefore even very late term shear stress, such as may be experienced with ocular injury, can dislodge a LASIK flap.

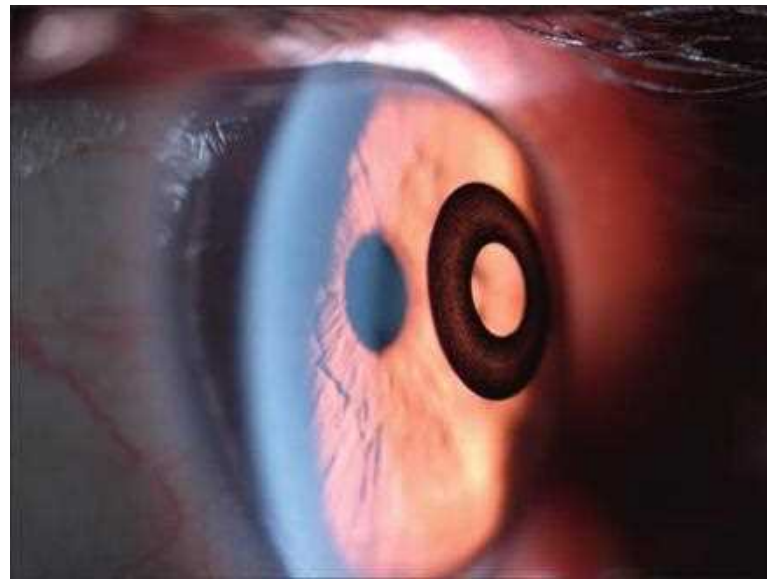
Although ablative keratorefractive surgery carries risk, it must be remembered that contact lens wear also carries risk that is cumulative over the many years a patient may wear contact lenses. For many patients, the risk of a keratorefractive procedure is comparable to the risk of contact lens wear and represents an acceptable alternative.

Both spherical errors and astigmatic errors are correctable with ablative keratorefractive surgery. Different refractive errors are corrected by altering the ablation pattern.<sup>34</sup> The correction of myopia is achieved by the simple ablation of a lenticule from the center of the cornea. Because tissue cannot be added by the excimer laser, however, steepening the central cornea as is required for the correction of hyperopia necessitates a more complicated ablation pattern. A torus (think of a doughnut or bagel sliced in half) is ablated from just outside of the center of the cornea to produce steepening centrally. However, the zone of uniform curvature, the optical zone, is necessarily smaller in a hyperopic treatment than in a myopic treatment.

The femtosecond laser may be used to carve a lenticule from the central cornea in a manner reminiscent of automated lamellar keratectomy. This lenticule is then withdrawn through a channel also carved into the cornea by the femtosecond laser. This procedure is known as small incision lenticule extraction or SMILE surgery and is relatively new.

## CORNEAL INLAYS

While the correction of presbyopia is not directly achievable by means of refractive surgery, a number of procedures have been introduced to alleviate some presbyopia symptoms. These procedures have in common the introduction of an implant into the substance of the cornea. Two corneal



**Fig. 2.4.11 The KAMRA Inlay Implanted Within the Cornea to Alleviate Symptoms of Presbyopia.** (December 2016 EyeWorld REFRACTIVE SURGERY section.)

inlays approved for use in the United States are the KAMRA and the Raindrop devices. The KAMRA inlay is a small opaque disc with an even smaller aperture in the center that functions as a as an optical pinhole. This inlay increases depth of field while reducing the amount of light that enters the eye. This increase in depth of field gives patients some degree of near vision. The KAMRA inlay is implanted in only one eye<sup>35</sup> (Fig. 2.4.11).

The Raindrop inlay is no longer available as of publication. It is a small clear lenticule and is also implanted in only one eye. Corneal inlays are introduced underneath a corneal flap or in a corneal pocket and sit within the corneal stroma.<sup>36,37</sup>

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# Ophthalmic Instruments

Neal H. Atebara, David Miller, Edmond H. Thall

# 2.5

**Definition:** From the earliest optical devices to the latest computerized imaging systems, technology has aided the clinician in the diagnosis and treatment of ocular disease.

## Key Features

- The ability of a transparent medium to bend a ray of light is the basis for most of the instruments used in ophthalmology today.
- Spherical lenses, prisms, mirrors, slit-shaped illumination, astronomical and Galilean telescopes, and a multitude of other optical components—both simple and complex—have been devised and manufactured for more than two centuries in order to study the human eye and its function.

## INTRODUCTION

In this chapter, the basic principles that underlie some of the more common instruments used in ophthalmology will be reviewed, including:

- Direct ophthalmoscope.
- Binocular indirect ophthalmoscope.
- Fundus camera.
- Optical coherence tomograph.
- Slit-lamp biomicroscope.
- Slit-lamp fundus lenses.
- Goldmann applanation tonometer.
- Specular microscope.
- Operating microscope.
- Keratometer and corneal topographer.
- Lensmeter (also known as lensometer).
- Automatic refractor.
- Magnifying devices.

## DIRECT OPHTHALMOSCOPE

The entire retina, if spread out and flattened, is about the size of a large postage stamp. The important structures themselves are rather small. For example, the optic nerve is 1.5 mm in diameter, and the major blood vessels are only 0.1–0.2 mm in diameter. Significant papilledema, with an elevation of the nerve head of 3.00 D, is equivalent to only a 1 mm change in elevation. Most of the important red and yellow details, including blood vessels, hemorrhages, and exudates, are seen against the light red background of the blood-filled choroid. Subtle changes in the pinkish white backscattered light of the optic disc announce major glaucomatous or neuro-ophthalmic alterations. The presence of the corneal reflection and the usual backscattered light of the healthy cornea and lens make the evaluation of fundus changes even more difficult.

In the face of these obstacles, it seems almost miraculous that the examiner is able to make a significant number of diagnoses using the direct ophthalmoscope. Fig. 2.5.1 illustrates how the ophthalmoscope directs the light rays of illumination and observation coaxially, while the observation system is essentially a peephole.<sup>1</sup> The lens and cornea of the patient's eye actually create the retinal image. Thus the observer does not really see the retina of the patient but an optical image of the retina.

To bring the red fundus reflex into sharp focus for the viewer, the modern ophthalmoscope has a disc of lenses. Because the compensating lens neutralizes the refractive error of both the physician and the patient

and the accommodation of each, its total power provides only a rough estimate of the patient's refractive state. The magnitude of a large amount of astigmatism may actually be estimated if the lens is focused on a blood vessel that travels parallel to the foveal reflex and then refocused on a vessel that travels perpendicular to the first vessel.<sup>2</sup>

Probably the most important advance in direct ophthalmoscopy was the use of the halogen tungsten bulb,<sup>3</sup> which has a number of advantages over the older tungsten bulb. A quartz jacket can withstand higher temperatures than can the glass jacket, thus the filament temperature may be raised higher than that in the conventional tungsten bulb to produce an increased lumen output.

The field of view of the modern direct ophthalmoscope averages about 10° and is limited by the most oblique pencil of rays that can pass from the outer edge of the observer's pupil to the opposite outer edge of the patient's pupil. To enlarge the field of view of the direct ophthalmoscope, the investigator's eye must be brought closer to the patient's eye with the patient's pupils dilated.

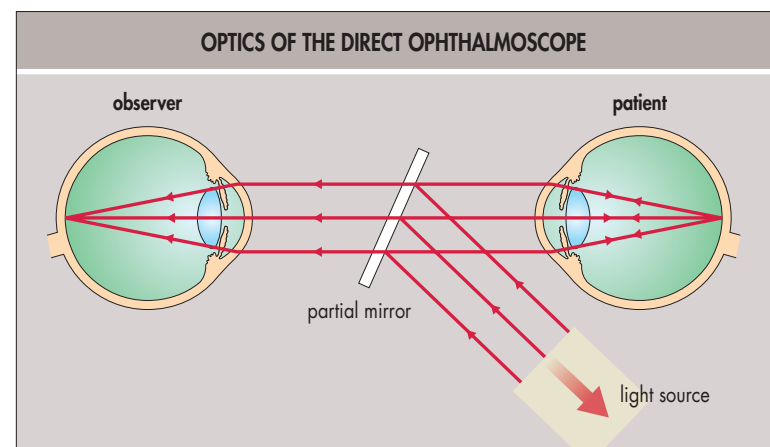
Because the enlargement capacity of any magnification lens usually is defined as one-fourth of the lens power, the retinal image in the typical emmetropic eye of 60 D may be considered to be magnified by 60/4, or  $\times 15$ . In aphakic eyes, from which a 20 D natural lens has been removed, the magnification for the observer is reduced to about 40/4 or  $\times 10$ .

## BINOCULAR INDIRECT OPHTHALMOSCOPE

Compared with the direct ophthalmoscope, the binocular indirect ophthalmoscope gives a wide field of view, a stereoscopic impression, and an image of high contrast. Of course, a small price must be paid for these advantages. The patient's pupil must be dilated, the instrumentation is larger, heavier, and more expensive, and the illumination is almost painfully bright for the patient.

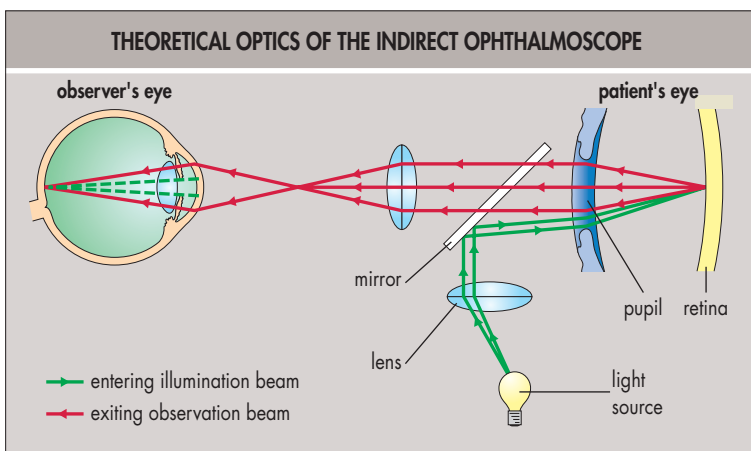
## Illumination System

In order to avoid corneal and lens reflection and scatter, the observation beam and the illumination beam is separated at the corneal and lens plane,<sup>4</sup> requiring a dilated pupil (Fig. 2.5.2). The filament of the bulb is actually brought to a focus in a portion of the patient's pupil. To minimize the loss of light, the condenser lens brings the observer's pupil to a focus

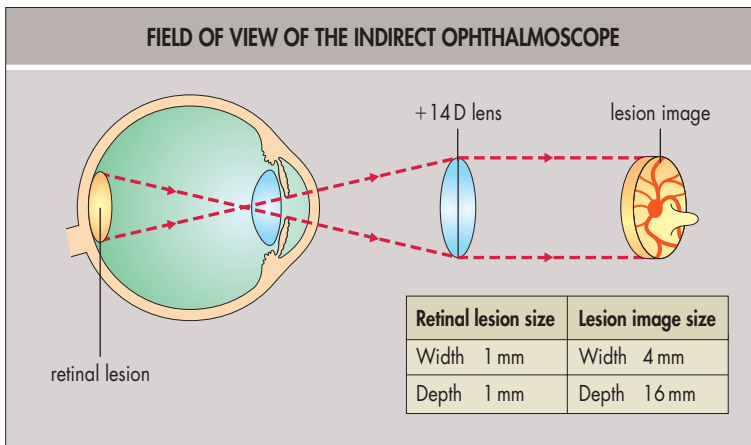


**Fig. 2.5.1 Optics of the Direct Ophthalmoscope.** With use of a mirror (either half-silvered or one that has a central aperture), the directions of the light of observation and the light incident to the patient are made concentric (coaxial).





**Fig. 2.5.2 Theoretical Optics of the Indirect Ophthalmoscope.** The illumination beam enters a small part of the pupil and does not overlap with the observation beam, and thus minimizes bothersome reflection and backscatter.



**Fig. 2.5.3 Field of View, Indirect Ophthalmoscope.** The focal length of the handheld lens determines the distance from the patient's eye at which to hold the lens. The tangent of the angle of field of view equals the lens diameter divided by the focal length.

in the patient's pupil. With patient and observer pupils conjugate, loss of light is minimized, and field of view is maximized.

## Observation System

### Contrast

Because the observation beam path is different from the illumination beam path, glare degradation from reflection and backscatter is minimized and subtle details are seen more easily. The observer must learn to tilt the handheld lens strategically to avoid reflection from the surface of the lens itself. This reflection is minimized (from about 4% of incident light to 1%) by a lens that has an antireflection coating.

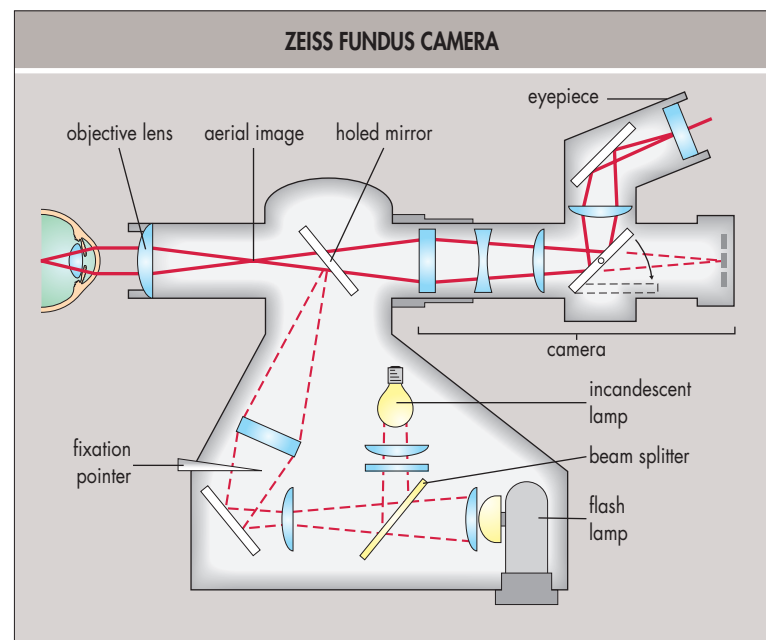
### Inverted Image

The handheld condenser lens creates a real, inverted aerial image of the illuminated patient's fundus, as expected from a positive lens. Thus the examiner must learn to reorient details from where they appear to be to where they actually are located.

### Field of View

Fig. 2.5.3 illustrates how the handheld lens produces the aerial image of the fundus. Rays that pass through the nodal point of the patient's eye and the edge of the handheld lens determine the size of the field of view. The distance of the handheld lens from the patient's eye also determines the angular subtense of the patient's fundus caught by the lens. This distance is optimal if it equals the focal length of the lens. Thus the field of view is determined by the expression  $d/F$ , where  $d$  is the diameter and  $F$  the focal length of the handheld lens.

For example, given equal diameters, stronger lenses (e.g.,  $F = 30$  D,  $f = 3.3$  cm) provide larger fields of view. However, a weaker lens may be made with a larger diameter because it is less vulnerable to spherical aberration.



**Fig. 2.5.4 Zeiss Fundus Camera.** See text for the description. (Adapted from American Academy of Ophthalmology. Home study course, optics and refraction. San Francisco, CA: American Academy of Ophthalmology; 1990.)

Thus a 20 D lens of 3 cm diameter yields almost the same field of view as a 30 D lens of 2 cm diameter.

### Magnification

Fig. 2.5.3 shows the chief ray that passes from the edge of the fundus view through the nodal point of the eye to the aerial image. The ratio of the fundal object to the aerial image is proportional to the ratio of the focal length of the patient's eye to the focal length of the condenser lens, or inversely proportional to the power ( $F$ ) of the eye (60 D) and the handheld lens. Thus for an emmetropic eye and a 20 D lens, the magnification =  $60 \text{ D}/20 \text{ D} = \times 3$ ; for a 30 D lens, the magnification =  $60 \text{ D}/30 \text{ D} = \times 2$ .

Ultimately, the distance of this mildly magnified aerial image from the observer determines the total magnification. If the observer has a large amplitude of accommodation, the aerial image is brought closer and its overall magnification increased.

### Stereopsis

The light beam that emerges from the patient's dilated pupils is directed through the handheld lens and into the two eyepieces (separation usually 15 mm) of the binocular indirect ophthalmoscope. Prisms then redirect the two beams into the examiner's eyes. A smaller distance between the two eyepieces than the interpupillary distance reduces the stereopsis appreciated by an observer (interpupillary distance of 60 mm) by about one-fourth. However, axial magnification (which equals one-fourth of the square of lateral magnification) augments the stereoscopic appearance. If the lateral magnification of a 20 D lens is  $\times 3$ , the axial magnification equals  $9/4$  or  $\times 2.25$ . Thus the ophthalmoscopic view through the handheld lens amplifies small changes in retinal topography. Using a lower power hand lens further increases this effect: for example, a 15 D lens results in transverse magnification of  $60/15 = 4\times$ , but axial magnification of  $16/4 = 4$ -fold.

Variations of indirect ophthalmoscopy include the scanning laser ophthalmoscope and various analyzers of the optic nerve head.

## FUNDUS CAMERA

### Lighting

The present illumination system of the Zeiss fundus camera is shown in Fig. 2.5.4.<sup>5,6</sup> Light from the incandescent lamp (for observation) and the flash lamp (for photography) is superimposed by means of the beam splitter, so that the light from the flash travels along the same path as that of the observation light. The lamp filaments are imaged in the vicinity of the holed mirror, which deflects the light toward the eye. The holed mirror is similar to the mirrors used in many retinoscopes, with a central hole to allow observation. In contrast to the retinoscope arrangement, the holed mirror in the fundus camera is imaged onto the plane of the patient's

pupil by the objective lens to ensure the necessary separation of illumination and observation pathways at the pupil. The objective lens corresponds to the condenser lens in the indirect ophthalmoscope; both lenses are designed with aspherical surfaces to provide the best possible image quality over a wide field of view.

Photographing through an undilated pupil was achieved by observation of the fundus using infrared light, which does not stimulate the retina. In such a system, the infrared light penetrates the 4–5 mm diameter pupil in a dark setting, is reflected off the retina, and is displayed on a monitor. Once the retina has been focused and framed, an electronic flash illuminates the retina before the pupil constricts.

## Reducing Reflections From the Cornea and Instrument

Anyone who has tried to evaluate subtle macular detail using a direct ophthalmoscope is familiar with the annoyance of corneal reflection. Gullstrand's table-mounted ophthalmoscope embodied his principle that the illumination system should not intersect the cornea in the same area as the rays that come from the observation system. In the Zeiss system, this principle is satisfied by a mirror that has a central hole. The mirror reflects a circle of light through the pupillary periphery while the fundus is viewed through the central hole of the mirror. Although such a system is not able to completely eliminate ocular and camera lens reflections, it successfully reduces them to a significant degree.

## The Observation System

Fig. 2.5.4 illustrates all the elements of the fundus camera. As noted before, light from the incandescent lamp and that from the flash lamp are folded into a common path, which ultimately strikes the holed mirror and is reflected into the patient's eye. This illumination system and the observation system are very similar to those of the indirect ophthalmoscope. In the case of the fundus camera, light reflected from the patient's retina passes through the hole in the mirror and focuses a real image in the film plane of the camera. A beam splitter diverts a portion of the light directed to the camera and sends it to the eyepiece. In essence, the eyepiece is like a simple microscope. It receives the real image of the fundus and processes it such that parallel light exits for the observer.

## Field of View

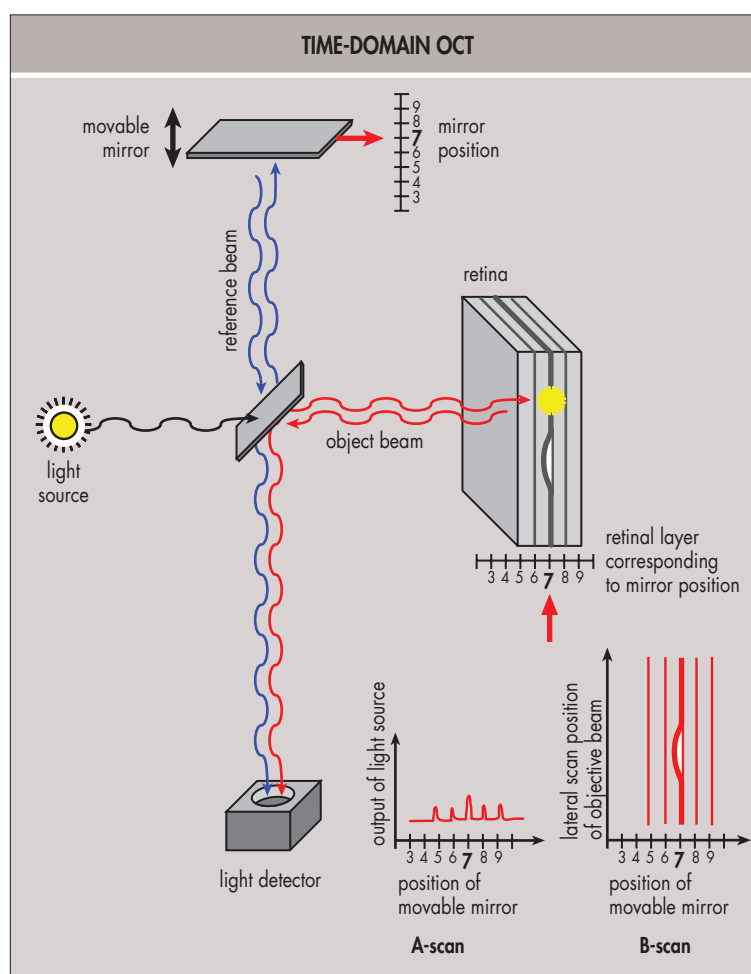
In theory, a 180° aerial image of the retina can be captured, even through a small pupil. In practice, however, because the rays from the equator exit the pupil at a very sharp angle, the collection of these rays can be accomplished only by a lens held very close to the pupil or a lens of very wide diameter. Of course, although wide-diameter lenses produce a greater field of view, they also introduce significant spherical aberration. For fields of view greater than 100°, therefore, the only sensible way to collect the sharply bent rays that come from the retinal periphery is to move the front lens close to the pupil. Thus in the equator-plus camera, the front lens of the system is a contact lens. Because the aerial image of such a large expanse of retina follows the globe's curvature, special lenses must be introduced into this system to flatten the image.

To photograph different fields of view, three different focal length lenses are used, much as the ophthalmologist might switch between +14 D, +20 D, and +28 D handheld lenses. The lens system that has the longer focal length (less dioptric power) produces a more magnified image. Thus the amount of field captured in a frame is smaller than that produced by the more powerful, shorter focal length lens. Theoretically, both the larger field and higher magnification could be obtained if the size of the film could be doubled.

Portions of the retina can be photographed beyond the traditional central 30° if the camera is directed to the peripheral area of interest. However, a camera aimed off axis by 30° or more with the 60 D ocular optical system induces 10–15 D of oblique astigmatism and results in fuzzy pictures.<sup>7</sup> Fortunately, well-designed fundus cameras anticipate off-axis photography and include a large range of cylindrical corrections with which to sharpen the peripheral views.

## OPTICAL COHERENCE TOMOGRAPHY

Optical coherence tomography (OCT) is based on the Michelson interferometer invented in the late 1800s. Originally the instrument was used to make extremely accurate measurements of length. A single beam of



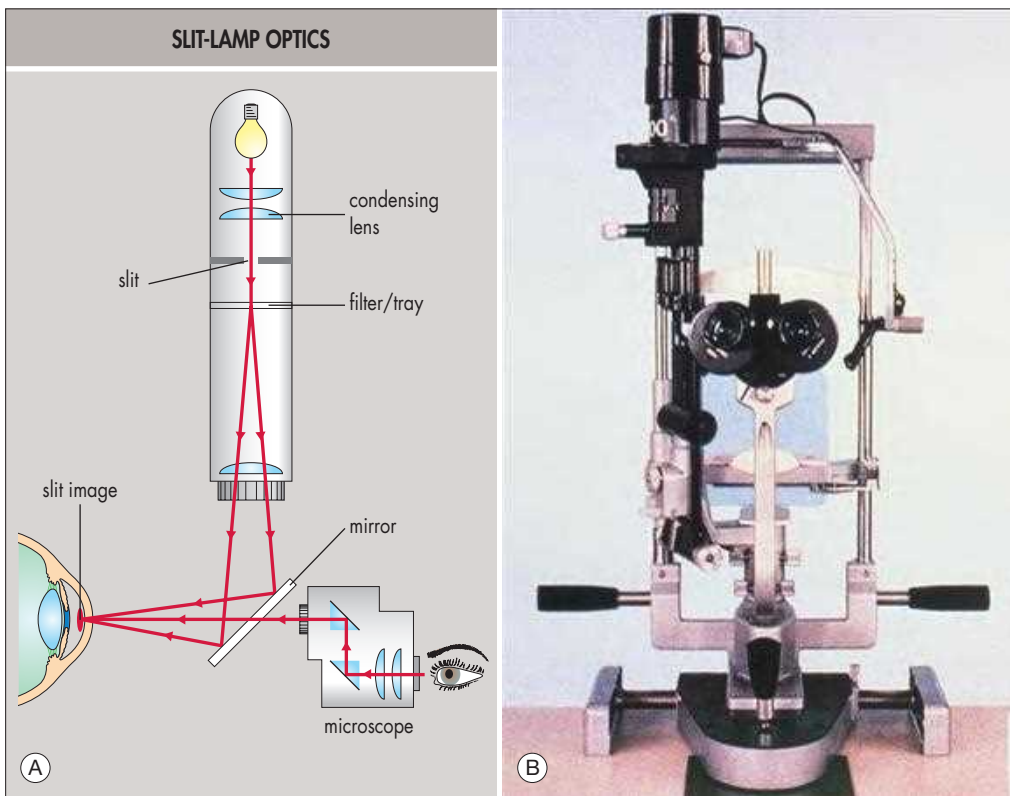
**Fig. 2.5.5 Optical Coherence Tomography (OCT).** Based on the principle of the Michelson interferometer, OCT analyzes the interference patterns between a reference beam and the object beam to create a precise cross-sectional reflectivity map of the internal retina.

white light is split into two beams moving in perpendicular directions. The beams are reflected back to, and recombine at, the beam splitter. When the beams recombine, interference fringes are observed, provided that the difference in optical path length (OPL) between the two arms of the interferometer is less than the coherence length of the light utilized. Michelson used white light with a coherence length of 1–2  $\mu\text{m}$ . One arm of the device had a fixed, known length, and the length of the other arm was varied until interference fringes were observed, at which point the difference in OPL between the two arms had to be less than 2  $\mu\text{m}$ . Submicron accuracy could be achieved by counting fringes.

If this technique were directly applied to retinal imaging, only a single layer's thickness could be measured because of the low coherence of white light. However, if a laser is used, the coherence length is too long and the position of a retinal layer could be localized only to within a few centimeters. The OCT utilizes a superluminescent diode that operates in the near-infrared and has a bandwidth of about 50 nm or about six times more coherent than white light but far less than the coherence of a laser.

The original clinical instruments incorporated two moving mirrors. One varied the length of one arm of the interferometer and was used every time the device scanned a narrow section of retina (Fig. 2.5.5). After a single scan was completed, the other mirror shifted the beam to the neighboring section of the retina and the next scan was repeated. An important limitation was the amount of time required to complete a scan. The time required to scan a single line of retina a few millimeters in length far exceeded even the best patient's fixation. Moreover, the eye itself is not dimensionally stable due to choroidal blood flow that varies with the cardiac cycle. Sophisticated software can overcome some fixation requirements, but limitations exist to this technique.

In spectral domain instruments one of the mirrors (which scans the reference arm) is replaced by a spectrometer that measures the reflection from each wavelength simultaneously, producing a much faster scan that not only improves accuracy but also enables a larger region of retina to be interrogated. It is important to realize that OCT measures optical path length not physical thickness. The presence of edema or other pathologies



**Fig. 2.5.6 The Slit Lamp.** (A) Some slit lamps first bring the light to a sharp focus within the slit aperture, and the light within the slit is focused by the condensing lens on to the patient's eye. The observation system of a modern slit lamp has many potential reflecting surfaces; antireflection coatings on these surfaces help reduce loss of light. (B) Slit-lamp apparatus. (Modified from Spalton DJ, Hitchings RA, Hunter PA. *Atlas of clinical ophthalmology*. New York: Gower Medical; 1984. p. 10.)

that differ in refractive index from the retina can distort the apparent thickness of the pathology, leading to imaging artifacts that can complicate interpretation of OCT images.

## SLIT-LAMP BIOMICROSCOPE

The slit lamp is the piece of equipment most frequently used by the ophthalmologist.<sup>8</sup> With the addition of auxiliary lenses, it can give unique, magnified views of every part of the eye. In conjunction with auxiliary devices it can be used to take photographs and to make quantitative measurements, including intraocular pressure, endothelial cell counts, pupil size, corneal thickness, anterior chamber depth, and others.

## Illumination

The modern slit lamp produces an intensity of about 200 mW/cm<sup>2</sup>. When operated at the rated voltage, halogen lamps have a higher luminance and color temperature than do conventional incandescent lamps. For slit-lamp work, a high color temperature (e.g., a greater amount of blue light) is useful. Because many of the ocular structures are seen via light scatter, and because the shorter wavelengths are scattered most, a light with a high blue component illuminates the structures best. The light is first brought to a focus at the slit aperture (Fig. 2.5.6), and the light within the slit is focused by the condensing lens onto the patient's eye.

## Improving Tissue Contrast

One of the great strengths of the modern slit lamp is the way in which contrast can be improved by various maneuvers:

- **Optical sectioning:** As the beam is narrowed, the scattered light of adjacent tissue is removed and greater detail of the optical section is seen.
- **Tangential illumination:** When the light is brought in from the side, highlights and shadows become stronger, and the texture (i.e., elevations and depressions) is seen better.
- **Pinpoint illumination:** The cells and flare in the anterior chamber in a patient who has iritis are best seen using a narrow beam focused into the aqueous, so that the black pupil becomes the background. The combination of the narrow beam and the dark pupillary background eliminates any extraneous light that would reduce contrast. The same principle holds when the examiner pushes the lower lid up to examine the tear meniscus. For example, the stagnant cell pattern of an obstructed tear duct is best seen using a narrow beam with the dark iris in the background.

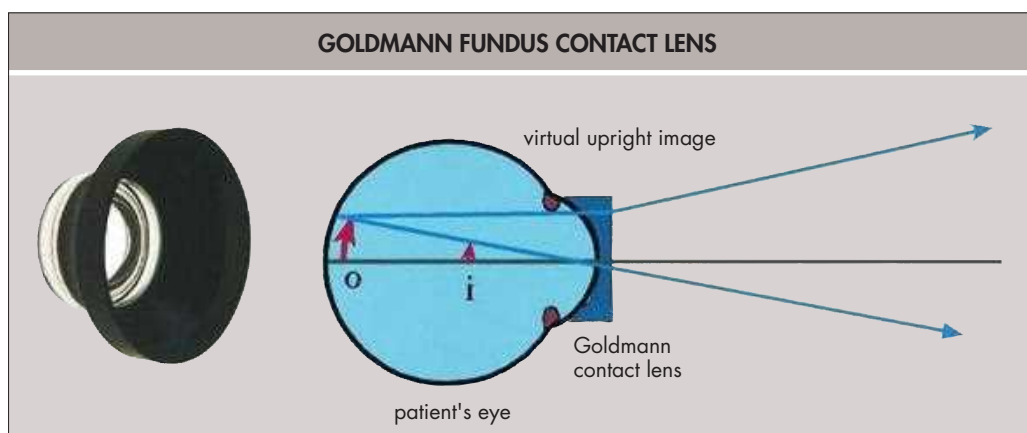
- **Specular reflection:** In this technique the angle of observation is set to equal the angle of illumination. In this way, the structure of the front surfaces of the cornea (i.e., ulcers, dry areas) and the rear surfaces (endothelial pattern) may be assessed.
- **Proximal indirect illumination:** In this technique a moderately wide beam is directed to the areas adjacent to the area of interest. Against a dark background, the backscattered light from the lesion yields a higher contrast, which often allows the observer to see the borders of the lesion more precisely. For example, when this technique is used, subtle corneal edema—with its minute pools of fluid—stands out more distinctly against a dark pupil.
- **Sclerotic scatter:** With the slit illuminator offset from its isocentric position, light is directed to the limbus. The light then follows the cornea as if it were a fiberoptic element and reaches the other side of the limbus. However, if a lesion or particles within the cornea exist, the backscattered light from the lesion or particles is seen clearly against the dark pupillary background.
- **Retroillumination from the fundus:** Light sent through the pupil to the fundus is reflected and yields an orange background. Holes in the iris or subtle wrinkles in the cornea become silhouetted and much easier to see.

## Observation System

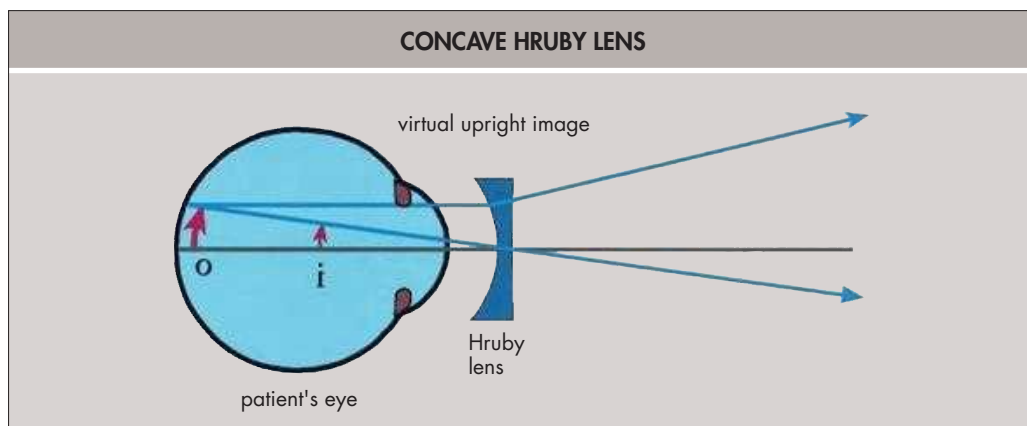
The observation system of the slit-lamp biomicroscope has a long working distance of about 3.9 inches (10 cm), which is about 100 times longer than that of a laboratory microscope. Prisms take the divergent rays from the patient's eye and force them to emerge as parallel pencils from each eyepiece. Thus a stereoscopic appreciation of the patient's eye is achieved without convergence of the observer's visual axis. Most slit-lamp microscopes offer magnifications between  $\times 5$  and  $\times 50$ , with  $\times 10$ ,  $\times 16$ , and  $\times 25$  being the most popular. Image resolution is ultimately limited by diffraction.

## SLIT-LAMP FUNDUS LENSES

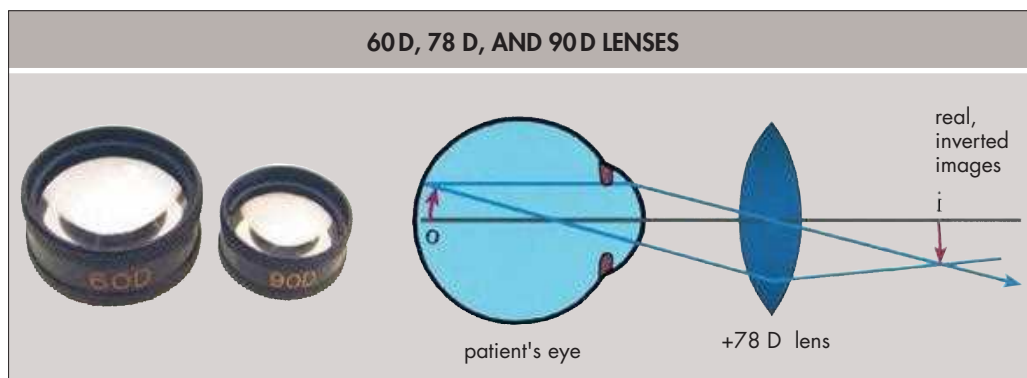
Because the cornea has such a high refractive power, the slit-lamp microscope can view only the first one-third of the eye.<sup>9</sup> Special lenses, in conjunction with the slit-lamp microscope, can be used to view the posterior vitreous and the posterior pole retina. The two ways to overcome the high corneal refractive power are (1) nullifying the corneal power, or (2) utilizing the power of the cornea as a component of an astronomical telescope in a manner similar to that exploited by the indirect ophthalmoscope.



**Fig. 2.5.7** The Goldmann fundus contact lens, or any similar plano-concave contact lens, nullifies the refractive power of the cornea, thereby moving the retinal image close to the pupillary plane and into the focal range of the slit-lamp microscope. The image formed is virtual, erect, and diminished in size.



**Fig. 2.5.8** The concave Hruby lens, when placed close in front of the patient's eye, forms a virtual, erect image of the illuminated retina that lies within the focal range of the slit-lamp microscope.



**Fig. 2.5.9** The 60 D, 78 D, and 90 D lenses produce inverted, real images of the retina within the focal range of the slit-lamp microscope in a fashion similar to that employed by the indirect ophthalmoscope.

The Goldmann contact lens (Fig. 2.5.7) and other similar lenses work in conjunction with the slit-lamp microscope to nullify the dioptric power produced by the corneal curvature and to bring the retina into the focal range of the slit-lamp microscope. These plano-concave contact lenses are placed on the cornea, forming virtual, erect, and diminished images of the illuminated retina near the pupillary plane within the focal range of the slit-lamp microscope.

The Hruby lens is a powerful plano-concave lens,  $-58.6$  D in power. It is held immediately in front of the cornea, forming a virtual, erect, and diminished image of the illuminated retina near the pupillary plane, bringing it within focal range (Fig. 2.5.8).

The 60 D, 78 D, and 90 D fundusoscopic lenses (Fig. 2.5.9) use a different approach to view the posterior vitreous and posterior pole retina. These lenses act as high-powered, biconvex, condensing lenses, projecting an inverted, real image in front of the lens within focal range. This is the same optical principle used by the indirect ophthalmoscope: the higher the power of the lens, the lower the magnification of the image.

The Goldmann three-mirror contact lens (Fig. 2.5.10), as its name implies, incorporates three internal mirrors. The contact lens nullifies the refractive power of the patient's cornea, and the three mirrors then reflect light from the patient's midperipheral retina, peripheral retina, and the iridocorneal angle, respectively. The posterior pole of the fundus can be visualized, also, in a manner similar to that of the Goldmann posterior pole contact lens.

The Quadraspheric, SuperQuad, and similar lenses are corneal contact lenses (Fig. 2.5.11).

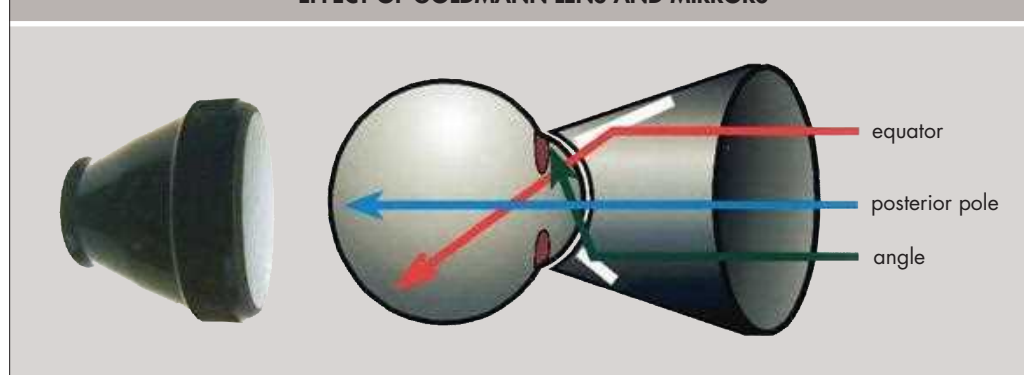
A real, inverted aerial image of the fundus is formed a few millimeters outside the large aspherical condensing lens, which is within the focal range of the slit-lamp microscope. Because the condensing lens is so close to the eye and has such a high power, the field of view is very wide, making these lenses specially suited for a wide-angle view of the posterior pole and midperipheral fundus.

## GOLDMANN APPLANATION TONOMETER

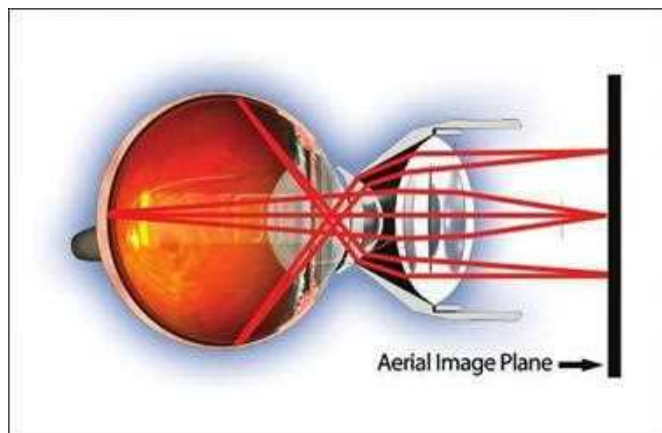
The applanation tonometer (Fig. 2.5.12) is used to measure intraocular pressure. It relies on an interesting physical principle. For an ideal, dry, thin-walled sphere, the pressure inside a sphere is proportional to the force applied to its surface. Unlike an ideal sphere, however, the human eye is not thin-walled and it is not dry, producing two confounding forces: (1) a force produced by the eye's scleral rigidity (because the eye is not thin-walled), directed away from the globe; and (2) a force produced by the surface tension of the tear film (because the eye is not dry), directed toward the globe (Fig. 2.5.13). Goldmann determined that when a flat surface is applied to the cornea with enough force to produce a circular area of flattening 3.06 mm in diameter, then the force caused by scleral rigidity exactly cancels out the force caused by surface tension. Therefore it is a very useful fact that the applanating force required to flatten a circular



## EFFECT OF GOLDMANN LENS AND MIRRORS



**Fig. 2.5.10** The contact lens of the Goldmann lens nullifies the refractive power of the patient's cornea, while the three mirrors then reflect light from the patient's peripheral retina (*orange ray*) and iridocorneal angle (*green ray*). The posterior pole of the fundus also can be visualized in a manner similar to that of the Goldmann posterior pole contact lens (*blue ray*).



**Fig. 2.5.11** The QuadrAspheric lens consists of a corneal contact lens and a high-powered, highly aspherical condensing lens. A real, inverted image of the fundus is formed, which is within the focal range of the slit-lamp microscope. (Courtesy Volk Optical.)

area of cornea exactly 3.06 mm in diameter is directly proportional to the intraocular pressure. Specifically, the force (measured in dynes) multiplied by 10 is equal to the intraocular pressure (measured in millimeters of mercury).

How does the observer know when the area of applanation is exactly 3.06 mm in diameter so that the intraocular pressure can be measured? The applanation tonometer is mounted on a biomicroscope to produce a magnified image. When the cornea is applanated, the tear film, which rims the circular area of applanated cornea, appears as a circle to the observer. The tear film often is stained with fluorescein dye and viewed under a cobalt-blue light to enhance the visibility of the tear film ring. Higher pressure from the tonometer head causes the circle to have a wider diameter because a larger area of cornea becomes applanated (*Fig. 2.5.14*). Split prisms, each mounted with their bases in opposite directions, are mounted in the applanation head, creating two images offset by exactly 3.06 mm. The clinician looks through the applanation head and adjusts the pressure until the half circles just overlap one another (*Fig. 2.5.15*). At this point, the circle is exactly 3.06 mm in diameter, and the reading on the

## GOLDMANN APPLANATION TONOMETER



**Fig. 2.5.12** Photograph of a Goldmann applanation tonometer in working position on a slit-lamp microscope.

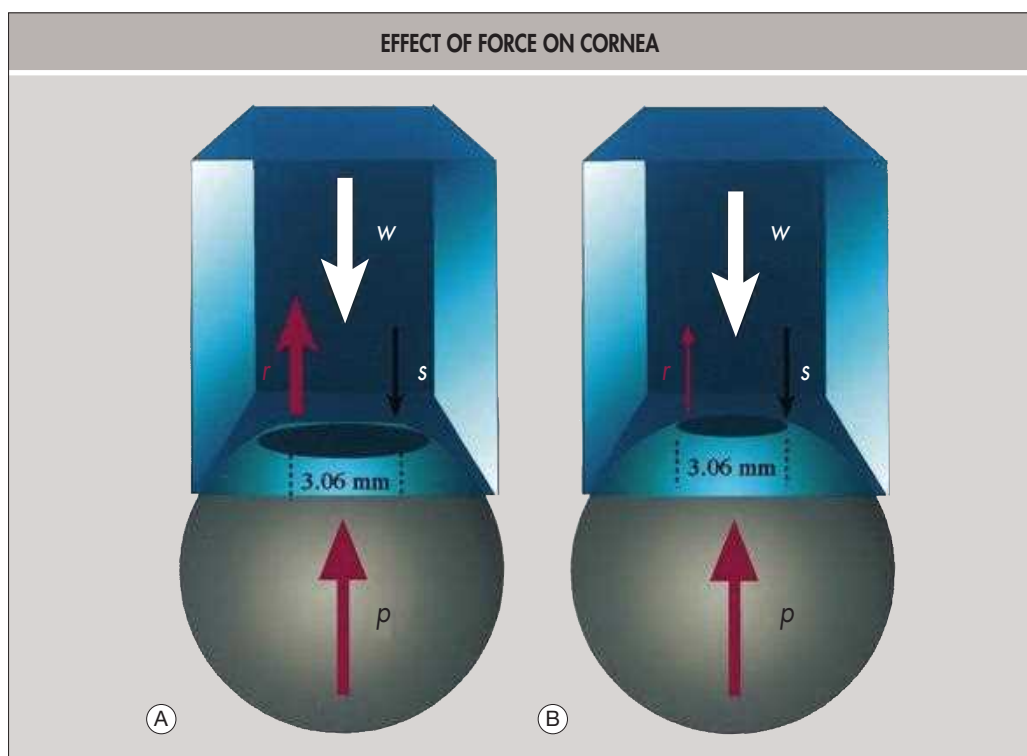
tonometer (multiplied by a factor of 10) represents the intraocular pressure in millimeters of mercury (*Fig. 2.5.16*).

## Specular Microscope

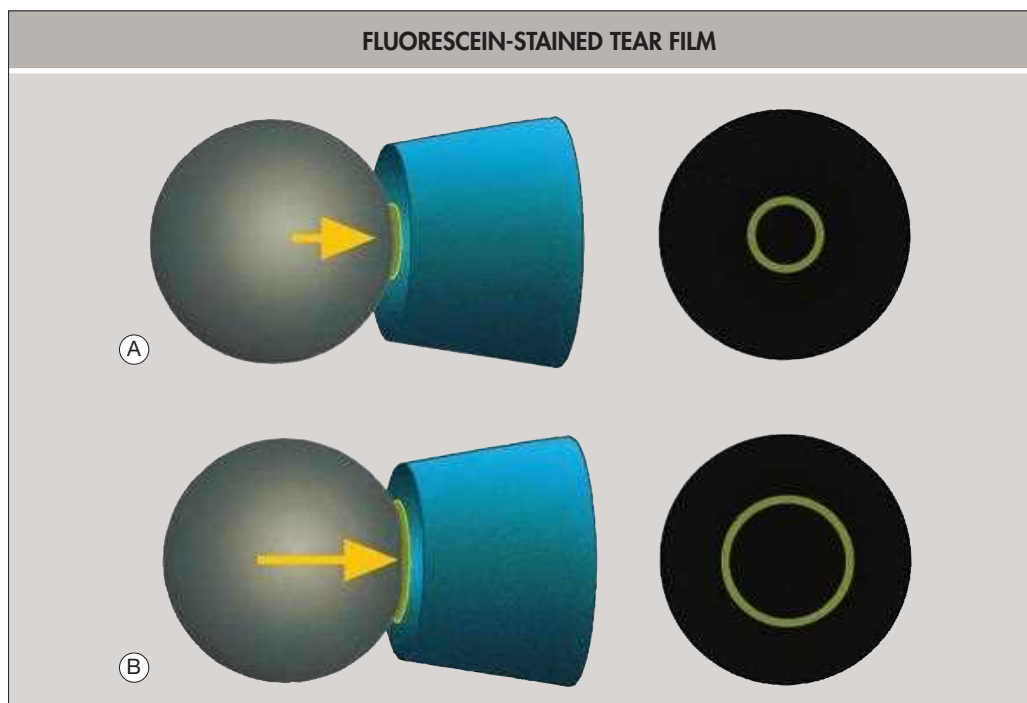
A number of significant obstacles stand in the way of easy microscopical observation of the living corneal endothelium. First, the reflection from the front corneal surface interferes with a sharp view of the endothelium. Second, the intervening stromal layers backscatter light, which decreases the contrast of the endothelial details. In addition, when the stroma becomes thick and edematous, the views of the endothelium become hazy. Finally, because of the small difference in index of refraction between the cornea (1.376) and the aqueous (1.336), only 0.02% of the incident light (for most angles of incidence) is reflected from the interface between corneal endothelium and aqueous.<sup>10</sup>

To eliminate the bothersome reflection from the front corneal surface, two approaches are used. An increase in the angle of incidence moves the anterior reflection to the side so it covers less of the specular reflection from the endothelium. This approach alone is used in the noncontact technique. If the cornea could be thickened artificially (without an increase in light scatter), this would move the surface reflection further to the side. With use of a contact lens that has a coupling fluid of index of refraction similar to that of the cornea, the surface reflection is eliminated and the corneal thickness may be assumed to include the contact lens thickness also. The reflection from the surface of the contact lens replaces that of the corneal surface. However, because of the thickness of the contact lens, the surface reflection is moved well over to the side (*Fig. 2.5.17*).

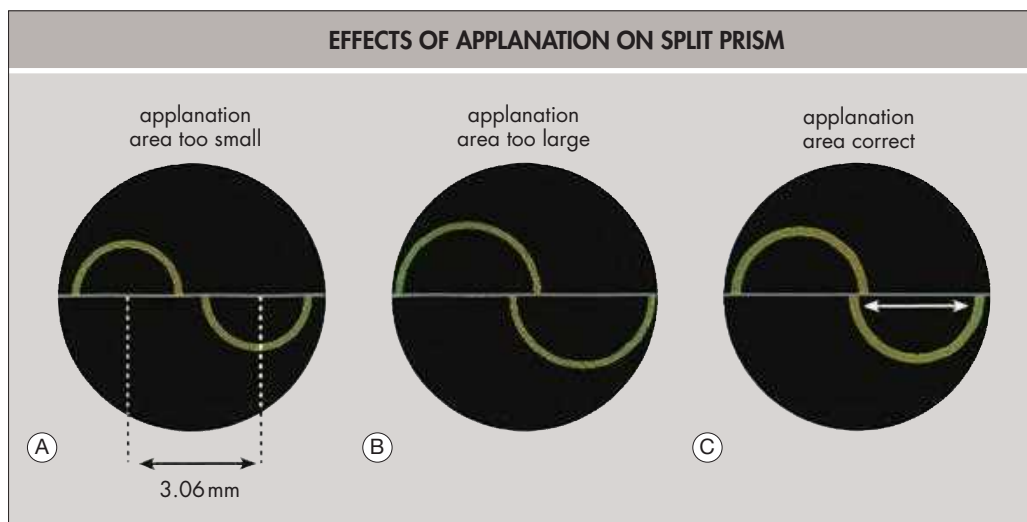
The magnification needed to yield important details about the shape and size of the endothelial cells lies between a magnification of  $\times 80$  and  $\times 250$ . Of course, a lower magnification photograph may allow an accurate count of the endothelium. In normal individuals the number of endothelial



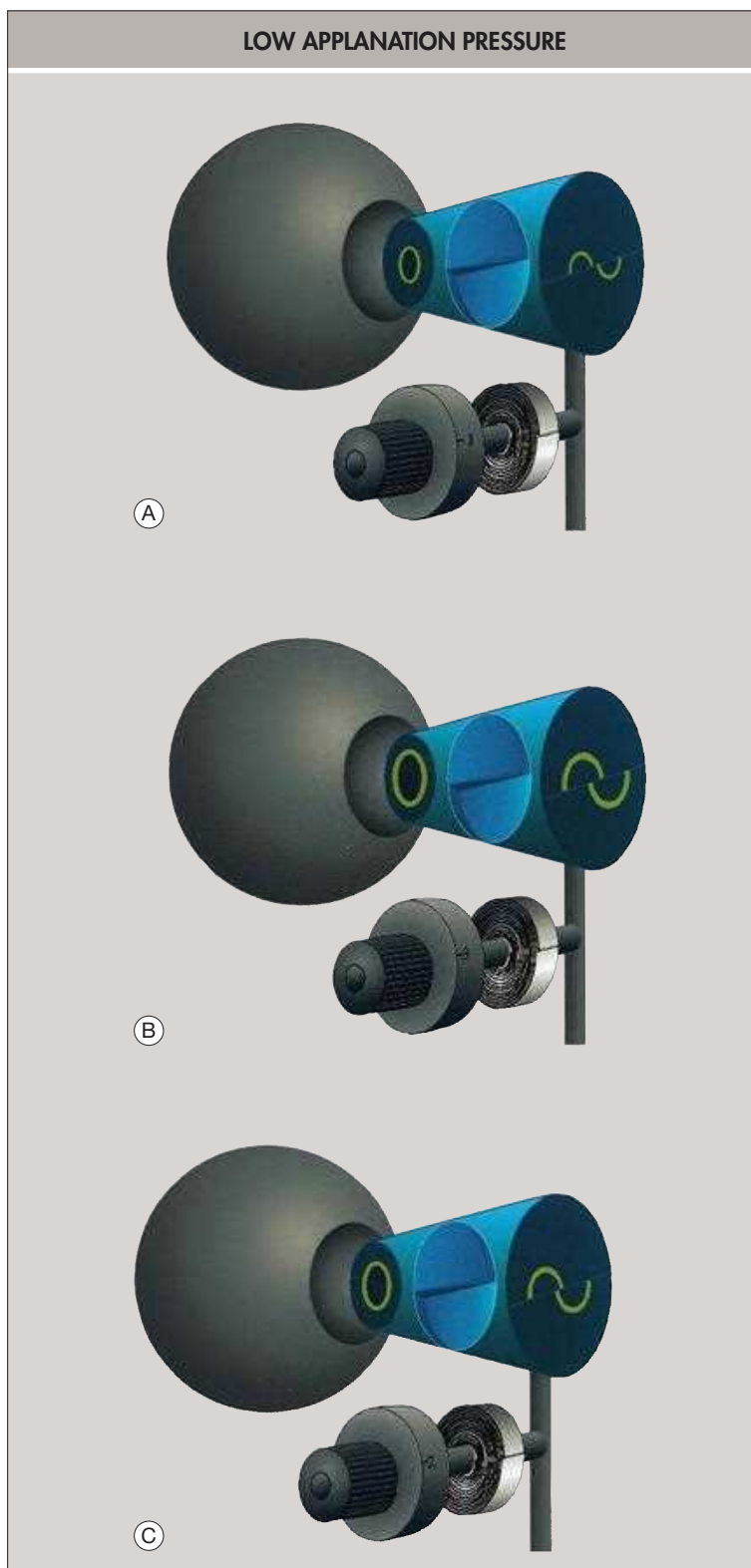
**Fig. 2.5.13 Effect of Force on Cornea.** (A) When a flat surface is applied to the cornea with enough force ( $w$ ) to produce a circular area of flattening greater than 3.06 mm in diameter, the force caused by scleral rigidity ( $r$ ) is greater than that caused by the tear film surface tension ( $s$ ). (B) When the force of the flat surface produces a circular area of flattening exactly 3.06 mm in diameter, the confounding forces caused by scleral rigidity and tear film surface tension cancel each other. The applied force ( $w$ ) then becomes directly proportional to the intraocular pressure ( $p$ ).



**Fig. 2.5.14 Fluorescein-Stained Tear Film.** When viewed through a transparent applanation head, the fluorescein-stained tear film appears as a circular ring (A). Greater applanation pressure causes the ring to increase in diameter (B).



**Fig. 2.5.15 Effects of Applanation on Split Prism.** The split prism in the applanation head creates two images offset by 3.06 mm, allowing greater ease in determining when the circular ring is exactly 3.06 mm in diameter. When the area of applanation is smaller than 3.06 mm, the arms of the semicircles do not reach each other (A). When the area of applanation is greater than 3.06 mm, the arms of the semicircles reach past each other (B). When the area of applanation is exactly 3.06 mm, the arms of the semicircles touch each other (C). This is the endpoint at which the intraocular pressure can be measured.

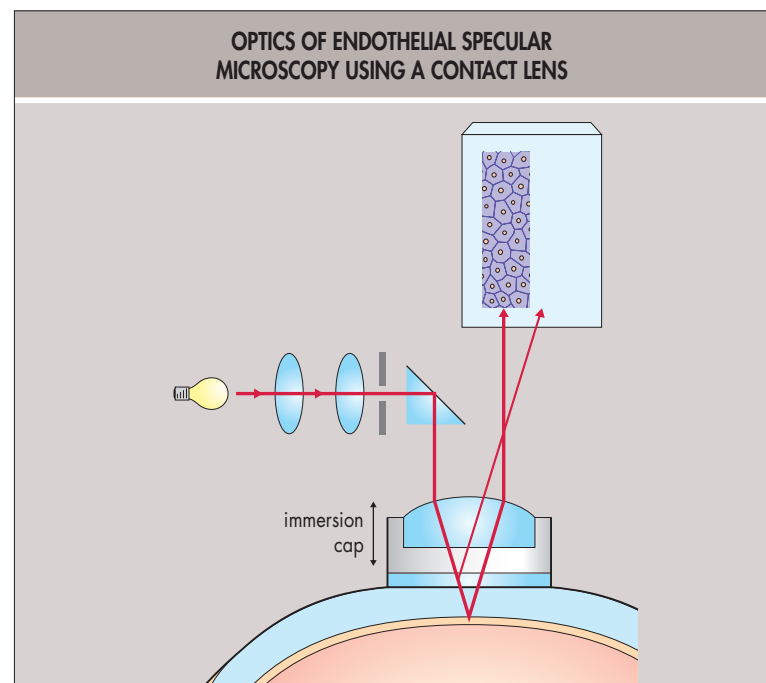


**Fig. 2.5.16 Low Applanation Pressure.** When the applanation pressure is too low (1.0 dyne in this illustration) the circular ring is smaller than 3.06 mm in diameter, and the arms of the ring do not reach each other in the split image (A). When the applanation pressure is too high (3.0 dynes in the illustration) the circular ring is larger than 3.06 mm in diameter, and the arms of the ring stretch past each other in the split image (B). When the applanation pressure creates a circular ring exactly 3.06 mm in diameter, the arms of the ring just reach each other in the split image (C). In this illustration, the endpoint is reached at 2.0 dynes of applanation pressure, which corresponds to an intraocular pressure of 20 mm Hg.

cells per square millimeter decreases with age, while the size of the cells increases with age.

## OPERATING MICROSCOPE

The operating microscope (Fig. 2.5.18) works on principles similar to those of the slit-lamp microscope. Both have the following optical components:



**Fig. 2.5.17 Optics of Endothelial Specular Microscopy Using a Contact Lens.** (Adapted from Bigar F. Specular microscopy of the corneal endothelium. In: Straub W, editor. Developments in ophthalmology, vol. 6. Basel, Switzerland: Karger; 1982. p. 1–88.)



**Fig. 2.5.18 External Photograph of an Operating Microscope.**

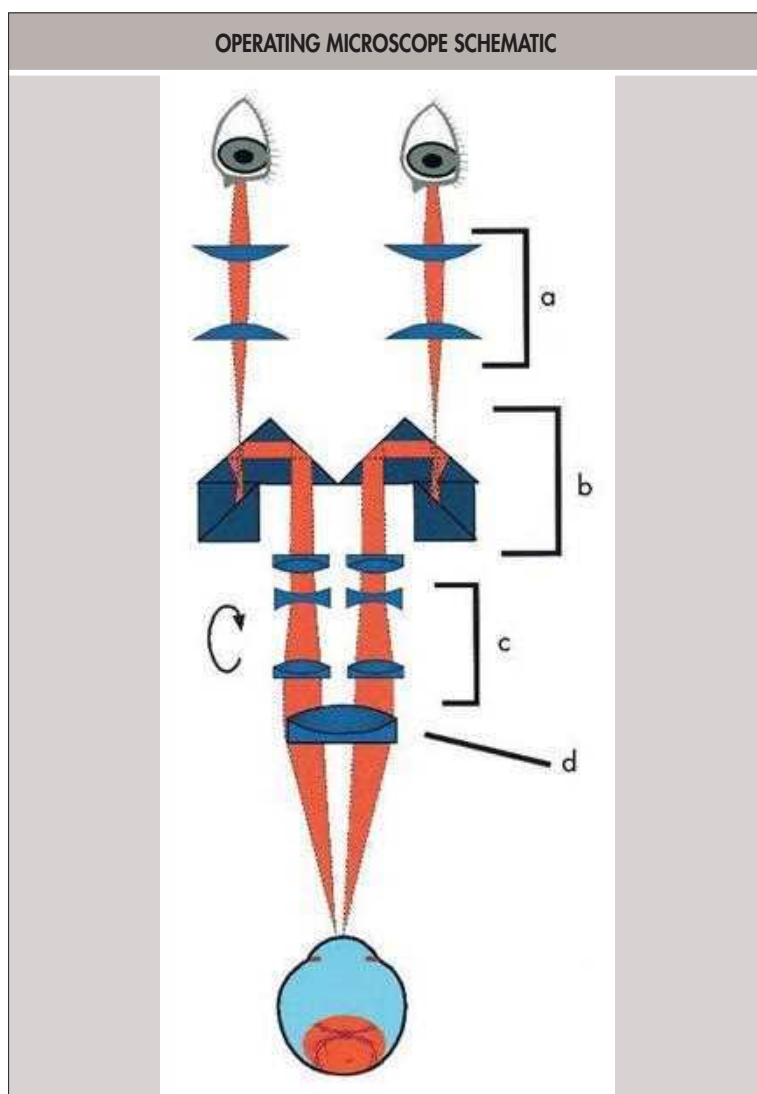
(1) astronomical telescope, (2) inverting prism, (3) Galilean telescope, (4) objective lens, (5) light source, and (6) binocular viewing system (Fig. 2.5.19). Unlike the slit-lamp microscope, the operating microscope's illumination source is not slit-shaped, and the working distance for the operating microscope (the distance from the objective lens to the patient's eye) is longer to accommodate the specific requirements of ocular surgery.

The working distance of this microscope is equal to the focal length of the objective lens. Commonly used objective focal lengths in ophthalmic surgery are 150 mm, 175 mm, and 200 mm. Use of the proper working distance can greatly lessen back and neck strain on the surgeon, especially during lengthy operations. A difference of 25 mm often can affect body comfort and the positioning of the surgeon's arms and hands.

The total magnification of the operating microscope is equal to the product of the magnifications of its various components. Because several different lenses are available for the objective and the eyepiece, magnification can be controlled. Smoothly variable magnification changers (zoom Galilean telescopes) are now incorporated into many operating microscopes. The  $\times 12.5$  eyepiece is the most popular choice for ophthalmic surgery, with magnification from  $\times 6$  to  $\times 40$ .

Various illumination systems are available, but the most important system for ophthalmic surgery is known as *coaxial illumination*. This





**Fig. 2.5.19 Schematic Diagram of an Operating Microscope.** The major components include: the eyepiece, an astronomical telescope system, which provides most of the magnification (a); an inverting prism, such as a Porro–Abbe prism, to correct for the inverted image produced by the eyepiece (b); a magnification changer, such as a Galilean telescope system, in which different lenses can be introduced in order to change the degree of magnification (c); and the objective lens, which adjusts the working distance (d). Two parallel optical systems, each a mirror image of the other, provide a stereoptic view of the patient's eye.

system is especially useful for visualization of the posterior capsule and for vitreous surgery. Fiberoptic delivery systems reduce heat near the microscope and facilitate the changing of bulbs during surgery.

## KERATOMETER AND CORNEAL TOPOGRAPHER

In the early 1600s Christopher Scheiner sat a person opposite a window. The subject's anterior corneal surface with its overlying tear film acted as a convex mirror and produced a small image of the window. Today we refer to that image as the first Purkinje image or simply the mire or mires. Scheiner compared the corneal mire to similar images produced by glass spheres of differing sizes and concluded the cornea had about the same shape as the sphere that produced the image most closely matching the mire.

The technique has been greatly refined. Today the mires are measured by an electronic camera, but the same basic principle introduced four centuries ago remains fundamentally unchanged. An object of known dimensions is placed in front of the cornea, which like any convex mirror produces a virtual erect image of the object. The dimensions of the mires are measured, and from this information an attempt is made to infer corneal shape and optical properties.

The basic problem, however, is that there is no definite relationship between the dimensions of the mires and the shape of the cornea.<sup>11</sup> Put another way, there are infinitely many corneas that can produce identical mires. Consequently, it is impossible to derive the shape of the cornea

from the shape of the mires. Implicit in all corneal measuring instruments based on Scheiner's method are two assumptions: (1) that the cornea is restricted to a specific geometrical class, and (2) that the instrument is aligned on the corneal axis. In many cases, at least one of the assumptions (and often both) is invalid.

Consider the simple case of a rotationally symmetrical cornea that can be described by two parameters: vertex curvature and eccentricity. Vertex curvature is directly proportional to power, and eccentricity describes how quickly the cornea flattens to influence aberrations. The two variables are independent, e.g., a 45.00 D hyperboloid can have many different eccentricities, and a hyperboloid of a given eccentricity can have many different powers. Thus to describe the shape and optical properties of a hyperboloid it is necessary to measure both eccentricity and power, but ophthalmometers such as the Bausch & Lomb keratometer or Javal–Schiotz measure neither.

Instead ophthalmometers assume the cornea is spherical. Under the spherical constraint the only remaining question is what is the radius of the sphere? The keratometer gives the radius of the sphere that produces the same mires as those produced by a hyperboloidal cornea. Two corneas with the same power but different eccentricities will produce different K-readings. Likewise, corneas of different power may produce the same K-readings.

It is important to realize that the keratometer was not intended to measure corneal shape or optical properties. The device was introduced shortly after World War II and was originally designed to assist in fitting rigid contact lenses that had spherical posterior surfaces, so the assumption of a spherical cornea was reasonable for the intended purpose. Originally, contact lens base curves had to be specified as a radius (in millimeters), so the keratometer was calibrated in millimeters. Some clinicians preferred to specify base curves in diopters, so later instruments were calibrated in diopters using the conversion formula:

$$\text{Diopters} = \frac{337.5}{\text{Radius (mm)}}$$

This conversion formula is not optically correct because it assumes the corneal refractive index is 1.3375, not the correct value of 1.376. The conversion underestimates the power of the anterior cornea and tear film. However, because the posterior corneal surface has negative power, this formula is a better estimate of overall corneal power. This was of no consequence at the time, because the only purpose of this formula was to allow laboratories to convert base curves specified in diopters into millimeters for purposes of fabrication. This formula had the advantage of making a radius of 7.5 mm exactly equal to 45 D. Today, ophthalmometers are available that give K-readings in millimeters, diopters, or both.

With the general acceptance of intraocular lenses (IOLs) in the mid-1970s, ophthalmometers gained a new clinical role for which they are not ideally suited—the estimate of corneal power to calculate implant power. Theoretical formulas incorporated K-readings as if they were actually accurate measurements of corneal power. It is fair to say that most of the clinical community did not fully appreciate the distinction between K-readings and corneal power. According to theory, if corneal power changes by 1.00 D, implant power should change by more than one diopter. It came as a complete surprise when the SRK equation—the first formula based on statistics rather than theory—suggested that a 1.00 D change in K-readings should change the implant power by only 0.9 D. This result proves that K-readings are not a measurement of corneal power.

Nevertheless, the SRK equation proved that corneal power and K-readings are correlated. The spherical aberration of a hyperboloidal cornea can be eliminated with the right eccentricity. Indeed, the eccentricity of most human corneas varies over a narrow range that is quite close to the optimal (spherical aberration free) value. Because corneal eccentricity normally varies over a limited range, K-readings correlate with—but are not measurements of—corneal power.

The success of the SRK formula should have alerted the clinical community to the limitations of the Scheiner approach, but it did not. With the advent of refractive surgery, ophthalmometers were again used to correlate changes in refractive error to K-readings. Again, it was soon found that K-readings did not correlate with changes in refractive error. The reason for the poor correlation is that keratorefractive surgical procedures change corneal eccentricity, destroying the statistical relationship that normally exists between power and eccentricity. The result is that K-readings no longer reflect corneal power in a predictable way.

Refractive surgeons quickly recognized the shortcomings of ophthalmometers but did not understand the underlying reason. Many believed



that the single circular mire interrogated only a small region of the cornea and additional rings would overcome the problem, but they do not. The fundamental problem, as stated before, is that no definite relationship exists between the mires and corneal shape, even when multiple rings are used.

Alignment is another critical factor affecting the “accuracy” of corneal topography systems. Most algorithms assume the instrument’s optical axis coincides with the corneal axis, but it does not. The early corneal topography instruments lacked any alignment method, which led to unreproducible results. Repeated measurements on the same patient were often wildly different, which obviously cast serious doubt on the reliability of these devices. Later instruments used the pupil, not the corneal vertex, for alignment. A consistent alignment procedure produced reproducible but not necessarily accurate measurements. Inappropriate alignment even in today’s instruments can produce artifacts that have been mistakenly attributed to early keratoconus.<sup>12</sup>

Despite their failings, most corneal measurement systems in clinical use are based on the Scheiner principle. Clinicians should use these systems with an appreciation for their limitations. Fundamentally, no relationship exists between the mires and corneal shape, because infinitely many different corneas can produce identical mires. However, the cornea is not infinitely variable, so correlations occur between the mires and the cornea that make it possible to use ophthalmometers and video keratometry to calculate IOL power and assist in other clinical evaluations. Clinicians should be aware, however, that the more irregular or misaligned the corneal and instrument axes, the more likely that the data are unreliable.

## LENSMETER

For most of the twentieth century, the lensmeter (also known as the lensometer or vertex meter) changed very little. However, in the 1970s a number of automatic lens analyzers appeared that eliminated almost all human involvement and quickened the determination of new prescriptions.

In this chapter, the basic principles of the traditional lensmeter are reviewed to outline its strengths and weaknesses and thus help to appreciate the usefulness of the automatic devices.

The lensmeter does not measure the focal length of the unknown lens. It measures the vertex power, which is the reciprocal of the distance between the back surface of the lens and its secondary focal point; this distance is known as the *back focal length*.

A simple lensmeter (Fig. 2.5.20) is an optical bench that consists of an illuminated, movable target, a powerful fixed-field lens, and a telescope eyepiece focused to infinity.<sup>13</sup> The key element is the field lens; without this, to measure the merest 0.25 D lens would require a lensometer of the optical bench type to be over 4 m long. The fixed-field lens is situated so that its focal point is on the back surface of the unknown lens being analyzed, which, in turn, sends parallel light to the observation telescope. Thus the small movement of the target is amplified optically and in such a way that the distance between the target and field lens always is directly

proportional to the power of the unknown lens (an example of Badal’s principle). Such an arrangement allows the instrument’s linear scale to be read in diopters.

To determine the power of each principal meridian of an unknown lens, the lens simply is inserted into the lensmeter, the principal meridian located, the target lines focused sharply, and the power recorded. The second target, set 90° from the first, is refocused and the new power recorded. Once the powers in the two principal meridians and the axes are known, the final prescription is calculated.

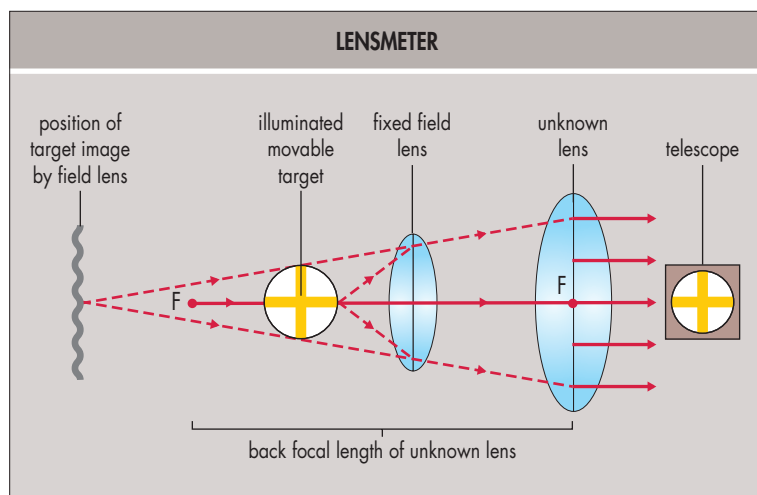
The automatic device rapidly measures the powers in all meridians, selects the meridians with the greatest difference in power between them, and designates these as the major meridians of the lens. The device is programmed to calculate the prescription and print out the result. The entire procedure takes less than 1 minute from spectacle insertion to printout.

The main advantage of the automated lensmeter is its elimination of human error. In today’s busy ophthalmic office, in which technicians and doctors juggle many mental tasks at the same time, a clear advantage exists to a device that does not need to be focused, have numbers written down, or require calculations to be made.

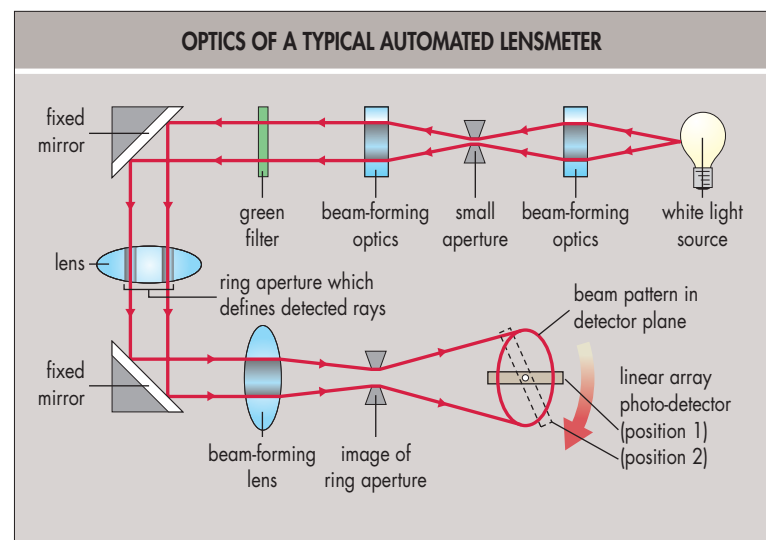
If an automated lensmeter does not focus a sharp image, how does it work? It simply measures the deflection of a fixed number of light rays produced by the unknown lens. To do this, the direction of the rays must be known before they enter the lens. The easiest way to accomplish this is to have them all enter parallel to one another. Fig. 2.5.21 shows a beam of collimated green light (which eliminates chromatic aberration) incident to the unknown lens. Thus a circle of light of a known dimension strikes the lens. The refracted light is passed through a ring aperture to tailor the size of the new beam to the size of the board of light detectors. By deflection of the parallel beam in its unique manner, the unknown lens produces a new pattern (i.e., a smaller or larger circle or an ellipse), which is detected and carefully measured by an array of photodiodes. These measurements yield deflection information that is fed into a small computer that calculates the lens parameters (powers, axis, adds, prisms), and a printer creates a record of the parameters. Because these devices measure ray deflections, if the lenses in the lensmeter are tipped at all, the deflection is altered and erroneous results are produced.

Another small error arises in the measurement of the add of a bifocal. All automated lensmeters are designed to measure the vergence of the light that exits a lens when parallel light enters it. However, light that enters the add when worn by a patient is typically divergent (i.e., originates at 16 inches [40 cm] or the reading distance from the spectacle plane). The error is significant only in high-powered lenses, such as for an aphakic correction. To minimize this error, the distance and near powers are measured using the back surface of the lens (in the position usually occupied by the front surface).

Accurate measurement of the progressive multifocal lens presents a problem with many lensmeters. The operator must first align the lens to measure the distance correction, bind then find and realign, and measure the area of the lens with the maximum add.



**Fig. 2.5.20 The Lensometer Resembles an Optical Bench.** The movable illuminated target sends light to the field lens, with the target in the endpoint position. Because the focal point of the field lens coincides with the position of the unknown lens, all final images are the same size (Badal principle).



**Fig. 2.5.21 Optics of a Typical Automated Lensmeter.** Parallel light strikes the unknown lens. The refracted light rays (which are confined to a pencil beam within an annulus) ultimately strike an array of electronic photoreceptors.

## AUTOMATED REFRACTOR

Any clinician who has asked enough patients “Is it better with lens 1 or lens 2?” must have dreamed of an automated refractor.<sup>14</sup> After all, the eye is a partial optical bench. The fundus can be a serviceable target if illuminated. The cornea and lens make a passable aspherical focusing system. To complete the optical bench, a positive lens needs to be placed before the eye to form a real aerial image of the fundus, as in indirect ophthalmoscopy. Except that distances are not standardized and calibration is not present, an indirect ophthalmoscope has most of the essential elements of an objective refractor.

Modern instruments have two sources of light. First, the target is illuminated with visible light for fixation and accommodation control and, second, a low-intensity infrared or near-infrared source sends light into the patient’s eye, which is “seen” by a sensor. The optometer must use “invisible” (or at least dim, unobtrusive) light for measurement to preclude an unwanted stimulus to accommodation and to allow comfortable fixation. These two (visible and infrared) systems usually are derived from a single incandescent lamp by the use of filters. For example, a cut-off filter of 800 nm allows only infrared light to enter the system.

The area of retina irradiated by infrared radiation produces a real image within the optometer. This image is analyzed by photoelectric means using an infrared-sensitive device. The use of infrared for focus evaluation presents a few problems. For example, an examiner cannot calibrate the focusing system “by eye” but must use an indirect method. In terms of accuracy, the eye’s chromatic aberration is a problem. Anyone familiar with the duochrome (red–green) test knows that the human eye focuses light of various wavelengths differently. Because the goal is to learn the eye’s refractive error in visible (yellow) light, a correction factor of about 1.00 D must be built into any infrared device.

It is valuable to consider some problems that had to be solved in the design of modern objective refractors: accommodation, subjective alignment, and focusing.

**Accommodation.** Accommodation associated with the use of a target that is optically distant but objectively near may induce errors in the measurement of refraction. Modern devices use a fogging lens through which the fixation target is viewed. The subject hopefully learns that accommodation tends to make the visible target even more blurred and thus relaxes accommodation. Occasional failure of accommodation to relax under a fog is presumed to occur because of an awareness that the target is not truly distant. This phenomenon has been termed *instrument myopia*.

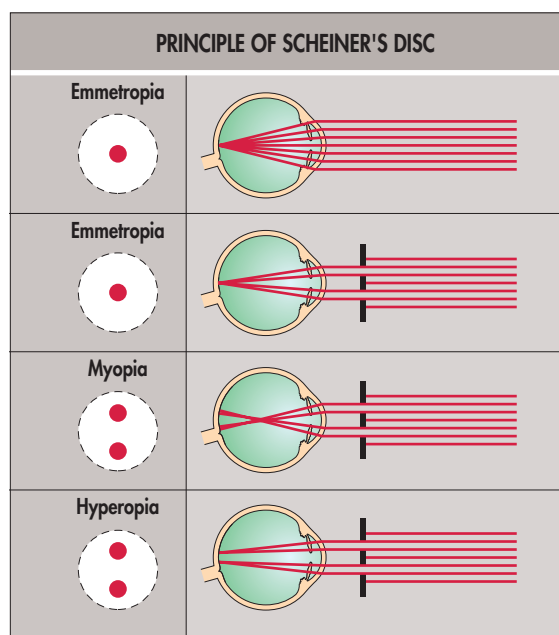
**Subjective alignment.** It is almost paradoxical to request a subject to simultaneously look at a fixation target and not attempt to clear it by accommodation. These divergent responses are required, however, if refraction is to be measured accurately for foveal vision. Accordingly, when the examiner aligns the optometer with respect to the subject’s pupil as the subject fixates the target, proper overall alignment must be ensured. At the same time, a fogging lens provides a disincentive to accommodate.

**Focusing.** Modern objective refractors are focused automatically, which eliminates the variability otherwise introduced by examiner accommodation. Automatic focusing for various meridians is accomplished swiftly, with the number and locations of meridians actually scanned depending on the method of image evaluation and on the approach to refractive error analysis used in the particular instrument. The computational power of the microprocessors found in today’s automated refractors allows refraction to be calculated within 10 seconds or less. This high speed tends to negate one of the major problems associated with older manual devices, such as momentary changes in fixation or accommodation or both that may take place during the course of measurement.

Most objective optometers use one of three methods for focus analysis: the retinoscopic principle, Scheiner’s disc principle, or the grating focus principle.

**Retinoscopic principle.** Bausch and Lomb’s Ophthalmometron was the first clinical automated refractor to utilize the retinoscopic principle.<sup>15</sup> No longer commercially available, this instrument used paired light sensors to register movement of the retinoscopic reflex. For example, if sensor 1 was stimulated before sensor 2, an analog of a retinoscopic “with” existed. Conditions that gave rise to a retinoscopic “against” caused sensor 2 to be stimulated first. In any event, a servomechanism found the focus in one meridian and attempted to maintain focus as each meridian was scanned in turn. The Ophthalmometron produced a graph that displayed the refraction in each meridian. Modern automated refractors are much more rapid and display refractive data directly in numeric form.

**Scheiner’s disc principle.** In the early seventeenth century, Fr. Christopher Scheiner observed that an in-focus candle is seen singly, whereas an out-



**Fig. 2.5.22**  
**Principle of Scheiner’s Disc.** Light enters the two pinholes and produces two images on the retina until the light is brought to a focus. (Adapted from Guyton DL. Automated clinical refraction. In: Duane T, editor. Clinical refraction, vol. 1. Baltimore, MD: Harper & Row; 1987. p. 1–43.)

of-focus candle is seen double when viewed through paired apertures separated by a distance slightly less than the diameter of the pupil. An automatic focusing device that uses Scheiner’s disc principle divides the rays that emerge from a subject’s eye into two bundles and then seeks the point at which these intersect. For example, a photoelectric sensing device might register an endpoint for a particular meridian under the condition that all the light falls on one sensing element rather than two. The 6600 Autorefractor<sup>16</sup> is an example of an instrument that operates on Scheiner’s principle (Fig. 2.5.22).

**Grating-focus principle.** In the grating-focus method, an image of a luminous target grating is formed on the retina. The sharpness of the aerial image of the illuminated “retina grating” is assessed continuously, usually by a scanning process. A high-speed servomechanism varies the focusing lenses until the actual grating image is as sharp as a standard in-focus image provided by the device.

## MAGNIFYING DEVICES

### Angular Magnification

In addition to transverse and axial magnification, angular magnification is another parameter used to characterize the performance of optical instruments. All focal optical systems (i.e., those with first order properties described by three pairs of points—focal, principal, and nodal) have an angular magnification of 1. Afocal systems such as telescopes that do not have focal, nodal, or principal points can have angular magnifications that differ from 1.

### Magnifying Glass

The simplest way to make an object appear larger is to move it closer to the eye, increasing the angular subtense of the retinal image (measured with respect to the eye’s posterior nodal point). The fundamental limitation to this approach is the eye’s near point, determined by accommodation. With placement of a single positive ancillary lens between the object and eye, the angular subtense can be increased beyond what can be achieved by accommodation alone. How much magnification is produced by a lens of a given power? The answer depends on where the object is placed relative to the ancillary lens.

The following analysis is based on paraxial optics, which is to say that all angles are small and aberrations are not involved. If the patient has  $A$  diopters of accommodation then in the unaided eye the object of height  $h$  at the near point subtends an angle of

$$\alpha = h(A).$$

If an auxiliary positive thin lens of power  $P$  (the magnifier) is placed in front of the eye such that the object is in the magnifier's front focal plane the angular subtense of the retinal image becomes

$$\alpha' = h(P).$$

The ratio  $(\alpha'/\alpha)$  compares the angular subtense of the retinal image when a magnifier is used divided by the image subtense without a magnifying lens and is the angular magnification.

$$Ma = \alpha'/\alpha = (P/A)$$

By convention, it is often assumed that the patient has 4 diopters of residual accommodation, so the formula becomes

$$Ma = (P/4)$$

The last equation is the standard formula often quoted in textbooks, but since accommodation varies from patient to patient, the last equation does not reflect the correct value in many cases. By preserving the patient's accommodation as a variable, the equation  $Ma = P/A$  more accurately reflects the magnification produced by a simple magnifier for a specific patient.

When the object is placed in the front focal plane of the auxiliary lens, however, the patient's accommodation is completely relaxed, which wastes some power that could be used for further magnification. The maximum amount of angular magnification is achieved when the ancillary lens produces a virtual image at the near point of accommodation. In which case the angular magnification becomes

$$Ma = 1 + P/A$$

or using the conventional value for  $A = 4.00$  D

$$Ma = 1 + P/4$$

which is another formula often cited in textbooks. Again, a more versatile equation is obtained by preserving the patient's accommodation as a variable. In any case, the lower the patient's accommodation, the greater the benefit of the simple magnifier.

## Galilean Telescope

To calculate the magnification of a telescope, the angle of incident parallel light is compared with the angle of the parallel rays of emergent light. From Fig. 2.5.23, the entrance angle is given by  $y_1/f_o$  (where  $f_o$  is the focal length of the objective lens), the emergent angle is given by  $y_1/f_e$  (where  $f_e$  is the focal length of the eyepiece lens), and the magnification is given by Eq. 2.5.1.

$$\frac{y_1/-f_e}{y_1/f_o} = \frac{-f_e}{f_o} \quad \text{Equation 2.5.1}$$

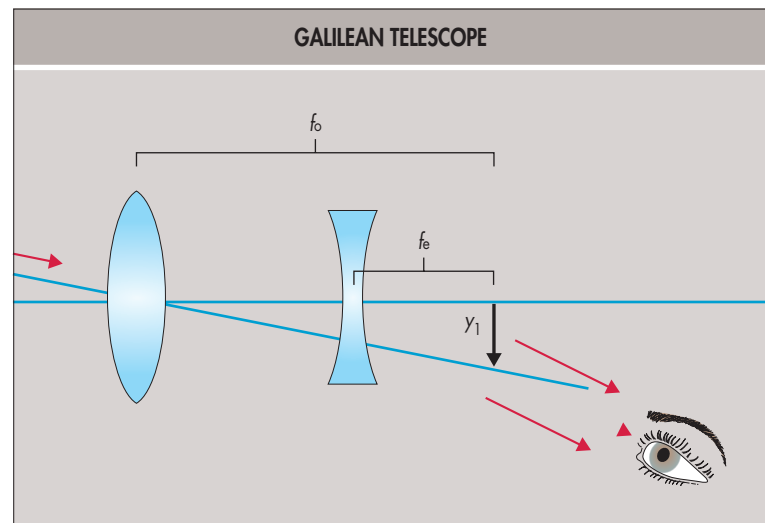
For example, if a Galilean telescope has an angular magnification of  $\times 3$  and the eyepiece is  $-12$  D, the power of the objective is given by Eq. 2.5.2.

$$3 = \frac{12}{f_o} \quad \text{Equation 2.5.2}$$

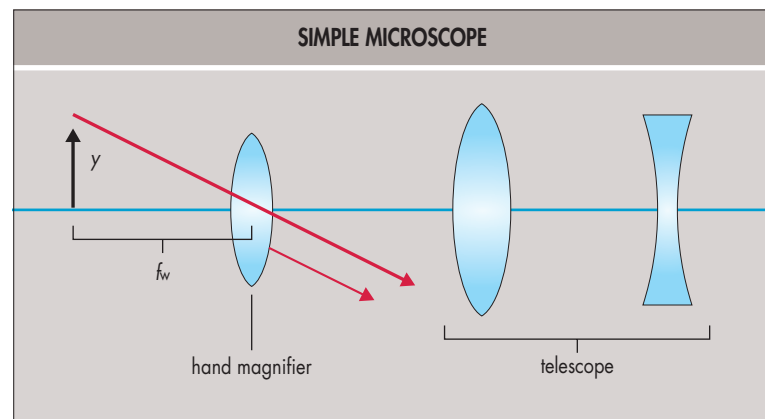
$$f_o = 4 \text{ D}$$

As another example, for a telescope of magnification  $\times 3$  and tube length ( $L$ ), the distance between objective and eyepiece, of 22 cm,  $f_o$ , and  $f_e$  are given by Eq. 2.5.3.

$$\begin{aligned} -3 &= \frac{f_o}{-f_e} \\ -3f_e &= f_o \\ L &= f_o - f_e \\ 22 &= -3f_e - (-f_e) \\ 22 &= -2f_e \\ -f_e &= -11 \text{ cm} \\ f_o &= 3.3 \text{ cm} \end{aligned} \quad \text{Equation 2.5.3}$$



**Fig. 2.5.23 A Galilean Telescope.** Note the objective lens takes parallel light and places a real image at the focal point of the negative eyepiece. The eyepiece takes the incident convergent light and renders rays parallel.



**Fig. 2.5.24 A Simple Microscope.** A positive lens (working distance lens) is placed in front of a Galilean telescope. This lens takes light from an object located at its focal point and renders the rays parallel for the Galilean telescope part of the device.

## Simple Microscope (Operating Loupe)

The principles of this device are similar to those of a Galilean telescope, even though it works only if it receives parallel light and a microscope is used to look at close objects.

However, if a magnifying lens ( $f_w$ ) is added, the focal length of which is the working distance, then the magnifying lens introduces parallel light to the telescope, as shown in Fig. 2.5.24, and the total magnification is given by Eq. 2.5.4.

$$\frac{f_w}{4} \times \frac{f_e}{f_o} \quad \text{Equation 2.5.4}$$

For example, for a loupe with a  $\times 3$  telescope and a  $+8$ D working lens (reading cap) the magnification =  $(8/4) \cdot 3 = \times 6$ .

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# Wavefront Optics and Aberrations of the Eye

Edmond H. Thall

# 2.6

**Definition:** An aberration is any deviation of the path of a ray of light from geometrically ideal behavior.

## Key Features

- Aberration theory is strictly confined to geometrical optics and ignores any aspects of physical optics such as diffraction and interference.
- Originally, wave aberrations were applied only to symmetrical optical systems, and each aberration was represented by a unique polynomial.
- Today other expansions, particularly the Zernike polynomials, are most commonly used, and usually each polynomial is a combination of pure aberrations.
- In any case, after defocus and regular astigmatism, the most important aberrations are coma and spherical aberration.

## INTRODUCTION

From a clinical perspective, aberration theory is simply an extended treatment of refractive error. Only hyperopia, myopia, and regular astigmatism are correctable by spectacles,<sup>1</sup> so in the past these were the only aberrations of clinical interest. The existence of other refractive errors was certainly recognized,<sup>2</sup> but because they were not correctable, clinicians had no need to study them in depth. Instead, the many aberrations not correctable by spectacles were relegated to a single broad category—irregular astigmatism. It is probably fair to say that even today many clinicians believe irregular astigmatism exists only in pathological cases and is not present in normal eyes.

For centuries, designers of optical instruments (e.g., telescopes, microscopes) had methods of correcting aberrations that could not be implemented clinically. Consequently, engineers have carefully characterized the individual aberrations that clinicians refer to collectively as irregular astigmatism.<sup>3</sup> With the advent of keratorefractive surgery came the intriguing possibility of correcting at least some refractive errors not correctable by spectacles. Keratorefractive surgery also brought the disconcerting complication of increased irregular astigmatism in some cases.<sup>4</sup> For the first time it was necessary for clinicians to explore irregular astigmatism more thoroughly. Fortunately, rather than reinvent the wheel, ophthalmologists can turn to the already well-developed aberration theory used by lens designers.

## RAY ABERRATIONS

Aberrations can be described by two different but closely related methods: ray and wave aberrations. When a ray is precisely traced through an optical system using the laws of geometrical optics (e.g., Snell's law) it is found that usually the ray does not exactly intersect the ideal image point. The displacement of the actual ray from the image point is the ray aberration. When a pencil of rays (by definition all originating from a single object point) are traced, the result is a spot diagram (Fig. 2.6.1).

For a specific and familiar example, consider the spot diagram for the axial object point at infinity of a theoretical eye with a 4 mm pupil and  $-1.00$  D of myopia and no other aberrations. A spot diagram can be calculated anywhere within an optical system, and typically several are calculated in the vicinity of the theoretical image plane. The set of through-focus spot

diagrams show that a stigmatic focus occurs about one-third of a millimeter anterior to the retina. The size of the spot diagram increases as the pupil enlarges, but the location of the stigmatic focus (and, therefore, the power of the corrective spectacle lens) does not change with pupil size, so the aberration is said to be pupil independent. Likewise, regular astigmatism is also pupil independent, which is why it is unnecessary to check pupil size to prescribe spectacles. The aberration known to lens designers as defocus encompasses both myopia and hyperopia.

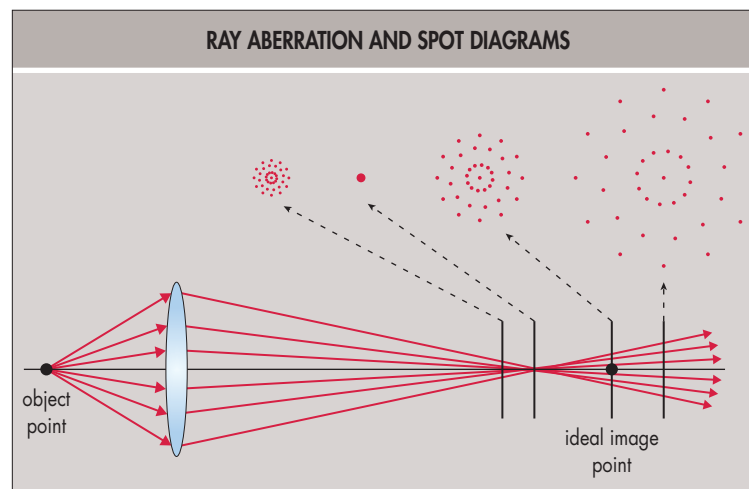
In 1857 Ludwig von Seidel described five basic monochromatic ray aberrations of rotationally symmetrical optical systems.<sup>5</sup> When studied individually, each aberration can be easily identified by its characteristic spot diagram. However, virtually all optical systems have many different aberrations. The spot diagrams of actual optical systems are a complex combination of several aberrations. It is difficult to identify and quantify the many individual aberrations from spot diagrams of actual optical systems.

In the early 1950s HH Hopkins developed a different, wavefront-based approach that simplified the definition, identification, and quantification of aberrations.<sup>6</sup> The two approaches, ray and wavefront, are not mutually exclusive but rather complementary.

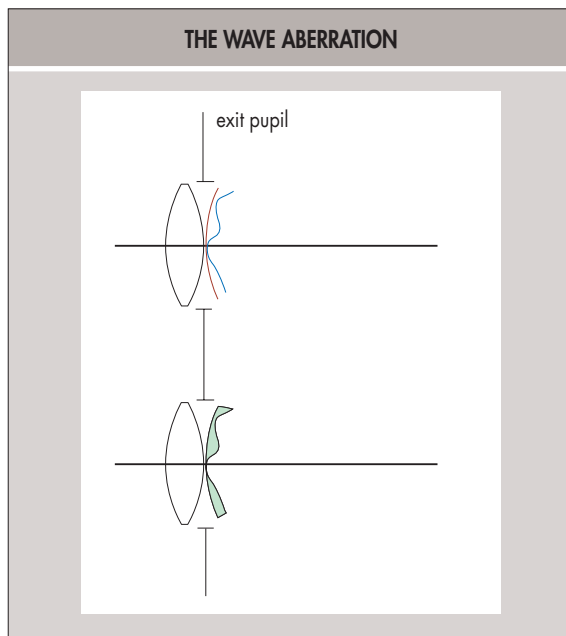
## THE WAVEFRONT APPROACH TO ABERRATIONS

Aberration theory falls within the discipline of geometrical optics,<sup>7</sup> so diffraction and other wave phenomena are completely ignored. In aberration theory, light propagation obeys the basic laws of reflection, refraction, and rectilinear propagation. All three laws are encompassed by Fermat's principle, which states that between any two points light travels the fastest path.

Ideally, a pencil of rays filling the entrance pupil of an optical system emerges from the exit pupil as a pencil converging to a perfect image point,<sup>8</sup> i.e., a stigmatic focus. The reference sphere is an imaginary spherical surface centered on the ideal (paraxial) image point and intersecting



**Fig. 2.6.1 Ray Aberration and Spot Diagrams.** In principle, the image ray should intersect the ideal image point but usually does not. The separation between any ray and the ideal image point is the ray aberration (for that particular ray). A spot diagram shows the intersection of multiple rays (from a single object point) in any plane perpendicular to the axis. Through-focus spot diagrams are a set of spot diagrams in the vicinity of the ideal image point showing the position of the best focus. In this case (but not usually), the best focus is stigmatic but in front of the ideal image point.



**Fig. 2.6.2 Definition of Wave Aberration.** The reference sphere is centered on the desired image point and intersects the center of the exit pupil (shown top, in red). An ideal optical system would produce an actual wavefront that coincides with the reference sphere. A real optical system produces a wavefront that does not coincide with the reference sphere (shown top, in blue). The difference between the actual wavefront and the reference sphere is the wave aberration (shown bottom, in green).

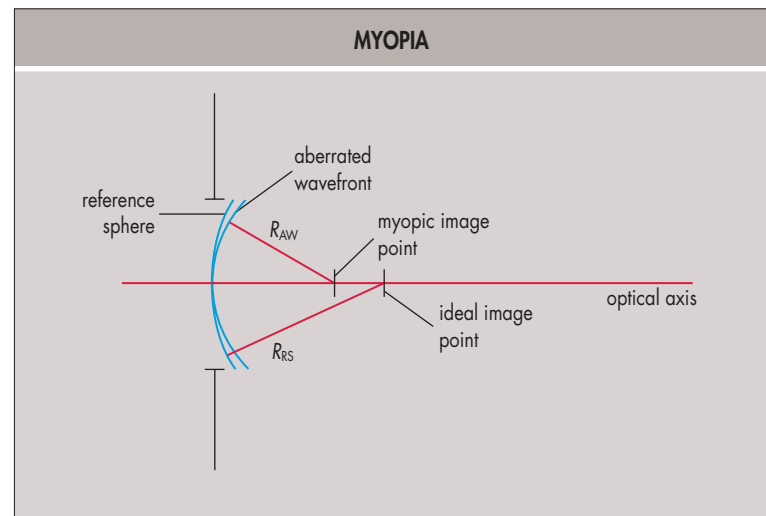
the center of the exit pupil.<sup>9</sup> According to Fermat's principle, to achieve a stigmatic focus, all light radiating from the object point at a particular instant must arrive simultaneously at the image point, or equivalently, must cross the reference sphere simultaneously.

In most cases, image rays do not emerge from the exit pupil as a pencil converging to a single point but rather converge to a small irregularly shaped region.<sup>10</sup> In other words, the focus is not stigmatic. It always is possible to draw a surface through the center of the exit pupil that all rays cross simultaneously, and when the focus is not stigmatic, that surface—called the actual wavefront—is not spherical. The difference between the reference sphere and actual wavefront is the wave aberration (Fig. 2.6.2).<sup>11</sup> The wavefront and reference sphere are both surfaces, and the difference between these two surfaces, the wave aberration, is likewise a surface. To give an analogy, consider the Earth's surface as the actual wavefront and sea level as the reference sphere. Height above (or below) sea level is analogous to the wave aberration.

The word wavefront is perhaps an unfortunate choice, suggesting that it is somehow related to the wave nature of light. However, as noted, aberration theory is based on geometrical optics that by definition ignores the wave properties of light. A pencil of object rays entering the optical system upon emerging from the exit pupil always “reaches” the wavefront simultaneously, so the wavefront is a surface of equal time. Arguably, the term isochrone (equal time) is more descriptive, but wavefront is too entrenched to change.

It is a common misconception that there is only one set of aberrations for each optical system. In fact, there is a different set of aberrations for every object point. This discussion began with a single pencil of object rays by definition from a single object point. Each object point produces its own pencil, and each object pencil has its own unique set of aberrations, although nearby object points have very similar aberrations.

Stigmatic focus means image rays converge to a *perfect* point either at the ideal image point or elsewhere.<sup>12</sup> Because of diffraction, the focus can never be stigmatic, but geometrical optics ignores diffraction. Using only refraction, reflection, and rectilinear propagation, focus can, in theory, be stigmatic. Some use the term “astigmatism” to refer to any focus that is not stigmatic, but the word astigmatism also has several other more specific meanings. To avoid confusion in this chapter, “nonstigmatic” refers to any focus that is not stigmatic. The term astigmatism is reserved for regular astigmatism or astigmatism of oblique incidence. When the focus is nonstigmatic, rays do not converge to a perfect point even at the best possible focus. As in defocus, aberrations can still exist even when the image is stigmatic. If rays converge to a perfect point but the image point is not at the position predicted by the vergence equation, then an aberration is present.



**Fig. 2.6.3 Myopia.** In myopia, the aberrated wavefront is spherical but has a shorter radius ( $R_{AW}$ ) than the reference sphere ( $R_{RS}$ ).

Returning to the example of a theoretical eye with  $-1.00$  D of myopia, the reference sphere is centered on the ideal image point. As shown earlier, in myopia, the image is stigmatic but anterior to the ideal image point. The wavefront emerging from the exit pupil therefore also is spherical but centered on a point anterior (i.e., to the left) of the ideal image point. The difference between the actual wavefront and reference sphere is the wave aberration surface (Fig. 2.6.3). It is worth noting that the maximum separation between the reference sphere and the wavefront is a mere  $1.5 \mu\text{m}$ , which is at the edge of the pupil. For midperipheral and central rays the wave aberration is less.

When wave aberrations are displayed on a graph, the optical axis is rotated  $90^\circ$  from horizontal to vertical. The wave aberration produced by myopia has a bowl shape.<sup>13</sup> All myopias, whether large or small, have the same characteristic bowl shape. The amount of myopia changes the bowl's depth and steepness of its edges but does not change its basic bowl shape. The wave aberration for hyperopia also is bowl shaped but the bowl is inverted (i.e., spills water). As both refractive errors have the same fundamental shape, lens designers classify them as the single aberration, defocus just as clinicians use “sphere” to specify either myopic or hyperopic correction when writing prescriptions. However, positive defocus is myopia and negative defocus is hyperopia, which may be counterintuitive to clinicians. The difference arises because lens designers classify defocus by the shape of the wave aberration, whereas clinicians think in terms of the power of the correcting lens.

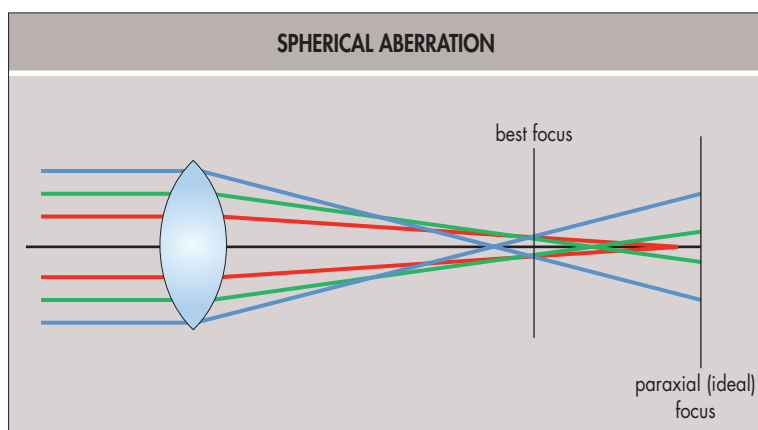
## SPHERICAL ABERRATION

In spherical aberration (SA), rays near the center of the lens focus at or close to the ideal image point, whereas more peripheral rays focus in a different location. In positive SA, peripheral rays focus in front of the ideal image point, and the more peripheral the ray the more anterior its focus (Fig. 2.6.4). In negative SA, peripheral rays focus behind the ideal image point and, again, the more peripheral the rays, the more posterior their focus. The wave aberration representing SA also has a bowl shape.<sup>14</sup> In fact, SA looks more like a bowl than does defocus. Compared with defocus, the wave aberration of SA has a flatter broader center and the edges become much steeper than the bowl representing defocus.

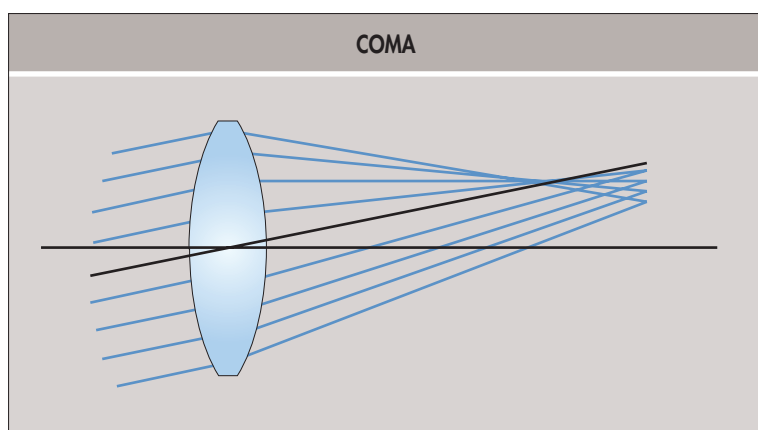
When SA is present, the location of the best focus is no longer at the ideal image point predicted by the vergence equation ( $U + P = V$ ). Positive SA shifts the best focus toward myopia, whereas negative SA shifts the focus toward hyperopia. However, even at the best position the focus is not stigmatic.

SA is strongly pupil dependent, because the position of best focus changes with pupil size. In positive SA, myopia increases as the pupil enlarges, which explains the uncommon clinical condition known as night myopia. In patients with a large amount of positive SA the increase in myopia under low light conditions is typically about  $-0.50$  D and produces symptoms of blurred vision and halos. The condition can be treated by a second pair of spectacles or clip-ons with an extra  $-0.50$  D over the daytime correction for night use.

SA can be reduced by aspherical refracting surfaces that flatten peripherally, which is typical of most corneas. Indeed, the cornea can flatten so



**Fig. 2.6.4 Positive Spherical Aberration.** Central rays (red) focus at the paraxial (ideal) image point but peripheral rays focus anteriorly. The more peripheral the ray, the more anterior its focus. In negative spherical aberration peripheral rays focus posterior to the ideal image point. Notice that spherical aberration shifts the position of the best focus.



**Fig. 2.6.5 Coma.** When rays are incident on a lens at an angle the focus flares out in a pattern suggestive of a comet's tail.

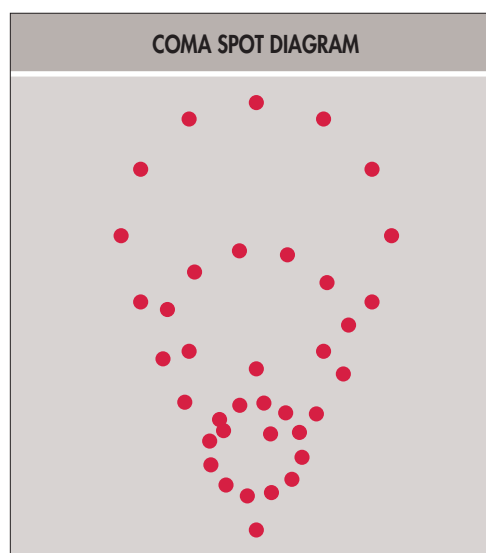
much that it overcompensates, producing negative SA. Theoretically, large amounts of negative SA would cause a hyperopic shift in low light conditions, but this is rarely if ever seen clinically. The Stiles–Crawford effect<sup>15</sup> (see later) also reduces the effect of SA on vision. The fact that refractive error usually does not fluctuate with pupil size in most eyes suggests that SA is adequately compensated over the typical range of pupil sizes.

It has been claimed that the crystalline lens compensates for corneal SA, and when the crystalline lens is removed, it should be replaced by an SA-compensating implant. However, studies that have measured SA in the cornea and crystalline lens separately have not found any tendency for the crystalline lens to compensate for corneal SA.<sup>16</sup> Also, corneal SA varies from person to person,<sup>17</sup> so an implant that corrects a fixed amount of SA is unlikely to benefit all patients. The patient's corneal SA should be measured preoperatively to properly compensate corneal SA with an implant, and an implant should be selected not only by its power but also by the amount of SA corrected, which is not current clinical practice.<sup>18</sup> Raytracing data on model eyes show that the amount of SA corrected by an implant varies substantially if the anterior chamber depth changes by tenths of millimeters or if the implant is tilted or decentered.<sup>19</sup> Refractive error rarely fluctuates with pupil size,<sup>1</sup> suggesting SA is not a problem in patients with conventional implants. SA increases depth of focus, so reducing it is not always desirable.

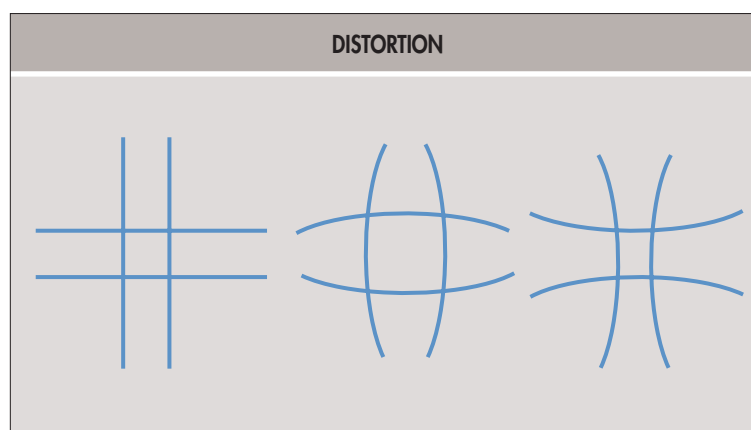
## COMA

Coma causes a pencil of rays to “flare out” from the image point in a fashion reminiscent of a comet's tail (Figs. 2.6.5 and 2.6.6). The shape of the wave aberration resembles a lounge chair.

Coma is increased when multiple optical elements do not share the same optical axis. Howland showed that after best spectacle correction, coma accounts for most of the residual aberration in otherwise normal eyes,<sup>20</sup> which is not surprising because none of the ocular media share a common axis.



**Fig. 2.6.6 Coma Spot Diagram.** Coma causes light from a single object point to flare out in the image giving the appearance of a comet's tail.



**Fig. 2.6.7 Distortion.** The original object consists of straight lines (left). Barrel distortion (middle) causes the lines to curve outward. Pincushion distortion (right) causes the lines to curve inward.

Clinically, coma rarely produces recognizable symptoms. However, coma can be symptomatic if there is a large amount present, which can occur (along with other higher-order aberrations) in off-axis keratorefractive surgery, dislocated or tilted crystalline lens or implant, or when the corneal vertex of a full-thickness graft is displaced by an unusual amount.<sup>21</sup>

## DISTORTION

Ideally, the image is geometrically similar to the object, which is to say that the image is a scale model of the object with all image distances proportional to corresponding object distances. Distortion is absent when the transverse magnification is constant over the entire image plane.

In pincushion distortion the transverse magnification increases as distance from the optical axis increases (Fig. 2.6.7). In barrel distortion magnification decreases as distance from the axis increases. Distortion is similar to defocus in that rays still focus stigmatically but in the wrong place. In defocus, rays focus stigmatically but in front or behind the ideal image point. In distortion, rays also focus stigmatically and in the same plane as the ideal image but too far (or too close) to the optical axis.

Pincushion distortion occurs in practically all spectacle-corrected, aphakic patients<sup>22</sup> and is occasionally seen in high myopes after clear lens extraction. Originally, one of the major reasons for the use of intraocular lens implants was to overcome the distortion suffered by spectacle-corrected aphakes. Once common, distortion is now rare since the introduction of intraocular lenses, although there has been a minor resurgence in patients undergoing clear lens extraction.

## FIELD CURVATURE (FC)

Ideally a flat object perpendicular to the optical axis is imaged as a flat object perpendicular to the axis. When field curvature is present, the object is imaged onto a curved surface (as in an IMAX theater). Field curvature

does not become significant until the image is outside the fovea, where retinal acuity is too low to detect the blurring produced by this aberration.

## OBLIQUE ASTIGMATISM (OA)

Oblique astigmatism is not to be confused with regular astigmatism. Seidel only considered rotationally symmetrical optical systems, which excludes regular astigmatism. Like field curvature, oblique astigmatism does not become significant until the image is outside the fovea where retinal acuity is too low to detect the blurring produced by this aberration.

## HIGHER-ORDER ABERRATIONS (HOA)

When the importance of aberration theory began to be appreciated, it was initially thought that understanding in detail the unique characteristics of many individual aberrations would be helpful. Theoretically, an infinite number of aberrations exist, so how many aberrations do clinicians really need to understand thoroughly?

Lens designers have found empirically that 36 aberrations adequately describe the imaging properties of even very complex optical systems. The number of aberrations required for clinical purposes is uncertain but is probably much less. However, lacking clear evidence to the contrary, many authors have adopted the use 36 polynomials based on engineering, not clinical experience.

The order of an aberration is defined rigorously later, but basically an order is a family of aberrations. The clinical triad of myopia, hyperopia, and regular astigmatism all belong to the family of second order wave aberrations. The five Seidel aberrations (coma, SA, FC, distortion, OA) are all fourth order aberrations. As the order increases so does the number of aberrations belonging to the order.

It now appears that besides a general familiarity with aberration theory, a thorough understanding of just a few specific aberrations is sufficient. In addition to defocus and regular astigmatism, the Seidel aberrations of SA and coma and perhaps a few others in specific cases are all that need to be understood in depth.

The situation has returned somewhat, but not completely, to the idea of lumping many aberrations into a single category. Whereas irregular astigmatism refers to any aberration higher than second order, “higher-order aberrations” generally refers to sixth order and above and thus excludes the Seidel aberrations.

In any case, it is clear that typically coma and SA account for most of the eye’s irregular astigmatism, with only small amounts of other aberrations contributing to the total irregular astigmatism. Higher-order aberrations may be increased in pathological cases or after some refractive procedures, particularly keratorefractive surgery.

## CHROMATIC ABERRATION

Wave aberration theory usually adopts the simplifying assumption that the light traversing the optical system is monochromatic. However, chromatic aberration has a significant effect on the image.

Longitudinal chromatic aberration (LCA) is the difference in image location between short and long wavelength light measured along the optical axis (Fig. 2.6.8). LCA is the basis for the duochrome test. The green half of the chart focuses anterior to the red half, and the power of the correcting sphere is adjusted until both sides appear equally sharp. In most cases there is about 0.50 D of separation between the two images.

Transverse chromatic aberration (TCA) is the difference in image location between short and long wavelength light measured in the image plane

(Fig. 2.6.9). Although the chromatic aberration of the eye is significant, color effects are rarely noticeable because of visual processing. Occasionally patients notice colored fringes around the edges of objects or letters when reading; these are usually produced by spectacle lenses made from highly dispersive materials. The problem generally is transient, but if not, can be overcome by using lenses fabricated from less dispersive (i.e., higher Abbe number) materials.

## MEASUREMENT OF OCULAR ABERRATIONS

In 1896 Tscherning was the first to observe irregular astigmatism (in his own eyes).<sup>23</sup> A small, distant source is viewed through a grid of pinhole apertures placed in front of an eye that is or has been rendered myopic (perhaps by fogging with, for example, +5.00 D lens). The grid divides the light into parallel pencils that focus in front of the retina then diverge, forming a pattern on the retina that is essentially the physical embodiment of a spot diagram. The grid will not be regularly spaced if aberrations (other than defocus) are present. If one draws the appearance of the grid, ocular aberrations can be estimated. Readers can easily reproduce this experiment for themselves just as Tscherning did.

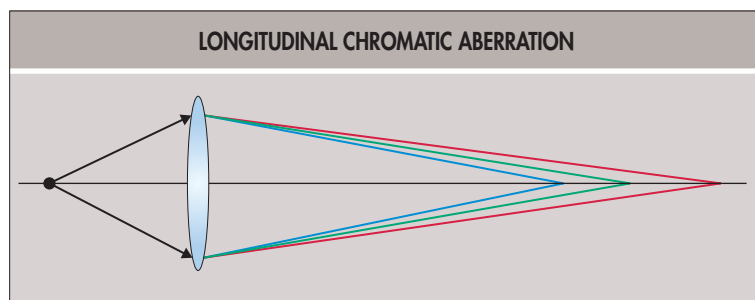
As a method for measuring aberrations, the Tscherning aberrometer suffers from the obvious limitation that it is subjective, relying on the patient’s ability to observe and accurately locate the displaced pencils. Nonetheless, it is a useful conceptual tool. The subjective limitations of Tscherning’s approach can be overcome by photographing the grid on the retina. However, photography introduces another problem—double pass. To be photographed, each grid spot on the retina acts as a light source, which passes through the eye, suffering its aberrations a second time. The second pass complicates the analysis of aberrations, although the Allegretto Wave Analyzer is based on this approach.<sup>24</sup>

There are several ways to overcome the double pass problem. One approach is to focus a laser (at low power of course) on the retina.<sup>25</sup> Since the laser traverses only a small amount of the pupil, it is essentially unaffected by ocular aberrations; practically speaking, this is a single pass technique. The small area of laser illuminated retina becomes a source from which light emerges from the eye. If the eye is aberration-free, the emerging light will have planar wavefronts, otherwise aberrations distort the wavefront shape.

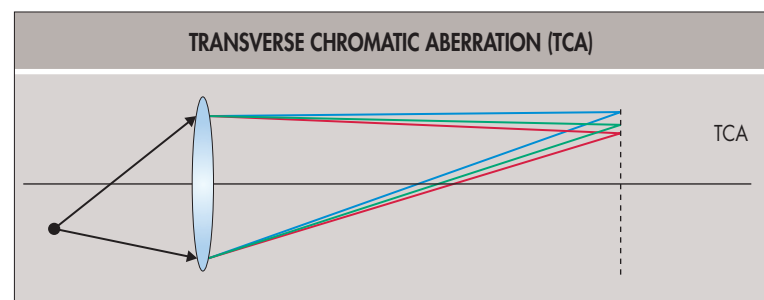
Using an approach suggested by Shack, the wavefront is sampled using a lenslet array that focuses small areas of the wavefront onto a detector. Each lenslet produces a small dot image on the detector that is displaced depending on the wavefront’s shape. The full wavefront is reconstructed from the displaced position of dots. The Hartman–Shack, as it is called today, is probably the most reliable way of measuring small amounts of higher-order aberration in an otherwise well-corrected eye or optical system. The technique is not as well suited to the measurement of large amounts of low-order aberrations.<sup>26</sup> Recent modifications of the technique improve the performance for low-order aberrations. Many aberrometers utilize some variation of the Hartmann–Shack approach.

Automated retinoscopy is another means of measuring aberrations and is incorporated into the ARK 10000 (Nidek). The Tracey uses the Tscherning approach but performs it sequentially by scanning a single laser beam over the pupil and observing the beam’s deviation on the pupil.<sup>27</sup> Besides being essentially a double pass system, movements during data acquisition are a potential problem.

It is important to realize that just because an instrument claims to measure aberrations does not mean it actually does so. It is very difficult to verify the accuracy of an aberrometer. Ocular aberrations, especially higher-order aberrations, change with the slightest change in tear film



**Fig. 2.6.8 Longitudinal Chromatic Aberration.** The image formed by short wavelength light is anterior to the image formed by longer wavelengths. This is the basis for the duochrome test used in subjective refraction.



**Fig. 2.6.9 Transverse Chromatic Aberration (TCA).** Highly dispersive materials may produce colored fringes at the image.



thickness, or changes in choroidal thickness that occur during the cardiac cycle, accommodation, hippus, ocular movement, head movement, or fixation change. The active optics photographic system that captures high resolution fundus images requires a bite bar for adequate head stabilization,<sup>28</sup> which no clinical aberrometer utilizes. Too often reproducibility is considered indicative of accuracy, but a stopped watch gives highly reproducible yet useless results. Accuracy cannot be inferred simply because a device gives reproducible results. Given the number of factors that affect ocular aberrations, an instrument that gives highly reproducible results, especially for higher-order aberrations, is suspect. Keep in mind that with all the advances in the clinical measurement of aberrations, there is still no objective measurement of hyperopia, myopia, or regular astigmatism that is consistently superior to subjective refraction. If low-order aberrations cannot be measured satisfactorily by objective methods, good reason exists to suspect that objective measurements of higher-order aberrations are somewhat inaccurate.

Regardless of the method used, all clinical measurements produce a set of discrete data points. The wavefront's shape between data points is not known. Mathematics, no matter how sophisticated, cannot create information beyond that present in the data. To summarize, the mathematical techniques do not find the actual wavefront, only the *most likely* wavefront given the data values, regardless of how the data were acquired (e.g., Hartman–Shack, Tscherning). More data points, provided they are accurately measured, and the more Zernike polynomials considered, the more likely the computed wavefront is a reasonable representation of the actual wavefront.

## Mathematical Considerations

There is no need to be intimidated by the mathematical aspects of aberration theory. Just as a spectacle lens is a combination of spherical and cylindrical contributions, total aberration is the combination of individual aberrations. The only difference is that in aberration theory several more individual aberrations occur, and they are less familiar to clinicians.

An individual aberration can be specified by a graph or its associated formula. As noted, when displayed graphically, the optical axis is rotated 90° from horizontal to vertical. Zernike polynomials are the formulas representing each individual graph.

Every Zernike polynomial has the same structure consisting of a coefficient that specifies the amount of the aberration (analogous to power, but in units of distance, not diopters), a radial polynomial, and usually a sine or cosine function. For instance,

$$\text{Secondary Astigmatism } X = Z_{11}(4\rho^4 - 3\rho^2)\cos 2\theta$$

The coefficient's subscripts (shown in purple) identify the individual aberration, the radial polynomial is  $(4\rho^4 - 3\rho^2)$ , is multiplied by a cosine function. The order of a Zernike polynomial is the sum of the largest exponent in the radial polynomial (red) and the coefficient of  $\theta$  (blue). Thus secondary astigmatism is a sixth order aberration.

Most Zernike polynomials come in pairs. For instance there is another sixth order Zernike polynomial:

$$\text{Secondary Astigmatism } Y = Z_{12}(4\rho^4 - 3\rho^2)\sin 2\theta$$

Note the difference in the coefficient subscripts. The shapes of these polynomials are identical except rotated around the vertical axis (i.e., the optical axis) by 90°.

A few Zernike polynomials are symmetrical about the optical axis and consequently have no trigonometric factor. For instance, fourth order primary spherical aberration is represented by the Zernike polynomial:

$$\text{Primary Spherical Aberration} = Z_{08}(1 - 6\rho^2 + 6\rho^4)$$

Zernike polynomials have only even orders (0, 2, 4, etc.). An order is a family of aberrations. For Zernike polynomials the number of aberrations within an order is always one more than the order itself. Thus there is one 0th order aberration, three 2nd order aberrations, five 4th order aberrations, and so forth. The variables  $\rho$  and  $\theta$  identify the position of a ray in the exit pupil, but it is important to understand the overall concepts without dwelling on mathematical detail.

A Zernike polynomial calculator is available on the Internet.<sup>29</sup> Users choose the amount of each individual Zernike aberration and the total aberration is calculated and displayed, which is a useful tool for those who wish to explore aberration theory in greater detail.

Infinitely, many Zernike polynomials exist, but as a rule, the higher the order of an aberration, the less it contributes to the total aberration. Usually there is no need to consider aberrations higher than a certain order. How many orders of Zernike polynomials must be calculated to obtain a reasonably accurate description of an optical system's aberrations? There is no definite answer, but lens designers have found empirically that 36 Zernike polynomials are sufficient for most purposes. Consequently, clinical aberrometers usually calculate 36 Zernike polynomials, but this is probably excessive. Lens designers usually deal with optical systems far more complicated than the eye. It is likely that far fewer aberrations are required for clinical work, although the precise number is not known, and currently no standard exists.

## AN OVERALL PERSPECTIVE ON ABERRATION THEORY

With the emergence of keratorefractive surgery came the possibility of correcting aberrations uncorrectable by spectacles. Initially some overly optimistic claims were made, including the possibility of achieving 20/6 acuity.<sup>30</sup> These claims were based on an incomplete understanding of aberration theory as well as other optical and nonoptical factors limiting acuity.

It is impossible to correct all aberrations by sculpting a single surface. Lens designers have known for centuries that correcting multiple aberrations requires multiple lenses. For this reason, high-quality optical systems corrected for many aberrations contain multiple lenses. At best, shaping just the anterior corneal surface can correct defocus, regular astigmatism, and SA. Correcting coma by keratorefractive surgery would probably be unwise even if it were possible, because coma is the result of misalignment between cornea and lens. The misalignment changes with age and following cataract surgery and could leave pseudophakic patients worse off.

Wave aberration data measures the entire eye, but keratorefractive surgery alters only the anterior corneal surface. Wavefront guided ablation attempts to improve outcomes by combining aberration data with corneal topography to improve visual results. However, corneal topography data has an accuracy of only  $\pm 5 \mu\text{m}$ , whereas the wavefront optimization requires accuracy better than  $1 \mu\text{m}$ . It appears that at this time corneal topography data is not sufficiently accurate to reap the theoretical benefits of wavefront guidance. Wavefront optimized ablation does not incorporate patient-specific data but simply flattens the ablation profile peripherally to reduce SA. As noted, corneal SA is patient specific, so results will vary.

Altering the shape of just the anterior corneal surface cannot, correct all ocular aberrations. No matter how technically advanced keratorefractive surgery becomes (and it still has a long way to go),<sup>31</sup> it will not be possible to eliminate all aberrations by this method. Even if it were possible to eliminate (or reduce to insignificance) all aberrations, other factors such as diffraction and intraocular light scattering would limit vision.

As noted, aberration theory is strictly limited to geometrical optics, completely ignoring diffraction, light scattering, and many other phenomena that affect visual function. After the correction of defocus and RA, for pupils smaller than about 2.5 mm, acuity is limited by diffraction not aberrations.<sup>32</sup> Consequently, the correction of higher-order aberrations would not lead to further visual improvement in patients with smaller pupils. Aberration theory also ignores intraocular light scattering, which can profoundly affect acuity.<sup>33</sup>

Although incompletely understood, neural mechanisms doubtless play an important role. It is speculative, but patients who have had uncorrected aberrations their entire lives may develop a form of refractive amblyopia, so again correction of irregular astigmatism in adults may not improve vision. Visual processing can decrease the influence of some aberrations but not all. The large amount of chromatic aberration present in most eyes is largely neutralized by visual processing.

In most cases the rays near the edge of the pupil are the most aberrant, in other words, focus farthest from the ideal image point. Wavefront apodization is a general term for any technique that diminishes the effect of peripheral rays on the image reducing the influence of aberrations. For example, rays striking the retina parallel to the photoreceptor outer segments produce more of a response than oblique incident rays (the Stiles–Crawford effect).<sup>34</sup> The Stiles–Crawford effect mitigates the influence SA and many higher-order aberrations.

For various reasons, apodization also can diminish image quality. Apodization is helpful provided the improvement in image quality gained by decreasing the influence of aberrations exceeds the loss of image quality produced by the apodization itself. Given the natural retinal apodization, the advantages of wavefront apodized IOLs may not be significant

or even beneficial. Keratorefractive surgery often increases HOA. The Stiles–Crawford effect may to some extent reduce the effect of HOA on vision-improving refractive outcomes.

Clinicians should be aware that irregular astigmatism is not uncommon but actually ubiquitous. All eyes have a large amount of uncorrected chromatic aberration. Considering only monochromatic aberrations, after correction of sphere and cylinder, almost all eyes will have some residual uncorrected irregular astigmatism. In most cases, coma is the dominant uncorrected aberration followed by SA to a lesser extent.

Aberration theory and wavefront methods were developed in the hope of improving the visual outcomes of keratorefractive surgery by correcting higher-order aberrations. Ironically, wavefront measurements have shown that more often than not keratorefractive surgery introduces more higher-order aberration than it corrects.<sup>35–37</sup>

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# Current Concepts, Classification, and History of Refractive Surgery

## 3.1

*Suphi Taneri, Tatsuya Mimura, Dimitri T. Azar*

**Definition:** Refractive surgery is the surgical correction of refractive errors of the eye such as myopia, hyperopia, astigmatism, and presbyopia.

### Key Features

- Established subspecialty of ophthalmology.
- Growing variety of well-established procedures.
- Adequate understanding of potential surgical complications, limitations, and alternatives.
- Blurring boundary with cataract surgery.

### Associated Features

- Alterations in optical aberrations after surgery.
- Mean uncorrected visual quality after modern procedures similar to preoperative spectacle correction.

## INTRODUCTION

Refractive surgery is one of the most rapidly evolving fields in ophthalmology. The introduction of the excimer laser, for example, has replaced corneal incisions for routine cases in a very short time. Additionally, over the past decade the femtosecond laser for laser-assisted in situ keratomileusis (LASIK) has added to the ease, safety, and efficacy of refractive procedures. Today, the femtosecond laser also is used for:

- Incisional refractive surgery.
- Corneal tunnels or pockets for the insertion of ring segments or disc-shaped implants into the stroma.
- Lamellar or penetrating corneal transplantations.
- Removal of corneal stromal lenticule to change the refraction of the eye small incision lenticule extraction (SMILE).
- (Refractive) lens exchange surgery.

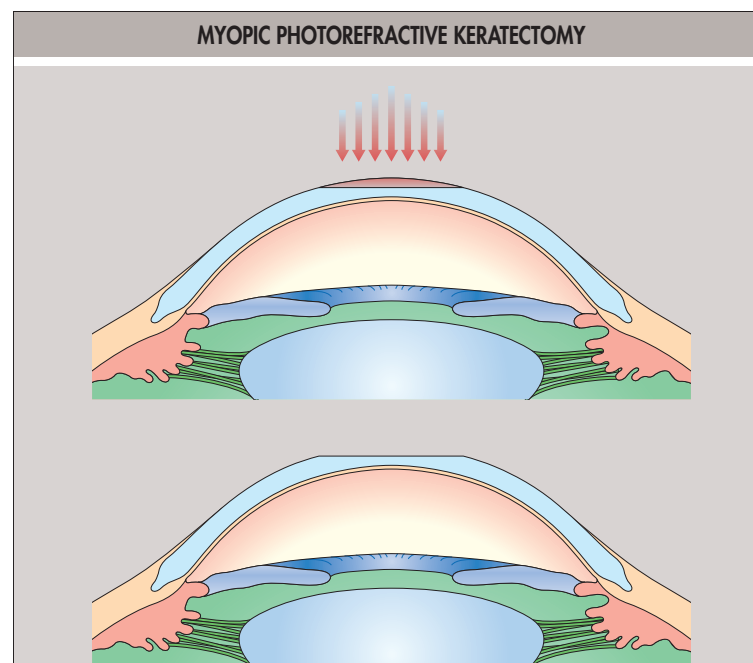
Many new approaches to correct presbyopia have been introduced in the last couple of years, including laser ablation profiles and intracorneal and intraocular implants. The greatest paradigm shift may have been the Nobel prize-winning method for adjusting the refractive power of an intraocular lens (IOL) after implantation into the eye by targeted radiation with UV light. Corneal cross-linking for the treatment of keratoconus is now a Food and Drug Administration (FDA)-approved treatment that also may have some potential as a refractive procedure.

In this chapter, we discuss excimer laser and ablation profiles; the classification of the different refractive surgery procedures, their utilization, advantages, and limitations; and briefly describe new procedures.

## EXCIMER LASER AND ABLATION PROFILES

Excimer laser corneal surgery was introduced as a precise tool for linear keratectomies by Trokel et al.<sup>1</sup> in 1983 but was later used for corneal reprofiling or photorefractive keratectomy (PRK) in 1988.<sup>2</sup> The ultraviolet laser (193 nm excimer or 213 nm solid state) allows the anterior corneal surface to be reshaped precisely to change its radius of curvature<sup>3</sup> (Fig. 3.1.1).

Numerous technological developments—such as flying-spot lasers, eye trackers, and use of femtosecond lasers for flap preparation—have



**Fig. 3.1.1 Photorefractive Keratectomy (PRK).** After removal of the corneal epithelium, the excimer laser is used to reprofile the anterior curvature of the cornea, which changes its refractive power.

improved clinical outcomes.<sup>4</sup> The advent of wavefront measurement technology also enabled the quantification of ocular aberrations.<sup>5</sup>

## Laser Ablation Profiles

The excimer laser can be used to flatten or steepen differentially the corneal meridians and hence to treat compound myopic and compound hyperopic astigmatism. Mixed astigmatism can be treated by flattening the refractively more powerful meridian or by steepening the weaker one.

There are currently several ablation profiles available for laser vision correction. Challenging cases include high and mixed astigmatism, higher degrees of defocus, large pupil size, higher amounts of higher-order aberration (HOA) or specifically spherical aberrations, thin corneas, pre-existing corneal opacification, or night driving problems. Assessment and treatment of an eye may be complicated by previous corneal or lenticular surgery leading to false measurements or an unpredicted response to the ablation. Moreover, a refractive procedure may have therapeutic aspects in recurrent erosion syndrome.

Existing laser ablation profiles include<sup>6</sup>:

- Munnerlyn's formula.<sup>7</sup>
- Wavefront-guided ablation.
- Wavefront-optimized or aspherical or Q factor-adjusted laser profile.
- Topography-guided ablation.
- Presbyopia correcting profiles.

In addition, combinations of these existing variants have been introduced recently, and even more are announced for the future (for example, ray-tracing optimized ablations).<sup>8</sup> Ablation profiles in corneal laser surgery



can be divided into those based on the total optical system and those based on the cornea.<sup>9</sup>

## Munnerlyn's Formula

The classic ablation profile for the correction of myopia and myopic astigmatism is based on Munnerlyn's formula,<sup>7</sup> which removes a convex-concave lenticule of corneal tissue with spherocylindrical surfaces to remodel the corneal curvature. The laser profile is based only on subjective and objective measurements of refraction. It does not take spherical aberrations into account, which may lead to an increase of spherical aberration, resulting in an oblate cornea. Munnerlyn's formula does not compensate for the loss of fluence in the periphery of the ablation zone, which occurs because the energy of a laser pulse is spread out over a larger area (i.e., an oval rather than a circle), nor the increased reflectance of the laser beam due to an oblique angle of incidence when the laser is not targeting the corneal apex.<sup>10</sup> Moreover, the reduction in tissue removal is greater than the reduction in fluence. These three laser-related factors together with different biomechanical and wound-healing responses in the periphery are now compensated for by algorithms proprietary to the laser manufacturer.

## Wavefront-Guided Ablation

The principles of wavefront deformation measurements are discussed in greater detail in Chapter 3.6. In a perfect optical system, all the refracted rays are focused on a single plane (wavefront). Optical aberrations induce deformations on this plane and can be quantified. They represent the optical performance of the entire visual system, not only the anterior surface of the cornea, as in corneal topography. The lower-order optical aberrations (sphere and astigmatism) can be corrected with spherocylindrical glasses. The HOA (including spherical aberration and coma) correspond to what is clinically known as irregular astigmatism (Fig. 3.1.2).

In theory, the higher the amount of HOA, the greater the benefit of performing a wavefront-guided ablation. However, wavefront-sensing may be negatively affected by the use of mydriatic eyedrops.<sup>11</sup> Furthermore, new HOA are induced by the laser treatment itself even if the radial loss of efficacy is compensated by less than perfect alignment of the ablation pattern on the cornea<sup>12</sup> and less than perfect eye-tracking,<sup>13</sup> including cyclo-torsional movements<sup>14</sup> before and during ablation. In addition, aberrations are induced when a LASIK flap is created.

Lenticular aberrations increase with age, whereas corneal aberrations remain fairly stable throughout our lives in the absence of anterior corneal disease or dry eye.

## Topography-Guided Ablation

Based on topography measurements by different topographers, including the Orbscan IIz (Fig. 3.1.3), the Pentacam (Fig. 3.1.4), and others, the elevation profile of the anterior corneal surface is calculated. The desired corneal surface is determined with the goal of correcting the refractive error and HOA induced at the cornea. The difference between the preexisting surface and the desired surface is used to calculate the ablation profile. Because of the calculated wavefront component of the cornea in this laser profile, the term *corneal wavefront ablation* is sometimes imprecisely used.

Topography-guided ablations have their greatest theoretical superiority in cases in which the problem is clearly located in the anterior cornea, like consequences of earlier surgery.<sup>15,16</sup> Examples include decentered laser ablations,<sup>17</sup> corneal grafts,<sup>15</sup> and corneal scars.<sup>18</sup> The reason is that a corneal topographer has a much higher resolution than wavefront sensors. A corneal topographer may evaluate the whole cornea, whereas ocular aberration measurements are only possible over the entrance pupil. Finally, a topographer directly evaluates the surface on which there are imperfections. Topography-guided ablations that were combined with collagen cross-linking were introduced in the treatment of keratoconus<sup>19</sup> or forme fruste keratoconus.<sup>20</sup>

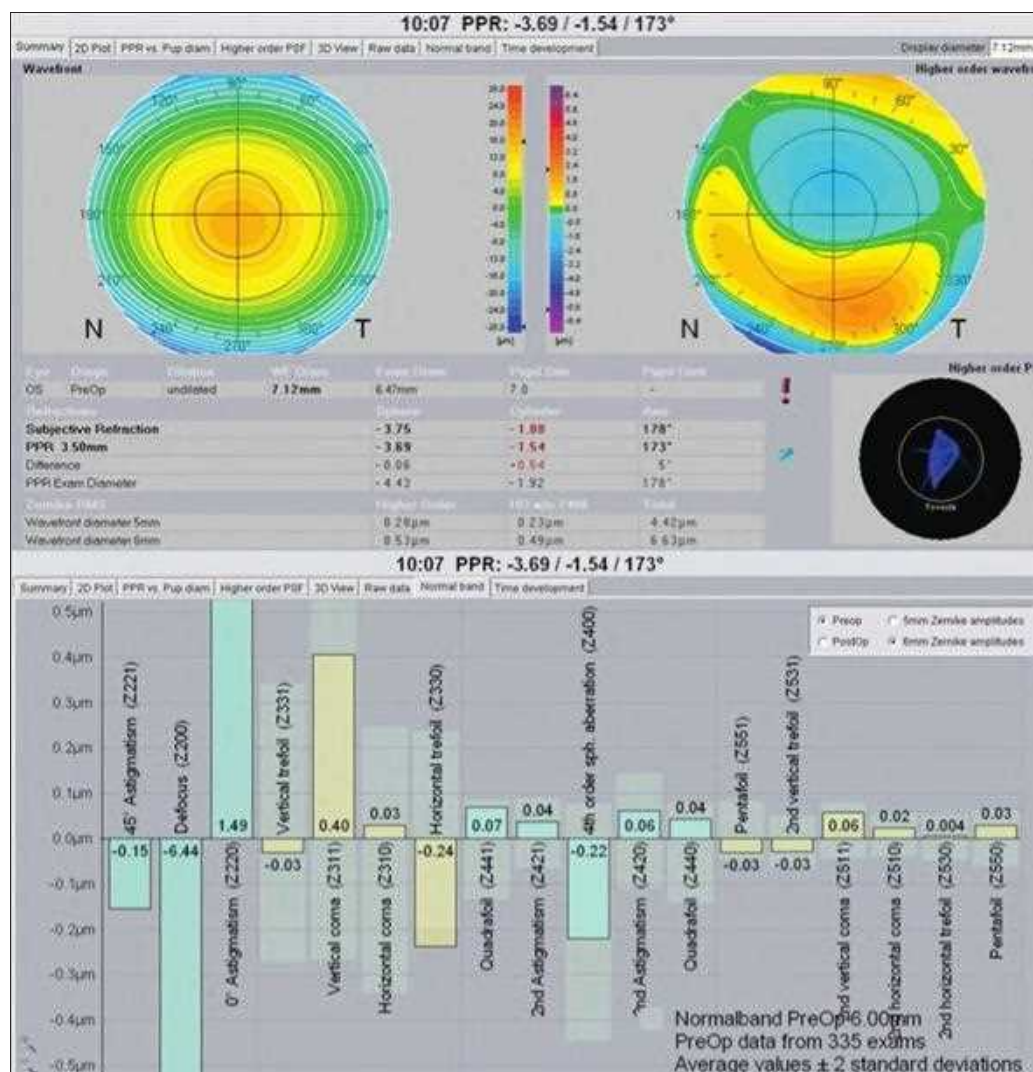
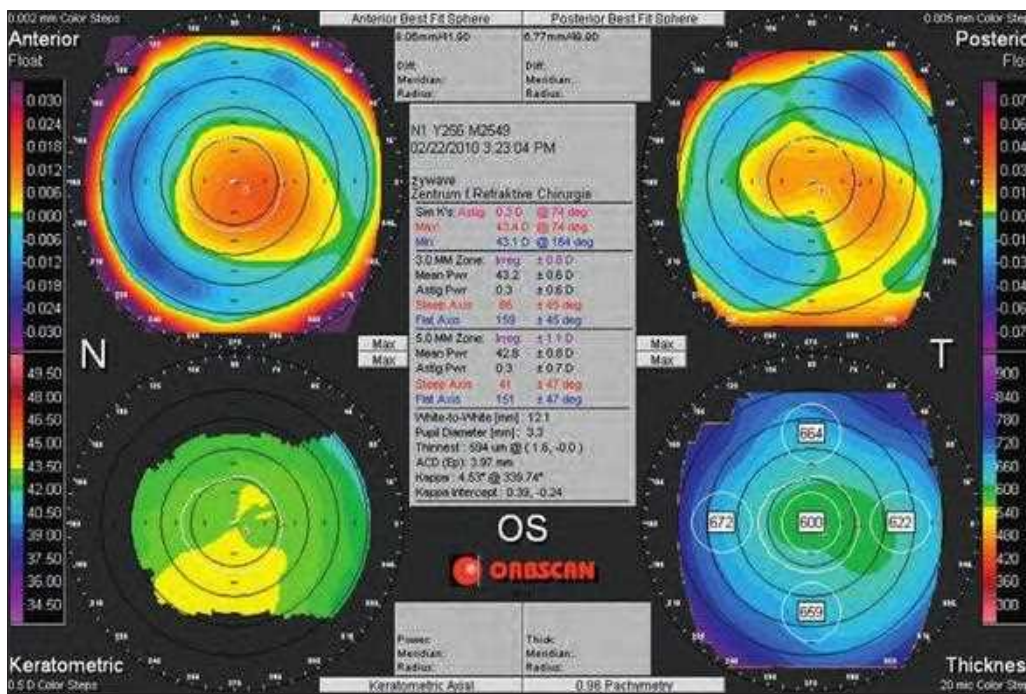
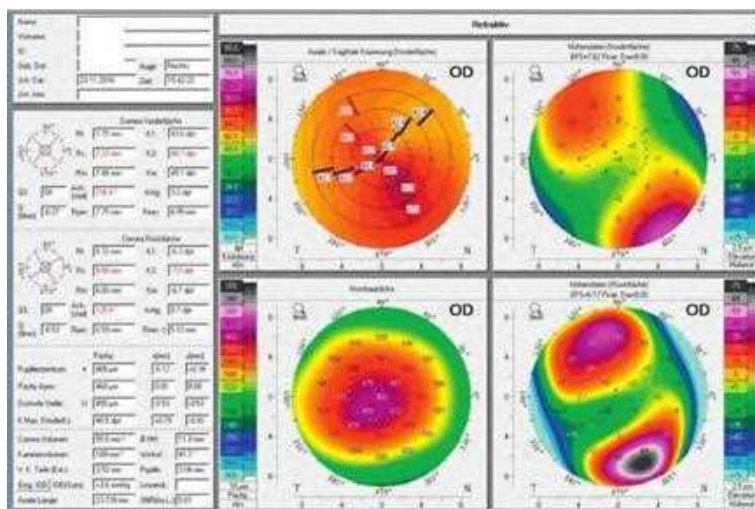


Fig. 3.1.2 Wavefront Measurements Over a Pupil Size of More Than 6 mm in a Myopic Astigmatic Eye.



**Fig. 3.1.3 Orbscan Examination.** Including anterior and posterior float, corneal topography, and pachymetry preoperatively in a 30-year-old patient.



**Fig. 3.1.4 Pentacam Examination of a Keratoconic Eye Showing Inferno-Nasal Steepening and Central Thinning of the Cornea.**

### Wavefront-Optimized<sup>21</sup>/Aspherical<sup>22</sup>/Q-Factor-Adjusted<sup>23–25</sup> Laser Profiles

The term *wavefront-optimized* refers to laser treatment software that has been designed with certain corrections preprogrammed, although a true and customized wavefront plan is not employed. Spherical aberrations are the most disturbing optical imperfections after the lower-order terms *sphere* and *cylinder*. Because standard spherocylindrical excimer ablations induce positive spherical aberrations,<sup>26,27</sup> wavefront-optimized laser profiles have been developed to preserve the eye's pre-existing optical aberrations without introducing new aberrations.<sup>28,29</sup>

The aim of preserving the natural cornea shape of each patient is propagated by other companies as aspherical or Q factor-adjusted ablation. This treatment is designed to improve the eye's optical quality by optimizing the asphericity of the cornea. The Q-factor is a measure of the asphericity of the cornea. In the normal population, the mean Q-factor is  $-0.25$ , which indicates a slightly prolate shape. After determining the ideal asphericity of the cornea in a model, some researchers have suggested the optimum Q-factor should be around  $-0.4$  or  $-0.5$ .<sup>30</sup>

### Presbyopia Correction

Presbyopia correction can be attempted by creating multifocal corneas<sup>31</sup> or hyperprolate corneas when aiming for a postoperative Q-factor close to  $-1.0$ . Attempts to address presbyopia by corneal ablation date back to the last millennium.<sup>32</sup>

## CONCEPTS IN DEVELOPMENT

An online pachymetry-guided ablation could aid in removing the anterior portion of the cornea without perforating Descemet's layer before a lamellar graft is transplanted.

In routine laser vision correction, the combination of existing principles will bring even better outcomes than we are used to today. Such a combination of a wavefront-guided ablation with an aspherical profile according to the cornea's preoperative asphericity has delivered excellent results in our hands.<sup>33</sup> Optical ray-tracing algorithms, on the other hand, may allow the highest degree of customization. The idea behind ray tracing is that no single measurement of an eye can provide all the data required to achieve utmost individualization of the ablation. Therefore the information of several types of measurements such as ocular wavefront, corneal topography including the topography of the cornea's back surface, corneal thickness, anterior chamber depth, lens thickness, and axial length may be considered. The systematic induction of HOA by means of wavefront-guided treatments may be overcome by such a method.<sup>8</sup>

## CLASSIFICATION OF REFRACTIVE PROCEDURES

The refractive power of an optical system, such as the eye, can be modified by changing the curvature of the refractive surfaces, the index of refraction of the different media, or the relative location of the different elements of the system.

Several classifications of keratorefractive surgery have been proposed based on the mechanisms of action of the surgery<sup>34</sup> or on the type of surgery.<sup>35</sup> A simplified classification in which the site of action of the surgery on the cornea—either over the optical zone or peripheral to it—is matched against the four different mechanisms of action of corneal surgery: addition, subtraction, relaxation, and coagulation-compression. The procedures that act on the optical zone are further subdivided into superficial or intrastromal (Table 3.1.1). In addition to keratorefractive surgery, the use of intraocular implants is the second class of procedures to modify the ocular refraction.

### Cornea

Approximately two-thirds of refraction occurs at the air-tear-corneal interface, which generally parallels the anterior surface of the cornea. The cornea is readily accessible, and its curvature can be modified as an extraocular procedure. Most keratorefractive procedures to date modify the radius of curvature of the anterior surface of the cornea.<sup>36</sup>

#### Central Cornea

Most procedures used to modify the corneal optical zone, or central cornea, change the relationship between its anterior and posterior surfaces; the thickness of the cornea is also modified. The central cornea may be modified either on the surface or intrastromally.



TABLE 3.1.1 Proposed Classification of Keratorefractive Surgical Procedures

Optical Zone	Addition	Subtraction	Relaxation	Coagulation–Compression
Superficial	Epikeratophakia Synthetic epikeratophakia	PRK, LASEK, epiLASIK, epi-Bowman keratectomy		Corneal molding
Intrastromal	Keratophakia Intracorneal lenses Intracorneal transplants	LASIK, Femto-LASIK Keratomileusis in situ Keratomileusis SMILE	Lamellar keratotomy	
Peripheral cornea	Intracorneal ring segments	Wedge resection	Radial keratotomy Hexagonal keratotomy Arcuate keratotomy	Thermokeratoplasty Compression sutures

LASEK, Laser subepithelial keratomileusis; LASIK, laser-assisted in situ keratomileusis; PRK, photorefractive keratectomy; SMILE, small incision lenticule extraction.

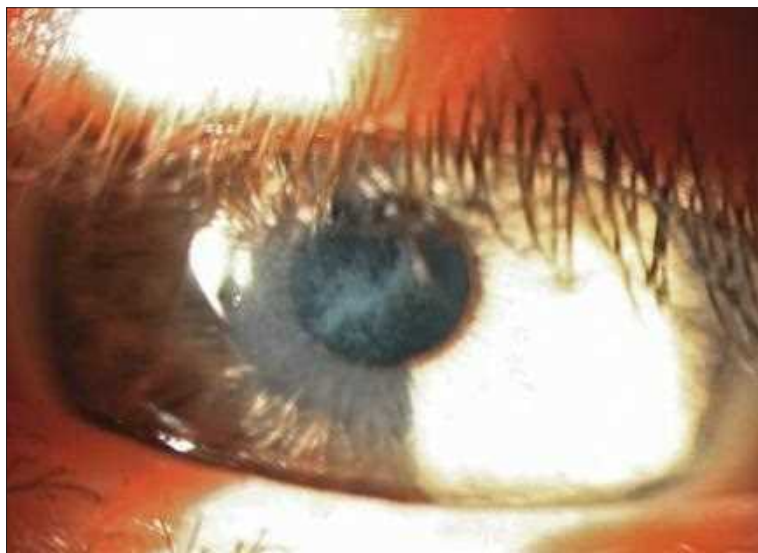


Fig. 3.1.5 Subepithelial Haze 3 Months After LASEK in a 28-Year-Old Man.

### Corneal Surface: Addition

**Epikeratophakia.** Epikeratophakia (also known as epikeratoplasty and onlay lamellar keratoplasty) was introduced by Werblin et al.<sup>37</sup> It involves removal of the epithelium from the central cornea and preparation of a peripheral annular keratotomy. A lyophilized donor lenticule (consisting of Bowman's layer and anterior stroma) is reconstituted and sewn into the annular keratotomy site.

Use of epikeratoplasty for the general treatment of myopia and hyperopia has been abandoned largely because of the potential loss of best-corrected visual acuity due to complications like irregular astigmatism, delayed visual recovery, and prolonged epithelial defects.

Synthetic materials<sup>38</sup> and improved means of attaching the lenticule to the cornea may allow epikeratoplasty to become a more useful refractive technique in the future.

### Corneal Surface: Subtraction

The surface ablation procedures PRK, laser subepithelial keratomileusis (LASEK), and epiLASIK have excellent results in terms of safety, efficacy, and stability with low-to-moderate myopic astigmatic corrections.<sup>39</sup> In prospective trials, no clinically significant superiority of any of these three methods could be established regarding epithelial closure time, pain perception, haze formation, safety, and efficiency.<sup>40</sup> Epi-Bowman keratectomy (EBK) is the latest variant of these surface ablation techniques.

**Photorefractive Keratectomy.** In PRK, the epithelium is removed by mechanical scraping, utilizing ethanol or with an excimer laser ablation, before the stroma is ablated to correct the ametropia. The stroma is eventually covered by the epithelium, which heals from the periphery toward the center in about 4 days. After PRK, the corneal epithelium undergoes a hyperplastic phase in which the refractive status of the eye may be modified.<sup>41</sup> The deposition of new collagen and glycosaminoglycans<sup>42</sup> by activated stromal keratocytes after PRK is a common phenomenon after deep ablations and in younger individuals (Fig. 3.1.5) and manifests as corneal haze or subepithelial scarring. The activation of the keratocytes seems to stem from interaction of epithelial cells and raw corneal stroma as the epithelium migrates to cover the defect or from activation of keratocytes by soluble tear factors that percolate through the initial epithelial defect after PRK. The haze may be associated with regression of the refractive

effect or focal topographical abnormalities; it peaks in humans 3–6 months after the operation and disappears after 1 year for most patients. Many surgeons now use mitomycin-C prophylactically during the initial treatment to prevent haze formation or therapeutically to remove haze.<sup>43</sup>

**Laser Subepithelial Keratomileusis.** LASEK involves cleaving the epithelial sheet at the basement membrane or at the junction of the epithelium to Bowman's membrane with dilute alcohol, applying the laser as in conventional PRK, and repositioning the epithelium afterward.<sup>44,45</sup> The first LASEK procedure was performed by Azar.<sup>46,47</sup> The term LASEK was coined by Massimo Camellin, who also popularized this method of surface ablation.

**EpiLASIK.** EpiLASIK is an abandoned surface ablation procedure designed to create an epithelial flap with an epikeratome that is equipped with a blunt separator instead of a sharp blade, as in microkeratomes used during LASIK.

**Epi-Bowman Keratectomy (EBK).** Epi-Bowman keratectomy was recently introduced and does not employ a metallic blade but a soft instrument to manually remove the epithelium before stromal ablation.

### Corneal Stroma: Subtraction

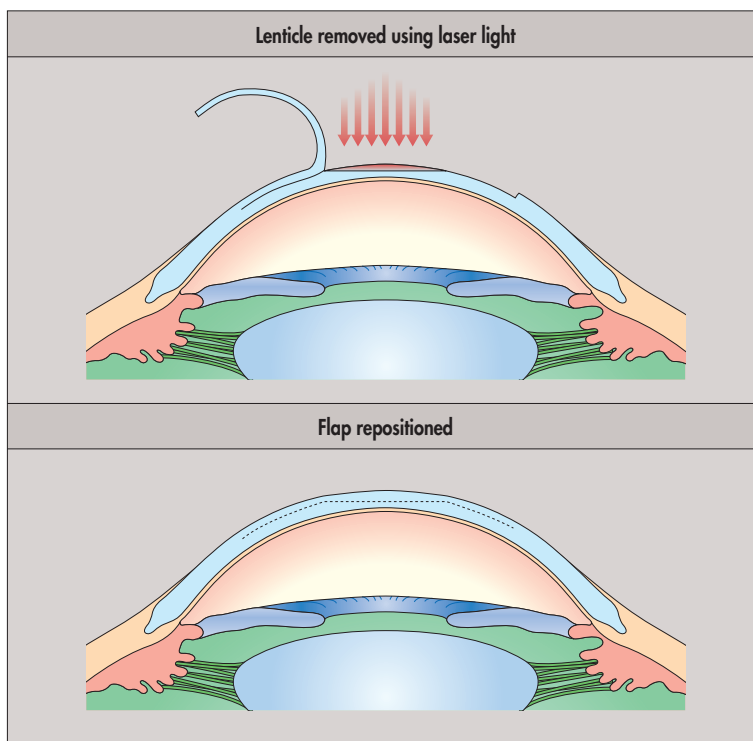
**Keratomileusis.** The term *keratomileusis* refers to the technique of “carving” (Greek *smileusis*) the cornea. Dr. José I. Barraquer first reported clinical results with the technique in 1964.<sup>48</sup>

Classic keratomileusis involves the excision of a lamellar button of parallel faces from the cornea with a microkeratome, freezing and reshaping the lamellar button, and replacing it in position with sutures. The procedure was modified by Krumeich and Swinger, who reshaped the disc with a second microkeratome pass without having to freeze it, in a procedure known as BKS (Barraquer–Krumeich–Swinger) keratomileusis. Ruiz and Rowsey<sup>49</sup> made further modifications by applying the second microkeratome pass to the stromal bed instead of the resected disc, in a procedure called in situ keratomileusis. Even though the refractive cut with the microkeratome gave a disc of parallel surfaces with no optical power, a dioptric effect was achieved because of the remodeling of corneal tissue, as described by Barraquer<sup>50</sup> in the law of thickness. The development of a mechanized microkeratome, or automatic corneal shaper, provided a more consistent thickness and diameter of the corneal disc and improved the predictability of the procedure. This procedure is known as automated lamellar keratoplasty (ALK). The fact that the corneal cap does not have to be modified led to the use of a hinged flap instead of a free cap. This, in turn, led to sutureless repositioning of the flap, which simplified the procedure further.

**Laser-Assisted in situ Keratomileusis.** LASIK refractive correction is the most commonly performed refractive surgery in the world today. The early model was first performed in rabbits by Pallikaris et al.<sup>51</sup> in a modification of Ruiz's keratomileusis in situ (Fig. 3.1.6). Buratto and Ferrari<sup>52</sup> first performed this procedure in humans after inadvertently obtaining a thin resection with the microkeratome while performing a modification of Barraquer's classic keratomileusis using the excimer laser instead of the cryolathe to modify the corneal cap.

In PRK, LASEK, and epiLASIK the laser is applied directly to Bowman's layer, whereas in LASIK it is applied to the midstroma after a flap has been lifted from the cornea. The flap is then replaced. LASIK causes a minimal degree of epithelial hyperplasia (much less than PRK) that causes regression of the effect.<sup>53</sup> No visually significant haze follows uncomplicated LASIK,<sup>54</sup> but when the flap is too thin, haze may occur, suggesting that a critical amount of unablated flap keratocytes is needed to inhibit haze formation after routine LASIK.

**Femto-LASIK.** Traditionally, the corneal flap cut during LASIK was created with a microkeratome blade. In contrast, Femto-LASIK uses the



**Fig. 3.1.6 Laser-Assisted in situ Keratomileusis (LASIK).** A flap with parallel sides is lifted using the microkeratome. The excimer laser is used to remove an exactly planned amount of tissue from the exposed corneal stroma. The flap, with its intact epithelium, is then folded back, and as it drapes over the modified stromal surface, the refractive power of the anterior corneal surface is modified. The dotted area in the bottom panel corresponds to the stromal tissue that was removed. No sutures are required.

femtosecond laser, which is coupled to the patient's eye with an interface fixated by suction. The femtosecond laser beam separates the corneal tissue by causing numerous microexplosions at a preprogrammed depth and position. The remaining tissue bridges between these cavitation bubbles are then bluntly dissected using spatula-like instruments. As no actual cut is performed with the femtosecond laser, in the rare event of a suction loss during flap preparation, a second attempt can be done immediately. This is not possible after a suction loss of a mechanical microkeratome, which necessitates changing to a surface ablation or waiting for approximately 3 months. This feature is a clear advantage to mechanical microkeratomers, but other flap-related complications like buttonholed flaps, flap striae, flap dislocation, and keratectasia may still happen. Transient light sensitivity—a new complication seen with initial femtosecond flap makers that occurred in some patients and resolved spontaneously after a couple of weeks—seems to be overcome with state-of-the-art femtosecond lasers by reducing the amount of energy delivered into the cornea.

**Intrastromal Laser Ablation.** Intrastromal, solid-state, picosecond lasers are being developed that are more compact and portable than excimer lasers. Intrastromal ablation is made to flatten the central cornea, the epithelium and Bowman's layer are spared, and thus fewer keratocyte fibroblastic responses are seen.

**Intrastromal Lenticule Extraction.** A new procedure, small incision lenticule extraction (SMILE), takes place entirely within the cornea and is performed exclusively with a femtosecond laser system, that is, no excimer laser is needed. The SMILE procedure consists of these steps (Fig. 3.1.7):

- The femtosecond laser is used to outline a small lens-shaped segment of tissue (lenticule) within the center of the cornea and a small incision in the midperiphery of the cornea.
- The lenticule is removed through this self-sealing incision and discarded.

The removal of the lenticule reduces the curvature of the cornea, thereby reducing myopia. Without a corneal flap, SMILE causes less postsurgical dry eye and may pose less risk for ectasia than LASIK. Also, without a corneal flap, no risk exists of flap displacement from trauma to the eye after surgery. SMILE has recently been approved by the FDA for the correction of myopia and myopic astigmatism and may soon become a popular alternative to LASIK for vision correction. However, currently it is not possible to perform SMILE for hyperopia.

### Corneal Stroma: Addition

**Keratophakia.** Keratophakia is the technique by which a corneal lens is inserted to change the shape of the cornea and modify its refractive power.<sup>55</sup> Traditionally, a lamellar keratectomy was performed with a microkeratome on the recipient's cornea. A fresh or preserved donor cornea also underwent a lamellar keratectomy. A stromal lens was created from the donor cornea and placed intrastromally in the recipient. In the future, lenticules obtained during a SMILE procedure may be reshaped according to the refractive needs of the recipient cornea and implanted in an intrastromal interface created by a femtosecond laser.

**Intracorneal Inlays.** Intracorneal inlays may prove beneficial in the treatment of various refractive errors. Barraquer, working in Bogotá, Colombia, performed experiments with corneal implants as early as 1949. Early inlays were composed of flint glass and Plexiglas for the correction of aphakia and high myopia. Claes Dohlman first described the use of a permeable lenticule in 1967 in Boston. Hydrogel inlays were developed so as not to impede metabolic gradients across the stroma, including nutrient flow to the anterior cornea.

Today, corneal inlays mainly are designed to treat presbyopia. The mechanisms behind the current generation of inlays can be divided into three categories:

- Small-aperture corneal inlays that increase the depth of focus.
- Space-occupying inlays that create a hyperprolate and thus multifocal cornea.
- Refractive annular addition lenticules that work as bifocal optical inlays to create separate distance and near focal points.

### Corneal Stroma: Relaxation

#### **Lamellar Keratotomy (Hyperopic Automated Lamellar Keratoplasty).**

In deep lamellar keratotomy (hyperopic ALK), a microtome performs a deep keratectomy to elevate a corneal flap that is replaced without additional surgery. The stromal bed then develops ectasia under the flap. Hyperopic ALK works best for low levels of hyperopia, but the predictability is low, and the risk of progressive ectasia ended the use of this procedure.

### Peripheral Cornea

Several keratorefractive procedures are used to change the shape of the central cornea through their action on the peripheral cornea. This is achieved without changing the thickness or the relationship between the anterior and posterior surfaces over the corneal optical zone.

### Peripheral Cornea: Addition

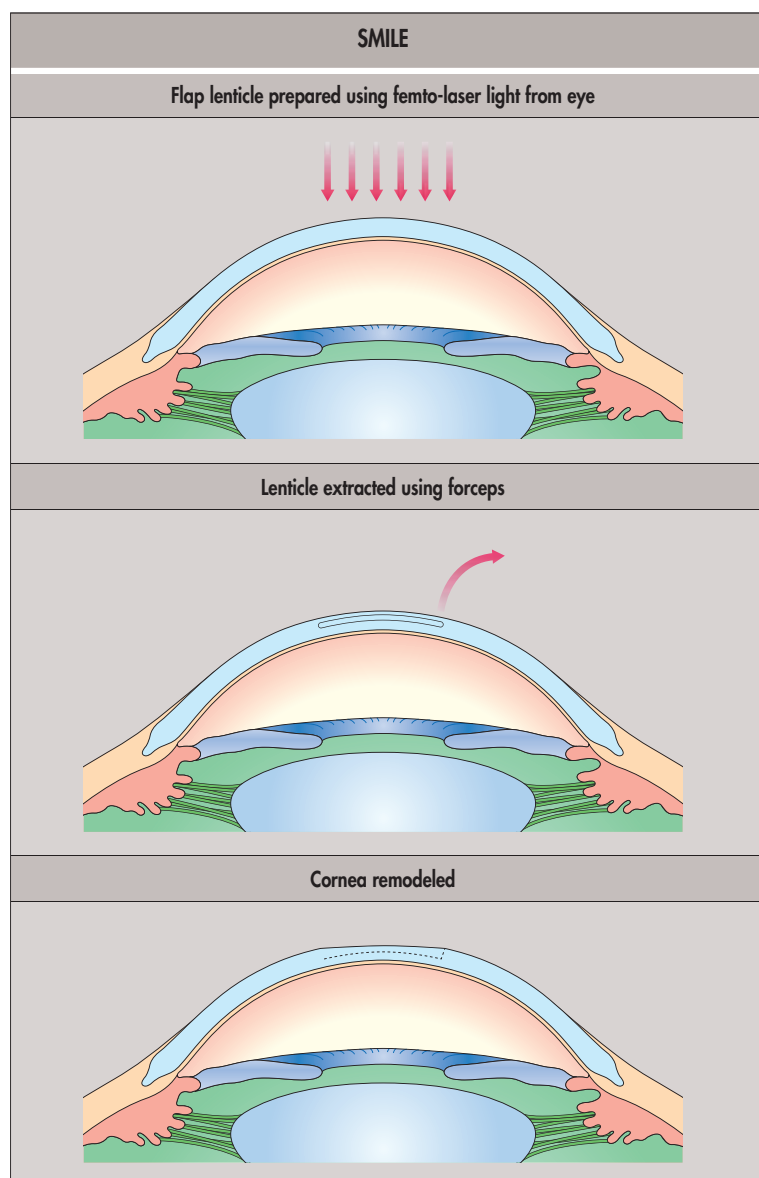
**Intracorneal Rings.** Krumeich<sup>56</sup> introduced the concept of titanium rings to alter the corneal curvature in keratoconic eyes or in combination with corneal transplant surgery (Fig. 3.1.8). In keratoconic eyes, first, a dedicated trephination system (GTS) is used to create a circular groove in which the ring is placed and secured with a double running antitorque suture. The suture may be removed after completion of wound healing. The rings may be inserted in the interface of corneal transplants. The idea was to modify corneal curvature by altering the shape of the implanted ring with special instruments. However, this concept yielded no sufficiently predictable effect, and extrusion of the rings has been observed.

**Intracorneal Ring Segments.** Intracorneal ring segments are placed in the peripheral cornea and take advantage of the fact that the arc of the cornea remains constant at all times, so when the anterior surface is lifted focally over the ring, a compensatory flattening of the central cornea occurs (Fig. 3.1.9). An advantage of intracorneal segments over other refractive surgical techniques is removability as opposed to reversibility, as at least the tunnel preparation is permanent. The main drawbacks are the limited range of correction and poor predictability compared with excimer laser ablative procedures. As a result, intracorneal ring segments today are almost solely used for high cylindrical corrections in keratoconic corneas and may be combined with corneal cross-linking.

### Peripheral Cornea: Subtraction

**Wedge Resection.** Troutman developed the use of wedge resections and resuturing in the flat meridian, often with relaxing incisions in the steep meridian. Although the procedure effectively decreases astigmatism, clinical results are highly unpredictable and it is now reserved for the correction of postkeratoplasty astigmatism of high degree. The use of the femtosecond laser to facilitate wedge resection surgery has been shown to be effective for postkeratoplasty astigmatism.





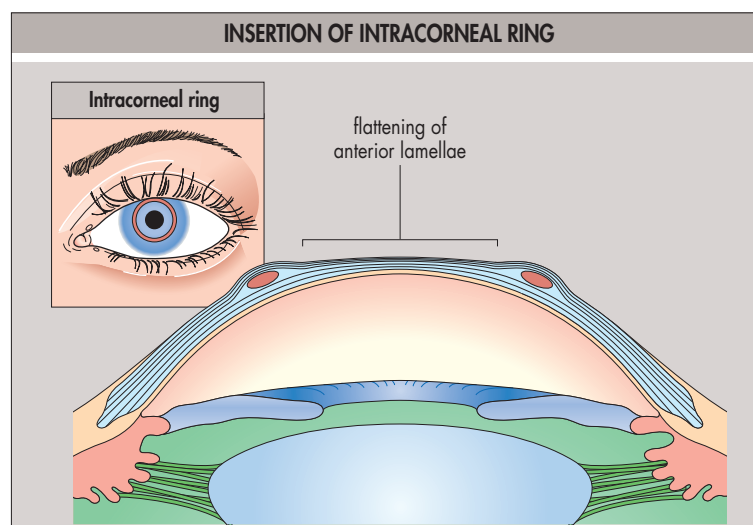
**Fig. 3.1.7 Small Incision Lenticule Extraction (SMILE).** A femtosecond laser fashions an intrastromal corneal lenticule. This lenticule is extracted through a small incision that flattens the anterior corneal surface. No flap and sutures are required.



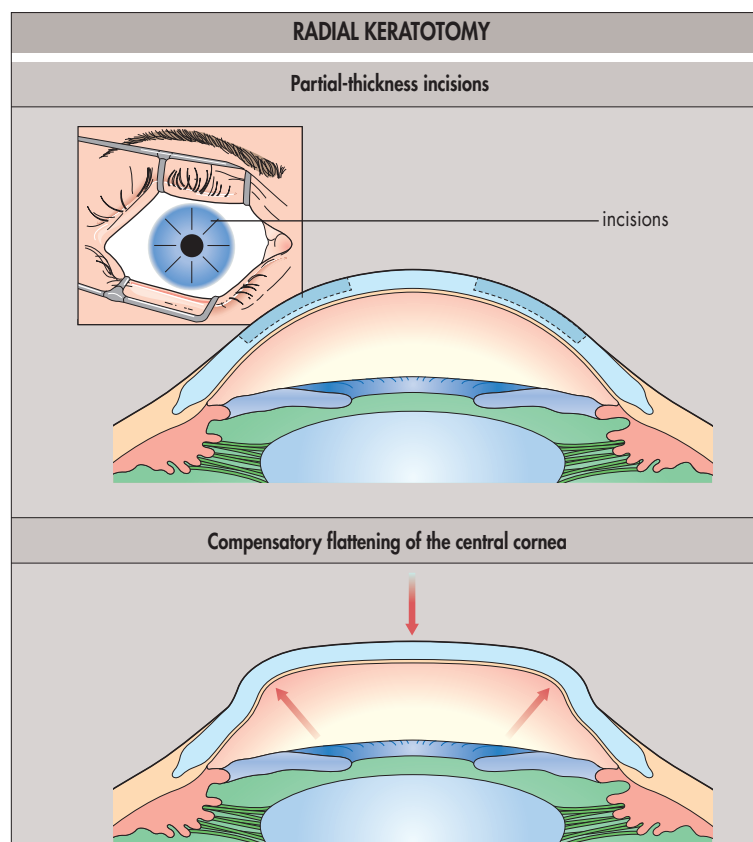
**Fig. 3.1.8 Intracorneal Titanium Ring as Devised by Krumeich.**

#### Peripheral Cornea: Relaxation

**Radial Keratotomy.** Radial keratotomy (RK) for myopia involves deep, radial corneal stroma incisions that weaken the paracentral and peripheral cornea and flatten the central cornea (Fig. 3.1.10). Sato et al.<sup>57</sup> in Japan used anterior and posterior corneal radial incisions to treat keratoconus,



**Fig. 3.1.9 Intracorneal Ring Segments.** After a peripheral circular lamellar dissection, two polymethyl methacrylate ring segments of predetermined diameter and thickness are inserted. The midperipheral anterior lamellae are lifted focally by the ring segments, which results in a compensatory flattening of the central anterior lamellae and hence a decrease in the refractive power of the central cornea.



**Fig. 3.1.10 Radial Keratotomy.** Partial-thickness incisions result in limited ectasia of the paracentral cornea and compensatory flattening of the central cornea.

astigmatism, and myopia. The procedure was abandoned because of the long-term complication of bullous keratopathy secondary to endothelial cell loss.<sup>58</sup> Anterior RK was performed by several ophthalmologists in the former Soviet Union in the early 1970s and was later popularized by Fyodorov and Durnev.<sup>59</sup> RK has been performed in the United States since 1978.<sup>60</sup>

The stability of refraction after RK is lower than with many other refractive surgical procedures. Therefore RK has been replaced by excimer laser procedures.

**Hexagonal Keratotomy.** Proposed by Gaster and Yamashita in 1983, hexagonal keratotomy, first performed in humans by Mendez in 1985, consists of making circumferential, hexagonal, peripheral cuts around a clear optical zone. It “uncouples” the central cornea from the periphery, which allows the cornea to bulge or steepen, thereby decreasing hyperopia. The

procedure has been largely abandoned because of the complications of poor healing and irregular astigmatism.<sup>61</sup>

**Astigmatic Keratotomy.** The first modern cataract extraction through a corneal incision, performed by David in France in 1747, introduced ophthalmologists to surgically induced astigmatism. Several investigators in the latter part of the nineteenth century, including Snellen, Schiötz, and Bates, attempted to correct corneal astigmatism with transverse relaxing corneal incisions. The first systematic study of the correction of astigmatism was performed by Lans<sup>62</sup> in 1898.

Astigmatic keratotomy (AK) involves making transverse cuts in an arcuate or straight fashion perpendicular to the steep meridian of astigmatism to produce localized ectasia of the peripheral cornea and central flattening of the incised meridian, thereby decreasing the astigmatism. Although important in its time, AK is no longer used except during a corneal graft.

For cataract surgery, limbal-relaxing incisions have gained popularity because they are more comfortable for the patient than are arcuate or transverse midperipheral incisions, although their effect is smaller as they are farther away from the corneal center.<sup>63</sup> However, today limbal-relaxing incisions are inferior to the implantation of toric IOLs during cataract surgery.

### Peripheral Cornea: Coagulation–Compression

**Thermokeratoplasty.** Radial intrastromal thermokeratoplasty shrinks the peripheral and paracentral stromal collagen to produce a peripheral flattening and a central steepening of the cornea to treat hyperopia. Unable to produce satisfactory results with relaxing incisions, Lans used cautery to selectively steepen a corneal meridian in rabbits. It was not until 1914 that Wray performed the procedure in humans in a case of hyperopic astigmatism. The procedure was later modified to correct hyperopia and popularized by Fyodorov. Although an initial reduction in hyperopia was observed, the lack of predictability and significant regression are persistent problems.

The solid-state infrared laser holmium:yttrium–aluminum–garnet (Ho:YAG) laser has been used in a peripheral intrastromal radial pattern (laser thermokeratoplasty) to treat hyperopia of 2.50 diopters (D) and less.<sup>64</sup> The long-term refractive stability of Ho:YAG laser thermokeratoplasty is poor. A handheld radiofrequency probe to shrink the peripheral collagen also has been employed.

**Microwave-Induced Thermokeratoplasty: Keraflex Procedure.** During an investigational Keraflex procedure, a microwave generator delivers a single low-energy microwave pulse lasting less than 1 second. Energy is applied to the cornea using a dielectrically shielded microwave emitter that contacts the epithelial surface. Through capacitive coupling, the single pulse raises the temperature of the selected region of corneal stroma to approximately 65°C, shrinking the collagen and forming a toroidal lesion in the upper 150  $\mu$ m of the stroma. The lesion created is intended to flatten the central cornea to achieve myopic correction without compromising the biomechanical integrity of the cornea.

**Circular Keratorrhaphy.** A suture placed in a circular fashion on the peripheral cornea to constrict the cornea and steepen the central cornea was first attempted by Krasnov in Russia in 1985 to treat hyperopia and aphakia. The principal problems are the development of irregular astigmatism by differential tension and loss of the effect as the suture elongates and “cheese-wires” through the tissue.

### Peripheral Cornea: Oppression

**Orthokeratology.** Orthokeratology is used as a nonsurgical option for the correction of myopia. An orthokeratology lens is flatter, looser, and larger than a conventional lens. Theoretically, the lens mechanically alters the central corneal contour over time.<sup>65,66</sup> Because of safety concerns, orthokeratology did not gain widespread acceptance.

Reverse-geometry lenses are fitted with a base curve flatter than the central corneal curvature to apply pressure to a central corneal zone that flattens during wear to reduce the myopic refractive error. The current approach to orthokeratology using reverse-geometry lens designs results in rapid reductions in myopic refractive error.<sup>67–71</sup>

## Intraocular Lenses and Refractive Lensectomy

### Refractive Lens Exchange

Extraction of the clear lens to correct high myopia was performed by Fukala<sup>72</sup> in Germany in 1890. The procedure was later abandoned because of an unacceptably high rate of complications. With more sophisticated operative techniques, recently there has been renewed interest in managing

high refractive errors by clear lens extraction. Because of retinal problems in high myopes, the procedure seems safer in high hyperopes.<sup>73</sup> For young patients, one major drawback is the loss of accommodation. To date, a variety of methods to restore near vision are available after lens removal, including correction with glasses and contact lenses, monovision, scleral expansion techniques, and various IOLs. However, none of them is perfect.

### Toric Intraocular Lenses

Intraocular lenses with a toric or bitoric surface with corrections of up to 5 D to correct even high amounts of astigmatism are available. They have demonstrated reasonable rotational stability.

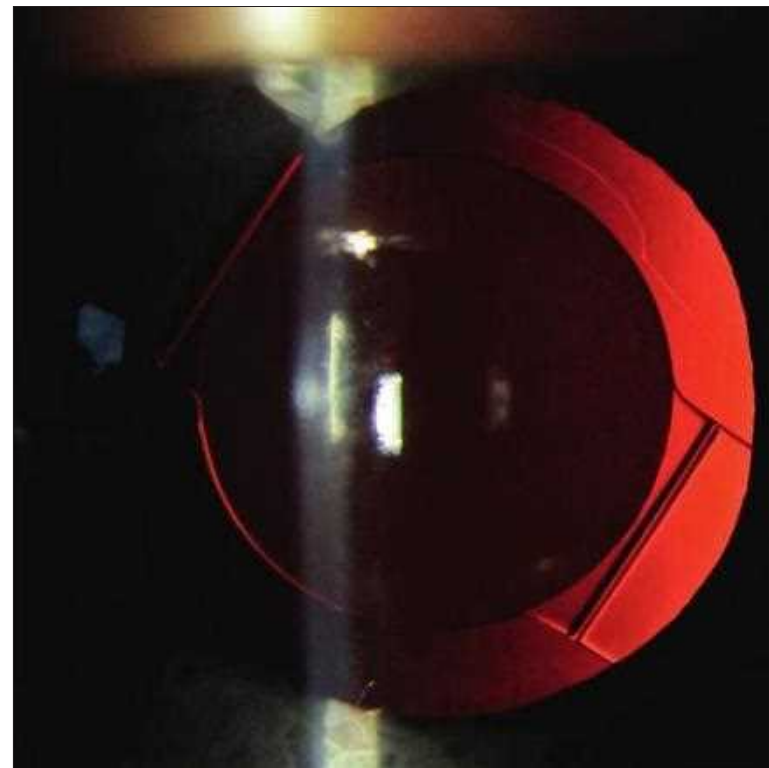
### Multifocal Intraocular Lenses

Pseudoaccommodative bifocal or trifocal lenses with a refractive and/or diffractive design have been in routine refractive surgical use for the last couple of years. For acceptable correction of presbyopia, the achieved refractive error must be negligible. However, this is often not the case after lens exchange alone even with toric multifocal IOLs, and the use of modern biometry devices, as well as sophisticated lens power calculation formulae. Then an enhancement with an excimer laser may be an option. However, even if emmetropia is achieved, compromises in night vision, glare, and halos remain inherent drawbacks of this approach.

### Potentially Accommodative Intraocular Lenses

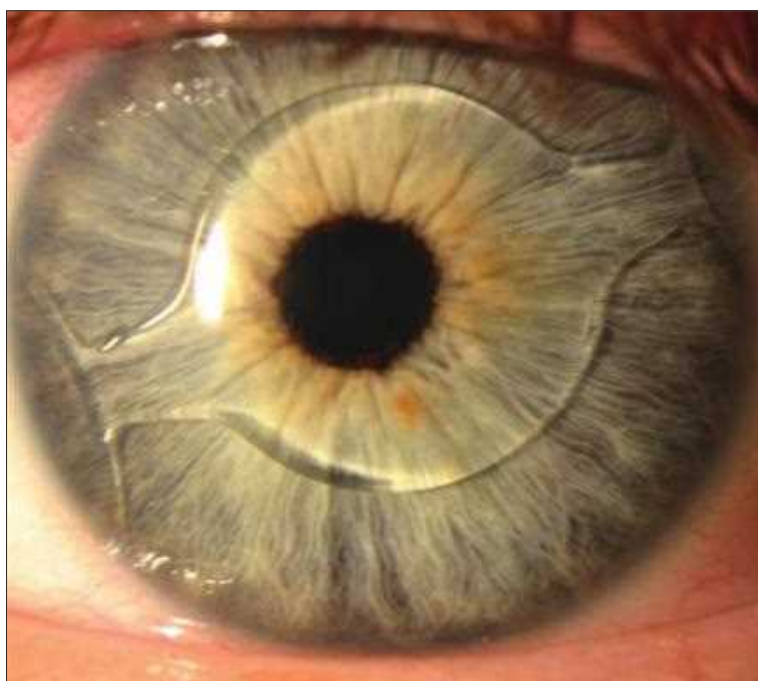
An alternative approach to a true accommodative IOL is to use the “focus shift” principle produced by an increase in effective lens power with forward movement of the optic.<sup>74–76</sup> The haptics of the accommodative IOL fixate in the capsular bag and allow the optic to move in reaction to the contraction of the ciliary muscle so that the patient can focus on nearby objects (Fig. 3.1.11). However, based on simple calculations, the forward shift possible in the capsular bag on its own is not sufficient to allow for the restoration of a reasonable amount of accommodation of 2–3 D for a single optic lens.

Another variant is to combine two optics that move relative to each other within the capsular bag into a single IOL (Synchrony dual-optic lens, Abbot Medical Optics, AMO, Santa Ana, CA). Using this intraocular telescope effect, small excursions may allow for sufficient accommodative response. The FluidVision IOL (PowerVision, Belmont, CA) uses liquid channels to harness the accommodative forces from the ciliary body expressed through the capsule similar to the crystalline lens. The NuLens (NuLens, Ltd., Herzliya Pituah, Israel) is a two-piece IOL that is placed outside the capsular bag. With the Tetraflex lens (Lenstec, St Petersburg,



**Fig. 3.1.11 Potentially Accommodative Intraocular Lens, “Crystalens.”** The IOL is fixated in the capsular bag. Forward movement or change in shape of the IOL in reaction to the contraction of the ciliary muscle may have an accommodative effect.





**Fig. 3.1.12** Angle-Supported Anterior Chamber Phakic Lens (© 2017 Novartis).

FL) the rationale is that accommodation results from an increase in HOA caused by deformation of the IOL through ciliary muscle contraction and/or increased vitreous pressure analogous to the natural lens. However, no long-term data are available yet for any of these potentially accommodating IOLs.

### Light-Adjustable Intraocular Lenses

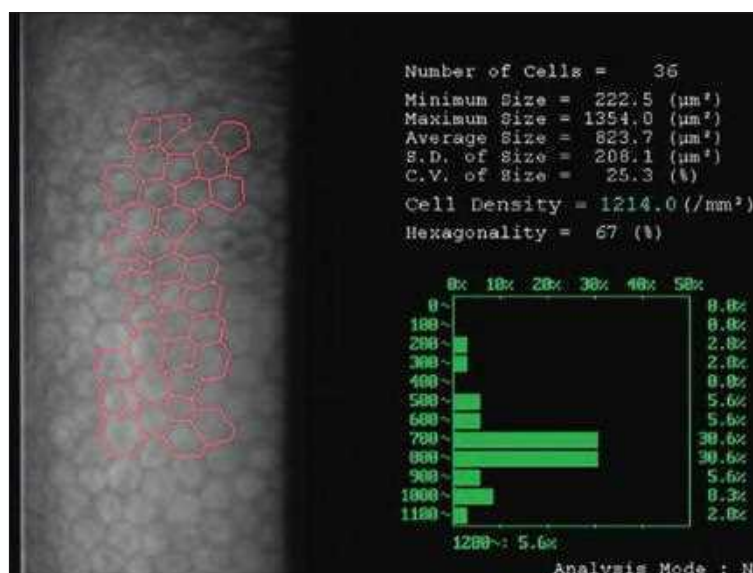
The Light Adjustable Lens (LAL, Calhoun Vision, Pasadena, CA) utilizes a Nobel prize-winning technology that allows it to change its refractive power after implantation in the eye. The LAL has properties similar to standard monofocal IOLs, but it differs with the special macromers incorporated in the makeup of the lens. These macromers are sensitive to light of a certain wavelength. When irradiated by such light, the macromers are photopolymerized.

After LAL implantation using a standard cataract surgery technique, allowing 2–3 weeks for corneal incisions to heal and refraction to stabilize, the lens in the eye will be irradiated for approximately 2 minutes with a digital light delivery device specially designed to deliver the exact dose and profile of light onto the lens. This light exposure is limited to certain portions of the lens and lets the macromers form an interpenetrating network via photopolymerization. Over the next 1–2 days, unreacted macromers from the nonexposed areas physically migrate to the irradiated areas, thus re-establishing a chemical equilibrium. This physical diffusion causes the irradiated parts to swell and change their curvature, which results in a change of refractive power. Myopia, hyperopia, and astigmatism may be corrected by customized irradiation patterns. Even multifocal treatments or the induction of positive or negative asphericity are thus possible. Once the targeted power adjustment is achieved, the entire lens is irradiated to polymerize the remaining unreacted macromers.

### Phakic Intraocular Lenses

In the 1950s, the use of phakic IOLs was attempted first by Strampelli and Barraquer but abandoned at that time because of multiple complications. Improvements in IOLs have renewed interest in the procedure. The iris-claw lens originally devised by Worst for the correction of aphakia was later modified by Fechner et al.<sup>77</sup> to correct high myopia in phakic patients. It is enclaved in the midperipheral, less mobile iris and presently requires a 6.0-mm incision for its insertion. The angle-supported phakic IOL was introduced by Baikoff and Joly<sup>78</sup> for the correction of myopia and has gone through several modifications (Fig. 3.1.12). Long-term follow-up has reported progressive pupil ovalization with an older model.<sup>79</sup>

The posterior chamber phakic IOL was introduced by Fyodorov et al.<sup>80</sup> in 1990. Several new models have been developed since. They must accommodate to the space between the posterior iris and the crystalline lens. Sizing is crucial. If the IOL vaults too much, pigment dispersion and even papillary block glaucoma can result. If it lies against the anterior surface of the crystalline lens, cataract can result.



**Fig. 3.1.13** Endothelial Cell Loss 4 Years After Implantation of an Iris-Claw Lens in a 29-Year-Old Woman.

Long-term follow-up is needed for all types of phakic IOLs regarding endothelial cell loss (Fig. 3.1.13), glaucoma, iris abnormalities, and cataract formation.

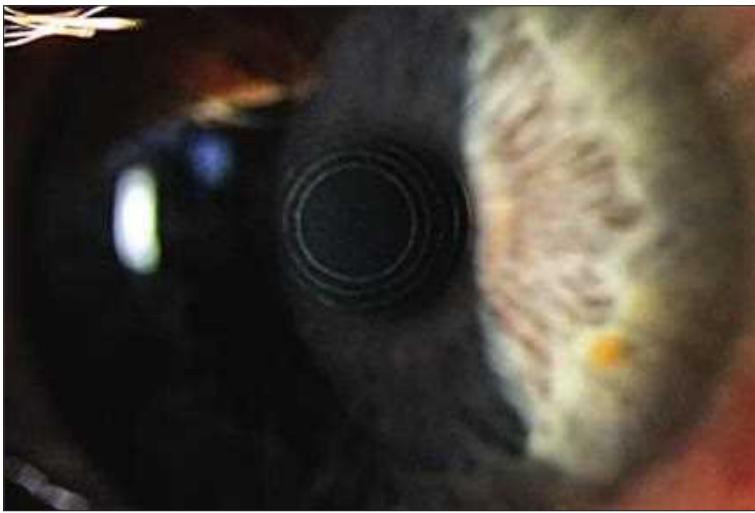
### Add-on Intraocular Lenses in Pseudophakic Eyes

In contrast to obsolete “piggyback” procedures in which two IOLs were implanted in the capsular bag, the “add-on” concept involves placement of an additional IOL in the sulcus ciliaris after routine implantation of another lens into the capsular bag. The first “add-on” lens (HumanOptics, Germany) was first implanted in 2000. An add-on IOL can be performed immediately following cataract surgery in a single session or years later. Its indications include correction of residual ametropia after cataract surgery (spherical and/or cylindrical) and the treatment of pseudophakic presbyopia. This method avoids the risk and hazards of IOL explantation from the capsular bag. The exchangeability of the additional IOL may be advantageous in cases with expected change of refraction as in keratoplasty patients, in pediatric patients after cataract surgery, and for refractive power compensation in vitrectomized eyes filled with silicone oil.

### New or Alternative Approaches

#### Photorefractive Intrastromal Cross-Linking (PiXL)

Corneal collagen cross-linking, recently FDA approved to halt progressive ectatic disorders, uses UV light and a photosensitizer (riboflavin) to strengthen chemical bonds in the cornea. A mild flattening of the corneal



**Fig. 3.1.14 IntraStromal Rings.** Rings formed by femtosecond laser bubbles 6 months after IntraCor placement in the nondominant eye. The patient perceived the rings without upset.

zonules have been made taut by either scleral expansion or infrared laser application. However, this theory of accommodation is not supported by independent studies. The studies undertaken all support the classic accommodative mechanism described by Helmholtz.

### Axial Length

Presently, procedures that modify the axial length of the eye—by either resection of the sclera or reinforcement of the posterior pole in cases of high myopia—have a role in the management of staphyloma but not in the management of refractive error.

### Refractive Indexes

Although not intended to be a refractive procedure, the use of compounds with a different index of refraction during retinal surgery must be considered. In an aphakic eye, a convex bubble of silicone oil (with a higher index of refraction) will act as a positive IOL, rendering the eye more myopic while the oil stays in place. A gas bubble with a lower index of refraction will act as a diverging IOL, rendering the eye hyperopic while the gas stays in place.

## SUMMARY

Refractive surgery is an established subspecialty of ophthalmology with a rapidly growing choice of long-term proven and novel procedures. The responsible and caring refractive surgeon must choose the procedure that best fits the needs and expectations for each particular patient from among all the techniques described in Part 3 Refractive Surgery. The patient should be fully aware of all the risks and benefits as well as all the optical alternatives to the proposed procedure, especially if a novel procedure is recommended. Presbyopia correction is targeted with multiple approaches, but to date none is perfect.

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# Preoperative Evaluation for Refractive Surgery

## 3.2

*Praneetha Thulasi, Joshua H. Hou, Jose de la Cruz*

### Definitions:

- Wavefront aberrometry is the measurement of the wavefront that emerges from an eye as a result of light reflecting from a focused light spot on the fovea. Application of Zernike polynomials allows characterization of a reconstructed estimated wavefront.
- Videokeratography is the computerized measurement of variation in curvature and dioptric power across the corneal surface that is typically based on the corneal reflection of the Placido pattern.
- Pachymetry is the measurement of corneal thickness.

### Key Features

- Preoperative evaluation for refractive surgery should involve documentation of refractive stability, review of both systemic and ophthalmic contraindications, manifest refraction, cycloplegic refraction, pupil measurements, pachymetry, wavefront analysis, corneal topography, slit-lamp examination, and dilated fundus examination.
- Care should be taken to identify patients at risk for postoperative corneal ectasia.
- Patient counseling is an important part of preoperative testing before refractive surgery.

## INTRODUCTION

Comprehensive preoperative evaluation of patients considering refractive surgery is often preceded by a brief screening examination to eliminate patients who are clearly not candidates for refractive surgery. Although it can help identify patients who would not benefit from refractive surgery, it also helps the surgeon plan the operative technique and further recommendations for a patient.

### General Considerations

#### Age

Laser corrective surgery is approved for those over 18 years of age who have had a stable refractive error over the previous 1–2 years. Although laser corrective surgery may be indicated in younger patients who are otherwise intolerant of traditional therapy, care must be taken because refractive error at this age often is unstable. A stable refractive error generally is defined as a  $\pm 0.5$  diopter (D) change in refraction over the past 1–2 years. Every patient presenting to a screening examination should be asked to discontinue all contact lens wear (1 week for soft nontoric lenses, 2 weeks for toric lenses, and at least 3 weeks for rigid lenses) and asked to bring their previous spectacles for assessment of refractive stability.

#### Degree of Correction

Although different laser platforms are approved for various thresholds of refractive correction, most surgeons opt to limit myopic correction to  $-10$  D and hyperopic and astigmatic correction to  $+4$  D to prevent postoperative corneal ectasia and haze and to avoid the unpredictability of correction at these higher refractions.

#### Patient Expectations

Perhaps the most important aspect of refractive surgery is appropriate counseling to set realistic expectations. Patients who are risk averse, who

### BOX 3.2.1 Systemic Contraindications to Photorefractive Keratectomy and Laser-in Situ Keratomileusis

#### Immunological Disease

- Autoimmune
- Collagen vascular
- Immunodeficiency

#### Pregnancy or Nursing (not absolute contraindication)

#### Abnormal Wound Healing

- Keloids (contraindicated for PRK only)
- Abnormal scars

#### Diabetes Mellitus (if corneal sensation is not intact)

#### Interference from Systemic Medications

- Isotretinoin
- Amiodarone hydrochloride

expect better vision than with glasses or contacts, or who have unrealistic expectations are likely not good candidates for refractive surgery. Appropriate counseling becomes even more important in patients between 40 and 50 years of age as presbyopia sets in and monovision may need to be a consideration. Another aspect to consider is a patient's occupation and hobbies. Those who perform activities that may put them at risk for flap dislocations should not be offered laser-assisted in situ keratomileusis (LASIK).

### Systemic Contraindications to Keratorefractive Surgery

A thorough medical history should be obtained from all patients considering refractive surgery. In particular, patients with a history of diabetes mellitus, pregnancy, autoimmune disease, collagen vascular disorders, thyroid disease, or abnormal wound healing may be at risk for poor outcomes postoperatively and should be identified before proceeding with surgery (Box 3.2.1).

#### Diabetes Mellitus

Uncontrolled diabetes not only leads to unstable refractions but also causes poor wound healing, persistent epithelial defects, and neurotrophic changes after laser surgery. A high risk of complications has been reported in the literature, including poor healing, worse refractive outcomes, and epithelial ingrowth.<sup>1,2</sup> Other studies did not show a significant complication rate in diabetes patients with well-controlled blood glucose.<sup>3,4</sup> Therefore it is recommended that refractive surgery be performed only in diabetes patients with tight blood glucose control ( $Hb A_{1c} < 7.9\%$ ) over the previous year, normal corneal sensation, and no signs of diabetic retinopathy.<sup>5</sup>

#### Pregnancy and Lactation

Refractive surgery during pregnancy is contraindicated because pregnancy can lead to transient changes in refractive error and cornea curvature and changes in tear quality. In addition, there are risks of fetal or infantile exposure to topical and systemic medications. There are multiple case reports of pregnancy-induced keratectasia following LASIK; it is important to counsel young female patients regarding this possibility.<sup>6–8</sup> Sharif reported a greater risk for corneal haze and myopic regression in women

who became pregnant within 5 months of photorefractive keratectomy (PRK). Starr also reported the case of a pregnant patient in whom overcorrection was induced and haze formation occurred.<sup>9,10</sup> It is recommended that patients wait 3 to 6 months after pregnancy and cessation of lactation before undergoing refractive surgery.

### Autoimmune Diseases

Uncontrolled collagen vascular disease is an absolute contraindication to undergoing laser refractive surgery, as it can lead to corneal melts and irregular healing. Patients with Sjögren's disease and thyroid-associated eye disease are predisposed to tear film irregularities and dry eyes.<sup>11</sup> Although most surgeons would agree that PRK will lead to poor healing in these patients, the debate is still ongoing whether patients with inactive or well-controlled collagen vascular disease can safely undergo LASIK.<sup>12</sup> Multiple studies have shown no additional complications with LASIK in patients with inactive disease and a normal ocular surface.<sup>3,13–15</sup> Case reports of severe complications also exist, however.<sup>11,16–19</sup> Appropriate counseling must be done in any patient with a collagen vascular disease interested in pursuing laser refractive surgery.

### Dermatological Keloid

Although dermatological keloid is listed as a precaution for LASIK and PRK, several studies have demonstrated good results without any additional complications after both PRK and LASIK.<sup>3,20,21</sup> Most surgeons at this point do not consider this a concern with laser surgery.

### Human Immunodeficiency Virus

A theoretical risk exists of transmission of human immunodeficiency virus (HIV) through laser plumes, but no reported cases have occurred to date that have shown such transmission. Nevertheless, adequate precautions must be taken while operating on patients with HIV. Hagen et al. used culture plates, and an excimer laser was used to ablate infected tissue.<sup>22</sup> None was culture positive. These patients also have a theoretical higher risk of infectious complications. Therefore only those on appropriate therapy and with adequate CD4 cell counts should be considered for refractive surgery.

### Medications

Multiple medications delay or inhibit wound healing after laser refractive surgery. Of these, amiodarone and isotretinoin need to be carefully considered before refractive surgery. Amiodarone is used to treat arrhythmias and can lead to multiple ocular side effects, including optic neuropathy, corneal and lenticular deposits, and halos around lights. Although there are reports of no increased complications, patients must be appropriately screened.<sup>23,24</sup> Isotretinoin is used to treat acne and can lead to dry eyes, blepharoconjunctivitis, and photosensitivity, all of which can complicate recovery.<sup>25</sup> Sumatriptan was previously considered to delay wound healing. However, recent reports do not show any significant adverse effects.<sup>26</sup> Various other systemic medications can exacerbate dry eye symptoms, and therefore patients on these should be appropriately counseled and treated.

## Ophthalmic Diseases

Multiple ophthalmic conditions necessitate special attention. Of note are disorders that lead to tear film deficiency, corneal dystrophies and ectasias, glaucoma, and other retinal and intraocular disorders (Table 3.2.1).

### Corneal Dystrophy

Any form of anterior corneal dystrophy is a contraindication for excimer laser use because this may lead to increased deposits.<sup>27</sup> Patients with epithelial basement membrane disease may benefit from PRK, as this can treat both the refractive error and the underlying pathology.<sup>28</sup> LASIK is contraindicated in patients with Fuchs' dystrophy because of the risk of corneal decompensation and potential for overestimation of corneal thickness in subclinical edema. There are case reports of safe performance of LASIK and PRK for posterior polymorphous corneal dystrophy.<sup>29,30</sup> Family history should be especially noted to ensure that any subtle changes of familial dystrophies are not missed.

### Corneal Curvature

Corneal curvature must be carefully examined because corneal ectasia after refractive surgery is a feared complication that can lead to severe loss of vision. Any signs or symptoms of corneal ectasia like keratoconus or pellucid marginal degeneration are a contraindication for laser refractive surgery. There are multiple criteria to evaluate and identify eyes at risk

TABLE 3.2.1 Ophthalmic Contraindications to Photorefractive Keratectomy

	Relative Contraindications	Absolute Contraindications
Ocular surface disease	Mild dry eye Lid disorders that affect the tear layer	Severe dry eye • Keratoconjunctivitis sicca • Exposure keratitis • Lid disorders that affect the tear layer Neurotrophic keratitis
Disorders that may be exacerbated by photorefractive keratectomy	Herpes zoster ophthalmicus/herpetic keratitis (if inactive for >1 year—unproved)	Herpes zoster ophthalmicus/herpetic keratitis (especially if active during the previous 6 months) Uncontrolled glaucoma
Abnormalities of corneal shape	Shape changes induced by contact lens Mild irregular astigmatism	Corneal ectasia • Keratoconus • Pellucid marginal degeneration • Keratoglobus High, irregular astigmatism
Other ophthalmic disorders	Posterior corneal dystrophies	Uveitis Diabetic retinopathy Progressive retinal disease

for postrefractive ectasias, but the key factors include abnormal topography, percent of tissue altered, thin corneal thickness, thin residual stromal bed, young age, and high myopia. Key elements of history such as rapidly changing refraction or a family history of ectasia can be helpful. Imaging using Placido-slit topography or Scheimpflug tomography can often identify suspicious changes in the anterior and posterior cornea.

### Ocular Surface Disease

Dry eyes are the most commonly experienced side effect after LASIK. Preoperative dry eye symptoms are at risk for worsening after laser surgery. It is important to optimize the ocular surface before refractive surgery. Although artificial tears are the mainstay of treatment, punctal plug placement during the LASIK procedure can decrease dry eye symptoms after LASIK.<sup>31</sup> Use of medications such as cyclosporine A after LASIK, while not significantly changing patient symptoms,<sup>32</sup> may improve refractive predictability.<sup>33</sup> Similarly, uncontrolled ocular allergy symptoms can lead to increased risk of perioperative complications; systemic treatment can decrease the risk of complications.

### Herpes Reactivation

Excimer laser treatment can lead to reactivation of herpes keratitis in both animal models and humans. Therefore refractive surgery was considered a contraindication. Recently however, de Rojas et al. presented a study in 48 patients who had inactive herpes keratitis for at least 1 year and in whom LASIK was performed while they were on oral and topical antiviral prophylaxis without any reactivation postoperatively.<sup>34</sup> The authors suggest careful patient selection, with inactive disease for at least 1 year, normal corneal sensitivities, and normal corneal parameters before proceeding. Given the risk of potentially devastating scarring if reactivation does occur, caution must be used while considering refractive surgery in this population.

### Glaucoma

Laser refractive surgery poses multiple complexities in patients with glaucoma. Although uncontrolled intraocular pressure is a contraindication for refractive surgery, patients with well-controlled glaucoma may be candidates. However, these patients often have ocular surface diseases that can complicate healing for LASIK or PRK. In addition, a change in corneal thickness can falsely change intraocular pressure measurements. Case reports exist of visual field, optic nerve, and nerve fiber layer changes occurring during the acute intraocular pressure elevation involved in LASIK flap creation,<sup>35,36</sup> and surface ablation procedures may be better suited in these patients. Another aspect to consider is the prolonged use of corticosteroids in patients undergoing PRK, which may lead to corticosteroid-induced intraocular pressure elevation, which occurs more commonly in patients predisposed to glaucoma.

### Other Considerations

Patients with visually significant or incipient cataracts must not undergo laser refractive surgery. Similarly, patients with significant retinal disease, latent strabismus, and monocular patients should not undergo laser refractive surgery.



**BOX 3.2.2 Ophthalmic Examination****Visual Acuity**

- Distance with and without correction
- Reading with and without correction

**Refraction**

- Current spectacle correction
- Manifest refraction
- Cycloplegic refraction with cyclopentolate 1%

**Topographical Analysis**

- Keratometry (measures central 3 mm)
- Computerized videokeratography

**Intraocular Pressure Measurement****External Examination**

- Ocular motility
- Ocular dominance
- Gross external examination measurements in bright and dim light

**Slit-Lamp Examination**

- Fluorescein stain
- Vital stain (if symptoms warrant)

**Dilated Funduscopy****Jones' Basal Tear Secretion Rate (if symptoms/signs warrant)****Pachymetry****OPHTHALMIC EXAMINATION**

The preoperative ophthalmic examination consists of determining patients' manifest and cycloplegic refraction, pupil diameter, ocular dominance, wavefront aberrometry measurement, corneal topography, pachymetry, slit-lamp examination, and dilated funduscopy (Box 3.2.2). Special care is required when manifest refraction is performed to avoid any errors. Cycloplegic refraction with 1% cyclopentolate is mandatory, especially in younger patients, to accurately measure refractive error in the absence of accommodation and to avoid myopic overcorrection.

A complete slit-lamp examination is important to identify problems with the lids, conjunctiva, cornea, or lens, which may lead to complications postoperatively. Eyelid malpositions, lagophthalmos, proptosis, and other external conditions that predispose the cornea to exposure must be recognized and treated before refractive surgery is attempted. Small interpalpebral fissures should be noted if LASIK is planned because of the difficulty in inserting the suction ring. Blepharitis and meibomian gland dysfunction should be treated aggressively before photoablation to reduce the risk of bacterial superinfection, to improve the quality of the tear film, and to prevent meibomian gland secretions and lash debris from becoming lodged in the interface between the flap and the corneal stroma.

Patients affected by significant corneal neovascularization extending within 1 mm of the ablation zone should be excluded from treatment. Extensive peripheral pannus should be noted and may be associated with bleeding following the keratectomy. Adequacy of the tear film should be assessed based on the Schirmer's test or tear meniscus height (approximately 0.3 mm) and tear-film breakup time ( $\geq 10$  sec).

An accurate preoperative measure of pupillary diameter in dim light should be obtained using an infrared pupillometer. Patients with scotopic pupil sizes  $\geq 6.5$  mm should be warned about the risks of night glare and halos following surgery, although the risk is lower with modern laser algorithms and blended ablation zones.<sup>37,38</sup>

In patients aged over 45 years, or those nearing the presbyopic age, a discussion regarding the postoperative need for reading glasses or the option for monovision correction should be discussed. Patients who are motivated to pursue monovision therapy should have ocular dominance assessed and should consider a trial of a monovision contact lens before surgery. Standard practice is to correct the dominant eye for distance and the nondominant eye for near sight in appropriate patients.

Keratometry should be measured to assess the power of the central cornea, to gauge the quality of the mires, and to provide a basis for later intraocular lens calculations. Tonometry, as part of a thorough examination, should also be obtained.

Dilated funduscopy should be performed to identify patients affected by progressive retinal disease, retinal holes, tears, or atypical lattice

degeneration, unrecognized diabetic retinopathy or myopic degeneration, and other pathologies that preclude photoablative treatment.

**ANCILLARY TESTING****Wavefront Measurement (Aberrometry)**

Recent advances in wavefront aberrometry have allowed for refined ablation profiles that correct for both higher- and lower-order aberrations in appropriate patients. Benefits to wavefront-guided LASIK include improved contrast sensitivity, reduced incidence of postoperative glare and halos, and reduced postoperative higher-order aberrations.<sup>39,40</sup> Wavefront testing should be the first examination performed before the eye is manipulated in any way. Any application of drops or tonometry can alter the results and thus should be avoided before testing. While waiting, patients should avoid reading magazines or other materials in the waiting room to minimize accommodation and dessication of the ocular surface. In all cases, wavefront measurements should be compared with the manifest and cycloplegic refractions to confirm consistency. Higher-order aberration indices, such as vertical coma, should be further reviewed for evidence suggestive of subclinical keratoconus.<sup>41</sup>

**Computerized Videokeratography**

Computerized videokeratography is crucial in the preoperative evaluation of patients for refractive surgery. Postoperative ectasia remains the most feared complication of photorefractive surgery; appropriate screening with corneal topography is absolutely essential. In any preoperative evaluation for refractive surgery, one must maintain a high degree of suspicion for ectatic disorders.

Care should be taken to establish the stability of patient corneal topography before surgery. Progressive changes in corneal topography may be indicative of ectatic disease or corneal molding (warping) due to rigid or soft contact lens wear. Because distortion from long-term contact lens wear may persist for a long time, patients should discontinue all contact lens wear before the preoperative examination. Prolonged contact lens cessation is warranted in patients who demonstrate poor stabilization of their corneal topography.<sup>42,43</sup>

**Pachymetry**

Pachymetry must be performed in all patients before LASIK. It is mandatory that the postablation corneal bed following LASIK be at least 250  $\mu$ m in thickness to avoid iatrogenic corneal ectasia and refractive instability. Residual bed thickness can be estimated from the baseline corneal pachymetry, the anticipated flap thickness, and the expected depth of ablation.

**Counseling**

Not all patients who meet medical and ophthalmic criteria for refractive surgery are necessarily good candidates for the procedure. Patients with unrealistic expectations are likely to be dissatisfied after surgery. Appropriate counseling regarding the risks of over- or undercorrection, postoperative dry eye, or postoperative glare and halos should be performed routinely. Patients should be informed of the potential need for spectacles after surgery for certain tasks such as driving at night. High hyperopes should be made aware of the decreased predictability of photoablative treatments in hyperopic cases. Presbyopic myopes should be made aware that the removal of distance glasses to achieve better near vision would no longer be possible after refractive surgery.

The preoperative evaluation of the patient for refractive surgery is lengthy and must be performed in an unrushed manner. However, it is time well spent because the best treatment for complications and disappointment is avoidance.

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# Excimer Laser Surface Ablation: Photorefractive Keratectomy (PRK), Laser Subepithelial Keratomileusis (LASEK), and Epi-LASIK

## 3.3

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### Definitions:

- Photorefractive keratectomy (PRK) is a procedure in which the cornea is reshaped using an excimer laser. PRK involves epithelial removal and photoablation of Bowman's layer and anterior corneal stromal tissue. In contrast to laser-assisted in situ keratomileusis (LASIK), there is no need for flap creation with a microkeratome.
- Laser subepithelial keratomileusis (LASEK) and epi-LASIK are corneal surface ablative refractive procedures.
- LASEK involves creating an epithelial flap with dilute alcohol and repositioning this flap after laser ablation.
- Epi-LASIK involves the use of a motorized epithelial separator to mechanically separate the corneal epithelium from the stroma.

### Key Features

- Excimer laser surface ablation results in removal of a precise amount of tissue from the anterior cornea. The central cornea is reprofiled to achieve myopic, hyperopic, or astigmatic correction.
- The refractive result is related to the depth of ablation and the diameter of the optical zone.
- Preoperative assessment plays a key role in determining a safe and effective outcome. It includes corneal pachymetry, topography, and cycloplegic refraction.
- Mitomycin-C is useful to prevent corneal haze and scarring in high myopic corrections.
- Wavefront guided ablations result in higher percentage of patients achieving uncorrected visual acuity of 20/20 or better compared with conventional ablations.
- PRK, LASEK and epi-LASIK are considered in patients with thin, steep, or flat corneas and in patients predisposed to flap trauma in thinner corneas, where creation of LASIK flap may leave less tissue than desired (usually 250  $\mu\text{m}$  of corneal tissue) remaining to the posterior stroma.
- Postoperative complications of PRK, LASEK, and epi-LASIK include epithelial healing, pain, infiltrates and infection, dry eye, and corneal haze.
- LASEK-related intraoperative complications include alcohol leakage, incomplete epithelial detachment, and laser-related complications.
- Epi-LASIK-related intraoperative complications include flap-related complications (when these occur the procedure may be converted to PRK) and laser-related complications.

### INTRODUCTION

The surgical treatment of myopia, hyperopia, and astigmatism has made great strides over time, with the introduction and advancement of the excimer laser PRK followed by LASIK surgery. Ultraviolet radiation at 193 nm wavelength utilized by the excimer laser can remove precise amounts of tissue from the anterior cornea. Use of the excimer laser for the treatment of myopia, hyperopia, and astigmatism is now well established.<sup>1-7</sup>

Other corneal surface ablative procedures include laser-assisted subepithelial keratomileusis (LASEK) and epi-LASIK. In principle, they combine the advantages of both LASIK (laser-assisted in situ keratomileusis) and PRK, while at the same time overcoming some of their problems.<sup>8-18</sup> LASEK was first conceived independently in 1996 by Azar,<sup>9</sup> as well as Cimberle and Camellin.<sup>10</sup> LASEK involves creating an epithelial flap with dilute alcohol solution and repositioning this flap after laser ablation, thus eliminating any inherent flap complications. Epi-LASIK makes use of a motorized epithelial separator to mechanically separate the corneal epithelium in toto from the stroma without the use of alcohol or chemicals.<sup>14,15</sup> This device makes use of a proprietary oscillating blade that separates the epithelial layer at the layer of Bowman's membrane without dissecting the corneal stroma.

Development of excimer lasers began in 1975 when Velasco and Setser<sup>19</sup> noted that metastable rare gas atoms such as xenon (Xe) could react under high pressures with halogens such as fluorine (F) to produce unstable compounds such as XeF.<sup>20</sup> These compounds rapidly dissociated to the ground state of the individual molecules associated with the release of an energetic ultraviolet photon and could be made to undergo light amplification by stimulated emission when they were excited by an electron beam, with the argon-fluorine (ArF) molecule emitting light with a wavelength of 193 nm.<sup>21</sup> The ablation thresholds, ablation rates, and healing patterns for different excimer wavelengths were described by Krueger and Trokel.<sup>22-24</sup> The ablation threshold for the cornea is the fluence at which tissue removal begins, which is approximately 50 mJ/cm<sup>2</sup> for 193 nm. The 193 nm light has very low tissue penetrance, enabling the laser to operate on the surface of the corneal tissue with precision and safety.

Large-area ablation with resculpting of the cornea to correct refractive errors is termed *laser keratomileusis*. Tissue is removed with great precision, and the corneal epithelium heals over the ablated area to create a smooth surface. About 0.24  $\mu\text{m}$  of tissue is removed with each laser pulse. Corneal epithelium ablates at a slightly faster and more irregular rate than corneal stroma, which is the reason that the epithelium is typically removed mechanically before ablation of the stroma for the PRK procedure. Bowman's layer ablates about 30% slower than the stroma, and fluorescein decreases the ablation rate by about 40%.

### ABLATION PROFILES

Munnerlyn<sup>25</sup> described the direct relation between the amount of tissue that must be removed to produce a certain refractive result and the optical zone size. The relationship can be simplified to:

$$\text{Depth of ablation } (\mu\text{m}) = [\text{diameter of optical zone (mm)}]^2 \times 1/3 \text{ power (D)}$$

As the optical zone is increased, the ablation depth needs to be increased. The optical zone size and depth are optimized to reduce excessive wound healing seen in deep ablations and the excessive halos, edge glare, and irregular astigmatism seen with small optical zones.<sup>26</sup>

In correction of spherical hyperopia, the cornea needs to be reshaped into a steeper convex structure. This can be achieved by a peripheral annular ablation with peripheral flattening creating central corneal

steepening. Generally, a larger (9–9.5 mm) ablation diameter is required to achieve permanent steepening of the cornea. It is more challenging to deliver larger-diameter hyperopic ablations than the equivalent myopic correction.

Excimer laser surgical correction of astigmatism requires that the cornea be ablated in a cylindrical or toric pattern. In the early excimer systems, the excimer laser beams were passed through a set of parallel blades that gradually open as directed by the computer algorithm. The orientation and speed of opening depends on the orientation and amount of astigmatism to be corrected. Flattening occurs perpendicular to the long axis of the slits. No change in power occurs along the axis of the slits. Another method of creating a toric ablation utilizes an ablatable mask. The laser first ablates the thinnest areas of the mask, thus allowing greater treatment of the cornea in areas where the mask is thinnest.<sup>27</sup> Any pattern can be created by differential protection of the cornea from treatment.

A computer-controlled scanning beam can be utilized to treat astigmatism. The size of the beam can be varied to create a transition zone, preventing a steep step off at the edges of treatment. With this method, it is possible to steepen, rather than flatten an axis, thus allowing for a more direct and tissue-conserving treatment of hyperopic astigmatism. Wavefront-guided customized corneal ablation profiles have been introduced for correction of irregular astigmatism (higher-order aberrations) as well as spherocylindrical refractive errors.

## INDICATIONS

PRK, LASEK, and epi-LASIK surface ablation may be performed in patients who are at low risk for subepithelial haze with low to moderate myopia and myopic astigmatism. The ideal candidates for LASEK and epi-LASIK are those with mild to moderate myopia up to −700 diopters (D).<sup>12,17</sup> LASEK has also been shown to be effective for hyperopia up to +4.00 D.<sup>28</sup>

Surgeons should consider these surface ablative refractive procedures for patients whose corneal characteristics render them at greater risk for LASIK, such as those with thin corneas where less than 250  $\mu\text{m}$  of residual stromal bed would be left and those with steep or flat corneas. These would also be the preferred surgical procedures in patients with lifestyles or professions that predispose them to flap trauma. LASEK may also be a better choice for patients with narrow palpebral fissures where the microkeratome cannot be well applied.

Contraindications for these procedures include exposure keratopathy, neuropathic keratopathy, severe dry eye (Sjögren's syndrome), keratoconus, central or paracentral corneal scars, unstable myopia, and irregular astigmatism.<sup>11,12</sup>

## PREOPERATIVE EVALUATION

As for any refractive procedure, the preoperative workup for PRK, LASEK, and epi-LASIK includes uncorrected and best-corrected distance and near visual acuities with a manifest and cycloplegic refraction. Ocular dominance testing, anterior segment and posterior segment examinations, keratometry, tonometry, pachymetry, aberrometry, and computerized topographical analysis are other important parts. A careful systemic and ocular history and examination is necessary to look for conditions that may require preoperative management or contraindicate the procedure (Box 3.3.1). For example, mild degrees of dysfunctional tear syndrome or dry eye (Fig. 3.3.1) can be managed preoperatively with lid hygiene, artificial tears, and topical cyclosporin for better early postoperative recovery. Meticulous preoperative counseling is also a very important aspect, as for any refractive procedure.

## PRK SURGICAL TECHNIQUE

### Patient Preparation and Epithelial Removal

The initial patient preparation is similar to all the three surface ablation procedures. The patient is positioned under the microscope, and the head is carefully aligned to make sure that the iris plane is perpendicular to the laser beam. After topical anesthesia (0.5% proparacaine or tetracaine), the eyelids and periocular skin are prepped with dilute povidone–iodine (Beta-dine) solution. A lid speculum is placed to provide adequate exposure of the globe. Careful centration with the eye aligned in the x-, y-, and z-planes is crucial.

It is important to perform the treatment as soon as possible after the proparacaine or tetracaine drops are instilled or have the patient close their eyes to prevent exposure keratitis from poor blinking. Drying of the

### BOX 3.3.1 Indications and Cautions

#### Potential Preference of PRK Over LASIK

- Thin corneal pachymetry
- Epithelial irregularities/dystrophies
- LASIK complications in the contralateral eye
- Predisposition to trauma
- Low myopia
- Irregular astigmatism
- Dry eyes

#### Cautions

- Postoperative pain intolerance/concern
- Keratoconus
- Glaucoma
- Pregnancy
- Advanced diabetes
- Collagen vascular disease
- Previous herpes (simplex or zoster) infection
- Severe dry eye
- Untreated blepharitis
- Neurotrophic cornea
- Peripheral ulcerative keratitis
- Patients on isotretinoin (Accutane), amiodarone (Cordarone), or sumatriptan (Imitrex)

inferior half of the cornea, as often occurs after anesthetic drops have been instilled, can lead to increased thinning inferiorly.

The epithelium is marked with a 7- or 8-mm optical zone marker centered on the pupil for myopia or a 9- or 10-mm marker for hyperopia or wavefront correction. It is helpful to remove a 1-mm larger area of epithelium than the planned ablation. Mechanical epithelial removal involves the use of a Tooke knife, disposable excimer spatula, or rotating brush. Alternatively, alcohol (18%–25% ethanol for 21–30 seconds) can be used to loosen the epithelium or excimer laser for partial or complete removal. The laser is typically set to a depth of approximately 45  $\mu\text{m}$ , and the epithelium being ablated by the laser beam can be visualized under blue fluorescence. The ablation is stopped when a change from a fluorescent pattern to a dark pattern is seen, indicating that the epithelium has been ablated. If fluorescence persists across the whole area after a 50  $\mu\text{m}$  ablation has been performed, an additional depth of 25  $\mu\text{m}$  should be set for the laser. It may be helpful to scrape the remaining epithelium. It is important to remove the epithelium totally. Any residual epithelium will create an uneven ablation and irregular astigmatism. Also, epithelial removal should be quick to avoid corneal hydration changes.

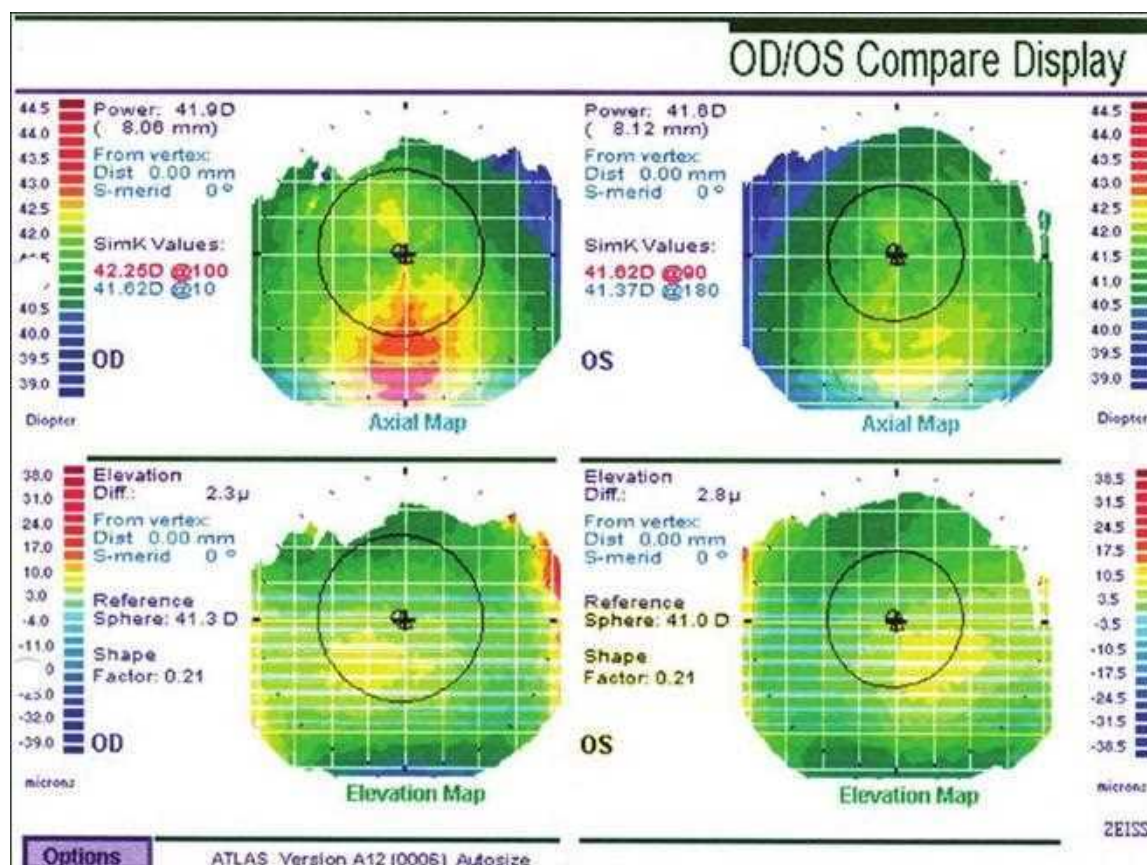
### Stromal Ablation

The ablation should promptly follow epithelial removal to prevent drying, which can lead to increased haze and scarring.<sup>29–30</sup>

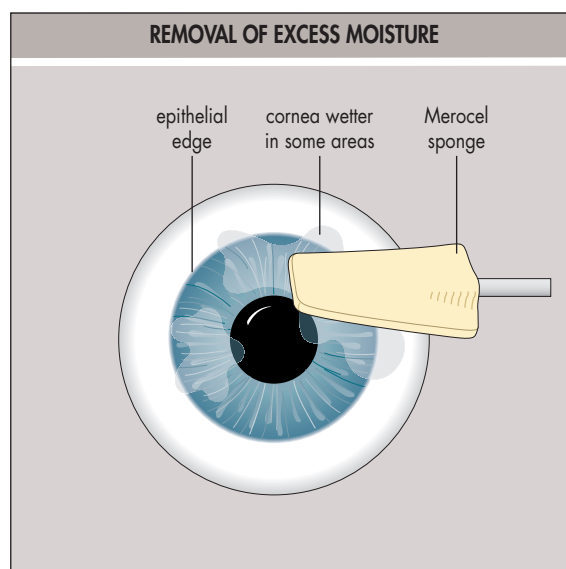
Centration is rechecked after epithelial removal. For astigmatic corrections, alignment on the proper axis should be verified by marking the patient's limbus at the 12 and 6 o'clock positions with gentian violet dye on a Sinskey hook at the slit lamp before the procedure. The ultraviolet excimer lasers used have wavelengths outside the visible spectrum; an auxiliary aiming device that is coaxial to the ablating laser is required to make certain the laser is centered on the eye. Helium–neon lasers, laser diodes, or a coaxial aiming target are commonly used for this. In automated systems with eye trackers, this is used only for initial alignment, but in manually controlled systems, it is used to align the eye during the entire procedure.

The ablation is begun, centered over the pupil with the patient looking at the fixation light. Eye movements should be minimized during the ablation to reduce irregular surfaces. The use of an eye tracker is helpful in maintaining centration.<sup>31–32</sup> It is important to make certain that the hydration status of the corneal stroma is uniform during the procedure. If excess fluid is detected, the procedure should be paused and the excess fluid removed by using a cellulose sponge to dry the cornea (Fig. 3.3.2). Likewise, if the cornea becomes too dry, a cellulose sponge can be used to evenly hydrate it. Inadequate or excessive tissue hydration leads to more or less tissue ablation per pulse, resulting in an overcorrection or undercorrection, respectively.





**Fig. 3.3.1 Inferior Steepening and Irregularity of the Topography Is Seen in This Young Patient With Dry Eye and Blepharitis.** This patient improved significantly with lid hygiene, artificial tears, and topical cyclosporin 0.05% for 1 month.



**Fig. 3.3.2 A Merocel Sponge Can Be Used to Remove Excess Moisture in a Uniform Fashion.** Maintaining proper central corneal hydration may improve results.

the cornea while the barrel of the marker is filled with two drops of 18% ethanol. After 25–35 seconds, the ethanol is absorbed using an aspiration hole followed by dry sponges (Weck-cel or Merocel, Xomed, Jacksonville, FL), to prevent alcohol spillage onto the epithelium outside the marker barrel. The ethanol application may be repeated for an additional 10–15 seconds.

One arm of a modified curved Vannas scissors or a jeweler's forceps is inserted under the epithelium and traced around the delineated margin of the epithelium, leaving 2–3 clock hours of intact margin, preferably at the 12 o'clock position. The loosened epithelium is peeled as a single sheet using a jeweler's forceps, spatula, or a Merocel sponge, leaving a flap of epithelium with the hinge still attached. The ablation is then initiated immediately using an excimer laser.

After ablation, a 30-gauge anterior chamber cannula is used to hydrate the stroma and epithelial sheet with balanced salt solution. The epithelial sheet is replaced on the stroma using the straight part of the cannula under intermittent irrigation. The epithelial flaps are realigned using the previous marks. The flap is then allowed to dry for 2–5 minutes.

A bandage contact lens is placed on the operated eye at the end of the procedure.

### Epi-LASIK Surgical Technique (Fig. 3.3.4)

The corneal epithelium is dried with sponges after proper positioning and ocular surface irrigation with balanced salt solution using an anterior chamber cannula. The cornea is marked with a standard LASIK marker.

The subepithelial separator is applied to the eye and suction is activated by a foot pedal. The oscillating blade separates the epithelium leaving a 2–3-mm nasal hinge, the suction is released, and the device is removed from the eye. The epithelial sheet is reflected nasally using a moistened Merocel sponge or a spatula. Laser ablation is then initiated immediately, with use of an excimer laser. The cornea is then irrigated with balanced salt solution. The epithelial sheet is carefully repositioned using the straight part of the cannula. The replaced corneal epithelial sheet is left to dry for 2–3 minutes to allow adhesion to the underlying corneal stroma. Some surgeons may choose to discard the epithelial flap instead. In this situation, the subepithelial separator would then simply remove the epithelium before the laser ablation.

At the end of the procedure, a bandage contact lens is placed on the operated eye.

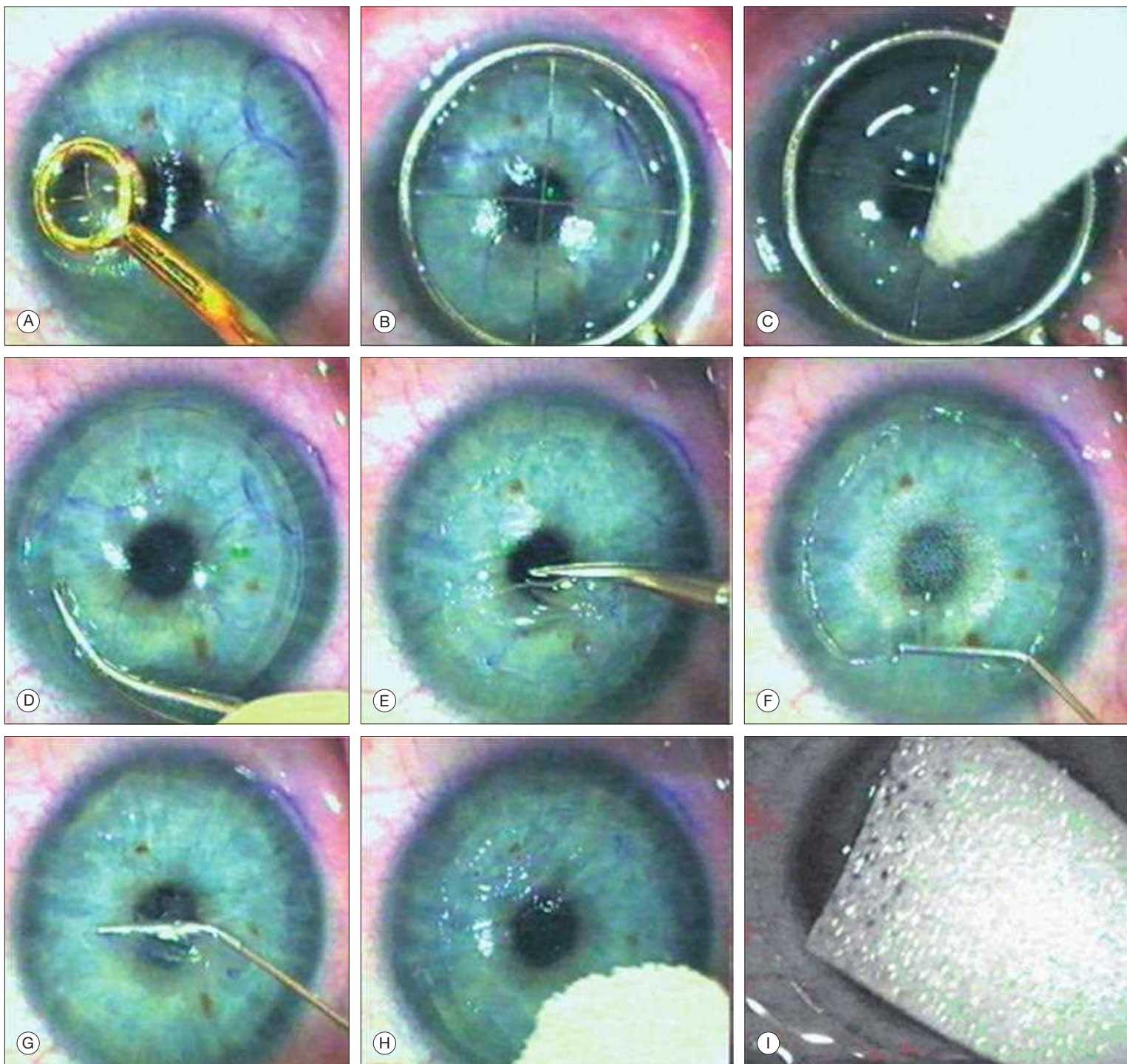
### LASEK Surgical Technique (see Fig. 3.3.3)

Patient is prepared and eye aligned as described earlier. Just before surgery, topical broad-spectrum antibiotics (e.g., tobramycin or a fluoroquinolone) may be applied prophylactically. Some surgeons use topical nonsteroidal anti-inflammatory drugs (NSAIDs) for pain relief. Dilute ethanol at a concentration of 18% is prepared by drawing 2 mL of dehydrated alcohol into a 12 mL syringe and diluting it with sterile water to 11 mL.<sup>9,12</sup>

The cornea is marked with 3-mm circles around the corneal periphery to allow the surgeon to have the precise reference points to realign the flap over the corneal bed. An alcohol dispenser consisting of a customized 7- or 9-mm semisharp marker (ASICO, Westmont, IL) attached to a hollow metal handle serves as a reservoir for the 18% alcohol.

Firm pressure is exerted on the central cornea and a button is pushed on the side of the handle, releasing the alcohol into the well of the marker. Alternatively, a 7-mm optical marker (Storz, St Louis, MO) is used to delineate the area centered on the pupil. Gentle pressure is applied on





**Fig. 3.3.3 Our Current LASEK Technique.** (A) Multiple marks are applied around the corneal periphery, simulating a floral pattern. (B) An alcohol dispenser consisting of a customized 7- or 9-mm semisharp marker attached to a hollow metal handle serves as a reservoir for 18% alcohol. Firm pressure is exerted on the cornea, and alcohol is released into the well of the marker. (C) After 25–30 seconds, the ethanol is absorbed using a dry cellulose sponge. (D) One arm of a modified Vannas scissors (note knob at tip of lower arm) is then inserted under the epithelium and traced around the delineated margin of the epithelium, leaving a hinge of 2–3 clock hours of intact margin, preferably at the 12 o'clock position. (E) The loosened epithelium is peeled as a single sheet using a Merocel sponge or the edge of a jeweler's forceps, leaving it attached at its hinge. (F) After laser ablation is performed, an anterior chamber cannula is used to hydrate the stroma and epithelial flap with balanced salt solution. (G) The epithelial flap is replaced on the stroma using the cannula under intermittent irrigation. (H) Care is taken to realign the epithelial flap using the previous marks and to avoid epithelial defects. The flap is allowed to dry for 2–5 min. Topical corticosteroids and antibiotic medications are applied. (I) A bandage contact lens is placed. (Reproduced from Azar DT, Taneri S. LASEK. In: Azar DT, Gatinel D, Hoang-Xuan T, editors. *Refractive surgery*. 2nd ed. Philadelphia: Elsevier; 2007. p. 239–47.)

### Surface Ablation With Mitomycin-C

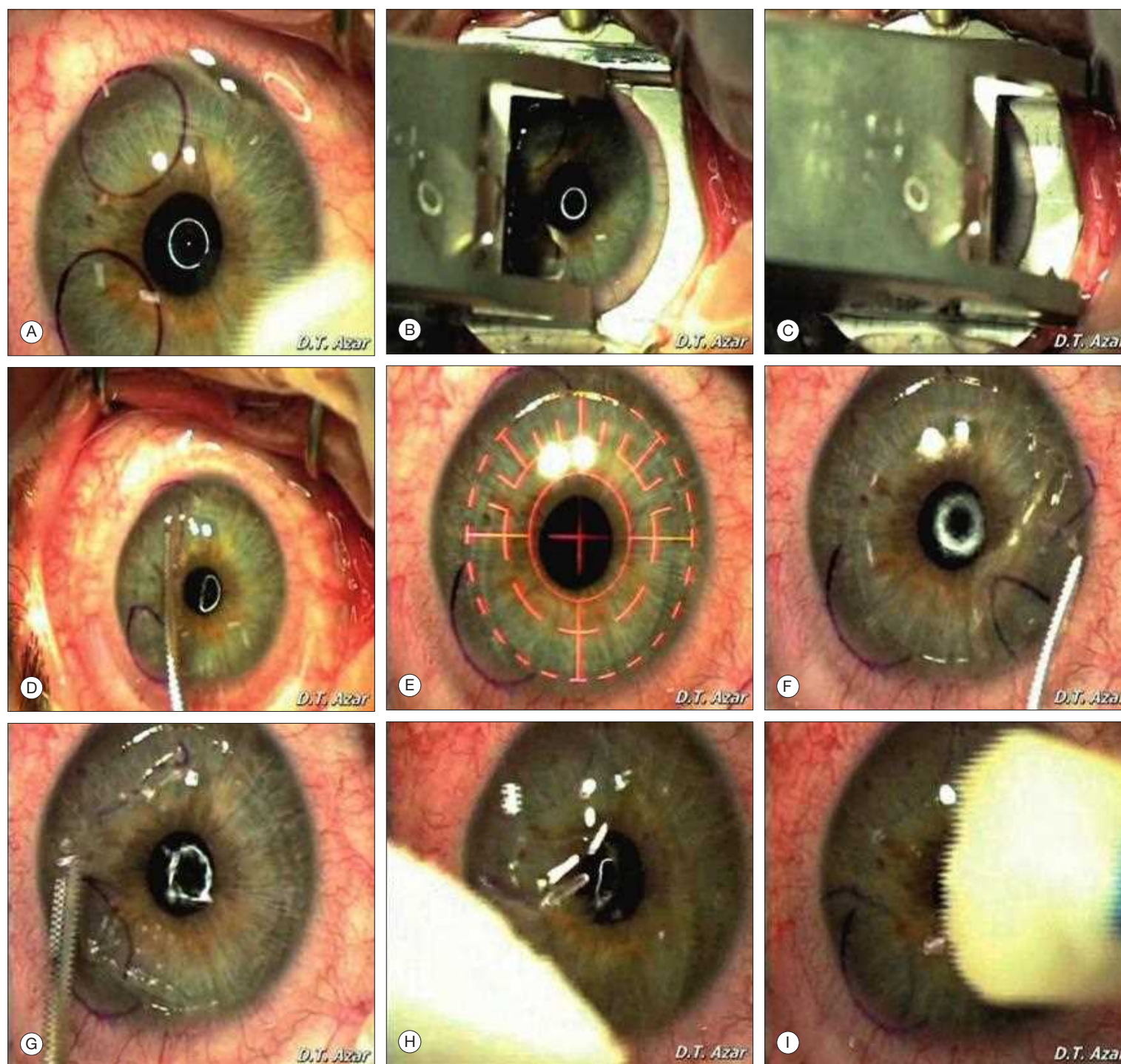
In refractive surgery, patients with high myopia are at a higher risk of haze formation.<sup>4,33–35</sup> Early haze formation has been more common with higher attempted corrections, smaller ablation zones (<4.5 mm), male gender, ablations deeper than 80  $\mu$ m, and discontinuation of topical corticosteroids.<sup>36–37</sup> Subepithelial stromal tissue reformation following photorefractive ablation is attributable to abnormal activation or proliferation of stromal keratocytes following surgical trauma to Bowman's layer.<sup>38–39</sup>

Mitomycin-C (MMC) is an alkylating antibiotic substance with anti-proliferative and antifibrotic actions. Topical MMC 0.02% (0.2 mg/mL)

application for 2 minutes on the exposed stromal bed has been used successfully to treat central subepithelial fibrosis after radial keratotomy (RK) or PRK.<sup>40–42</sup> It also has a role in prevention of corneal haze formation after PRK for treatment of myopia and hyperopia.<sup>43</sup> The typical application times range between 1 and 2 minutes, although as little as a 12-second application of 0.02% MMC has been found effective for prevention of corneal haze.<sup>44</sup> Application is performed immediately after the laser ablation. The corneal surface and the entire conjunctiva are then vigorously irrigated with 20 mL of cold normal saline to remove any residual MMC.

PRK with MMC application may offer a good alternative for patients with high refractive error, where the cornea is not thick enough for a safe





**Fig. 3.3.4 The Epi-LASIK Technique.** (A) Marks are applied around the corneal periphery. (B,C) The epikeratome is applied to the eye with suction; the oscillating blade separates the epithelium. Once the separator reaches its final position, suction is released and the device is removed from the eye. (D) With the use of either a moistened Meroel sponge or a metallic spatula, the epithelium is reflected to reveal the corneal stroma. (E) Laser ablation is performed. (F,G) The cornea is irrigated with balanced salt solution and the epithelial sheet is carefully repositioned. (H,I) The replaced corneal epithelial sheet is left to dry for 2–3 minutes, and a bandage contact lens is placed. (Reproduced with permission from Azar DT, editor, Ghanem RC, DVD editor. Refractive surgery. 2nd ed. St Louis: Mosby Elsevier; 2006.)

LASIK procedure or if LASIK is contraindicated for other reasons. It has also been tried in post keratoplasty, post RK, and immediately after the occurrence of the LASIK flap buttonhole with successful results.<sup>45–47</sup>

### Wavefront-Guided Surface Ablation

Conventional laser treatments tend to increase the higher-order aberrations (HOA) in an attempt to treat the lower-order aberrations by altering the corneal shape from its normal prolate to a more oblate configuration. Spherical aberration is the most common of these, causing mainly loss of contrast sensitivity rather than Snellen visual acuity.<sup>48</sup> Wavefront-guided laser utilizes the preoperative wavefront of the patient and compares it to the desired postoperative wavefront. The difference is used to generate a three-dimensional map of the planned ablation. Thus customized,

computer-generated, complex patterns of ablation are delivered in an attempt to decrease the pre-existing HOA as well.

## RESULTS

### Photorefractive Keratectomy for Myopia and Astigmatism

Outcomes have improved over time as techniques and lasers have evolved based on the experience gained from early studies. Treatments limited to low myopia (less than  $-6.00$  D) have achieved a final mean spherical equivalent refraction between  $-0.04$  D and  $-0.44$  D postoperatively. Over various studies, 25.9%–80% of patients have achieved a postoperative

uncorrected visual acuity (UCVA) of 20/20 or greater, whereas about 82%–91.5% of patients received a best-corrected visual acuity (BCVA) of 20/40 or greater. Loss of BCVA, a measure of safety, is typically 2%–4% but rises significantly in studies treating high and very high myopia.<sup>13,49–53</sup>

The numbers for high myopia fall to about 27%–30% of patients achieving 20/40 or better vision for more than –10.00 D of myopia, with 39% of these within 1.00 D of emmetropia.<sup>34,54</sup> Another study reported 42.9% of eyes within 1.00 D of intended correction 6–9 years after PRK for myopia  $\geq 6.00$  D.<sup>55</sup>

From the 1.5- and 6-year follow-up studies it was reported that all myopic PRK ablations were accompanied by a hyperopic shift that increased with the magnitude of myopic correction followed by a period of regression that compensated for the hyperopic shift, finally stabilizing in 3–6 months. The standard deviation of the postoperative endpoint increased with an increase in attempted correction. No significant regression occurred after 1.5 or after 6 years.<sup>2,56–57</sup> Refractive stability, in fact, continues for up to 12 years, as reported by Rajan et al.<sup>58</sup>

It has been shown that refractive results in flap-based and PRK-based procedures are comparable in mild-to-moderate myopia patients but are better in high-myopia patients.<sup>59</sup> Visual rehabilitation after PRK is slower than after LASIK. A recent report comparing the two procedures showed similar visual acuity efficacy in the treatment of eyes with high myopia ( $\geq -10.00$  D) in the long term, with LASIK having superior efficacy and safety over PRK within the first 2 years after surgery.<sup>60</sup>

Astigmatism correction is more complicated than myopia or hyperopia correction because it involves both the amount and the orientation of the astigmatism. More recent trials have shown promising results in treating astigmatism. In general, results in those with low and moderate levels of astigmatism have greater predictability and safety than those with high astigmatism. PRK for the correction of mixed astigmatism is a useful technique in terms of efficacy, safety, and predictability with conventional as well as customized ablation techniques.<sup>61</sup>

## Photorefractive Keratectomy for Hyperopia

The treatment of hyperopia with excimer laser PRK has lagged behind that of myopia. Reproducible steepening of the cornea has been more difficult to obtain than flattening, and regression has been more of a problem.

Hyperopic PRK shows good predictability and safety in those with low and moderate hyperopia; results for high hyperopes are less impressive. In a study by Pacella et al.,<sup>59</sup> including hyperopia up to +4.75 D, 100% of patients achieved 20/30 acuity or better and the mean postoperative spherical equivalent was –0.01 D. In contrast, for patients with between +11.00 and +16.00 D of hyperopia, only 37% had a spherical equivalent within 1 D of emmetropia.<sup>62</sup>

The long-term efficacy and stability of spherical and astigmatic PRK have been found to be similar to LASIK.<sup>63</sup> Nevertheless, the epithelial healing time was predictably longer for the PRK group. Eyes that underwent LASIK experienced less pain/discomfort and faster visual recovery. Mitomycin-C has been shown to prevent haze formation and improve predictability and efficacy of PRK.<sup>64</sup>

## Wavefront-Guided PRK

Custom PRK has been shown to be safe and effective for the correction of low to moderate and high myopia, compound myopic astigmatism, and hyperopia. In a recent study, the mean refractive spherical equivalent was  $-0.16 \pm 0.45$  1 year after custom myopic PRK, with 96.6% of eyes within  $\pm 1.00$  D of intended correction. In another study, 80% of eyes achieved uncorrected distance visual acuity (UDVA) of 20/20.<sup>65–67</sup> A randomized, prospective, contralateral eye study comparing custom and conventional PRK showed that the mean uncorrected and corrected visual acuity did not differ significantly in the two groups. Higher order aberration was less in the custom group, but this did not seem to correlate with clinical outcomes.<sup>68</sup> We must realize that it is not possible to totally eliminate these HOA with wavefront treatment either.<sup>69</sup>

Compared with wavefront-guided LASIK, wavefront-guided PRK had similar efficacy, predictability, safety, and contrast sensitivity. In one study, wavefront-guided PRK induced statistically fewer HOA than wavefront-guided LASIK.<sup>53,66,70</sup> Wavefront-guided PRK with MMC has been used to successfully treat residual myopia/hyperopia in eyes with prior RK, with a mean improvement of three lines of uncorrected acuity in both the groups.<sup>71</sup>

## COMPLICATIONS

### General Complications for All Surface Ablation Procedures

#### *Undercorrection or Overcorrection*

Corneal wound healing response after surface ablation is more complex than after LASIK for the same amount of correction.<sup>72</sup> Therefore complications such as regression, overcorrection, and haze are more common. Refractive regression is a manifestation of postoperative stromal keratocyte healing or, less importantly, epithelial hyperplasia. Excessive fluid or desiccation of the corneal stroma intraoperatively can result in an undercorrection or overcorrection.

In cases of undercorrection with residual myopia, the simplest form of management is to use spectacles or contact lenses. Contact lens use can be highly successful after surface ablation. An attempt can be made to reduce wound healing in patients with mild undercorrection by using corticosteroids; mixed results have been reported with this technique. Residual myopia also can be managed by further refractive surgery, including additional PRK or LASIK.

Overcorrection is a desired result in the first few months after surface ablation, as there is usually regression of 5%–10%. If the patient has a greater degree of overcorrection than is expected at 1 month or longer after surgery, an attempt may be made to increase wound healing by tapering the corticosteroids rapidly. If additional stromal remodeling occurs during this corticosteroid taper, a decrease in the amount of hyperopia will occur. A rapid taper of corticosteroids may induce corneal haze in some patients, so monitoring is important. Also, as previously mentioned, refractive modulation with corticosteroid therapy is not always successful.

#### *Epithelial Problems*

Hyperopic ablation is limited by the large epithelial defect created. Normally, the defect heals in 3–4 days. Inadequate healing can lead to persistent epithelial defects. Pre-existing dry eye, autoimmune connective tissue disease, or diabetes mellitus predispose to it. Medication toxicity can lead to superficial punctate keratitis (SPK). Discontinuation of such medication can be considered along with use of preservative-free artificial tears. Persistent defects need to be treated aggressively with pressure patching, autologous serum, punctual occlusion, or cyclosporine as per the individual case. This is necessary to avoid corneal haze, scarring, and a possible risk of infection.

#### *Corneal Haze/Scar Formation*

Transient haze after surface ablation, which can be visually significant and can cause loss of BCVA (Fig. 3.3.5), may result from the corneal wound-healing process. The haze formation can be visually significant and cause loss of BCVA (see Fig. 3.3.5). In most cases, it appears within a few weeks as a mild, diffuse, whitish anterior stromal opacity, which increases in severity for 2–4 months and then fades. Late-onset haze is defined as haze presenting 4–14 months postoperatively.<sup>73</sup> It has been linked to ultraviolet exposure; patients should be cautioned to always wear ultraviolet protection when outdoors for the first few years following the procedure. Corneal scar development may be prevented by the prophylactic use of mitomycin-C 0.02% in patients with higher spherical equivalent corrections.<sup>44</sup> Surgical removal of the scar with the excimer laser can improve visual function in these patients.

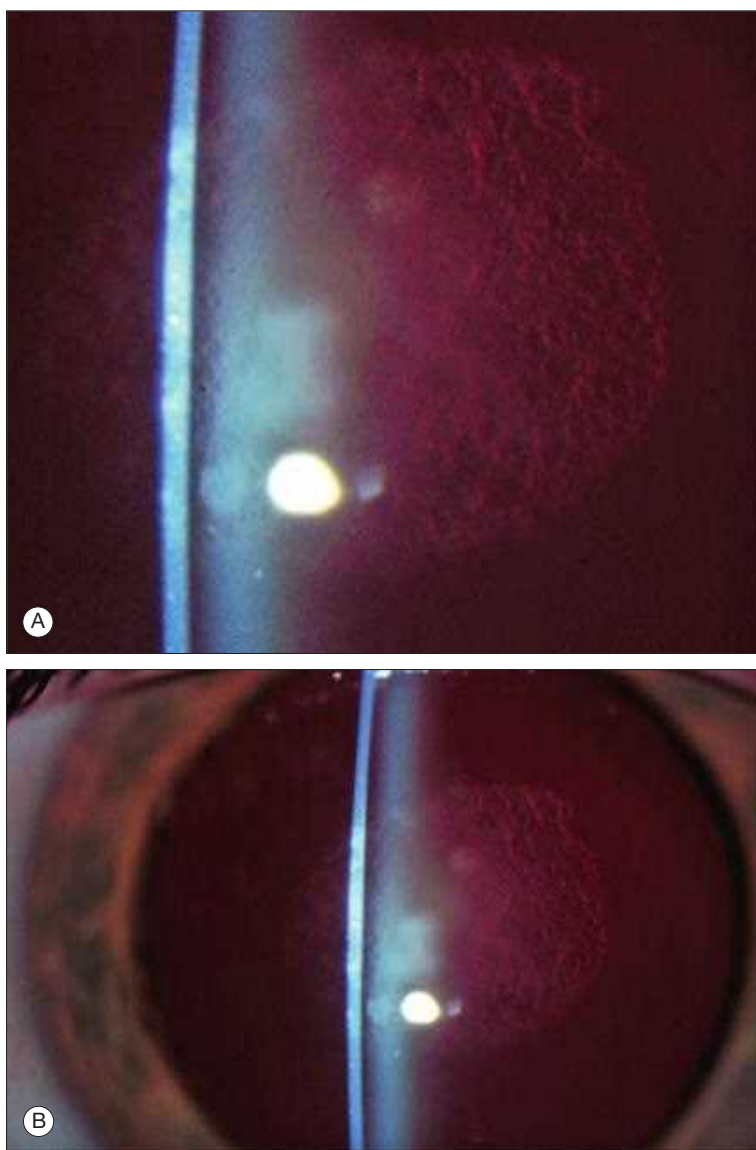
#### *Dry Eyes*

Dry eye symptoms are thought to be less common following surface ablation procedures compared with LASIK. The reinnervation process is speedier after these, because the ablated nerve endings are located close to the epithelial surface.<sup>74</sup>

#### *Infectious Keratitis*

Although rare, infectious keratitis can be a devastating complication of any refractive surgery. The breakdown of the corneal epithelium as a barrier and the use of an extended wear bandage contact lens are predisposing factors for development of corneal infection. In addition, the use of topical corticosteroids may suppress the immune response to infection. Staphylococcus species have been noted as the most common causative organisms and streptococcus species as the next, with *Pseudomonas aeruginosa* also causing bacterial keratitis.<sup>75</sup> Opportunistic organisms such as *Mycobacterium chelonae* and fungal infections have been reported. Prophylactic broad-spectrum antibiotics such as fourth-generation fluoroquinolones





**Fig. 3.3.5 Corneal Haze After PRK in a Patient With Prior LASIK When No Mitomycin-C Was Used.** (A) Slit beam of subepithelial haze. (B) Haze evident over area of photoablation.

currently are the most commonly prescribed to try to reduce the potential for infection in the postoperative period.

## Specific Intraoperative Complications Related to LASEK

### *Alcohol Leakage During Surgery*

Alcohol leakage may occur during LASEK and spill over to the limbal and conjunctival epithelium. When this happens, it should be immediately absorbed with a sponge and the area irrigated thoroughly with balanced salt solution. No significant long-term complications are likely to occur if prompt irrigation is performed.

### *Incomplete Epithelial Detachment*

Insufficient alcohol exposure and poor surgical technique may lead to incomplete epithelial detachment. This may in turn result in tearing of the flap, fragmentation, or creating a buttonhole. If epithelial detachment is difficult, additional application of alcohol usually is sufficient to facilitate complete detachment of the epithelial sheet. If this still fails, then the

remaining epithelium may be scraped off and the procedure easily converted to PRK.

## Specific Intraoperative Complications Related to Epi-LASIK

The major difference between LASEK and epi-LASIK is that the separation of the epithelial sheet is performed mechanically without exposing the cornea to alcohol or other chemical agents that may be toxic to the epithelial cells.<sup>76,77</sup> The use of a motorized epithelial separator, however, creates a different set of flap-related problems, such as a free or incomplete epithelial flap and tearing, fragmentation, or buttonhole of the flap. However, unlike the flap-related complications of LASIK, when these occur in epi-LASIK, the residual epithelium may be removed mechanically and the procedure easily converted to a standard PRK with equally good results. This is where epi-LASIK offers advantages over LASIK, where the corneal flap-related complications often require that the LASIK procedure be abandoned.

## CONCLUSIONS

The excimer laser surface ablation procedures include PRK, LASEK, and epi-LASIK. The techniques are still developing, and there will certainly be significant advances in the future. Developments of customized corneal ablation using wavefront analysis, laser registration systems, and use of mitomycin-C have been the most recent significant achievements to date in laser vision correction. Although LASIK continues to be the preferred surgical procedure in most situations, PRK, LASEK, and epi-LASIK are useful alternatives in patients with thin corneas and in patients prone to flap dislocation such as military personnel or contact sports athletes. An increased understanding of the optics of refractive surgery and the corneal wound-healing response may help us to improve our results and modulate the patient's postoperative healing to further our goal of predictable, safe refractive surgery.

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# LASIK

Patricia B. Sierra, David R. Hardten

# 3.4



**Definition:** Laser-assisted in situ keratomileusis (LASIK) is a form of lamellar corneal surgery that employs an excimer laser ablation of the corneal stroma beneath a hinged corneal flap.

## Key Features

- Combines lamellar surgery with the accuracy of the excimer laser.
- Hinged flap may be created either with a microkeratome or a femtosecond laser, however, femtosecond lasers produce thinner, more predictable flaps with fewer complications.
- Most widely used refractive surgery technique.
- Excellent option for refinement of refractive errors in pseudophakes especially with presbyopic and toric lenses.
- Recent advances including wave-front guidance, wavefront optimization, and topography guidance improve visual results and predictability.
- Recent rates of ectasia continue to fall due to better pre-operative screening and awareness.

## Associated Features

- PRK and other surface procedures are an alternative for patients in whom LASIK may not be ideal.
- Intraoperative ablation and postoperative complications.
- LASIK in complex cases: after radial keratotomy (RK), PRK, and penetrating keratoplasty.
- IOL after LASIK.

## HISTORICAL REVIEW

Refractive corneal surgery principles date back at least to the nineteenth century.<sup>1</sup> However, lamellar refractive surgery was not described until 1949, when Dr. José I. Barraquer realized that the refractive power of the eye could be altered by subtraction or addition of corneal tissue.<sup>2</sup> The term *keratomileusis*, which is derived from the Greek roots *keras* (hornlike = cornea) and *mileusis* (carving), was used to describe the lamellar techniques.<sup>3-5</sup> Unfortunately, there were many disadvantages to the procedure (i.e., complex instrumentation, steep learning curve, high rate of complications, and corneal scarring<sup>4</sup>), and the initial enthusiasm soon dissipated.

It was not until Dr. Luis Ruiz turned to keratomileusis in situ that the technical difficulties of the previous techniques were overcome. The introduction by Ruiz in the early 1980s of a microkeratome propelled by gears was a significant milestone for the development of modern refractive surgery. Dr. Leo Bores in 1987 performed the first keratomileusis in situ in the United States. This technique was still difficult to perform and had a significant complication rate.<sup>5,6</sup>

Within a few years, advances in instrumentation allowed for the lamellar keratoplasty to be performed with greater accuracy of the resections; this became known as automated lamellar keratoplasty (ALK). Results of ALK for myopia showed improvement over previous lamellar techniques but still were far from predictable, with significant induction of irregular astigmatism and reduction of best-corrected visual acuity (BCVA).<sup>7</sup>

The introduction of the excimer laser has had a greater impact on the practice of refractive surgery than any other event in the past 25 years.<sup>6</sup> Trokel et al. suggested PRK after studying the effect of the excimer laser on animal corneas in 1983.<sup>8</sup> It was later revealed that in myopia greater than 6.00 diopters (D), PRK resulted in significant central corneal haze, regression of the refractive effect, and poor predictability.

Buratto reported the use of the excimer laser in situ after a cap of corneal tissue was removed.<sup>9</sup> In a further improvement of his technique, Pallikaris came up with the idea of combining the precision of PRK with the technique of ALK and creating a hinged flap that was replaced after treatment of the lamellar bed with the laser.<sup>10-12</sup> In this way LASIK was introduced, designed, and developed at the University of Crete and the Vardinoyannion Eye Institute of Crete, Greece.<sup>12</sup> LASIK avoided the inaccurate positioning of the corneal cap, which produced significant irregular astigmatism. Guimaraes et al. then reported that suturing could be eliminated by briefly drying the flap.<sup>13,14</sup>

In summary, it was the combination of an old technique (keratomileusis) with new technology (excimer laser) that redefined corneal refractive surgery at the close of the twentieth century.<sup>9</sup> Buratto<sup>9</sup> and Pallikaris<sup>12</sup> are credited with combining lamellar surgical techniques developed by Barraquer<sup>2,5</sup> and excimer laser technology in a procedure they termed laser-assisted in situ keratomileusis.

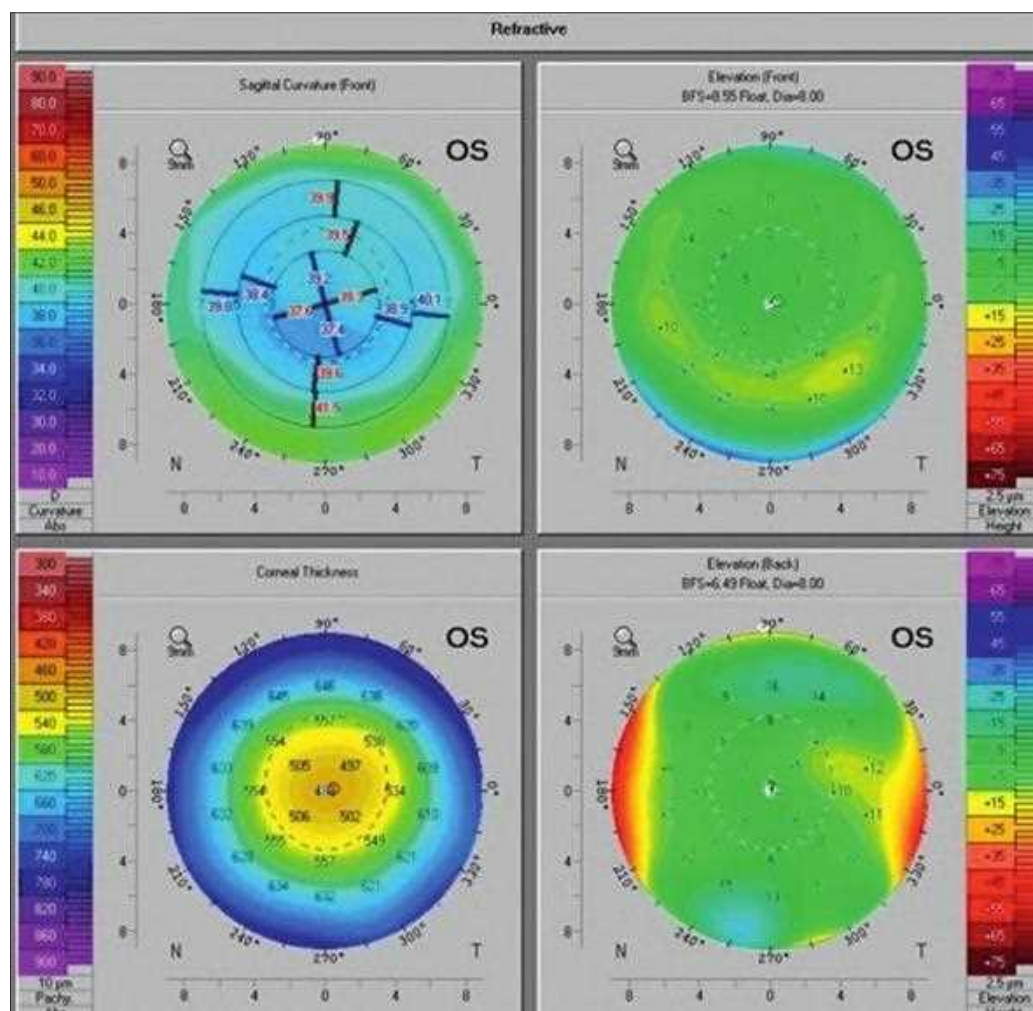
## LASIK

LASIK combines lamellar corneal surgery with the accuracy of the excimer laser. It involves the excimer laser ablation of the corneal stroma beneath a hinged corneal flap that is created with a microkeratome or a femtosecond laser.

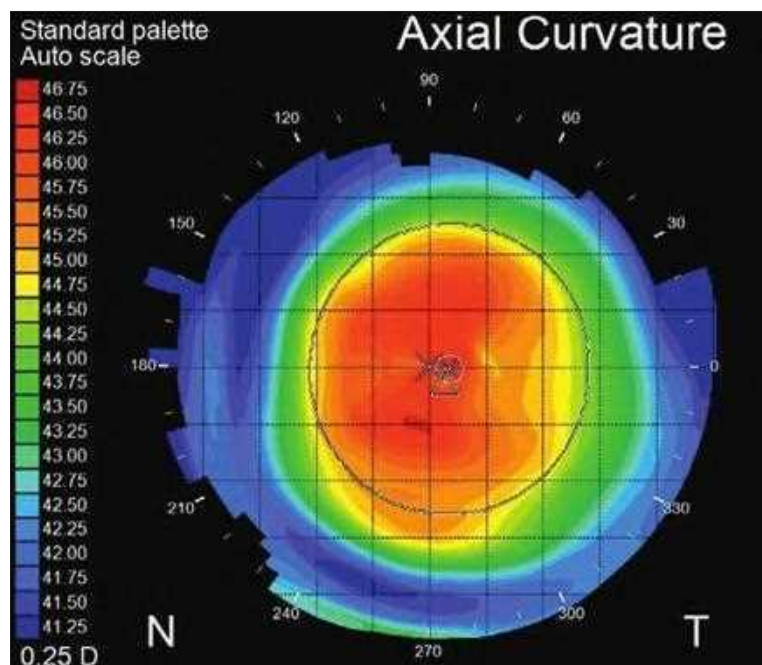
LASIK has been used to correct up to 15.00 D of myopia, 6.00 D of hyperopia, and up to 6.00 D of astigmatism. The range of corrections utilized has not been clearly defined, and many surgeons have treated patients beyond these ranges with success. The results in the clinical evaluation of the procedure as far as predictability (percentage of eyes within a given postoperative target, i.e.,  $\pm 0.5$  D), efficacy (percentage of eyes with loss of best-corrected vision postoperatively, i.e., loss of two or more lines), stability (evaluation of stability of refraction at a certain interval postoperatively), and quality of vision (incidence of adverse visual phenomena, such as halos, glare, etc.) have been better in lower ranges than in higher ranges of correction.<sup>15</sup> Most surgeons now limit their levels of correction to less than 8.00–10.00 D of myopia and 4.00 D of hyperopia.<sup>16</sup>

The normal cornea has a prolate shape (greater curvature centrally than peripherally). Laser vision correction procedures for myopia reverse this natural prolate shape of the cornea and decrease the central corneal curvature to create an oblate shape (Fig. 3.4.1). Corneal surgery for hyperopia differs in several important respects from surgery for myopia. The corneal refractive power must be increased to treat hyperopia, whereas it must be decreased to treat myopia. Excimer laser ablations for treatment of hyperopia are applied in the midperiphery and result in steepening of the





**Fig. 3.4.1** Postmyopic LASIK With Scheimpflug Imaging. Note the central corneal flattening on sagittal curvature and anterior elevation maps with corresponding thinning on pachymetry map.



**Fig. 3.4.2** Posthyperopic LASIK Imaging on Placido Disc Topography. Note central corneal steepening.

central cornea and relative flattening of the periphery with minimal ablation occurring at the center of the cornea (Fig. 3.4.2). Effective treatments for hyperopia have a larger ablation diameter than those for myopia.

Hyperopic astigmatism treatment is accomplished with the excimer laser by removing tissue along the paracentral area, promoting steepening

of the flat meridian. Cylindrical ablation patterns for correction of mixed astigmatism include the bitoric and the cross-cylinder techniques. The bitoric LASIK technique consists of flattening the steep meridian with a cylindrical ablation in combination with a paracentral ablation over the flat meridian to steepen this axis. The cross-cylinder technique corrects astigmatism by dividing the cylinder power into two symmetrical parts. Half of the correction is treated on the negative meridian, and half is treated on the positive meridian.

## Excimer Lasers

The excimer laser is used to reshape the surface of the cornea by removing anterior stromal tissue. The process by which the excimer laser removes corneal tissue is nonthermal ablative photodecomposition.<sup>17</sup>

Laser delivery patterns include broad beam, scanning slit, and flying spot. Some lasers have a combination of mechanisms that allow for large and small treatment areas through a system termed variable spot scanning. This combines the advantage of a shorter treatment time by treating large areas all at once and the flexibility of treating smaller areas asymmetrically when needed with a small-diameter beam.<sup>18</sup>

There are four basic types of excimer laser treatment profiles: conventional, wavefront-optimized, wavefront-guided, and topography-guided.

*Conventional LASIK*, also called standard or traditional LASIK, was the first profile to receive Food and Drug Administration (FDA) approval and still is used commonly today. Conventional LASIK applies a simple spherocylindrical correction obtained through a manifest refraction and based on the removal of tissue using Munnerlyn's equation.<sup>19</sup> However, conventional LASIK to treat myopia induces positive spherical aberration dependent on the amount of attempted correction.<sup>20</sup>

In standard treatments, the best point to use for centration during the refractive procedure is still not clear, with the options of the corneal intercept of the visual axis, the entrance pupil, or the corneal light reflex.<sup>21,22</sup> Eye-tracking devices rely on infrared lasers or cameras to follow small eye movements and move the laser ablation beam accordingly.



Studies have shown improvements in uncorrected visual acuity (UCVA), BCVA, and centration with eye-tracking devices.<sup>23,24</sup> Larger ablations and blend zones may reduce the incidence of glare and halos.<sup>25</sup>

**Wavefront-guided (WFG) LASIK**, also called custom LASIK, is a variation in which the excimer laser ablates a sophisticated pattern based on measurements from an aberrometer. The goal of WFG LASIK is to achieve an improved ablation based on the optical aberrations measured with the wavefront aberrometer, not just sphere and cylinder (lower-order aberrations). There are other types of optical aberrations in the visual pathway of the eye, such as coma and spherical aberration, collectively called higher-order aberrations (HOA). Wavefront technology measures both the lower-order aberrations and HOA,<sup>26,27</sup> improving the precision of refraction to 0.1 D or smaller. There are several methods that can be used to measure the wavefront: Tscherning, dynamic skiascopy, ray tracing, and Hartmann-Shack. All methods evaluate how light is modified as it passes through the lens and cornea, and a wavefront is constructed by analyzing the exiting light rays. The shape of the wavefront describes the total aberration of the eye. The size of the wavefront (cross-sectional area) is determined by the size of the entrance pupil.

The first step in the wavefront-based LASIK technique is an examination with a wavefront device that measures the aberrations. The profile to correct these aberrations is created and imported into an excimer laser and used to guide the ablation during LASIK. (Fig. 3.4.3A). As the ablation patterns and treatments become more complex and more specific for the individual, the importance of precise registration of these patterns on the cornea increases. Significant cyclorotation could introduce significant postsurgical aberrations.<sup>22,28,29</sup> Iris registration is able to compensate for pupil centroid shifts due to variable illuminations and pupil sizes by referencing to the outer iris boundary with improved centration of wavefront ablations.<sup>30</sup>

The wavefront data can provide useful information in the postoperative setting, where it can be used to identify and describe specific HOA that may be consistent with a patient's subjective visual symptoms.

**Wavefront-optimized** treatment profiles are population-based corrections designed to reduce or eliminate the induced spherical aberration of conventional LASIK.<sup>31</sup> The wavefront-optimized treatment is based on a spherocylindrical correction that is adjusted by an internal algorithm to remove additional tissue in the periphery of the ablation zone, thereby creating a more prolate corneal shape.

In traditional myopic corrections, laser pulses at the peripheral cornea have a diminished effect due to the oblique angle of the laser beam, which induces spherical aberration. To compensate for this effect in a wavefront-optimized ablation, extra laser pulses are applied to the corneal periphery (Fig. 3.4.3B).<sup>32,33</sup>

**Topography-guided LASIK** uses information from both the corneal shape and the refractive spherocylindrical correction to determine the excimer laser ablation profile (Fig. 3.4.3C).

Topographers, which are not limited by pupil size, can measure greater and wider points of curvature on the cornea compared with wavefront devices. Topography-guided treatments can be used successfully for highly aberrated eyes (such as corneas with opacities or irregular astigmatism) and are not affected by the state of accommodation, early cataracts, or vitreous opacities.<sup>34</sup>

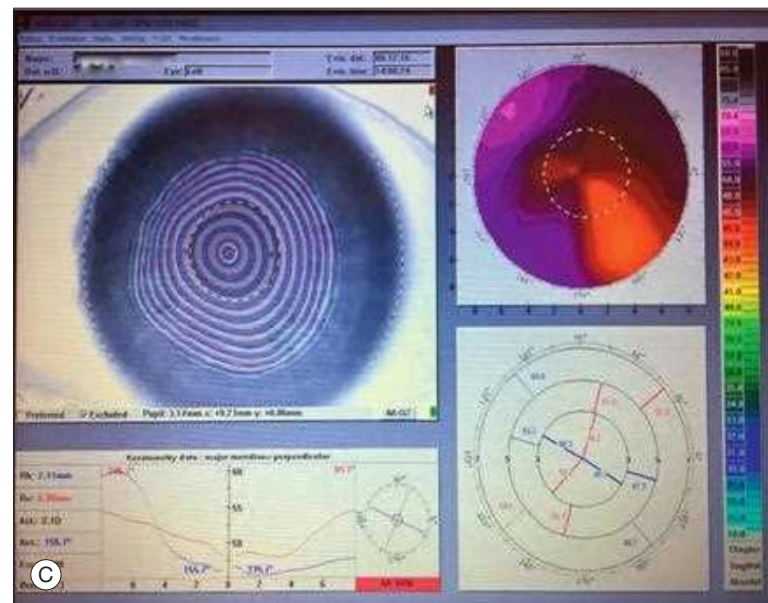
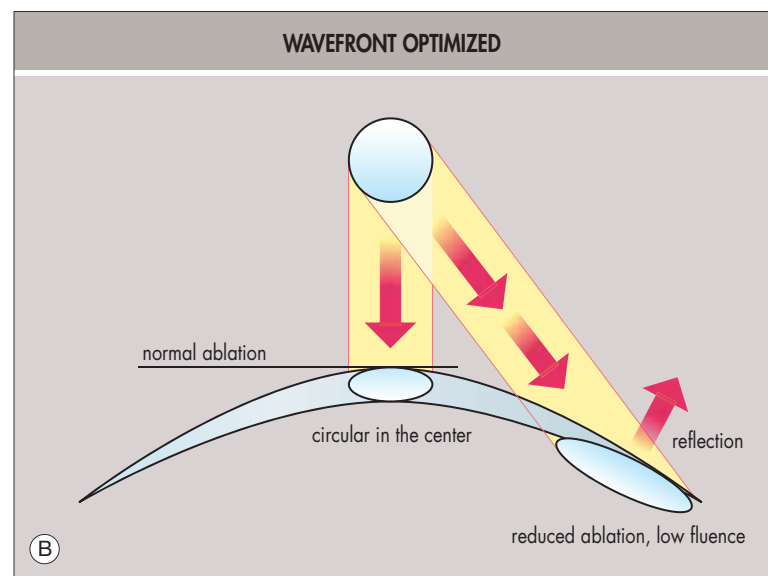
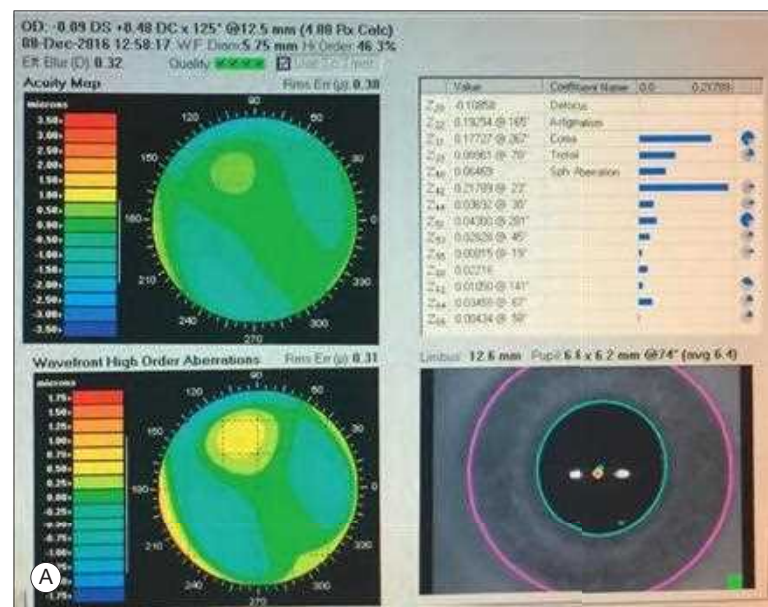
## Patient Selection

### Preoperative Evaluation and Diagnostic Approach

The first step in the evaluation should be to determine the goals of the patient in seeking refractive surgery and assess whether the patient has realistic expectations. Patients should understand the risks, benefits, and alternatives to the LASIK procedure. A stable refraction is important. Most surgeons now limit the upper range of correction to treatment of 8–10 D of myopia even though the lasers are capable of treating higher corrections.

Also important is a review of ocular and systemic conditions. Visual acuity is measured using manifest and cycloplegic refraction. The refraction is compared with prior spectacle corrections to assess the stability of refraction for the given eye. In addition, the wavefront refraction can be used as the baseline to obtain the wavefront-adjusted manifest refraction (WAMR). Pupil size, ocular dominance testing, and distance and near vision with and without correction should also be documented. Anterior and posterior segment examinations are performed to rule out other conditions that may adversely affect the surgical result.

Measurement of the central corneal thickness is an important element of the preoperative evaluation. WFG and optimized procedures usually remove more stromal tissue compared with conventional treatments. An



**Fig. 3.4.3 Wavefront-Guided, Wavefront-Optimized Ablations, and Topography-Guided Lasik.** (A) Wavefront-guided treatment plan based on aberrometry demonstrating lower and higher aberrations. Note: eye with significant degree of higher order aberrations despite low refractive error. (B) Wavefront-optimized treatments deliver additional pulses to the peripheral cornea to compensate for energy loss (beam ovalization and reflection) and decrease spherical aberration. (C) Topography-guided ablation. Overview display of patient's topographical data utilized to guide excimer laser treatment. Data include reduced camera image of measurement, keratometer data, color coded topographical image, and values.

estimated residual stromal bed is needed for surgical planning, because it is one factor that may predict postoperative ectasia. It is computed by subtracting the anticipated flap thickness and maximum ablation depth from the central corneal thickness measurement. The minimal residual bed for LASIK remains controversial, although 250–300  $\mu\text{m}$  is generally recognized as a minimum.

Ectasia can occur with even thick residual stromal beds in eyes with keratoconus features. To account for variations in actual flap thickness, the stromal bed can be measured after the flap has been retracted to allow for a more precise determination of the residual bed. A percentage of anterior tissue depth altered (PTA)  $\geq 40$  at the time of LASIK was significantly associated with the development of ectasia in a study of eyes with normal preoperative topography.<sup>35</sup>

Computer-assisted videokeratoscopy, corneal tomography, and Scheimpflug imaging are now available and used routinely in the preoperative and postoperative assessments of refractive surgery patients. These tools can help to screen for subclinical keratoconus or other corneal diseases.

Rigid contact lens wearers should remove their lenses for 3–4 weeks before examination, and soft contact lens wearers should have 2 weeks without lenses.

The possibility of monovision should be discussed with patients near or of presbyopic age; the discussion should include glare and halos, the possibility of under- and overcorrection, and any special considerations. Appropriate reading materials are helpful for patient education.

Informed consent should include a discussion of the most frequent side effects and potential risks involved with the surgery.

Alternative refractive treatments such as PRK should be discussed and may be preferred to LASIK in patients with anterior basement membrane dystrophy (ABMD), thin corneas, small and deep-set orbits, anterior scleral buckles, glaucoma after trabeculectomy, optic nerve disease, a risky occupation or activity, and corneal ectasia.<sup>36,37</sup>

The option of phakic IOL implantation can be offered to patients with high myopic corrections, very thin corneas, or abnormal corneal topography and/or tomography. Natural lens replacement is an option for patients nearing cataract age or requiring higher hyperopic corrections.

### Limitations and Contraindications

Laser vision correction may have a higher risk in patients with collagen vascular disease,<sup>38</sup> patients with autoimmune or immunodeficiency diseases, women who are pregnant or nursing, patients with signs of keratoconus, and those taking isotretinoin or amiodarone. Other conditions potentially associated with more adverse outcomes include Fuchs' corneal dystrophy, strabismus, ophthalmic herpes simplex or herpes zoster, and other systemic diseases likely to affect healing, such as diabetes and atopic disease.<sup>17,39–41</sup> Caution should be exercised for patients with abnormal corneal topographies or with ocular abnormalities as well as systemic conditions that are likely to affect wound healing.

## Microkeratomes and Femtosecond Lasers

A critical step in LASIK is the creation of the corneal flap. Several different microkeratomes are available for use in LASIK, ranging from modern automated steel microkeratomes to femtosecond lasers.<sup>42</sup> The choice depends on the surgeon's access and preference. In the past decade, the femtosecond laser has gained popularity and is replacing mechanical microkeratomes for LASIK flap creation in the United States.<sup>43,44</sup> Femtosecond lasers use laser pulses to cause microcavitation bubbles at a preset depth in the corneal stroma. The cavitation bubble is composed primarily of water and carbon dioxide. Multiple cavitation bubbles coalesce, and an intrastromal cleavage plane is created. Hinge placement, flap diameters, and flap thickness can be set to exact specifications. The chance of a flap buttonhole or incomplete, decentered, or free flap appears to be reduced. Flaps are thinner and of uniform thickness from the center to the periphery. Femtosecond flap creation is very precise and flap thickness is usually within  $\pm 14 \mu\text{m}$  of the intended result.<sup>43–45</sup> These differences in flap creation between femtosecond lasers and mechanical microkeratomes are thought to be responsible for better LASIK outcomes with the femtosecond laser.

## Operative Technique

Careful candidate selection, as discussed earlier, is critical for optimal outcomes. Surgeon preparation, including a thorough knowledge of the patient, procedure, parameters, and equipment, is essential. Patient preparation, including preoperative explanation regarding the steps, sights,

and sounds of the procedure, serves to maximize comfort and minimize anxiety. Approximately 5–10 minutes before the procedure, a mild sedative can be given to the patient to alleviate the anxiety of undergoing the procedure and to help them sleep postoperatively.

When performing a WFG LASIK procedure, obtaining an accurate capture of ocular aberrations is critical to ensure accurate measurements and optimal results (Fig. 3.4.3A).

### Microkeratome Surgical Technique

Topical anesthesia is applied to the eye. The eyelids are prepared with dilute povidone-iodine solution. A lid speculum is inserted to open the eyelids. Eyelashes should be kept away from the surgical field by the use of adhesive drapes or a closed bladed lid speculum. The contralateral eye is taped shut to prevent cross-fixation and drying. The microkeratome should be inspected for any defects in the blade or function of the moving parts. It is vital to confirm that the excimer laser will be able to deliver treatment after the corneal flap is reflected.

The cornea can be marked with ink before creating the corneal flap with the microkeratome to more easily realign the corneal flap in the event that a free flap is created.

The suction ring is placed using a bimanual technique in which the shaft of the suction ring is held in the fingers of one hand and a finger from the other hand provides additional support on the ring itself. Once adequate placement has been achieved, the suction is engaged by foot control (usually done by the technician). Adequate intraocular pressure (above 65 mm Hg) is then verified, with one useful method being an applanation lens (Barraquer tonometer). When adequate suction is achieved, the patient will confirm the temporary loss of visualization of the fixation light.

Before the pass of the microkeratome, several drops of artificial tears are placed on the cornea. This lubrication reduces the likelihood of a corneal epithelial defect occurring during the microkeratome pass. If using a two-piece microkeratome, the head is slid onto the post of the suction ring and advanced until the gear on the microkeratome head engages the track. It is important to again verify that the suction ring is still firmly attached to the globe at this point by gently lifting the suction ring upward, making sure that the suction is not lost. The surgeon then activates the microkeratome using forward and reverse foot control, the suction is turned off after the microkeratome pass, and then the suction ring can be carefully removed. Prompt attention at this point is extremely important in the case that a free cap or buttonhole has been created. In cases in which the stromal bed is too small or irregular for a good result, the laser ablation should not be performed, and the flap should be placed carefully back into position.

Before the flap is lifted, a wet cellulose sponge is used to prevent any cells, debris, or excess fluid from getting onto the stromal bed. With use of a flat cannula, iris sweep, or smooth forceps, the flap can be lifted and directed toward the hinge. Assessment of the thickness of the residual corneal bed may be performed by using ultrasound pachymetry. Microkeratome flap thickness may vary, with differences in thickness occurring even with the same microkeratome, making this measurement more important in eyes that may require a deeper ablation with the excimer laser, thus leaving less tissue in the residual corneal bed.

### Femtosecond Laser Flap Creation

The femtosecond laser is a highly precise, computer-guided laser that enables surgeons to program flap parameters, such as diameter, depth, hinge location, and edges, based on patients' anatomical characteristics or surgeons' preferences (Video 3.4.1). Flap parameters such as pattern, hinge position, flap depth, flap diameter, bed energy and spot separation, side cut angle and energy, hinge angles, and pocket parameters need to be carefully programmed or reviewed by the surgeon before the surgical procedure is initiated.

A suction ring is applied to the eye with slight downward pressure, and suction is then enabled to affix the ring firmly to the eye. Proper centration is extremely important and is a critical step that ensures greater accuracy of all subsequent steps of flap creation (Fig. 3.4.4). With the eye fixated, the cornea is then fully applanated. Centration and flap size should be confirmed on the monitor before the laser is initialized for treatment. It is critical to instruct the patient to abstain from eyelid squeezing during this step to prevent suction loss (Fig. 3.4.5A).

Once the procedure is complete, suction can be released and the same technique can be repeated on the contralateral eye.

Lifting femtosecond flaps can be quite different from lifting a microkeratome flap and is rather a blunt dissection, best accomplished with the use of a spatula (Fig. 3.4.5B). The spatula should be entered near the hinge

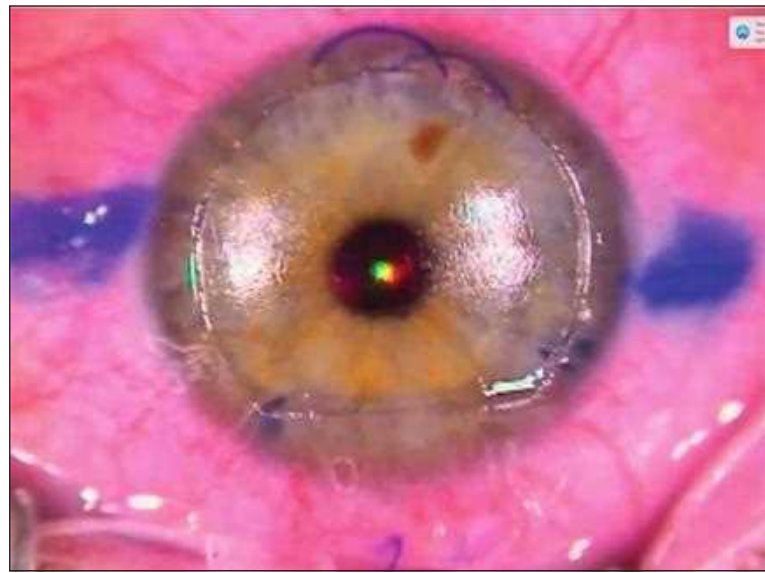


See clip:  
3.4.1





**Fig. 3.4.4** Suction Ring Centration Is a Critical Step That Ensures Accuracy of All Subsequent Steps of Femtosecond Laser Flap Creation.



**Fig. 3.4.6** Patient Fixation on Target Light Under Laser and Tracker Fixation on Pupil Width Should Be Maintained at All Times During Excimer Treatment.

and gently elevated in one to four swipes. The flap is then reflected, and the surgeon can proceed with excimer laser treatment.

### **Excimer Laser Ablation**

The patient should be positioned under the microscope with the head carefully aligned to make sure that the iris is perpendicular to the laser beam. Careful centration with the eye aligned in the x, y, and z planes is crucial. Alignment is even more critical with wavefront-guided laser treatments because most HOA are not radially symmetrical. Torsional misalignment—either cyclotorsion or head tilt—during surgery can result in undercorrection of the aberration or even in the induction of additional aberrations. The most basic technique to ensure alignment is to mark the limbus, typically at the 3 and 9 o'clock positions, immediately before surgery while the patient is seated. These marks are then used to align the head when the patient is lying under the laser. Most modern laser systems are now equipped with either pupil tracking or iris registration.

The surgeon should always verify the entered computer data before starting the ablation. The microscope should be adequately focused on the corneal surface. A dry cellulose sponge is then used to carefully remove any excess fluid from the stromal surface. Hydration of the stromal bed needs to be adjusted evenly and consistently in all cases. It is important at this point to minimize the procedure time in order to prevent stromal dehydration and subsequent overcorrection. Uneven hydration can lead to central islands and/or irregular astigmatism. Excess pooling of fluid often can be found near the hinge after folding back the flap and should be wicked away. The patient should be instructed to fixate on the target light. Adequate centration over the pupil should be reassessed (Fig. 3.4.6).

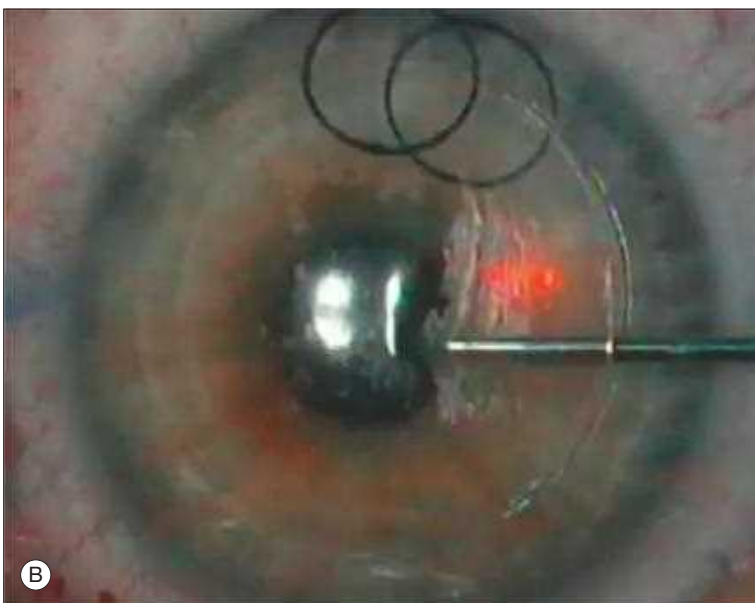
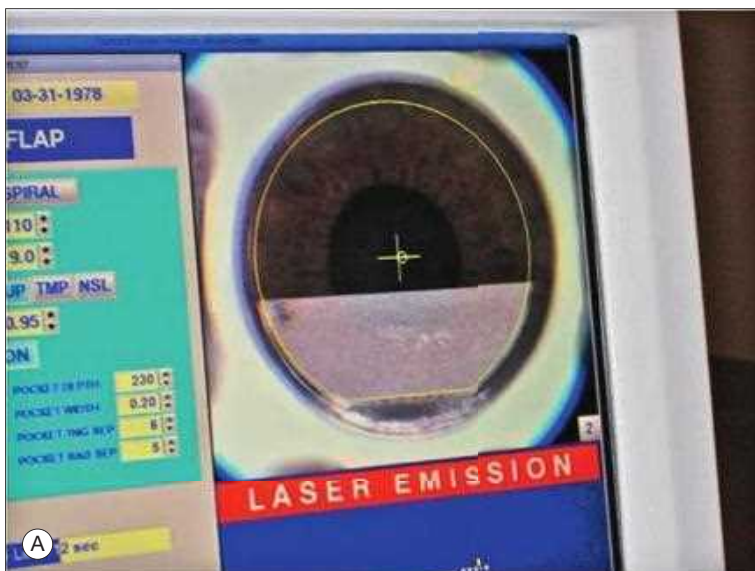
The laser eye tracker and iris registration are activated, and the laser ablation initiated. If fluid starts accumulating over the stromal surface, the laser ablation can be halted, and the fluid should be removed with a cellulose sponge. The hinge should be protected if it is within the ablation zone.

After the ablation, the flap is then repositioned onto the bed using an irrigation cannula or an iris sweep. Saline solution is used to remove debris from the interface (Fig. 3.4.7). A wet cellulose sponge is then used to realign the flap. Sweeping movements should be performed from the hinge toward the periphery of the flap.

Good adhesion of the flap is verified by stretching the flap toward the gutter. If good adhesion is present, there is minimal space in the gutter and no movement of the flap occurs when stroking the flap with a dry sponge. When the flap is felt to be securely in position, a drop of an antibiotic, a corticosteroid, and a lubricating agent may be applied to the cornea before removal of the speculum. If bilateral LASIK will be performed, the operated eye is covered and the procedure repeated in the contralateral eye. Both eyes are then protected with transparent plastic shields until the following day.

### **Postoperative Care**

Postoperative care of the typical patient who has undergone LASIK is still quite important. Generally, some tearing and burning occurs immediately



**Fig. 3.4.5** Raster pattern flap creation with Intralase femtosecond laser (A). Femtosecond flap dissection with blunt spatula. (B).



**Fig. 3.4.7 Irrigation Under the Flap Can Remove Debris From the Interface.** Care must be taken not to overirrigate, as this can increase the risk of flap striae from overhydration.

after surgery, for which it is recommended that the patient take a 2-hour nap. The patient is placed on topical prophylactic antibiotics and topical corticosteroids four times per day for 1–2 weeks. Preservative-free lubricating drops are helpful in most patients for the first several weeks after surgery, and frequent use should be encouraged.

On the first postoperative day, careful evaluation of the corneal flap should be performed at the slit lamp. The patient may resume most activities if the postoperative examination is normal. Instructions not to rub the eyes or swim underwater should be reinforced to prevent flap displacement or infectious keratitis.

## Complications

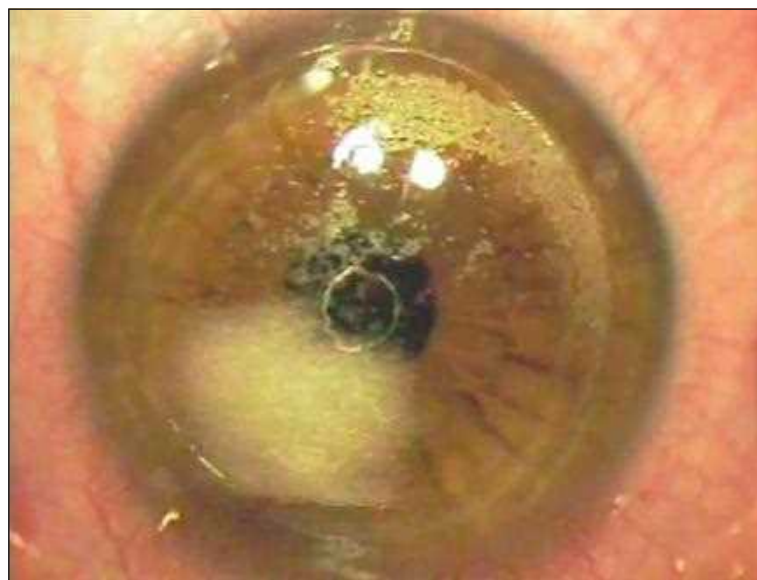
### Intraoperative Complications

An *incomplete flap* may result from the premature termination of the microkeratome advancement or ineffective passes or suction loss during a femtosecond flap creation. Reasons for a microkeratome incomplete pass include inadequate globe exposure due to interference of eyelid, lashes, speculum, and/or drape as well as loss of suction during the pass. If there is not enough room beneath the flap to perform the ablation, then the surgeon should reposition the flap and abort the surgery. Incomplete flaps also can result when the femtosecond laser cannot photodisrupt the corneal stroma in portions of the intended interface or if there is resistance between the interface from scar tissue. Typically, surface laser treatment with mitomycin-C can be used later to complete the refractive correction.<sup>46,47</sup>

When suction loss occurs during a femtosecond LASIK flap creation, resulting in an incomplete flap, a second femtosecond pass can create an intact flap. Tomita and colleagues reported successful immediate lamellar recut in their series of eyes with suction loss.<sup>48</sup> Some controversy surrounds the rationale for immediate recut, as other authors have demonstrated the potential for creating new cleavage planes if immediate recut is undertaken.<sup>49</sup> When suction loss occurs during the side cut or just before starting the side cut, a repeat side cut can be performed with a smaller diameter.

A *flap buttonhole* is one of the most serious flap complications, and the excimer laser ablation should be aborted. The flap should be repositioned and smoothed into place. Treatment of the second eye is not advisable at the same setting, as the same complication is likely to happen in the presence of a steep cornea or poor suction. However, these almost always occur in the second eye with a thinner flap in mechanical microkeratomers.<sup>50,51</sup> Femtosecond laser flaps also are prone to similar complications, albeit usually from a different mechanism: *vertical gas breakthrough*.<sup>52</sup> Epithelial ingrowth or haze may occur in the area of the buttonhole and may require further intervention. Typically, retreatment can be performed immediately or later with phototherapeutic keratectomy (PTK)/PRK and mitomycin-C.<sup>53,54</sup>

A *free cap* can occasionally occur when using a microkeratome to create a flap, and the surgeon should be prepared to deal with this problem. If the cap is small and/or decentered, it should be replaced without ablation and the procedure aborted. If it is well centered and of adequate size, the cap is typically placed on the conjunctiva with the epithelial side down during the



**Fig. 3.4.8 Opaque Bubble Layer (OBL).** Note gas bubbles trapped inside the stoma. The OBL can make lifting of the flap difficult and, if over the pupillary area, may interfere with an eye-tracking mechanism during excimer laser ablation.

photoablation. Care must be taken to reposition the cap into the same orientation after the ablation. Adequate drying time should be allowed for the cap to adhere without sutures. The most frequent cause of a free cap is a flat or small cornea in which there is less tissue to be brought forward into the microkeratome. Poor suction also can cause small free flaps. Marking of the cornea before flap creation can facilitate alignment in the event of a free cap.

*Epithelial defects* can be prevented with adequate lubrication of the cornea before the microkeratome pass. Also, toxic anesthetics should be kept to a minimum before the procedure. If a large epithelial defect occurs during the microkeratome pass, the ablation should be aborted in the affected eye. It is not recommended to proceed with flap creation in the contralateral eye, as the same complication is likely to occur. On the other hand, if the epithelial defect is small, a contact lens can be placed over the cornea to decrease significant discomfort to the patient. An epithelial defect may lead to greater flap edema with poorer adherence in the area of the defect, increasing the risk of epithelial ingrowth and diffuse lamellar keratitis.

*Epithelial breakthrough* is a rare complication during femtosecond laser corneal flap creation and is generally observed in patients with prior corneal incisions in the ablation zone. In these situations, increasing femtosecond energy or microkeratome flap creation should be considered. In patients with severe corneal scars that obscure visualization of anterior segment structures, femtosecond flap creation should be avoided. It is important to be attentive for this complication intraoperatively and to abstain from lifting the flap to prevent more serious flap problems such as buttonholes or flap tears.<sup>55</sup>

An *opaque bubble layer (OBL)* and anterior chamber gas bubbles can present during corneal flap creation with a femtosecond laser. An OBL forms when gas bubbles created by laser photocavitation are trapped inside the stoma. Gas also can appear in the anterior chamber and persist up to several minutes or even hours. The OBL can make lifting of the flap difficult, and care must be taken to perform a gentle blunt dissection to prevent a flap tear in the area of the OBL. If the OBL or anterior chamber bubbles are over the pupillary area, they may interfere with an eye-tracking mechanism during excimer laser ablation. In these situations, it is usually recommended to wait for bubbles to dissipate before proceeding with laser treatment.<sup>56</sup> Other factors associated with increased frequency of OBL include steeper, thicker corneas and a hard docking technique. Although the OBL makes the LASIK procedure more difficult, it does not appear to affect the postoperative optical quality and visual outcome (Fig. 3.4.8).<sup>57</sup>

### Ablation Complications

*Central islands* are small central elevations in the corneal topography that may occur for a variety of reasons.<sup>58,59</sup> Beam profile abnormalities, increased hydration of the central corneal stroma, or particulate material falling onto the cornea may block subsequent laser pulses. This was more common with broad-beamed lasers.<sup>60</sup> Typically these central islands resolve with time as epithelial remodeling fills in the surrounding area.



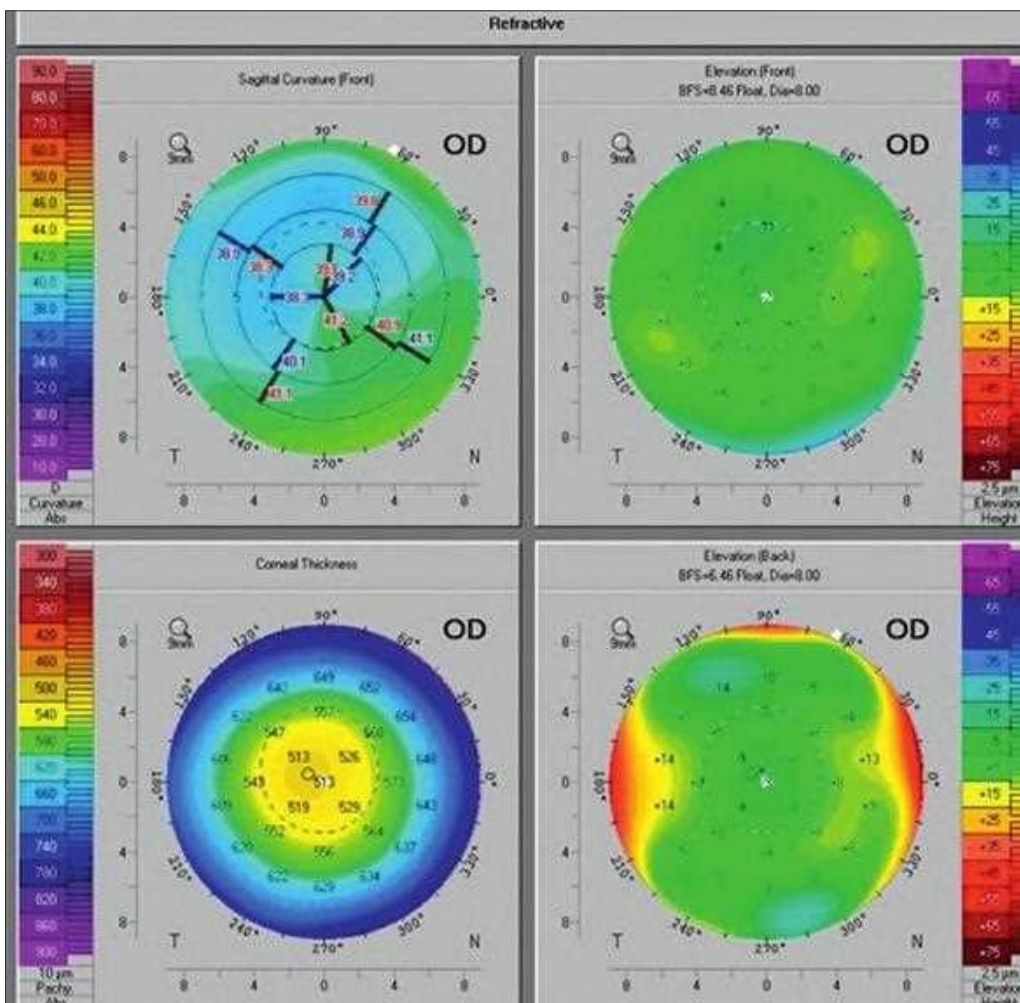


Fig. 3.4.9 Superior Decentration on Scheimpflug Imaging Following Myopic Excimer Ablation.

**Decentration** (Fig. 3.4.9) can result from poor fixation and alignment, eye movement during the laser procedure, significant pupil shift with light, or asymmetrical hydration of the cornea. The higher the myopic correction, the greater the risk of a decentered ablation, which can result in glare, irregular astigmatism, and a decrease in BCVA.<sup>22,61,62</sup> Low-contrast visual acuity is a more sensitive measurement of visual function than high-contrast Snellen acuity and can be used to assess these patients more accurately.<sup>63</sup> Decentration may be decreased with the use of current lasers with incorporated eye-tracking systems and iris registration, yet careful attention must still be paid to patient fixation.<sup>64</sup> Typically, if the ablation is more than 1 mm decentered, the irregular astigmatism that occurs is symptomatic. Management of decentration by treatment based on wavefront or topographical information may decrease symptoms in patients with an unsatisfactory outcome with the first procedure.<sup>65</sup>

**Under- and overcorrection** may result from errors of refraction, improper surgical ablation, malfunctioning of the excimer laser, abnormal corneal hydration status, or an excessive or inadequate wound-healing response. It is crucial to maintain consistent hydration of the cornea, because excessive fluid on the cornea results in an undercorrection. If desiccation of the corneal stroma is present, then overcorrection and haze may occur. The higher the refractive error, the greater the chance of regression.<sup>63</sup> Many surgeons find that adjusting the amount of treatment using a nomogram based on their actual surgical results improves their refractive outcomes.

### Postoperative Complications

**Interface debris** is common even with aggressive interface irrigation. The most frequent source of debris is meibomian gland material from the lids that is trapped in the interface. Careful draping of lashes and cleaning of the flap interface with balanced salt solution before and after the flap is floated into position can help to reduce the incidence of this problem.<sup>66</sup>

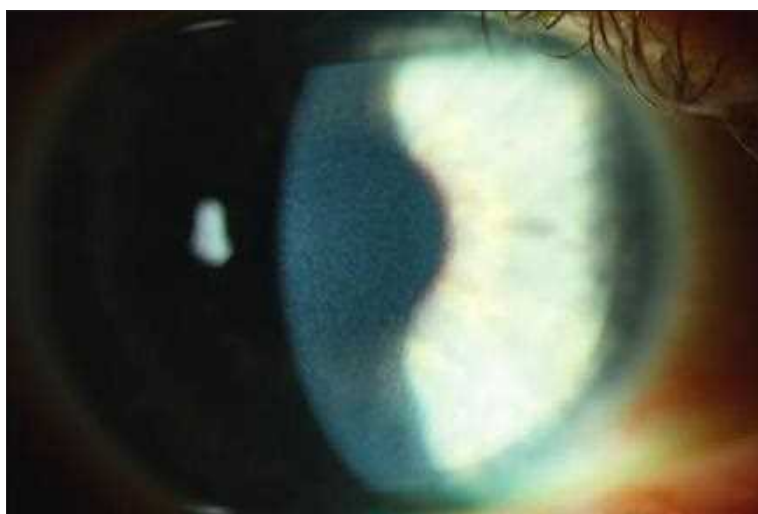
**Flap displacement** usually occurs in the first 24 hours postoperatively. When a flap displacement occurs, it should be lifted and repositioned as soon as possible.<sup>67</sup> The epithelium at the flap edge grows remarkably fast to cover the stromal bed. Care must be taken to clean the bed and back of the flap of debris and epithelial cells. Stroking the cap with a cellulose

sponge can minimize persistent folds in the flap and properly line up the cap with the bed.

**Punctate epithelial keratopathy** (dry eye) is the most frequent complication of LASIK.<sup>68</sup> Several possible mechanisms contributing to LASIK-induced dry eye have been proposed. The mechanisms include injury to the afferent sensory nerve fibers, a reduction in neurotrophic influences on epithelial cells, a decreased blinking rate, decreased tear production, altered tear-film stability and distribution, increased tear evaporation, and injury to limbal goblet cells. The preponderance of data supports the hypothesis that the most important factor in the pathophysiology of LASIK-induced dry eye is the transection of afferent sensory nerves in the anterior third of the stroma during the lamellar cut.<sup>69,70</sup> The disorder tends to be more common and more severe in the context of underlying chronic dry eye. It has become evident, however, that the disorder is multifactorial.<sup>71,72</sup> Studies in patients in whom the flap was created with a microkeratome showed significantly more signs and symptoms of LASIK-induced dry eye than those in which a femtosecond laser was used for flap creation.<sup>73</sup> Treatment involves frequent lubrication of the ocular surface with artificial tears, topical anti-inflammatory therapy, and punctal plugs; management of any eyelid disorder also may be of benefit.

**Diffuse lamellar keratitis** (DLK), also known as *Sands of Sahara syndrome*, is an interface inflammatory process that occurs in the early postoperative period after LASIK (Fig. 3.4.10).<sup>74</sup> Patients are initially asymptomatic and often have no visual impairment. A fine granular-appearing infiltrate that looks like dust or sand typically presents initially in the interface periphery. If left untreated, the inflammation can progressively worsen and may lead to corneal scarring with resultant irregular astigmatism. The cause of DLK is likely multifactorial. Bacterial toxins or antigens, debris on the instruments, eyelid secretions, or other factors may play a role.<sup>74-77</sup> Femtosecond LASIK flap creation has been associated with a higher risk for DLK than microkeratome flap creation.<sup>78</sup> Studies suggest that newer generation femtosecond lasers with higher frequency are associated with decreased DLK rates because lower energy settings are used in creating LASIK flaps.

Treatment involves frequent topical corticosteroids, and if severe enough, interface irrigation.<sup>79,80</sup> However, some authors have reported



**Fig. 3.4.10 Diffuse Lamellar Keratitis (DLK).** The image shows stage II DLK, and identification of this should be followed by increased topical corticosteroid administration and close follow-up.

excellent results in the treatment of severe DLK with high-dose topical and oral corticosteroids without flap lifting and interface irrigation.<sup>81</sup>

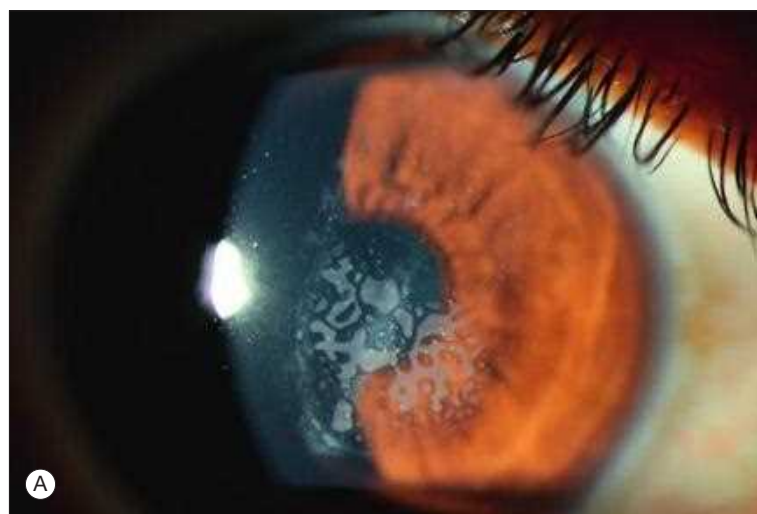
*Flap striae and microstriae* are common complications after LASIK. Most striae are asymptomatic and can be visualized if the flap is carefully examined with retroillumination.<sup>66</sup> When microstriae occur over the pupil or when macrostriae exist, irregular astigmatism with visual aberrations and monocular diplopia may result. In such cases, the flap should be lifted again, hydrated, and stretched back into position.

*Epithelial ingrowth* into the interface between the flap and the stromal bed occurs in up to 3% of patients following myopic LASIK surgery (Fig. 3.4.11). Known risk factors for this complication include epithelial defects at the time of surgery, history of recurrent corneal erosions, corneal basement membrane epithelial dystrophy, history of ingrowth in the other eye, hyperopic LASIK correction, flap striae or folds (as when the flap dislocates after surgery because of trauma or poor adhesion), flap instability, type 1 diabetes, and repeated LASIK surgeries.<sup>82,83</sup> Rarely, the epithelial ingrowth progresses into the central visual axis, causing irregular astigmatism and loss of BCVA. In some cases, the epithelial cells will block nutritional support for the overlying stroma and lead to flap melt.<sup>66</sup> If this is the case, the flap should be lifted, and careful scraping of the epithelium should be performed at the stromal bed as well as under the flap. In recurrent cases, suturing or flap gluing may help to reduce the incidence of recurrent epithelial ingrowth.<sup>84</sup> Nd:YAG laser application has been described as a technique for the treatment of epithelial ingrowth after LASIK surgery.<sup>85</sup>

*Corneal haze* can occur following LASIK. With fears of corneal ectasia following LASIK, surgeons continue to aim for thinner flaps. Although thin-flap LASIK has been reported to be successful,<sup>86</sup> there have been reports of interface haze formation with thin-flap femtosecond LASIK (<90  $\mu\text{m}$ ), especially in young patients<sup>87</sup> and could be related to focal disruptions of the Bowman's layer and injury to the epithelial basement membrane.<sup>88</sup>

*Infectious keratitis* after LASIK is a devastating, vision-threatening complication. Fortunately, the estimated incidence is low and reported to be between 1 in 1000 and 1 in 5000 procedures.<sup>89,90</sup> Reported organisms include *Mycobacterium* spp., fungi, *Nocardia* spp., *Staphylococcus aureus*, *Streptococcus viridans*, coagulase-negative *Staphylococcus* spp., and *Streptococcus pneumoniae*.<sup>91</sup> The most common organism cultured in a worldwide survey was methicillin-resistant *Staphylococcus aureus* (MRSA).<sup>93</sup> Symptoms may include pain, photophobia, watering, decreased visual acuity, ghost images, and halos. Slit-lamp examination may reveal ciliary injection, epithelial defect, anterior chamber reaction, and hypopyon. In the case of mycobacteria and fungi, presentation is usually delayed several weeks after the LASIK procedure and then has a smoldering course. Clinically, the mycobacteria and fungi usually are seen in the interface, often with a feathery or indistinct margin. Gram-positive infections are usually seen shortly after the procedure, often at the flap margin, and usually have distinct, sharp margins.

It is important to maintain a high suspicion for atypical organisms. The flap should be lifted and cultures should be inoculated on blood, chocolate, Sabouraud and Lowenstein-Jensen agar, and blood-heart infusion. Smears



**Fig. 3.4.11 (A)** Central epithelial ingrowth under LASIK flap following traumatic flap displacement. **(B)** Peripheral epithelial ingrowth with associated flap melting.

should also be taken for Gram, Giemsa, and Calcofluor white stains as well as Ziehl-Neelsen for acid-fast bacteria.

The mycobacteria species associated with keratitis following LASIK belong to the nontuberculous mycobacteria group. These species are resistant to chemical disinfectants such as chlorine, which is probably why such infections may occur after surgical procedures. Clarithromycin and amikacin are the antibiotics of choice, but poor penetration of topical medications leads to persistent infection. Early flap lifting and soaking of the flap and bed with amikacin 0.08% and/or clarithromycin 1% followed by aggressive topical therapy leads to the best results.<sup>92</sup>

Perhaps the most important factor within our control is prevention. Meibomian gland disease should be treated before LASIK. Instruments must be properly sterilized, and intraoperative sterile techniques should be employed, including the use of sterile gloves and drapes and disinfection of the skin and eyelids with povidone-iodine. During the procedure, instruments should be sterile and sterile plastic bags used for the nonsterile portions of the laser. Efforts should be made to avoid irrigating meibomian secretions into the interface. Suction lid specula may be helpful in removing excessive fluids and debris. Postoperatively, the patient should be instructed to wear shields and not to rub the eye. Prophylactic antibiotics should be used for 1 week postoperatively.

### Keratectasia

Retrospective analysis of patients with ectasia suggests the following risk factors for progression of ectasia after laser vision correction: (1) abnormal preoperative topography, (2) low residual bed thickness, (3) young age, (4) low preoperative corneal thickness, and (5) high myopia.<sup>94,95</sup> General agreement exists on leaving 250–300  $\mu\text{m}$  of untouched posterior cornea stroma. Ablation below that limit may cause biomechanical weakening, causing the cornea to bulge forward.<sup>96</sup> Another important cause of iatrogenic keratectasia is LASIK performed on unrecognized keratoconus suspects.<sup>97</sup> Videokeratographic clues for a keratoconus suspect may include steep



keratometry, inferior steepening of the cornea, asymmetry of the corneal curvature, or nonorthogonal astigmatism. Iatrogenic keratectasia has been reported as early as 1 week and as late as 2 years postoperatively.<sup>98</sup>

Although ectasia is rare after laser vision correction, many management options are available. Most are similar to those available for naturally occurring keratoconus. Most patients can still function well with nonsurgical options, such as contact lenses.<sup>99,100</sup> Intracorneal ring segments may be used to manage patients with ectasia after refractive surgery.<sup>101–103</sup> Corneal collagen crosslinking (CXL) with riboflavin and ultraviolet-A (UVA) radiation is now being used to treat keratoconus and post-LASIK ectasia; the principal goal of the technique is to stabilize the progression of these corneal diseases.<sup>104,105</sup> In previous studies of CXL outcomes, patients had improvement in corrected distance visual acuity (CDVA), uncorrected distance visual acuity (UDVA), maximum and average keratometry (K) values, several corneal topography indices, and corneal and optical HOA.<sup>106–108</sup>

Although corneal transplantation (penetrating or lamellar) is not often required, transplantation does have a high rate of success in eyes with keratoconus and would likely yield similarly good results in eyes with ectasia after refractive surgery.<sup>109,110</sup>

## Results

The efficacy and predictability of laser refractive surgery have greatly improved in recent years, even with standard conventional techniques. Most of this improvement is due to the development of flying spot lasers,<sup>18,111</sup> tracking systems,<sup>112,113</sup> and 8- to 9-mm transition zones that allow for blending the steep step at the periphery of the ablation zone.<sup>114,115</sup>

With traditional LASIK, the accuracy is greater for lower degrees of myopia. In one study of 130 eyes with an average preoperative spherical equivalent (SE) of  $-3.61$  D followed for 12 months after LASIK, 98% obtained a correction within  $\pm 1$  D from target and 93% obtained 20/40 or better UCVA.<sup>116</sup>

Another study showed that in low myopia ( $-0.75$  D to  $-6.00$  D of myopia and  $0$ – $0.75$  D of preoperative astigmatism), 50% of eyes achieved 20/25 or better and 90% of eyes achieved 20/40 or better at 1 month postoperatively, and the SE was within  $\pm 1.00$  D of emmetropia in 89% of the patients. In high myopia ( $-6.00$  to  $-20.00$  D of myopia and  $0$  to  $4.5$  D of preoperative astigmatism), at 1 month, 35% of eyes were 20/25 or better and 71% of eyes were 20/40 or better, and the mean SE was within  $\pm 1.00$  D of emmetropia in 63%.<sup>117</sup> The results of this and other studies suggest more predictable results for low myopia without astigmatism than for high myopia correction or in eyes requiring astigmatic correction.<sup>118,119</sup>

Data obtained from multicenter trials on wavefront-guided LASIK ablation for low to moderate myopia and astigmatism revealed that 98% of eyes achieved 20/20 UCVA, and 71% were at 20/16 or better uncorrected. What is even more impressive is the fact that postoperative UCVA was better than the preoperative best corrected results in 47% of patients.<sup>120,121</sup>

Ongoing improvements in the custom wavefront treatments have resulted in more precise treatments and postoperative results even for higher corrections. The results achieved with VISX Star S4 laser (Advanced Medical Optics, Inc.; Santa Ana, CA) treatment of high myopia and astigmatism with Custom Vue customized ablations were remarkable. The mean preoperative refractive spherical error was  $-8.00$  D ( $\pm 1.4$  D, range  $-5.5$  to  $-11.3$  D). The average cylinder was  $-1.00$  D ( $\pm 1.00$ , range  $0.0$  to  $-5.3$  D). The manifest refraction spherical equivalent (MRSE) was  $-8.5$  D ( $\pm 1.3$ , range  $-6.4$  to  $-11.8$  D). At 6 months, 98% of the eyes were seeing 20/40 or better uncorrected, 84% were 20/20 or better, and 65% were 20/16 or better. Three quarters had the same or better postoperative UCVA compared with their preoperative best spectacle-corrected visual acuity (BSCVA). Among the spherical myopes, 99% were at 20/20 or better uncorrected, with 84% at 20/16 or better at 6 months. Patients' satisfaction with their quality of vision was also high. This demonstrated that the customized approach offers excellent quantity as well as quality of vision even for higher corrections.<sup>120</sup>

Low to moderate levels of spherical hyperopia, simple hyperopic astigmatism, and compound hyperopic astigmatism can be effectively and safely corrected with LASIK. The results of a study evaluating patients with primary and secondary hyperopia who underwent traditional LASIK demonstrated that patients with primary hyperopia and a mean manifest SE of  $+1.73 \pm 0.79$  D before surgery obtained a postoperative SE of  $-0.13 \pm 1.00$  D at 6 months after surgery and an SE of  $-0.18 \pm 1.08$  D at 1 year after surgery. At 6 months, 84% of patients with secondary hyperopia had a UCVA of 20/40 or better; 76% were within  $\pm 1$  D of emmetropia. At 1 year, 85% had a UCVA of 20/40 or better and 85% were within  $\pm 1$  D of emmetropia. No patients with secondary hyperopia lost two or more

lines of BCVA at 1 year.<sup>122</sup> For higher levels of correction, the predictability within  $\pm 1$  D of attempted correction decreases to approximately 50%–80%, and the loss of BCVA generally ranges from 0% to 7%. However, LASIK for hyperopia greater than  $+5.00$  D is not recommended, as it may result in a loss of BSCVA in a significant number of eyes (13%–15%).<sup>123–128</sup>

Multicenter clinical trials of wavefront-guided LASIK for the correction of hyperopia and hyperopic astigmatism demonstrated significant improvements compared with traditional LASIK. Mean preoperative spherical error was  $+1.67 \pm 1.00$  (up to  $+4.59$  D), the average astigmatism was  $+0.65 \pm 0.48$  D (up to  $+2$ ), and MRSE was  $+1.99 \pm 1.00$  D (up to  $4.84$  D). At 6 months, 95% of the eyes had a UCVA of 20/40 or better, 62% were at 20/20 or better, and 20% were at 20/16 or better. The UCVA at 9 months was 20/16 or better in 24% of eyes and 20/20 or better in 72% of eyes.<sup>120</sup>

For mixed astigmatism, multicenter trials for custom wavefront LASIK results 6 months after surgery were a UCVA of 20/40 or better in 96% of eyes and 20/20 or better in 60% of eyes.<sup>120</sup>

Wavefront-guided and wavefront-optimized procedures attempt to minimize induced aberrations in different ways. Aspherical or wavefront-optimized ablation profiles have been developed to avoid inducing spherical aberrations.<sup>129,130</sup> Stonecipher and Kezirian reported 3-month results of an FDA trial for LASIK with the Allegretto Wave comparing wavefront-optimized versus wavefront-guided LASIK for myopic astigmatism, finding no statistically significant differences between either treatment group in regard to visual acuity and refractive outcomes. They stated that 93% of patients in each group had achieved 20/20 vision or better.<sup>131</sup> These results are comparable to those reported in a prospective, randomized study by Mirafat et al., who compared wavefront-guided and wavefront-optimized LASIK in contralateral eyes with myopia up to 7.00 D and astigmatism up to 3.00 D, also reporting no statistical differences in the UCVA, BCVA, or contrast sensitivity between both groups with 20/20 vision or better in 83.8% of the wavefront-optimized eyes and 89.2% of the wavefront-guided eyes.<sup>132</sup>

Stonecipher and Kezirian concluded in their study that wavefront-guided treatments may be considered if the magnitude of preoperative root mean square (RMS) HOA is  $>0.35$   $\mu\text{m}$ , and in their study population, 83% of eyes had preoperative RMS HOA of  $<0.3$   $\mu\text{m}$ .<sup>131</sup>

Studies using topography-guided LASIK have been encouraging. A prospective study of topography-guided LASIK using the WaveLight Allegretto Wave Eye-Q Laser included 249 eyes of patients with up to  $-9.00$  D of SE myopia at the spectacle plane with up to 6.00 D of astigmatism. Topography-guided treatment resulted in a significant reduction in MRSE and cylinder, reaching stability at 3 months after treatment. The mean MRSE was  $0.06 \pm 0.33$  D at 3 months and  $0.00 \pm 0.2700$  D at 1 year. At 1 year, 94.8% of eyes were within 0.50 D of plano. At 1 year, 15.7% of eyes saw 20/10 or better without correction; 34.4% of eyes saw 20/12.5 or better; 64.8% of eyes saw 20/16 or better; 92.6% of eyes saw 20/20 or better; and 96.5% of eyes saw 20/25 or better. Eyes treated with topography-guided treatment achieved an improvement in UCVA compared with preoperative BSCVA, with 29.6% of eyes gaining one or more lines of UCVA and 89.9% of eyes seeing at least as well without correction postoperatively as they did with best spectacle correction preoperatively.<sup>133</sup>

In a comparative study, both topography-guided and wavefront-optimized LASIK for myopia in virgin eyes provided excellent results. However, topography-guided LASIK was associated with better contrast sensitivity, lower induction of HOA, and a smaller amount of tissue ablation.<sup>134</sup>

With regard to patient satisfaction following LASIK, a comprehensive literature review was conducted in 2008 by the Joint LASIK Study Task Force. The results showed that 95% of patients were satisfied with their visual outcome after myopic and hyperopic LASIK.<sup>135</sup>

Modern LASIK outcomes support the safety, efficacy, and patient satisfaction of the procedure and appear better than those reported in summaries of the safety and effectiveness of earlier laser refractive surgery systems approved by the FDA. In a recent literature review of LASIK articles published between 2008 and 2015, the aggregate loss of two or more lines of corrected distance visual acuity was 0.61% (359/58653). The overall percentage of eyes with a UCVA better than 20/40 was 99.5% (59503/59825). The SE refraction was within  $\pm 1.00$  D of the target refraction in 98.6% of eyes (59476/60329), with 90.9% (59954/65974) within  $\pm 0.50$  D. In studies reporting patient satisfaction, 1.2% (129/9726) of patients were dissatisfied with LASIK.<sup>136</sup>

In addition, Price et al. compared visual satisfaction between LASIK and contact lens wear over a 3-year period. Current LASIK technology improved ease of night driving, did not significantly increase dry eye symptoms, and resulted in higher levels of satisfaction at 1, 2, and 3 years of follow-up.<sup>137</sup>



## LASIK ENHANCEMENTS

The initial consideration when deciding to perform a LASIK enhancement is to determine the possible reason for failure of the prior procedure. Errors may be related to inadequate preoperative refraction, improper laser ablation, abnormal corneal hydration during the procedure, an excessive or inadequate healing response, or induced corneal ectasia. A careful analysis of anterior and posterior corneal elevation maps should be performed to rule out a decentered ablation or iatrogenic corneal ectasia.<sup>138,139</sup>

Patient selection and appropriate timing are key for a successful LASIK enhancement. It is recommended to wait at least 3 months before considering an enhancement.<sup>140</sup> Patients with refractive instability should not undergo an enhancement procedure.

Another important consideration is the measurement of the central corneal thickness. If less than 250–300  $\mu\text{m}$  of residual untouched stromal bed will be available after the enhancement laser ablation or PTA is less than 40%, the risk of inducing corneal ectasia probably outweighs the benefit of the procedure.<sup>35</sup>

Regarding the decision of whether to recut the cornea versus lift the flap, studies have shown the effectiveness and predictability of using different techniques.<sup>141,142</sup> Flap lifting is probably the preferred method in most patients.<sup>143</sup> The flap edge can be marked at the slit lamp and lifted before the laser ablation. Unfortunately, this method requires flap manipulation and has been reported to be associated with a higher risk for epithelial ingrowth.<sup>143,144</sup> Flap recutting, however, may be associated with a higher risk of an inadequate flap or in loose lamellar wedges of stromal tissue. Therefore it is recommended to relift a flap when performing early enhancements in most patients. Some surgeons, however, advocate a deeper cut to avoid the previous interface.<sup>145</sup>

Femtosecond laser-created flaps are significantly stronger than microkeratome-created flaps and may be associated with increased difficulty of flap lift and a higher risk of complications.<sup>146,147</sup> To avoid these difficulties and possible complications of relifting or recutting LASIK flaps, a newer alternative is to utilize a femtosecond laser for the creation of a second side cut, within the border of the original LASIK flap (i.e., smaller than the original flap diameter).<sup>148</sup> Despite some reports of good results, epithelial ingrowth or irregular flaps can still result, and therefore most surgeons do not utilize these techniques.

A third alternative to flap lifting or recutting is PRK with the use of mitomycin-C on the LASIK flap.<sup>149</sup> This is a less invasive technique for the correction of residual refractive errors in patients with low residual stromal bed or in patients seeking an enhancement 2 or more years after the initial LASIK procedure, even though it is associated with a longer recovery.<sup>150,151</sup>

## LASIK IN COMPLEX CASES

### LASIK After Radial Keratotomy

Various studies have proven LASIK to be safe and effective in treating residual myopia and RK-induced hyperopia.<sup>152,153</sup>

A stable refraction for at least 6 months before LASIK is mandatory. A careful evaluation of the RK incisions is mandatory because the presence of epithelial inclusion cysts can predispose the patient to subsequent epithelial ingrowth after LASIK; LASIK should be avoided in these patients.

During the LASIK procedure, the flap should be manipulated with extreme care to prevent the RK incisions from splaying.<sup>154</sup> Careful observation of the patient during the postoperative period should be granted, as the risk of epithelial ingrowth is higher in this group of patients.<sup>155</sup> The epithelial ingrowth can be particularly difficult to manage and may even require fibrin glue for effective treatment.<sup>84</sup> With the availability of mitomycin-C to reduce haze in patients having PRK after prior surgery, many surgeons are now using PRK to treat patients with residual refractive errors after RK.<sup>156–158</sup>

### LASIK After Photorefractive Keratectomy

PRK has been proven to be a safe and effective method for treating low to moderate myopia.<sup>159</sup> Regression as well as the development of corneal haze are the main limiting factors in the correction of higher refractive errors, which are greater in patients treated for more than 6.00 D of myopia.

PRK retreatment for undercorrections should be approached with caution because there is a risk of further regression, increased haze, and loss of visual acuity.<sup>160,161</sup> LASIK appears to be a better approach in this

group of patients, and it has been proven to be a safe, effective, and predictable procedure for treating eyes with no or low haze after PRK.<sup>162</sup> Some surgeons suggest that the postoperative care should be the same as after primary PRK, with prolonged use of topical corticosteroids.<sup>163</sup>

In most cases, though, because of the underlying process that led the surgeon to decide on PRK in the first procedure (thin corneas, ABMD), the authors typically utilize PRK for enhancement procedures.

## LASIK After Penetrating Keratoplasty

Residual refractive errors after penetrating keratoplasty (PKP) are usually responsible for decreased visual acuity despite a clear graft. The mean amount of astigmatism that has been reported after PKP for keratoconus is usually between 2 and 6 D with only 15%  $>5.00$  D.<sup>164</sup> Visual rehabilitation with spectacles or contact lenses should be considered initially, followed by the possibility of incisional refractive surgery if the patient is intolerant to either of these alternatives.

Several studies have shown that LASIK has significant advantages over other surgical procedures in the management of refractive errors after PKP.<sup>165–170</sup>

LASIK should be delayed at least 12 months after PKP because of the risk of corneal dehiscence during the creation of the flap. Although the precise safety interval between PKP and LASIK has not been established, some surgeons have performed LASIK as early as 8 months after PRK,<sup>171</sup> while others advise a minimum period of 2–3 years.<sup>167,168</sup> All sutures should be removed before performing the lamellar surgery.

LASIK is more effective in treating myopia than astigmatism after PKP. In a study by Donnenfeld et al., the mean SE of patients before surgery of  $-7.58 \pm 4.42$  D improved to  $-1.57 \pm 1.20$  D at 12 months after LASIK. Also, the mean cylinder of  $3.64 \pm 1.72$  D before surgery improved to  $1.29 \pm 1.04$  D by 12 months after. SE anisometropia was reduced from a mean of  $6.88 \pm 4.4$  D to  $1.42 \pm 1.05$  D at the final examination. BCVA remained the same or improved in 21 of 23 eyes and decreased by one and three lines in two patients.<sup>171</sup>

Our experience in 57 eyes treated for myopia and astigmatism after PKP was a mean SE decrease from  $-4.19 \pm 3.38$  D (range,  $-0.75$  D to  $-15.25$  D) preoperatively to  $-0.61 \pm 1.81$  D 2 years after LASIK. The mean preoperative refractive astigmatism decreased from  $4.51 \pm 2.2$  D (range,  $0.5$ – $10.00$  D) to  $1.0 \pm 1.35$  D for the 28 eyes with follow-up. The UCVA was 20/40 or better in 12 eyes (43%), and the BCVA was 20/40 or better in 86%.<sup>169</sup> These results are very similar to those of a recent study by Malecha et al. in which the preoperative SE was reduced by 3.93 D and the mean cylinder was reduced by 2.83 D from the preoperative values at the last follow-up visit. The UCVA was 20/40 or better in 73.7% of the eyes after LASIK.<sup>172</sup> The long-term results also appear to be quite stable in most eyes.<sup>171</sup>

In conclusion, LASIK after PKP is in general less predictable than in eyes with no history of surgery, partly because of larger corrections and the effect of the graft–host interface.<sup>171</sup> Still, significant improvement in uncorrected vision as well as anisometropia make this treatment attractive for patients with a healthy endothelium and a transplant large enough to place the ablation within the transplanted cornea. It is important to remember that the realistic goals of LASIK after PKP are to decrease the degree of anisometropia and ametropia to levels at which spectacle correction or contact lenses can be tolerated.

## LASIK After Intraocular Lens Implantation and Bioptics

Bioptics, popularized by Roberto Zaldivar, is the planned combination of phakic or aphakic IOL surgery with corneal surgery to correct large refractive errors.<sup>173</sup> Typically the maximum IOL power is used, and the residual refractive error is corrected by corneal ablation surgery (PRK or LASIK). The surgeries can be staged, with the lens surgery performed first followed later by PRK or LASIK. Alternatively, the LASIK flap can be made before the time of the lens surgery and lifted several weeks or months later for the laser ablation. Bioptics can be performed with either phakic or aphakic IOLs to correct any residual refractive error. Bioptics is especially useful in high myopia with astigmatism, and it is preferable to laser corneal ablation alone because of the reduced risk of visual aberrations, contrast loss, glare, and halos that are associated with extremely large myopic laser ablations.<sup>174,175</sup>

Similarly, LASIK can be extremely useful in treating ametropia after clear lens extraction or cataract surgery with multifocal IOL implantation with good refractive outcomes and improved patient satisfaction.<sup>176,177</sup>

## Intraocular Lens Calculations After LASIK

Postrefractive surgery patients who develop a cataract expect excellent UCVA after cataract surgery, just like after their previous refractive procedure. Experience with eyes after myopic refractive procedures indicates that use of postoperative average standard keratometric readings in standard IOL power predictive formulas frequently results in substantial refractive errors, hyperopia being the unexpected surprise in patients who undergo myopic refractive procedures, and myopia in those undergoing hyperopic procedures.<sup>178–180</sup>

Calculation of IOL power in cataract surgery is based on the measurements of corneal power/radius of curvature, axial length, and estimation of postoperative anterior chamber depth (effective lens position, ELP).

The main reason for underestimation of IOL power after refractive corneal surgery lies in the inaccurate determination of keratometric power.<sup>181</sup> The keratometer is inaccurate in this setting, because it measures only four points of the cornea in a paracentral region, ignoring flatter (after myopic refractive surgery) or steeper (after hyperopic refractive surgery) more central regions.<sup>182</sup> Computerized videokeratography (CVK) overcomes some of these limitations. However, both keratometry and CVK are inaccurate in eyes that have had myopic PRK or LASIK, because the standardized value for the corneal index of refraction (1.3375) used in both devices is not valid for measuring these corneas.<sup>180,183,184</sup> A second important factor accounting for inaccuracies when using conventional IOL calculations is the ELP, or predicted position of the IOL along the axial length of the eye.

Because preoperative data frequently are not available, and performance of IOL calculations can be time consuming using various individual methods, the American Society of Cataract and Refractive Surgery developed an online Internet-based IOL power calculator to assist surgeons with these difficult IOL calculations. A recent study by Wang et al. evaluated the accuracy of various methods of IOL power prediction using this online IOL power calculator after previous myopic LASIK or PRK. Methods using surgically induced change in refraction as well as methods using no previous data gave better results than methods using pre-LASIK/PRK K values.<sup>185</sup>

As with all refractive procedures and because of the possibility of residual refractive errors, it is important that the patient should have realistic expectations and that the desired target refraction be discussed beforehand.

## SUMMARY

LASIK is an extremely useful technique that combines safety, rapid visual recovery, and flexibility in its ability to be enhanced or combined with other procedures. As the techniques continue to improve, with newer advances in femtosecond and excimer lasers, refractive surgery will continue to evolve and will change the way we assess our refractive expectations and outcomes.

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# Small Incision Lenticule Extraction (SMILE)

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3.5



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**Definition:** Small incision lenticule extraction (SMILE) is a laser refractive procedure in which a corneal stromal lenticule is created with a femtosecond laser and removed through a small incision in order to correct the refractive error.

## Key Features

- SMILE preserves the corneal integrity better than laser-assisted in situ keratomileusis (LASIK) with its flap-free design eliminating risk of microfolds and flap dislocation.
- Perioperative complications include epithelial abrasions, suction loss during femtosecond laser application, and minor tears of the lenticule or incision edges during lenticule removal.
- Corneal haze is the most common early postoperative complication.
- Early dry eye symptoms can occur, although it spares the subbasal nerve density better than flap-based LASIK, with faster sensitivity recovery.
- Enhancements can be performed with the CIRCLE procedure, where the cap is converted to a flap and followed by excimer ablation of the stromal bed or with surface ablation.

## INTRODUCTION

Over the past decade, femtosecond laser-assisted in situ keratomileusis (FS-LASIK) has become a well-established technique for correcting myopic refractive errors. Femtosecond laser technology allows a more reproducible corneal flap of predetermined thickness, compared with microkeratome.<sup>1</sup> Femtosecond lenticule extraction (FLEX) was later introduced as an alternative to FS-LASIK after development of the VisuMax femtosecond laser (Carl Zeiss Meditec, Jena, Germany). FLEX still required a corneal flap to enter the corneal stroma, as with LASIK. However, FLEX allowed corneal tissue removal by creating a stromal lenticule instead of laser ablation. It proved beneficial to further improve on this and develop a laser refractive technique that did not require use of a corneal flap, minimizing the trauma on the corneal surface and removing the risk of microfolds or flap dislocation.<sup>2,3</sup>

Small incision lenticule extraction (SMILE) was introduced as a next-generation stromal lenticule refractive procedure, further optimizing FLEX.<sup>4,5</sup> As a flap-free technique, an intrastromal lenticule was cut by a femtosecond laser and removed through a small corneal incision. With use of only a small incision (2–4 mm in width) for removal of the lenticule, the corneal integrity was left almost intact.

## FEMTOSECOND LASER SYSTEM

The femtosecond laser ( $10^{-15}$  seconds) that is used for SMILE is a Nd:YAG solid-state laser that emits energy into a focal point with a 1043 nm wavelength and has been discussed in previous sections in this chapter.

## TREATMENT RANGE FOR SMILE

SMILE with VisuMax is approved outside the United States for myopia up to –10.00 diopters (D) in sphere and up to 5.00 D of cylindrical component. SMILE for myopia and astigmatism with VisuMax was Conformité Européenne (CE) marked in 2009. In 2016, the US Food and Drug Administration (FDA) approved VisuMax for myopia from –1.00 D and up to –8.00 D in sphere and astigmatism of 0.50 D or less. Patients with more than –10.00 D in sphere still remain a surgical challenge. For now, VisuMax does not have an approved algorithm for treating hyperopia. Initial studies have tested an improved lenticule shape that removes more tissue in the midperiphery than in the center. Although the technique is promising, it still needs refinement to be on par with the state-of-the-art excimer laser treatments for low to moderate hyperopia.<sup>8–10</sup>

## PATIENT EVALUATION

Patients referred to SMILE should preferably be 18 years or older with a stable refraction for more than 2 years. Standard preoperative evaluation includes uncorrected and corrected distance visual acuity, pupil size, tonometry, pachymetry, tomography, slit-lamp examination, and dilated funduscopy. Tomographic measurements of the corneal front and back curvature should be carefully examined to exclude irregular tomographic patterns or subclinical keratoconus. The patient should not wear contact lenses 2 days (soft lenses) or 2 weeks (hard lenses) before tomographic evaluation. Contraindications for SMILE include corneal scars, corneal dystrophies, and severe dry eyes. Very anxious patients may not be candidates for SMILE, due to the increased risk of perioperative suction loss. LASIK is still the chosen technique to achieve monovision in presbyopic patients, as they often require surgical enhancements, which are done more easily after a flap-based procedure.<sup>11</sup> SMILE may be preferred over LASIK in patients who are involved in contact sports or perform jobs with increased risk of eye trauma, because there is no risk of traumatic flap displacement or dislodgement. Studies suggest that SMILE may also be the best option for moderate to high myopic correction due to higher predictability than after LASIK.<sup>12</sup>

## SURGICAL PROCEDURE

SMILE can be performed under topical anesthesia. Bilateral sequential treatment is usually performed. The patient is positioned supine under the femtosecond laser, and the untreated eye is covered and taped to prevent corneal dehydration. Two drops of 0.8% oxybuprocaine tetrachloride are applied 5 minutes before operation and again just before the lid speculum is installed. A contact glass interface that consists of a peripheral ring of small suction ports is attached to the femtosecond laser. The curved contact glass ensures precise contact to the corneal surface during laser application and is available in various sizes (S, M, L, and type KP). The size of the contact glass should correspond to the white-to-white distance of the patient. A small (S)-sized contact glass is generally preferred, especially in Asian patients with small white-to-white distances. The patient is positioned under the laser head. It is important to dry the ocular surface, especially the inferior fornix, with a sponge to remove any excess tear fluid or ocular surface secretions. This can be performed by placing a disposable sponge in the inferior fornix while the patient is being aligned to the interface cone. Some surgeons advocate the use of a speculum with a



suction device to remove excess tear fluid. Once the patient is under the laser head, the bed is elevated to allow contact with the interface and the anterior corneal surface. Before contact the patient is asked to fixate on a green light from the femtosecond laser for accurate centration. The bed then is elevated further to allow complete contact with the corneal surface. The degree of contact with the ocular surface can be ascertained by the spread of the tear fluid meniscus. In most cases when the tear fluid has spread to three quarters of the width of the cornea, suction is applied. Following suction, the patient is still able to fixate on the green light due to a low intraocular pressure rise.<sup>13,14</sup> Good centration is important because no built-in tracker exists.<sup>15</sup> Patients who have high astigmatism treatments should be marked in the horizontal axis on the slit lamp before the laser procedure. Once under the interface and suction applied, the interface can be rotated to ensure that the marked horizontal axis on the eye is in alignment with that of the horizontal meridian through the right eyepiece in the microscope of the laser, to counter any cyclotorsion.<sup>14</sup>

## Femtosecond Laser Application

SMILE is performed with four sequential laser cuts to create a corneal lenticule and a tunnel incision<sup>4</sup>: (1) a posterior lenticule surface cut in a spiral-in pattern (refractive cut), (2) a vertical cut along the circumference of the lenticule, (3) an anterior lenticule surface cut in a spiral-out pattern (corneal cap), and (4) a superiorly placed 2–4 mm tunnel vertical incision cut that gives access to the lenticule from the corneal surface (Fig. 3.5.1). We prefer to rotate the incision to the superior temporal side in the right eye and superior nasal in the left eye to ease the access for a right-handed surgeon and to avoid any superior pannus and intraoperative bleeding, which maybe be common in patients who wear contact lenses.

The spiral-in pattern of the posterior lenticule cut maximizes the time the patient can focus on the fixation target and minimizes the risk of suction loss due to eye movements. Cutting the posterior surface first ensures that the gas bubbles do not block the laser application of the anterior surface cut. The spiral-in and spiral-out laser firing sequence has also been shown to cause minimal disruption to the collagen lamellae.<sup>7</sup> The laser refractive application takes approximately 20–25 seconds depending on the laser settings. Suction is released automatically after treatment.

The following laser settings can be altered by the surgeon and to determine the lenticule thickness and treatment zone. For the lenticule: lenticule diameter, minimum lenticule thickness, and lenticule side cut angle. For the corneal cap: cap thickness, cap diameter, incision position, incision width, and incision side cut angle. The laser settings are determined by the preoperative refractive status, together with the preference and experience of the surgeon. Surgeons starting with SMILE should perform cases with lenticule thickness of above 70  $\mu\text{m}$  (minimum lenticule thickness of 15  $\mu\text{m}$ ) because it will be easier to perform the removal.<sup>16</sup> Surgeons with more experience with the procedure may perform treatments of  $-1$  D.

## Lenticule Removal



See clip:  
3.5.1

Lenticule removal includes several key stages (Fig. 3.5.2) (Video 3.5.1). The eye can be fixated with a pair of forceps to avoid sudden eye movements during the intrastromal maneuvers. The incision is opened with a Sinskey hook. The two lenticule planes are identified in each corner of the incision. The remaining tissue bridges of the upper surface are broken with a blunt spatula and the lenticule is separated from the cap. The blunt spatula should be gently maneuvered over the lenticule with no major resistance from the remaining tissue bridges. A gentle sweeping movement is advocated ensuring that the dissection passes over the complete area of the anterior surface of the lenticule. The same maneuver is performed on the posterior surface of the lenticule. The lenticule then can be removed through the incision using a pair of forceps. Some surgeons flush the intrastromal pocket with balanced salt solution to remove remaining debris and minimize the risk of epithelial ingrowth. However, the fluid may possibly induce small fluid pockets in the interface and can delay the immediate visual recovery.<sup>17</sup> After lenticule removal, the cap can be massaged with a sponge to remove residual tension folds to the periphery, to minimize irregularities and microfolds on the visual axis when correcting highly myopic patients.<sup>18,19</sup> One drop of fluoroquinolone and corticosteroid are then applied at the end of the procedure.

## Postoperative Management

A postoperative regimen may include a combination of topical dexamethasone and antibiotics, typically 4 times a day for 2 weeks, then tapered to

twice a day for 2 weeks.<sup>16</sup> The patient should use lubricating drops hourly for the first week to ease the discomfort in the postoperative period. Daily activities can be performed, but the patient should avoid swimming pools and extensive eye rubbing during the first 2 weeks. Slit-lamp examination should be performed 1 day, 1 week, and 1 and 3 months after the operation. We normally assess refractive outcome with formal refraction at 1 and 3 months.

## COMPLICATIONS

SMILE has an advantage over LASIK; flap dislocation and detachment are not seen because of the flap-free approach. Nevertheless, specific complications related to the lenticule cutting and removal do occur. Before operation, the surgeon should be aware of how to avoid and manage the most frequent peri- and postoperative complications (Table 3.5.1).<sup>20</sup>

### Perioperative Complications

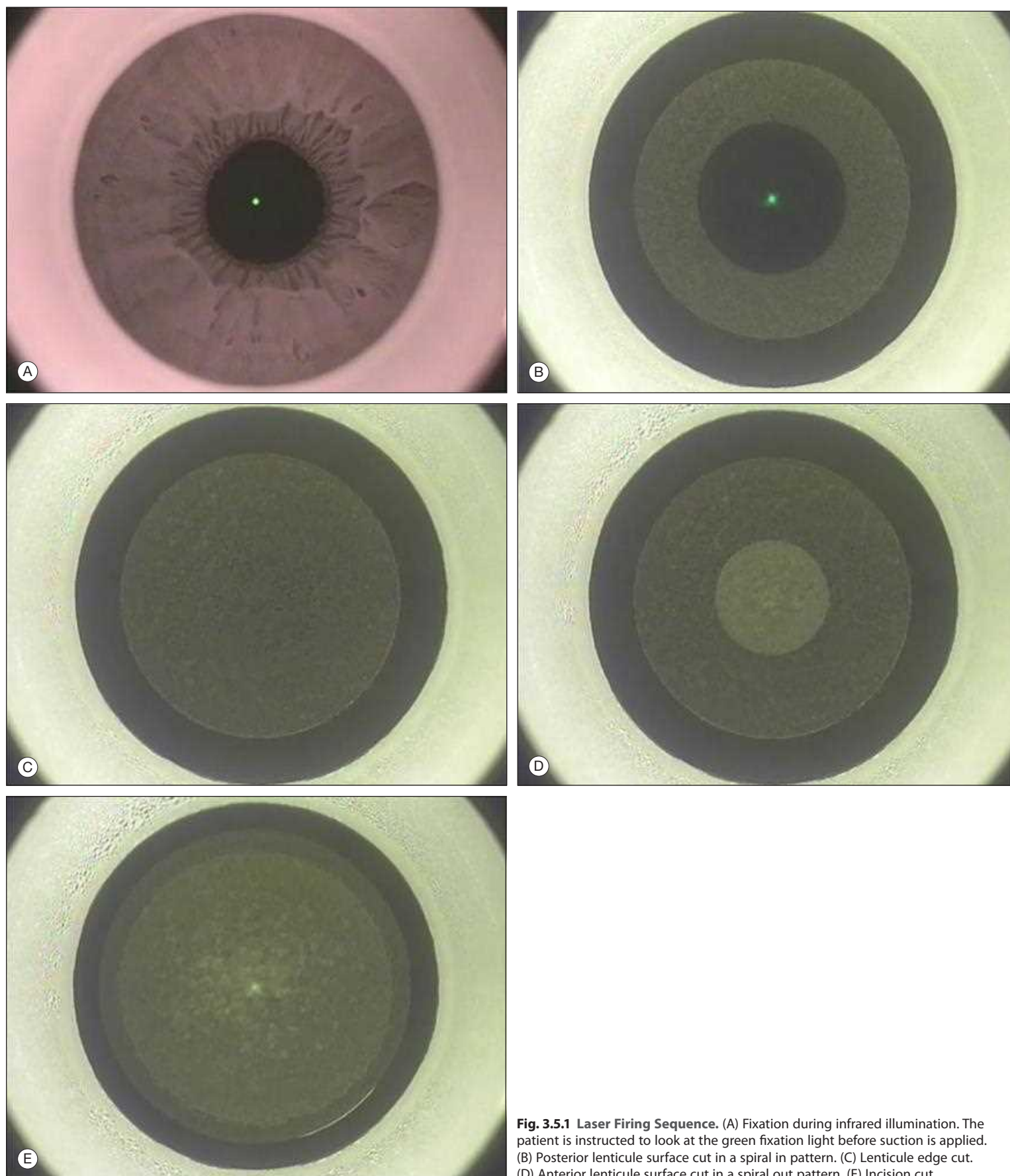
*Epithelial abrasions* (5.2%) are the most common complication after SMILE but rarely cause sequelae. Central abrasions (0.2%) can be treated with a bandage lens for few days. Epithelial abrasions have been associated with an increased risk of postoperative interface inflammation. Intensive treatment with topical dexamethasone every hour eases the inflammation.<sup>21,22</sup> Incisional abrasions may be seen more commonly in older patients (e.g., in their 40s).

*Minor and major tears* (1.8%) of the lenticule or incision edges are a common complication after SMILE and depend on the width of the incision (Fig. 3.5.3A). Small tears will normally heal with minor scar formations outside the optical zone. Nevertheless, they should be avoided to reduce the risk of postoperative epithelial ingrowth. The incision width should be altered depending on the surgeon's experience, usually 2–3 mm for experienced surgeons but up to 5 mm for inexperienced. Minor tears in the lenticule edge most commonly occur in thin lenticules and after uneven laser application (opaque bubbles or “black areas” where energy was not transferred to the stromal tissue due to opacities).

*Lenticule extraction difficulties* (1.6%) may occur after inadequate laser cutting and/or dissection. Difficulties with lenticule removal may increase the risk of tearing the lenticule, with lenticule tags left in the stromal pocket (0.04%) leading to induced postoperative irregular astigmatism. In those cases, the original incision may be used to remove the lenticule tag.<sup>23</sup> Adequate dissection to remove any remaining stromal bridges anterior and posterior to the optical zone (see earlier) can avoid this complication. The most common reason that may lead to difficulty with removal of the lenticule occurs when the dissection is performed inadvertently on the posterior surface first. This pushes the anterior surface of the lenticule up against the cap, which if unrecognized can cause difficulties in removal. This is particularly common when performing corrections for low myopia. Adequate delineation of the anterior and posterior surfaces of the lenticule at the beginning of the procedure—and custom-made instruments that allow removal of the lenticule from the posterior surface—can help in this situation.<sup>24</sup> Prolonged stromal manipulation may lead to delayed postoperative visual quality.

*Intraoperative suction loss* (1%) with detachment of the contact glass may occur at any time throughout the procedure and will automatically terminate laser application. Common reasons for suction loss include eye squeezing or head movements, often seen in anxious patients, or excess tearing on the ocular surface.<sup>20,21,25,26</sup> Detailed counseling of what visually to expect during the laser application are important. Hence, the surgeon's experience with the technique and patients' counseling may decrease the risk of suction loss.<sup>27</sup> Increased tear production or local anesthesia can induce fluid ingress and detachment between the contact glass and cornea. Small palpebral apertures and a large cap diameter also increase the risk of suction loss.<sup>26,27</sup>

If suction loss occurs before completion of the posterior surface, the surgeon will not be allowed to complete the SMILE procedure, but is given the option to convert to FS-LASIK. The option then is to convert to FS-LASIK. Retreatment can be performed after a few minutes or postponed to another day. If suction loss appears after completing the vertical lenticule side cut, the surgeon can aim to redock and complete the procedure. However, it can be problematic to achieve the exact alignment because of the gas bubble layer obscuring the pupil. Gentle compression on the ocular surface with a wet sponge will allow dispersion of the cavitation bubbles and improve visualization for the patient. Increasing the anterior cap diameter following suction loss will help ensure adequate alignment during redocking to repeat the anterior cut. In a study of suction loss



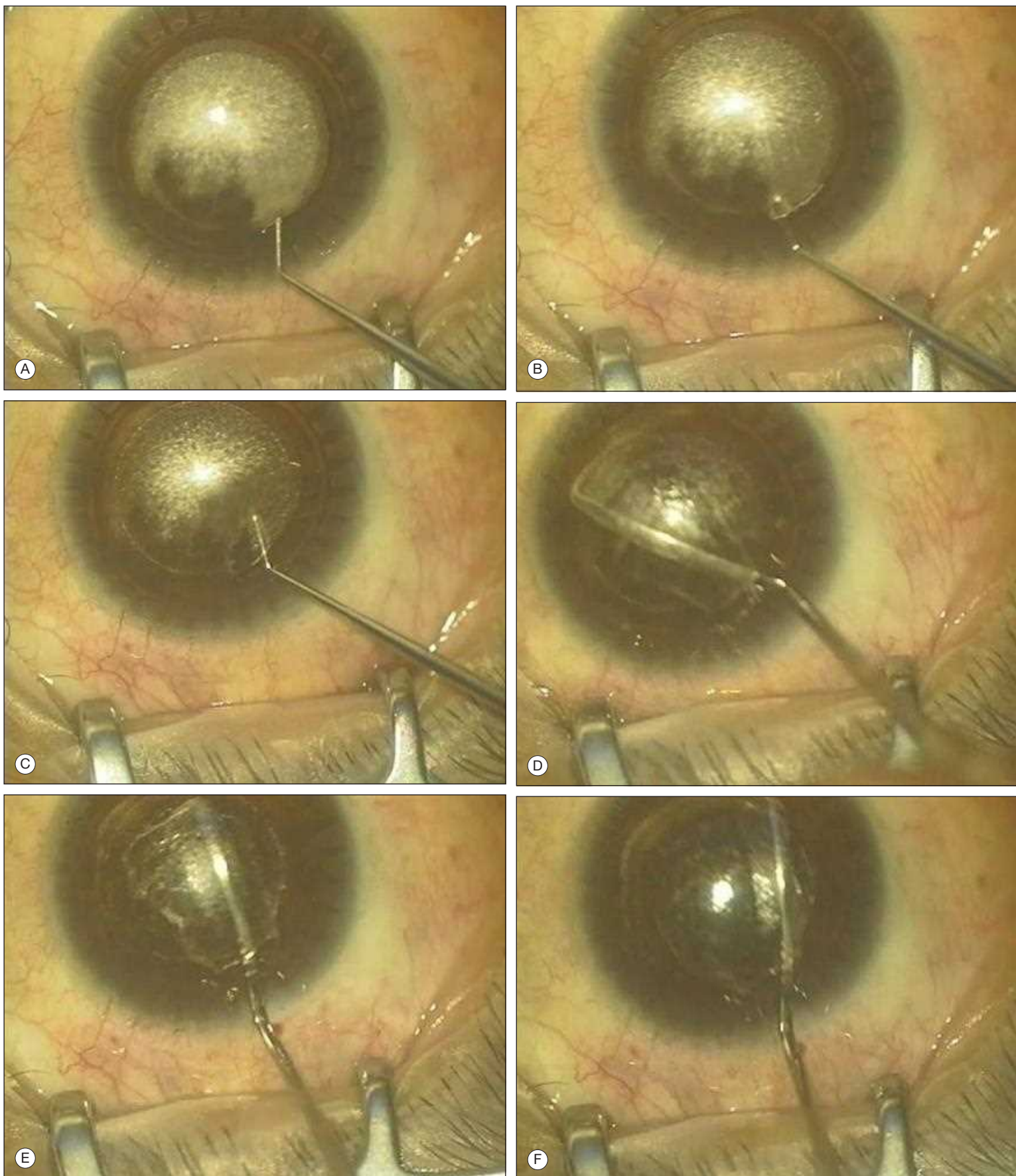
**Fig. 3.5.1 Laser Firing Sequence.** (A) Fixation during infrared illumination. The patient is instructed to look at the green fixation light before suction is applied. (B) Posterior lenticule surface cut in a spiral in pattern. (C) Lenticule edge cut. (D) Anterior lenticule surface cut in a spiral out pattern. (E) Incision cut.

and redocking during SMILE, uncorrected distance visual acuity (UDVA) was 20/30 or better in 73% of the patients after 3 months (mean preoperative sphere of  $-5.81$  D and cylinder up to  $1.09$  D).<sup>25</sup> In a paired-eyed case study of 35 patients with suction loss in one eye, corrected distance visual acuity (CDVA) was significantly worse after 1 week in the complicated eye but with no significant differences in UDVA and CDVA after 3 months.<sup>21</sup>

## Postoperative Complications

**Corneal haze** (5.6%) is a well-known early postoperative complication after almost all laser refractive procedures and is associated with corneal keratocyte apoptosis and wound healing.<sup>28,29</sup> The corneal haze usually decreases over time. In cases with moderate corneal haze, CDVA had normalized within 2 years after the operation.<sup>21</sup>





**Fig. 3.5.2 Lenticule Dissection and Removal.** (A) Opening of the side cut incision with a Sinskey hook. (B) Demarcation of the anterior lenticule surface. (C) Demarcation of posterior lenticule surface. (D) Dissection of the anterior surface. (E) Dissection of the posterior surface. (F) Peripheral dissection of posterior lenticule surface. (G) Dissection of the edge, ensuring the lenticule is detached. (H) Removal of the lenticule with a pair of forceps.

*Continued*



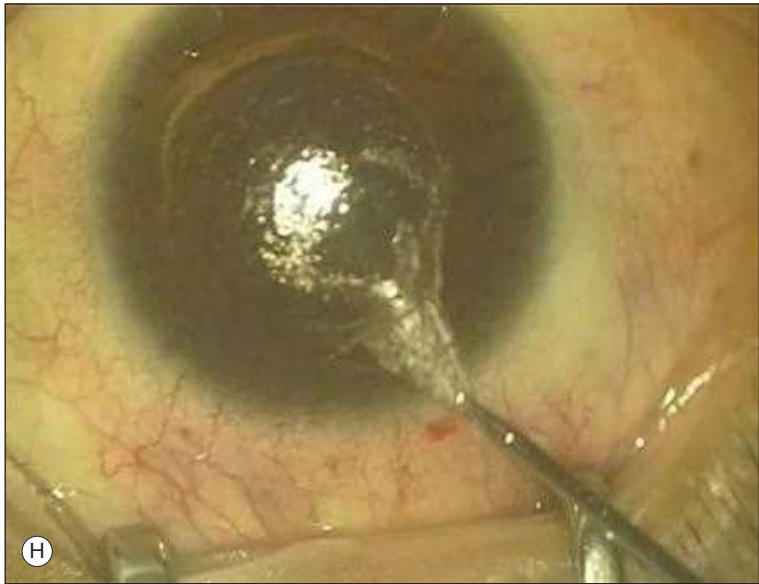
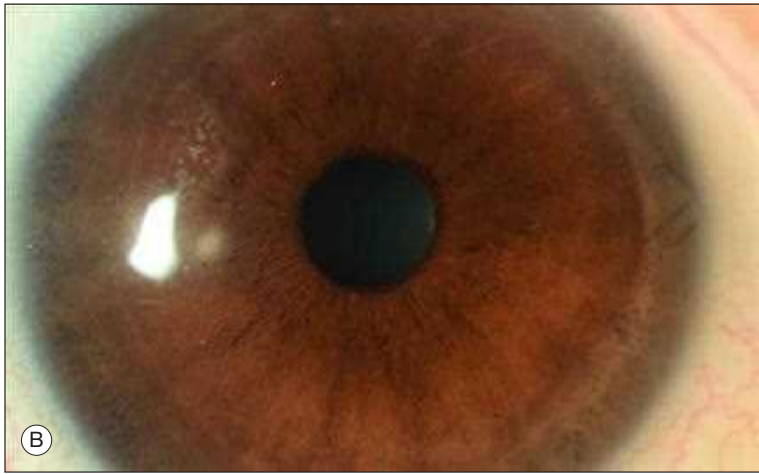


Fig. 3.5.2, cont'd



**Fig. 3.5.3** (A) Minor tear at the incision edge are a common complication after SMILE. Usually, they will heal with minor scar formations and no influence on the visual outcome. Nevertheless, they should be avoided due to increased risk of epithelial ingrowth. (B) Epithelial ingrowth 6 weeks after operation due to seeding of epithelial cells through the incision. The epithelial ingrowth was left untouched because it was located outside the visual axis and the patient did not have any visual complaints. (Courtesy Dr. C Chan.)

TABLE 3.5.1 Incidence of Peri- and Postoperative Complications Following SMILE.	
Perioperative Complications	Postoperative Complications
Peripheral (5.2%) and central (0.2%) epithelial abrasions	Corneal haze/nontransparency (5.6%)
Minor and major tears (1.8%)	Dry corneal surface, day 1 (3.2%)
Lenticule extraction difficulties (1.6%)	Epithelial ingrowth (0.5%)
Suction loss (1%)	Irregular corneal topography (0.5%)
Fiber in interface (0.2%)	Visually insignificant microstriae (0.4%)
Remaining lenticule remnant (0.04%)	Diffuse lamellar keratitis (0.2%)
	Monocular ghost images (0.2%)

Early dry eyes (3.2%) at day 1 may be seen in combination with corneal haze. In several studies, the flap-free approach has been shown to preserve the subbasal nerve layer density better after SMILE compared with FS-LASIK in both short- and longer-term studies.<sup>30–32</sup> Corneal sensitivity recovery has been shown to be faster after SMILE. However, early postoperative dry eye symptoms are comparable with flap-based procedures.<sup>30,33</sup> Tear break-up time (TBUT), Schirmer’s test, and tear meniscus height were similar after SMILE and FLEX up to 6 months after operation in a contralateral eye study.<sup>30</sup>

Epithelial ingrowth (0.5%) is seen when epithelial cells proliferate at the incision site or are displaced into the interface during lenticule removal (Fig. 3.5.3B). Epithelial ingrowth to the interface is more rarely seen after SMILE than after LASIK. Epithelial islands may be spotted at the incision site, often in relation to a minor tear after lenticule removal difficulties.

The epithelial islands may be left alone if no progression is observed. They also can be scraped off the border of the incision using a pocket epithelial remover or treated with Nd:YAG laser. Only in very severe cases with epithelial ingrowth to the interface center does it become visually significant.<sup>34</sup> In such situations if the epithelium cannot be removed through the small incision, an alternative option would be to perform a conversion of the pocket to a flap to allow a more extensive irrigation of the stromal interface.

Diffuse lamellar keratitis (DLK) (0.2%), also known as Sands of Sahara or interface inflammation, typically appears after 1–3 days, accompanied by decreased visual acuity, pain, and photophobia.<sup>35</sup> High laser energy settings during photodisruption increase the risk of diffuse lamellar keratitis.<sup>36</sup> Thin stromal lenticules may increase the risk of DLK, because gas bubbles after photodisruption accumulate within a small stromal area and provoke a strong inflammatory response.<sup>35</sup> DLK is frequently reported in conjunction with central aberrations and postoperative epithelial defects.<sup>21</sup> DLK may be successfully treated with topical corticosteroids or flushing the interface in some cases. In rare cases, a bacterial or fungal organism can be the cause of the inflammation and should always be considered if the patient does not respond to the treatment.<sup>37</sup> From the authors’ experience a higher incidence of DLK has been reported when the interface has not been irrigated following the procedure.

HIGHER-ORDER ABERRATIONS

Increased postoperative higher-order aberrations (HOAs) may promote visual complaints such as glare, halos, reduced contrast sensitivity, and poor night vision.

Preoperative patient evaluation includes pupil size and should be taken into consideration when the lenticule diameter is determined for the operation. Patients with large pupils may be more troubled by postoperative spherical aberrations if a small lenticule diameter is chosen. In particular, spherical aberrations may induce halos and decreased night vision due to the myopic shift with a large pupil (night myopia). However, a large lenticule diameter requires a thick lenticule to gain the same amount of correction and may not be acceptable when correcting highly myopic patients. Coma may increase after decentered laser treatment and can lead to symptoms of halos and monocular diplopia. In contrast to state-of-the-art excimer lasers, the VisuMax laser lacks an eye-tracking system. The alignment relies on the patient's cooperation and the surgeon's objective adjustment. Nevertheless, VisuMax is on par with the MEL 90 laser used for LASIK when it comes to centration during surgery.<sup>38,39</sup> Studies have reported an increase in coma and HOAs but not in spherical aberrations after SMILE.<sup>40–44</sup> A minor decrease is seen years after the operation, probably explained by remodeling of the epithelial layer.<sup>45</sup> Corneal aberrations after SMILE have been shown to be less than after FS-LASIK,<sup>42–44</sup> although one study reported a similar shift in aberrations after SMILE and LASIK.<sup>46</sup>

## BIOMECHANICAL STABILITY

In contrast to a flap-based LASIK procedure, SMILE involves the creation of a cap. Thus SMILE may be able to better preserve the corneal tectonic integrity because the small incision leaves most of the anterior corneal collagen intact. Most of the corneal strength is located in the anterior third of the cornea and is crucial to withstand the intraocular pressure.<sup>47</sup> From earlier ex vivo studies of the depth-dependent tensile strength, Reinsteint et al.<sup>48</sup> developed a mathematical model to predict the tensile strength following SMILE, LASIK, and photorefractive keratectomy (PRK). The model demonstrated greater postoperative tensile strength after SMILE than after LASIK and PRK, due to the creation of the corneal cap. Several studies have assessed the postoperative corneal biomechanical properties in vivo after SMILE and LASIK by using the Ocular Response Analyzer and Corvis ST (Scheimpflug-based tonometry). In a randomized pair-eyed study of SMILE and LASIK, both corneal hysteresis (CH) and corneal resistance factor (CRF) decreased after operation, but with no significant differences between the two methods.<sup>49</sup> Likewise, a randomized pair-eyed study of SMILE and FLEX reported no significant differences in terms of CH and CRF between the two methods after 6 months.<sup>50</sup> For now, no studies have performed a randomized pair-eyed study with Corvis ST. Retrospective studies using the Corvis ST on LASIK, FLEX, and SMILE reported similar reduction in the corneal biomechanical properties with regard to the deformation pattern during the airpuls.<sup>51,52</sup>

Iatrogenic ectasia with corneal protrusion and decreased visual acuity is a rare but severe complication after LASIK (0.05%).<sup>53</sup> The general recommendation for preventing ectasia is a minimum residual bed thickness of 300  $\mu\text{m}$  in LASIK. The use of the same recommendations in SMILE has been a topic of discussion because the cornea may be more biomechanically robust with less risk of iatrogenic ectasia.<sup>48</sup> Nevertheless, a few cases of iatrogenic ectasia have been reported after SMILE, although the preoperative evaluation of the patients may have shown abnormal preoperative topographical patterns.<sup>54–58</sup>

## REFRACTIVE AND VISUAL OUTCOME

SMILE has shown to be comparable with LASIK in terms of efficacy, predictability, stability, and safety.<sup>21,42,43,59,60</sup> However, the learning curve of SMILE is likely to affect the postoperative results in the early phase.<sup>6,27,60</sup> This can possibly be avoided with proper supervised training and earlier experience with corneal surgery.<sup>61</sup> In a study of SMILE for low myopia (mean spherical equivalent [SE] of  $-2.61$  D and cylinder up to  $1.50$  D), UDVA was 20/20 or better in 96% of the patients after 1 year.<sup>62</sup> In terms of CDVA, 9% lost one Snellen line but no eyes more than two. Postoperative SE was within  $\pm 0.50$  D and  $\pm 1.00$  D in 84% and 89%, respectively. Minor regression was reported from 3 to 12 months, where SE changed more than  $0.5$  D in 8% of the patients. A study of SMILE for moderate to high myopia (mean SE of  $-7.18$  D and cylinder up to  $1.50$  D), UDVA was 20/40 or better in 97% of the patients after 3 months.<sup>6</sup> CDVA improved slightly but significantly from baseline to 3 months, and with 2.4% loss in CDVA of two Snellen lines or more. In eyes with emmetropia as target refraction, 80% and 94% were within  $\pm 0.50$  D and  $\pm 1.00$  D, respectively. Studies with up to 5 years of follow-up report stable visual outcomes but a minor myopic regression of  $0.48$  D.<sup>45,63,64</sup> A study of SMILE for astigmatism ( $1.81$  D in mean cylinder, range  $0.75$  D– $4.00$  D) reported an astigmatic undercorrection of 11%

of attempted correction after 12 months.<sup>65,66</sup> Postoperative undercorrection tended to increase with higher attempted astigmatic correction and may be taken into consideration if the surgeon chooses to personalize the nomogram for astigmatic treatments.<sup>67</sup>

## RETREATMENTS

With improvement of the VisuMax nomogram, SMILE has proven to be accurate and predictable for correcting myopia and myopic astigmatism.<sup>5,6,45,68,69</sup> Still there is a risk of postoperative under- or overcorrection, but it does not seem to be related to the intended refractive correction.<sup>6</sup> Furthermore, the minor but significant myopic drift may require further enhancements years after SMILE.<sup>45,63,64</sup> It raises the question of how to correct patients already treated with SMILE. After LASIK or FLEX, the surgeon would simply lift the flap and perform excimer reshaping in the earlier treated zone. Several techniques for postoperative enhancement have been suggested, and the chosen technique should always be based on an extensive evaluation of the postoperative tomography, the degree of correction required, and the visual complaints of the patient.<sup>70</sup>

In the CIRCLE procedure available with VisuMax, the corneal cap can be converted to a flap with use of the previous upper surface and lenticule edge cuts.<sup>71,72</sup> With the femtosecond laser, the surgeon creates a circular incision in relation to the edge of the previous cap and leaves a hinge in the superior position. A lamellar cut connects the new circular cut with the previous SMILE optical zone. Lifting the flap gives access to the stromal bed, where reshaping can be done with excimer laser. The visual and refractive outcomes after the CIRCLE procedure followed by excimer laser surgery have proven to be reliable. Reportedly, 95.8% of patients with emmetropia as target refraction reached a UDVA of 20/20 or better 3 months after the CIRCLE procedure, with a residual refractive error of  $0.10$  D (mean preoperative SE:  $-0.74$  D, range  $-2.98$  D– $0.38$  D).<sup>71</sup> Another technique involves topography-guided PRK in patients with postoperative irregular topography.<sup>73</sup> Corneal haze has been reported after the PRK treatment even after minimal ablation depths. Perioperative mitomycin-C may be beneficial to prevent postoperative haze. In one case study, enhancement was performed with SMILE using the original cap. The laser application was stopped after the new lower surface and lenticule edge was cut, and the new lenticule was removed though the original incision.<sup>74</sup>

## CONCLUSIONS

SMILE has emerged as a new technique for correcting myopia and astigmatism. SMILE preserves the corneal integrity by creating a corneal cap with no risk of flap displacement as may be seen after LASIK and FLEX. Several studies have shown SMILE to have high efficacy, predictability, stability, and safety with fewer postoperative HOAs than after LASIK. In future, the development and refinement of SMILE may open up new ways of correcting hyperopia by removal of a piece of tissue that flattens the corneal curvature. Until then, LASIK and PRK are the recommended corneal treatment for correcting low hyperopia.

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# Wavefront-Based Excimer Laser Refractive Surgery

## 3.6

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**Definition:** Wavefront-customized excimer laser refractive surgery corrects pre-existing lower- and higher-order aberrations. Wavefront-optimized treatments preserve pre-existing corneal optical aberrations (customizing for spherical aberration).

### Key Features

- Zernike polynomials and Fourier transforms are used to represent and analyze the ocular wavefront.
- Optical properties influence image quality.
- Different devices measure ocular aberrations differently.
- Wavefront-customized and wavefront-optimized ablations result in better visual acuity and mesopic contrast sensitivity.

### INTRODUCTION

The eye is a complex, imperfect optical system. As light rays from distant objects pass through the optical components of the eye, they refract at the tear film and at corneal and crystalline lens interfaces. Any deviation from a perfectly focused optical system is referred to as aberration. Most of these aberrations reflect myopia, or hyperopia, and regular astigmatism, known as lower-order aberrations (LOA), which can be corrected with spherocylindrical spectacles.<sup>1</sup> Other optical aberrations are commonly referred to as irregular astigmatism and include spherical aberration, coma, trefoils, and quadrifolds. Irregular astigmatism encompasses higher order aberrations (HOA).

HOA may decrease the quality of vision and cause symptoms in up to 15% of the general population.<sup>2</sup> Rigid contact lenses can correct HOA that are generated at the anterior corneal surface. More advanced treatments involve the use of a personalized wavefront-guided laser refractive technique to reshape the surface of the cornea that leads to a more optically desired outcome.<sup>1</sup>

A customized corneal shaping requires wavefront analysis of the eye (aberrometry). For reproducibility, the waveform can be decomposed into components, using either Zernike polynomials or Fourier analysis.<sup>3-5</sup> The wavefront map is digitally interfaced with an excimer laser to control the delivery of a laser beam across the cornea in a customized fashion.

In the majority of the population, other noncustomized treatments may use epidemiological data to predefine ablation profiles that may be suitable to improve high-order aberration, especially spherical aberration. Although these treatments are not personalized for each patient, they are based on epidemiological information of wavefront analyses and are commonly known as wavefront optimized treatments.<sup>6</sup>

### WAVEFRONT OPTICS

The wavefront is the locus of points in an optical pathway having the same phase. If all incoming rays are parallel, and the eye is free from any aberrations, the resultant emerging wavefront is a perfectly flat surface. In other words, all light rays coming from a point source located at infinity focus at a single point on the retina. In reality, though, the focusing properties of a real eye are not completely uniform: Some areas bend light more strongly than others. The wavefront aberration is the deviation of a particular eye's wavefront from the ideal wavefront in the pupillary plane. Its magnitude is

entirely dependent on the diameter of the pupil; a larger diameter leads to a larger wavefront error (Fig. 3.6.1).<sup>4,7,8</sup>

### HIGHER-ORDER ABERRATIONS

HOA are monochromatic refractive disorders that may limit the vision of healthy eyes to less than the retinal detection threshold. HOA cannot be corrected with spherocylindrical lenses or with standard refractive surgery.<sup>5,8</sup> They have been categorized using Zernike polynomials by radial order and by angular frequency, with third order and higher constituting HOA.<sup>5</sup> The higher the order, the less visually significant the aberration. The two most frequently discussed aberrations are spherical aberration (which causes halos and night vision disturbances) and coma (which is associated with monocular diplopia).<sup>4,9</sup> The wavefront in spherical aberration is spherical in the center of the pupil but changes its curvature toward the edge of the pupil, giving concentric rings of focus that result in point images with halos. In coma, the wavefront is asymmetrical, producing a comet-shaped pattern (Fig. 3.6.2). Trefoil, quadrifoil, pentafoil, and secondary astigmatism are other HOA (see Fig. 3.6.2).

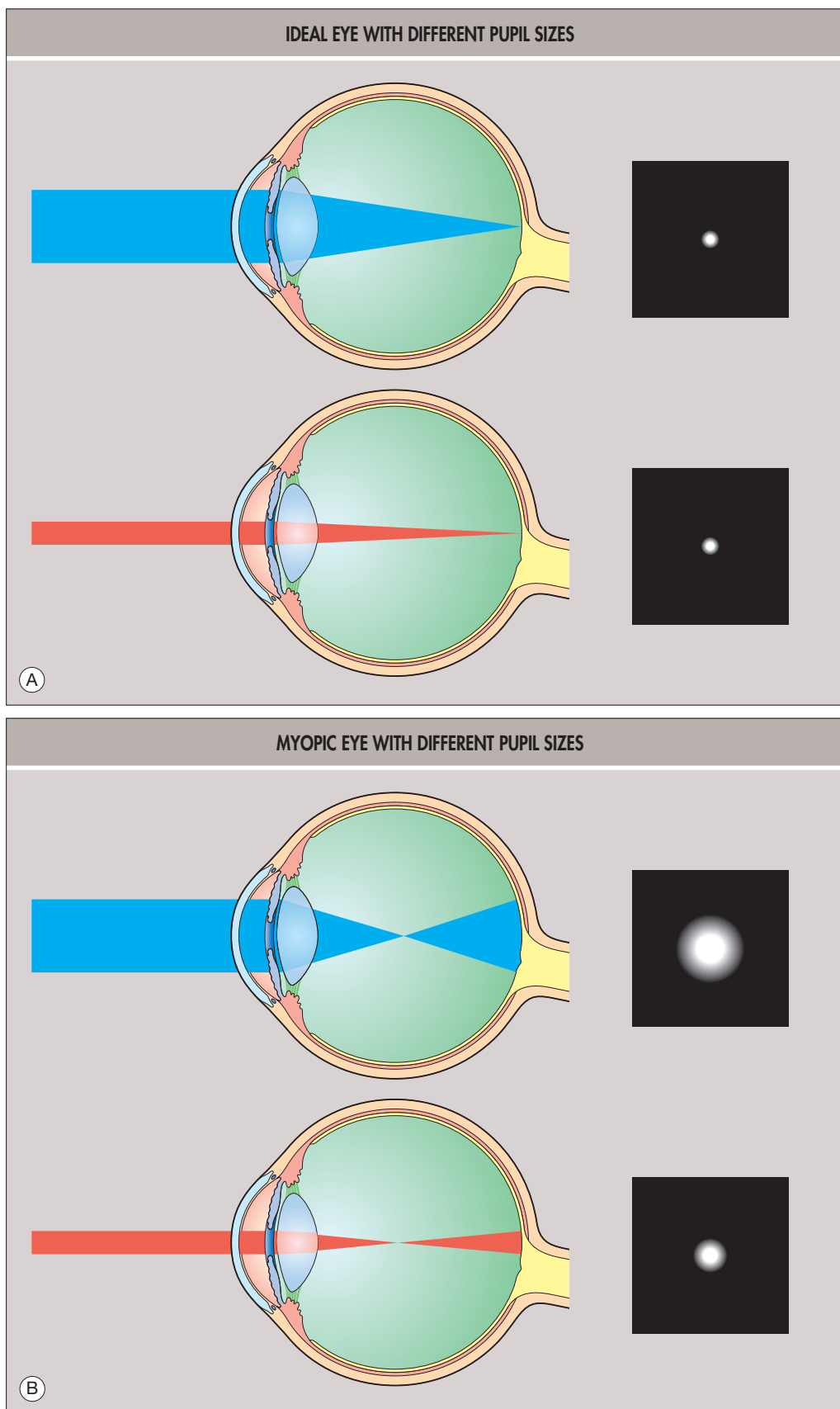
### IDEAL CORNEAL SHAPE

The shape of the cornea is prolate (more curved in the center) to allow for a lower total HOA.<sup>10</sup> The Q-value of the central cornea (5–7 mm) in a normal population varies from –0.21 to –0.27, meaning that the central cornea has a stronger curvature than the periphery.<sup>11</sup> This aspherical shape allows for focusing of rays coming from the periphery and those coming from the center on one point, correcting for inherent spherical aberration of spherical lenses. Any change in the average prolate corneal shape toward a more oblate profile (less curved in its center) leads to induction of spherical aberrations and consequently a decrease in night vision and contrast sensitivity.

### MEASUREMENTS OF WAVEFRONT ABERRATIONS

Zernike polynomials and Fourier transforms are used to analyze the detected ocular wavefront.<sup>5,12</sup> Zernike polynomials are a sequence of polynomials based on a radial model, whereas Fourier transforms represent nonradial mathematical functions of frequency. Most aberrometers used for customized laser surgery rely on Zernike polynomials to decompose the wavefront aberrations (Fig. 3.6.2). They can, in principle, measure an infinite number of aberration orders. Clinically, data up to the Zernike fifth order capture nearly all the aberration variance typically found in normal human eyes.<sup>7,8</sup> The Fourier analysis can decompose an image into spatial frequency components with a higher resolution of the surface (Fig. 3.6.3).

The measured wavefront errors are represented as root mean square deviations (RMS), which are correlated to the absolute deviation of an ideal wavefront. Applegate and colleagues<sup>4,5</sup> evaluated the effect of individual Zernike modes on visual quality and noted large differences in their subjective impact, with those in the middle of a given Zernike order influencing vision more than those at the periphery. For example, in the second radial order, defocus degrades vision more than astigmatism. Similarly, in the third and fourth order, coma and spherical aberration degrade vision more than trefoil and quadrifoil, respectively (see Fig. 3.6.2).



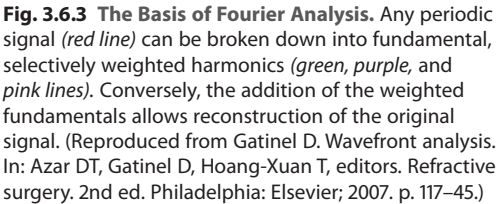
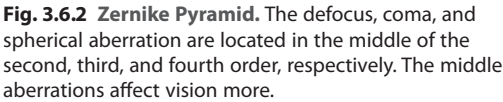
**Fig. 3.6.1 Aberrations of the Eye With Different Pupil Sizes.** (A) In an ideal eye with no ocular aberrations, a point source of light focuses on the retina. Image quality is not influenced by pupil size. (B) In an eye with an error of refraction (here with axial myopia), pupil size plays an important role in image quality. Rays striking the cornea further away from the center are bent differently from those striking the corneal center due to the intrinsic corneal shape. The formed aberrated wavefront is greater in the dilated eye compared with the miotic eye.

## QUALITY OF VISION AND MEASURES OF OPTICAL QUALITY

Visual assessment has two parts, acuity (quantity) and quality. A good visual acuity can be achieved on a high-contrast eye chart by correcting LOA using the standard refractive ablation. Vision quality refers to all fine details, colors, and shades of images after they are in focus—it is especially compromised in dim light. It can manifest as double vision, ghosting, glare, halos, starbursts, and reduced contrast sensitivity.

Standard approaches to quantification of the optical quality of the eye describe either the optical properties of the eye (aberration maps, wavefront error maps) or the effect these properties have on image quality (abnormality of an image of a point light source or of a sinusoidal grating).<sup>13</sup>

Aberration maps measure the undulating wavefront from an aberrated eye at the pupillary plane; they are quantified by the RMS wavefront error. Despite the fact that RMS wavefront error is not a good predictor of the subjective impact of aberrations on vision, it usually gives a rough estimate of the overall aberrations of the eye.<sup>10,13,14</sup>



to the image is called the modulation transfer function (MTF) and phase transfer function (PTF), respectively. The eye's OTF includes both the MTF and PTF.<sup>13,14</sup>

Several methods for assessing the wavefront aberrations in human eyes are currently available. Each method has its own way of measuring the



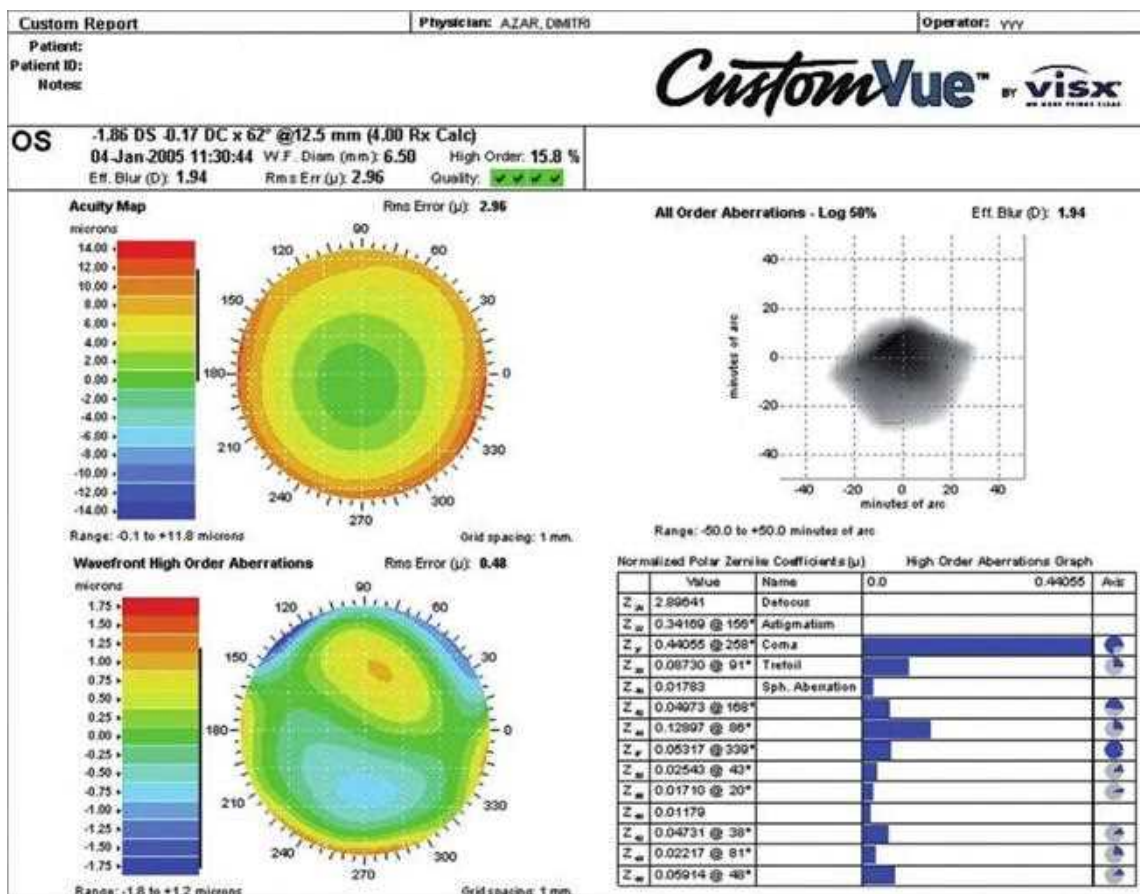


Fig. 3.6.4 VISX WaveScan Map Showing a High Amount of Coma.

displacement of a ray of light from its ideal position. They can be generally classified as outgoing or ingoing aberrometers.

Devices based on the Hartmann–Shack principle are currently the most widely used. These devices analyze an outgoing light that emerges or is returned from the retina and passes through the optical system of the eye.<sup>15,16</sup> A narrow beam of light is projected onto the retina, and its image passes through the lens and the cornea and exits the eye. The Hartmann–Shack sensor has a lenslet array that consists of a matrix of small lenses.<sup>15,16</sup> The light that emerges from the eye is focused on a charge-coupled device (CCD) camera through each lenslet to form a spot pattern. The spot pattern of an ideal subject with a perfect wavefront will be exactly the same pattern as the reference grid; a distorted wavefront will create an irregular spot pattern. Displacement of lenslet images from their reference position is used to calculate the shape of the wavefront. The advantages of this system include the fact that it measures wavefront in one shot; hence it is faster, leading to a higher resolution and a higher repeatability (Figs. 3.6.4 and 3.6.5).

Tscherning aberrometry analyzes the ingoing light that forms an image on the retina.<sup>17</sup> A grid pattern formed by multiple spots is projected through the optical system of the eye and forms an image on the retina. This image is observed, evaluated, and captured on a CCD similar to a fundus camera. The distortion of the grid pattern enables calculation of the aberrations of the optical system of the eye.<sup>17</sup>

Ray-tracing aberrometry measures ingoing light that passes through the optical system of the eye and forms an image on the retina.<sup>17</sup> It measures rays sequentially making it much slower (the total time of scanning is 10–40 milliseconds) and decreasing its precision. The iTrace aberrometer (Tracey Technologies, Houston, TX) is the only one based on the retinal ray-tracing technology and is not currently linked to any customized laser platform.<sup>18</sup>

The scanning slit refractometer is a double-pass aberrometer (slit skioscopy) that is based on retinoscopic principles.<sup>19</sup> Both the projecting system—consisting of an infrared light source—and the receiving system rotate at high speed around the optical axis synchronously, with 360° meridians measured in 0.4 seconds. A group of photodetectors is located above and below the optical axis at 2.0, 3.2, 4.4, and 5.5 mm, and they detect the time needed for reflected light to reach them. The time difference depends on the type and amount of refractive error and is converted into the refractive power.<sup>19</sup> This principle is used in the ARK 10000 Optical Path Difference Scanning System (OPD-Scan) distributed by Nidek.

## WAVEFRONT-BASED SURGERY

The aim of wavefront custom ablation, in addition to spherocylindrical correction, is to adjust for the pre-existing aberrations and those that may be induced by conventional laser vision correction.<sup>20,21</sup> To achieve this aim, preoperative ocular higher-order aberration wavefront measurements should be accurate, and the laser ablation profiles should be precise—hence efficient eye-registration and tracking devices, a small laser spot size, and a sufficient corneal bed thickness become paramount for achieving superior clinical results.

Wavefront measurements should be accurate; the alignment of the line of sight is important to avoid artifacts. Common clinical conditions, such as tear film abnormalities or opacities, may present challenges to wavefront measurements.<sup>15</sup> Eyes with small-diameter pupils may be difficult to measure and provide information beyond the 3-mm optical zone and therefore require pharmacological dilatation. However, some variations in the wavefront maps have been seen with some pharmaceutical agents. It has been reported that cyclopentolate eyedrops lead to a significant difference in the preoperative refractive error wavefront compared with the subjective refraction, whereas Neo-Synephrine does not significantly influence measurements.<sup>22</sup> An eye with marked aberrations such as scars or keratoconus may be difficult to measure because of complete light scatter and the inability of the source testing light to reach to the retina and reflect back to the CCD camera.<sup>15</sup>

The algorithm for converting measurements into an ablation profile should be faithful to the original maps. It should be optimized to provide the best optical quality over the optical zone and tapering of the ablation in the surrounding zone (Figs. 3.6.6 and 3.6.7).

Another important issue for successful custom ablation surgery is eye registration and eye tracking during corneal laser ablation. The wavefront data must be transferred to the laser machine and applied to the same location on the eye from which they were captured. A small misalignment in the axis can have significant impact on the results of the procedure. It may actually cause new HOA due to misalignment of the pattern of treatment to the actual wavefront error on the eye. It is common to have 5°–7° of cyclotorsion when changing from sitting position to supine position. It has been reported that 50% of the visual benefit correction of HOA is lost with a 250 μm decentration or a 10° eye rotation.<sup>23</sup> Ideally the wavefront must be centered and registered with respect to a fixed ocular structure to avoid misalignment between the captured wavefront and the delivered laser. No

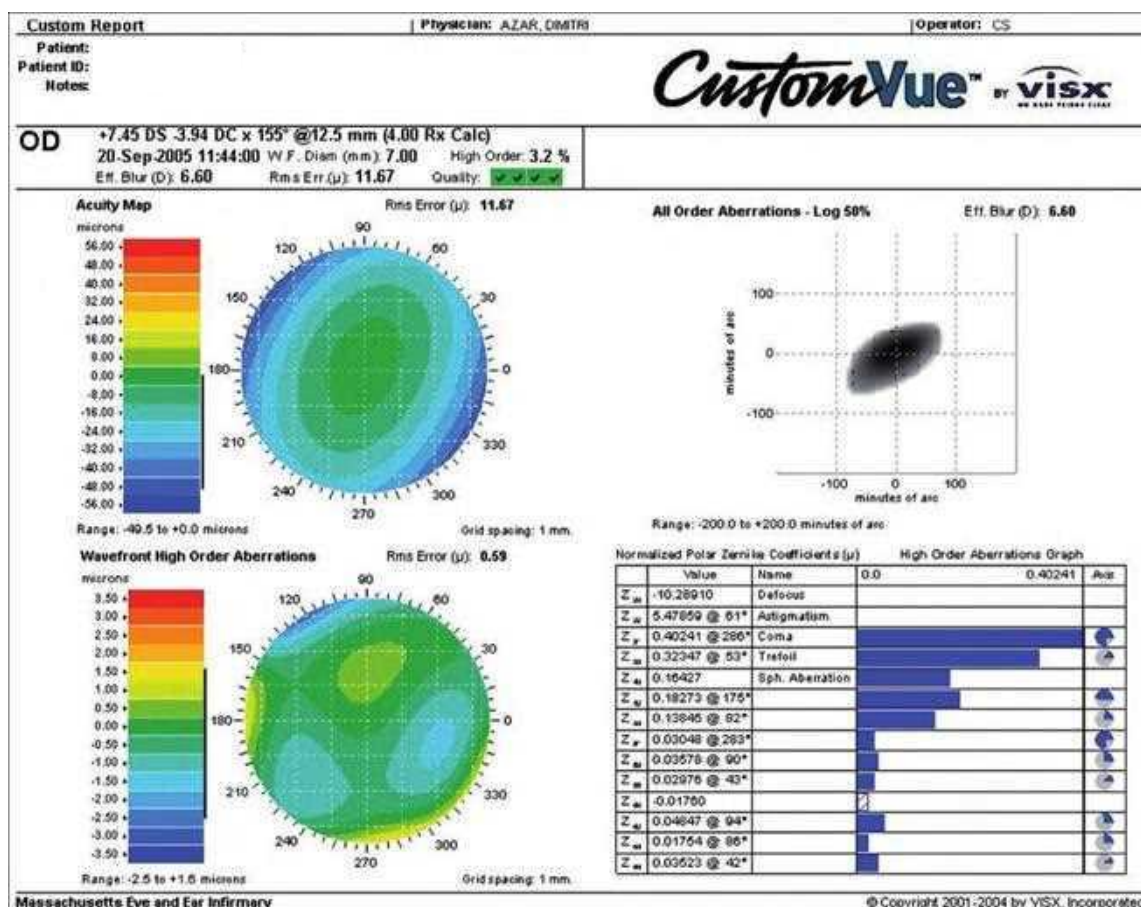


Fig. 3.6.5 VISX WaveScan Map Showing High Amount of Trefoil.

TABLE 3.6.1 Table Comparing Different Available Wavefront Platforms for Customized Lasik Treatment

Aberrometer	Manufacturer	Wavefront Sensor	Minimum Resolution (Points per mm <sup>2</sup> )	FDA Approved	CE Approved
Wavelight Allegro Analyzer	Alcon	Tscherning	3.3	Yes	Yes
Zywave 3	Bausch & Lomb	Hartmann-Shack	10.7	Yes	Yes
OPD Scan III	Nidek	Dynamic skiascopy	35.5	No	Yes
Schwind Peramis	Schwind	Hartmann-Shack	572.9	No	Yes
Itrace	Tracey Technologies	Ray tracing	6.6	Yes	Yes
IDesign	Abbott Vision	Hartmann-Shack	31.2	Yes	Yes

confusion should exist regarding axis alignment of wavefront-based treatments. Considering that they are based on a detailed map of the entrance pupil, centration of the treatment is unquestionably done over the pupil. All concerns about kappa angle or centration on different axes only apply to noncustomized treatments.

Two main methods of using wavefront information in refractive surgery are wavefront-optimized ablation and wavefront-customized ablation. Wavefront-optimized ablation aims at preserving the eye's pre-existing optical aberrations using adjustments based on population averages and at optimizing the asphericity of the cornea. The ablation profile is based on an ideal model without evaluating the patient's own aberrometry, therefore it is not a customized treatment. Wavefront-customized ablation leads to having an individual treatment ablation profile based on the patient's own aberrometry; therefore it would be able to correct for pre-existing HOA.

## RESULTS

Sakimoto et al. reviewed the outcomes for wavefront-customized LASIK in low to moderate myopia using three separate laser platforms.<sup>21</sup> The postoperative manifest spherical equivalent (SE) was within  $\pm 1.00$  diopters (D) in 96% of eyes and within  $\pm 0.50$  D in 81%. Ninety-eight percent of patients had postoperative uncorrected visual acuities (UCVA) better than 20/40, and 89% had UCVA equal to or better than 20/20. A loss of best spectacle-corrected visual acuity (BSCVA) of more than two lines was seen in 0.5% of patients. Wavefront-customized LASIK seems to be most successful in patients with low myopia: 95% of the patients with  $-2.00$  D or

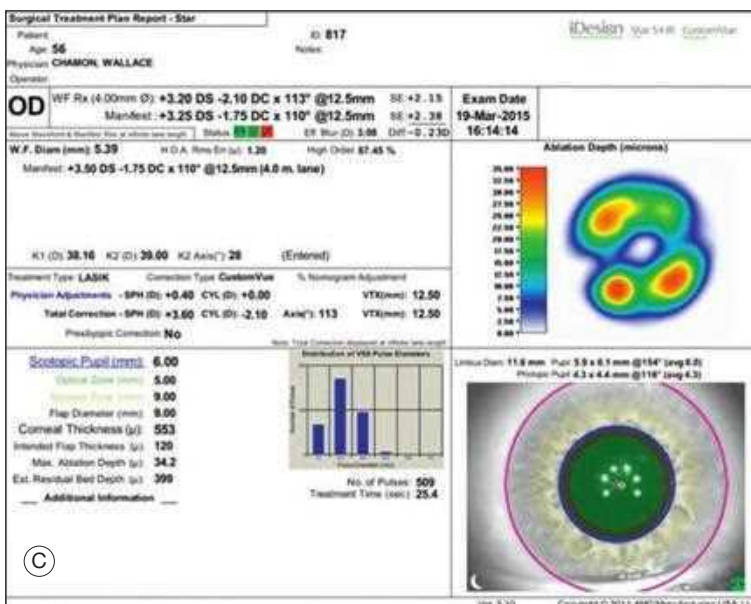
less SE achieved UCVA of 20/20 or better, as did 91% of patients with preoperative SE of  $-2.00$  to  $-4.00$  D. A marked difference in 20/20 or better postoperative UCVA was seen between the wavefront-customized and conventional LASIK treatments. In wavefront LASIK, 89% of myopic patients achieved this level of vision, whereas 72% of patients treated with conventional treatment achieved 20/20 or better. Feng et al. did a meta-analysis comparing 458 eyes with wavefront-customized and 472 eyes with wavefront-optimized LASIK treatments for myopia (SE between  $-0.25$  and  $-9.75$  D).<sup>24</sup> No statistically significant difference was detected in eyes achieving 20/20 UCVA or better, nor in eyes achieving postoperative SE within  $\pm 0.50$  D, nor in the average change in HOA. No eye lost two or more lines of BSCVA.<sup>24</sup>

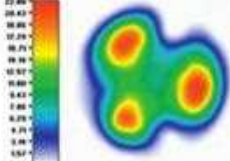


## WAVEFRONT PLATFORMS (TABLE 3.6.1)

## CONCLUSIONS

Knowledge of ocular aberrations can lead to better understanding of the quality of vision. Adequate interpretation of ocular wavefront maps can help in planning for custom LASIK treatment. Our quest for achieving perfect vision following laser vision correction is still ongoing. Despite falling short of the high expectations of supervision with wavefront-guided ablations promised by earlier studies, wavefront-based treatments still shows superiority over conventional treatment profiles.





Surgical Treatment Plan Report - Star				iDesign	
Patient Age: <b>56</b>		O: <b>817</b>		View: <b>40.00</b> Customizable	
Physician: <b>CHAMBERLAIN, WALLACE</b>		Notes:			
Operator:					
<b>OS</b>	WF Rx (4.00mm Ø): <b>+0.64 DS -0.93 DC x 158° @12.5mm</b> SE: <b>+0.17</b>		Exam Date		<b>19-Mar-2015</b>
	Manifest: <b>+1.25 DS -1.50 DC x 165° @12.5mm</b> SE: <b>+0.50</b>		16:40:20		
Wave Front Map (at 6.00mm Ø): <b>1.10</b> R.O.A. Ring Error (µ): <b>0.81</b> High Order: <b>87.95 %</b>		ET Star (C): <b>1.43</b> Diff: <b>-0.330</b>			
Manifest: <b>+1.50 DS -1.50 DC x 165° @12.5mm (4.0 mm. lase)</b>					
K1 (D): <b>41.88</b> K2 (D): <b>43.02</b> K2 Axis (D): <b>29</b>		[Design]			
Treatment Type: <b>LASIK</b> Correction Type: <b>CustomVue</b>		% Nonsymmetry Adjustment:			
Physician Adjustments - SPH (D): <b>+0.00</b> CYL (D): <b>+0.00</b>		VTK (mm): <b>12.50</b>			
Total Correction - SPH (D): <b>-0.64</b> CYL (D): <b>-0.93</b>		Axis (°): <b>158</b> VTK (mm): <b>12.50</b>			
Pre-scan Corneal: <b>No</b>					
<b>Scoliosis/Pupil (mm): 6.00</b> Diffus. Zone (mm): <b>5.00</b> 9.00 9.00 Flap Diameter (mm): <b>9.00</b> Corneal Thickness (µ): <b>551</b> Intended Flap Thickness (µ): <b>120</b> Max. Ablation Depth (µ): <b>21.8</b> Ext. Residual Bed Depth (µ): <b>409</b>				UPIUM Dmm: <b>11.8 mm</b> Pupil: <b>6.1 x 6.2 mm @17° (avg 6.2)</b> Pre-scan Pupil: <b>4.8 x 4.8 mm @163° (avg 4.7)</b>	
____ Additional Information ____ Manifest Cyl. is greater than WF Cyl. by <b>0.60 D</b> .		No. of Pulses: <b>274</b> Treatment Time (sec): <b>13.7</b>			

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# Phakic Intraocular Lenses

Ramon C. Ghanem, Vinícius C. Ghanem, Norma Allemann, Dimitri T. Azar

# 3.7



IN THIS CHAPTER  
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**Definition:** Phakic intraocular lenses (IOLs) are artificial lenses implanted in the anterior or posterior chamber of the eye to correct refractive errors. They preserve the natural crystalline lens to maintain accommodation.

## Key Features

- Three models of phakic IOLs are described: anterior chamber angle-supported, anterior chamber iris-fixated, and posterior chamber IOLs.
- Improved IOL designs and better preoperative screening are providing increased safety and efficacy for the correction of severe ametropias.

## Associated Features

- Early models of phakic IOLs were made of rigid polymethyl methacrylate (PMMA). Newer lenses are foldable, requiring a smaller incision and providing a faster visual recovery.
- Complications are IOL specific and include over- and undercorrection, glare and halos, endothelial cell loss, glaucoma, pigment dispersion, and cataract formation.
- Surgical peripheral iridectomy or preoperative YAG laser iridectomies are necessary to avoid postoperative pupillary-block glaucoma in most IOL models.

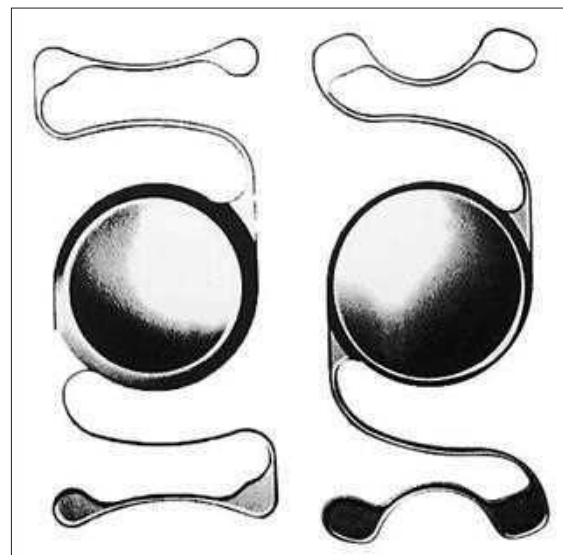
## INTRODUCTION

If high ametropia occurs, laser corneal refractive surgery (photorefractive keratectomy [PRK] and laser-assisted in situ keratomileusis [LASIK]) is limited by decreased safety, predictability, and efficacy of postoperative results. Now a growing interest exists in the use of phakic intraocular lenses (IOLs) to correct these refractive errors. Phakic IOL implantation has the advantage of preserving the architecture of the cornea. Additionally, it may provide more predictable refractive results and better visual quality than surgical techniques that manipulate the corneal curvature.

## HISTORY OF PHAKIC LENSES

Clear lens extraction for the correction of myopia was a concept introduced in the early 1800s, becoming increasingly popular from 1850 to 1900.<sup>1</sup> After the discovery of sterilization in 1889, a rush for myopia correction by clear lens extraction was started by Fukala in Austria/Germany ("Fukala surgery") and Vacher in France.<sup>1</sup> It was not until the end of the nineteenth century, however, that complications of this operation (e.g., retinal detachment and choroidal hemorrhage) began to be reported, and the technique largely fell out of favor.

In the 1950s, an emergence of the idea of correcting myopia by inserting a concave lens into the phakic eye was seen. At this time, Strampelli, Barraquer,<sup>2</sup> and Choyce experimented with anterior chamber (AC) angle-fixed lenses, which they eventually abandoned because of corneal edema, chronic iritis with pupil ovalization, and iris atrophy. In the 1980s



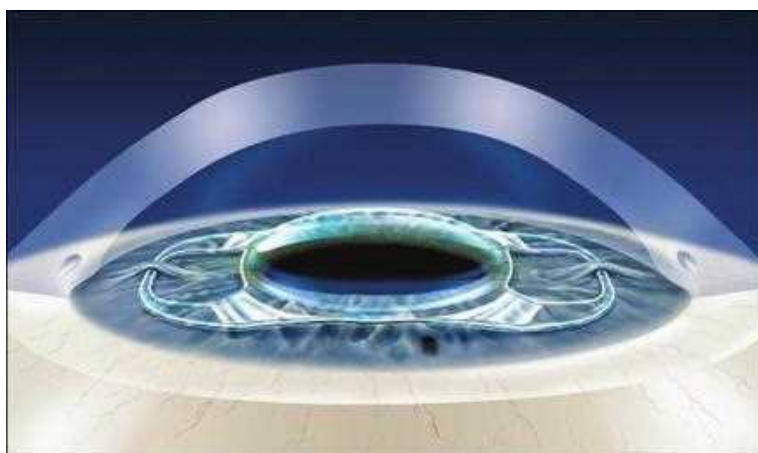
**Fig. 3.7.1** Angle-supported Baikoff ZB5M (left) and the NuVita MA20 (right).

and 1990s several PMMA angle-supported AC phakic IOLs were introduced, but subsequently discontinued due to the same complications. The most important were the Baikoff<sup>3,4</sup> lens, ZB and ZB5M models (Fig. 3.7.1), which were based on the multiflex Kelman anterior chamber IOL and the ZSAL-4 (Morcher GmbH, Stuttgart, Germany).<sup>3,5-9</sup> The ZB5M was later modified to implement thinner optics, greater effective optic diameter, flatter anterior face, and improved loop profile to reduce angle trauma. It was called NuVita MA20 (Bausch & Lomb, Rochester, NY) (see Fig. 3.7.1).

The first iris-fixated lenses were sutured to the iris stroma. The claw fixation method rendered iris stitching unnecessary. Worst introduced his final conceptual model of the midperipheral fixation iris-claw lens for secondary lens implantation. For many years, the iris-claw lens was used as a primary implant after intracapsular and extracapsular cataract extraction because of good tolerance and refractive results; it is still used today as a standby lens in cases of posterior capsule rupture. In 1986 Worst and Fechner<sup>10,11</sup> modified this IOL to a biconcave AC lens for the correction of myopia. To increase the safety of this IOL and minimize the possibility of IOL–cornea contact, the biconcave design was changed in 1991 to a convex–concave model with a lower shoulder, a thinner periphery, and a larger optic diameter (Fig. 3.7.2). This lens was called the Worst myopia claw lens. The name of the lens then was changed to the Artisan–Worst lens (Ophtec BV, Groningen, Netherlands) and Artisan–Verisyse lens (Abbott Medical Optics, Inc., Abbott Park, IL).

In the mid-1980s, the implantation of posterior chamber IOLs in phakic eyes was reported by Fyodorov.<sup>12</sup> The original lens design was a "collar-button" type, with the optic located in the anterior chamber and the haptics behind the iris plane. The design, modified by Chiron-Adatomed to produce a silicone elastomer posterior chamber lens, was reported to have a high incidence of cataract formation.<sup>13</sup> Further modification, the phakic refractive lens (PRL) (Ioltech/CIBA Vision, La Rochelle, France) (Fig. 3.7.3), had a greater vaulting, decreasing the incidence of cataract but causing zonular lesions.<sup>14</sup> Currently, the implantable collamer lens (ICL) (STAAR Surgical Co., Monrovia, CA) is the only posterior chamber phakic IOL available (Fig. 3.7.4).

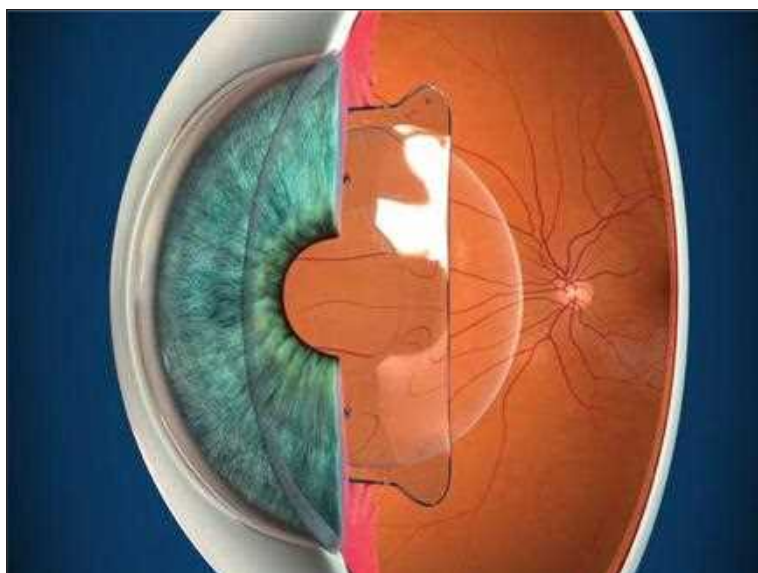




**Fig. 3.7.2** Iris-fixated Verisyse Lens in situ.



**Fig. 3.7.3** Posterior Chamber Phakic Refractive Lens (PRL) for Myopia (top) and Hyperopia (bottom).



**Fig. 3.7.4** Posterior Chamber Sulcus-Supported Implantable Collamer Lens (ICL) in situ.

### BOX 3.7.1 General Criteria for Implanting Phakic IOLs

- Age >21 years
- Stable refraction (less than 0.50 D change) for 1 year
- Clear crystalline lens
- Ametropia not suitable/appropriate for excimer laser surgery
- Unsatisfactory vision with/intolerance of contact lenses or spectacles
- Functional and occupational requirements
- Anterior chamber depth (measured from endothelium)\*  
Artisan–Verisyse / Artiflex–Veriflex:  $\geq 2.7$  mm  
ICL:  $\geq 2.8$  mm for myopia,  $\geq 3.0$  mm for hyperopia
- A minimum endothelial cell density of:  
 $\geq 3000$  cells/mm<sup>2</sup> at 21 years of age  
 $\geq 2600$  cells/mm<sup>2</sup> at 31 years of age  
 $\geq 2200$  cells/mm<sup>2</sup> at 41 years of age  
 $\geq 2000$  cells/mm<sup>2</sup> at 45 years of age or more
- No ocular pathology (corneal disorders, iris or pupil anomaly, glaucoma, uveitis, maculopathy, etc.)

\*Güell JL, Morral M, Kook D, Kohnen T. J Cataract Refract Surg. 2010;36:1976–93.

## INDICATIONS OF PHAKIC LENSES

Regardless of the type of phakic IOL, careful patient selection is critical for successful outcomes. General criteria should be followed (Box 3.7.1).

### Moderate and High Myopia

Patients who are poor candidates for laser correction may be candidates for phakic IOL. Food and Drug Administration (FDA)–approved excimer lasers can treat myopia of up to  $-12.00$  diopters (D). However, the higher the intended correction, the thinner and flatter the cornea will be postoperatively. For LASIK surgery, one must preserve a safe residual corneal stromal bed of at least  $250\ \mu\text{m}$ . A more conservative value would be  $300\ \mu\text{m}$  and a percentage of tissue altered (PTA) no more than 40%.<sup>15,16</sup> There is a limit to the amount of central flattening one can induce in the cornea, which is usually around  $35.00$  to  $36.00$  D (final keratometry). Beyond these limits, there is an increased risk of developing corneal ectasia due to thin residual stromal bed and loss of visual quality and night vision problems due to excessive corneal flattening. It was shown that LASIK also induces significant spherical and coma aberrations compared with phakic IOLs for high myopia.<sup>17</sup> Because of these risks, a current trend exists toward reducing the upper limits of LASIK and PRK to around  $-8.00$  to  $-10.00$  D. Above these limits, and in cases of keratoconus or keratoconus-suspect, or the cornea is too thin or too flat for laser surgery, phakic IOLs become the major alternative.

Most phakic IOLs for myopia can correct up to around  $-20.00$  D (Table 3.7.1). In 2004 the FDA approved the first phakic IOL designed to correct high myopia. The Verisyse (AMO/Ophtec, USA Inc.), also known as Artisan–Worst iris-claw lens, was approved for myopia ranging from  $-5.00$  to  $-20.00$  D with astigmatism less than or equal to  $2.50$  D. In 2005 a second phakic IOL was approved by the FDA. The Visian ICL was approved for myopia ranging from  $-3.00$  to  $-20.00$  D with astigmatism less than or equal to  $2.50$  D.

### High Hyperopia

The upper limits for hyperopic laser surgery are around  $+5.00$  to  $+6.00$  D. Higher attempted corrections can cause excessive steepening of the cornea (above  $50.00$  D), usually with a small optical treatment zone, leading to induced aberrations, especially spherical and coma aberrations and degradation of optical quality. Phakic IOLs may be indicated for the correction of hyperopia up to  $+22.00$  D (see Table 3.7.1). In many cases, however, these eyes have insufficient AC depth, limiting its implantation. For hyperopia, refractive lens exchange (refractive lensectomy) with IOL implantation is the main alternative for laser surgery in the presbyopic age group.<sup>18,19</sup>

### High Astigmatism

LASIK is the treatment of choice for astigmatism of up to around  $5.00$ – $7.00$  D. One may consider implanting toric phakic IOLs in cases of high degrees of astigmatism whether associated with myopia or hyperopia (see Table 3.7.1). Both spherical and cylindrical corrections can be combined

TABLE 3.7.1 Current Phakic IOLs, Either FDA Approved or With European Conformity Mark

Type of Lens	Name/Model	Power Range (D)	Optic Size (mm)	Length (mm)	Incision Size (mm)	Material	Manufacturer
AC Angle-Supported	Kelman Duet (two parts)	−8.00 to −20.00	5.5	12.5–13.5 (0.5 steps)	2.0 (foldable)	Silicone optic PMMA haptic	TEKIA
	Acrysof Cachet	−6.00 to −16.5	6.0	12.5–14.0 (0.5 steps)	2.0 (foldable)	Hydrophobic Acrylic	Alcon
AC Iris-Fixated	Artisan 202 Pediatric	−3.00 to −23.5	5.0	7.5	5.2	PMMA	Ophtec/Abbott
	Artisan 203 Hyperopia	+1.00 to +12.00	5.0	8.5	5.2	PMMA	Ophtec/Abbott
	Artisan Toric	+6.5 to −23.00 Cyl +1.00 to +7.5	5.0	8.5	5.2	PMMA	Ophtec/Abbott
	Artisan 204 Myopia	−1 to −15.5	6.0	8.5	6.2	PMMA	Ophtec/Abbott
	Artisan 206 Myopia	−1.00 to −23.5	5.0	8.5	5.2	PMMA	Ophtec/Abbott
	Artiflex/Veriflex	−2.00 to −14.5	6.0	8.5	3.2 (foldable)	Polysiloxane optic PMMA haptics	Ophtec/Abbott
PC Sulcus-Supported	Artiflex/Veriflex Toric	−1.00 to −13.5 Cyl +1.00 to +5.00	6.0	8.5	3.2 (foldable)	Polysiloxane optic PMMA haptics	Ophtec/Abbott
	ICL	−23.00 to +22.00 Cyl +1.00 to +6.00	4.65–5.5	11.0–13.0 (0.5 steps)	3.0 (foldable)	Collamer	STAAR

AC, Anterior chamber; FDA, Food and Drug Administration; ICL, implantable collamer lens; IOLs, intraocular lenses; PC, posterior chamber, PMMA, polymethyl methacrylate.

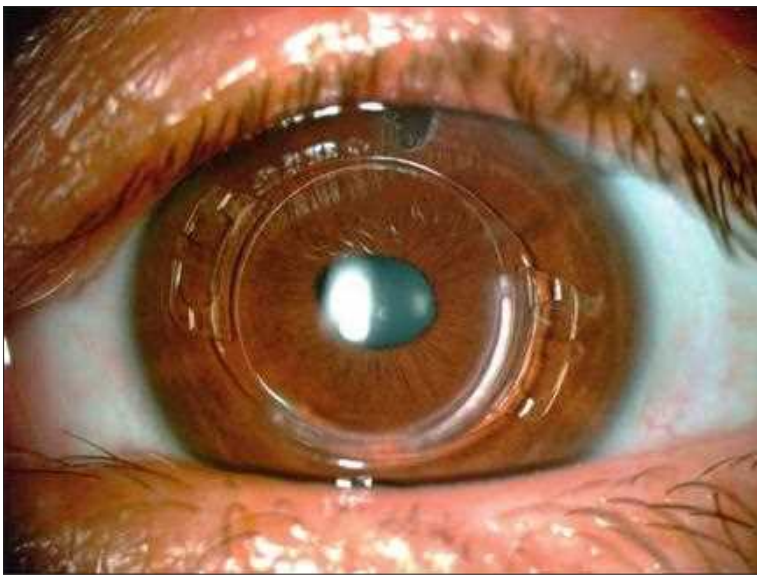


Fig. 3.7.5 Toric Artiflex to Correct Residual Myopic Astigmatism After 6-mm Intracorneal Ring Segment Implantation in a Patient With Keratoconus.

in these lenses, which aims to correct the total refractive error, but to date, only spherical corrections are FDA approved. The sum of minus sphere and cylinder cannot exceed −14.50 D with Artiflex toric and −23.00 D with Artisan toric.

With irregular astigmatism or if toric models are not available, astigmatism can be reduced with relaxing procedures such as limbal relaxing incisions, arcuate keratotomy, intrastromal rings<sup>20</sup> (Fig. 3.7.5), and with toric pseudophakic IOLs in cases where the crystalline lens is opaque. LASIK or PRK could be performed after phakic IOLs to correct residual ametropia (myopia, hyperopia, and/or astigmatism), also called bioptics (discussed later in the chapter).

## ADVANTAGES AND DISADVANTAGES OF PHAKIC IOLS

For the advantages and disadvantages of phakic IOLs, see Table 3.7.2.

## INTRAOCULAR LENS POWER CALCULATION

Van der Heijde<sup>21</sup> proposed the theoretical basis for IOL power calculations based on studies of patients implanted with a Worst and Fechner lens, which are directly applicable to other phakic IOLs. The power calculation is independent of the axial length of the eye. Instead it depends on: (1) central corneal curvature (power)–keratometry (K); (2) AC depth; and (3) patient refraction (preoperative spherical equivalent). With current IOL formulas and nomograms great accuracy occurs on IOL power calculations.

TABLE 3.7.2 Advantages and Disadvantages of Phakic IOLs

Advantages	Disadvantages
<ul style="list-style-type: none"> <li>Preserves corneal architecture</li> <li>Potential to treat a large range of myopic, hyperopic, and astigmatic refractive error</li> <li>Allows the crystalline lens to retain its function, preserving accommodation</li> <li>Excellent visual and refractive results (induces less coma and spherical aberration than LASIK)</li> <li>Removable and exchangeable</li> <li>Frequently improve BSCVA in myopic eyes by eliminating minimization effect of glasses</li> <li>Results are predictable and stable</li> <li>Flat learning curve for some models</li> </ul>	<ul style="list-style-type: none"> <li>Potential risks of an intraocular procedure (e.g., endophthalmitis)</li> <li>Nonfoldable models require large incision that may result in significant residual postoperative astigmatism</li> <li>Highly ametropic patients may require additional laser surgery (bioptics) for fine-tuning the refractive outcome</li> <li>May cause irreversible damage (e.g., endothelial cell loss, cataract formation, glaucomatous optic neuropathy)</li> <li>Implantation in hyperopic patients is limited by shallow anterior chambers and can be followed by loss of BSCVA due to loss of magnification effect of glasses</li> <li>Other complications are not rare: pupil ovalization, induced astigmatism, chronic uveitis, pupillary block, pigment dispersion</li> </ul>

BSCVA, Best spectacle-corrected visual acuity; IOLs, intraocular lenses; LASIK, laser-assisted in situ keratomileusis.

## Sizing the Phakic IOLs

The eye's anterior segment anatomy differs significantly among individuals, affecting the indications of phakic IOLs in different refractive errors.<sup>22</sup> Most of the complications of these lenses are related to inappropriate sizing and inaccurate measurements of the AC dimensions.

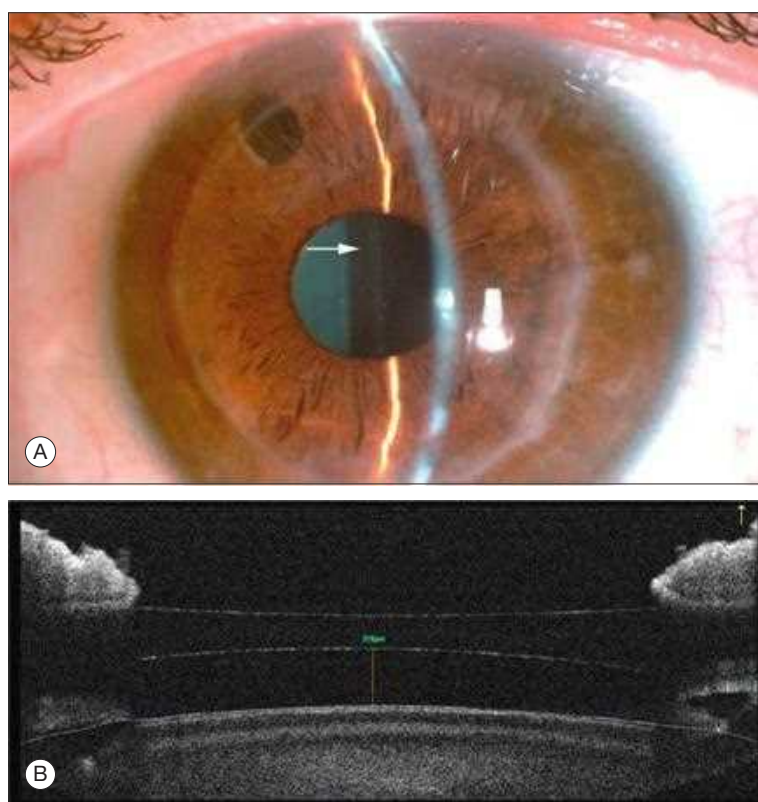
For the iris-fixated phakic IOLs (i.e., Artisan and Artiflex), sizing is not an issue because these IOLs are fixated to the midperipheral iris, not the angle or sulcus, having the advantage of being one-size-fits-all length (8.5 mm).

For the sulcus-supported phakic IOLs (i.e., implantable collamer lens), different sizes of overall length are manufactured to suit normal variations in intraocular anatomy (e.g., 12.1, 12.6, 13.2, and 13.7 mm). The relationship of the selected overall diameter of the implanted lens to the dimensions of the posterior chamber represents an important determinant of the achieved postoperative vault, which is the term used to describe the measurable distance between the anterior capsule of the crystalline lens and the posterior surface of the ICL (Fig. 3.7.6).<sup>23</sup>

The white-to-white (WTW) diameter (external measurement from limbus to limbus) is the most important factor in determining the ICL size. It provides an approximate estimation of the AC (angle-to-angle [ATA]) and sulcus-to-sulcus (STS) diameters. The WTW is usually measured with the IOLMaster or the Lenstar biometers and checked with manual calipers between the 3 and 9 o'clock meridians. Alternative methods include tomographers such as the Galilei (Ziemer), Pentacam (Oculus), and the Orbscan IIz (Bausch & Lomb). Most studies have used the WTW measurement plus 0.5 mm, rounded to the nearest 0.5 mm increment.<sup>12,24</sup>

The WTW measurement, however, is well known to suffer from significant inaccuracies.<sup>25,26</sup> In a study comparing vertical and horizontal WTW





**Fig. 3.7.6** (A) ICL-V4 in a patient with previous deep anterior lamellar keratoplasty. Observe adequate vaulting (arrow). (B) ICL vault measured with anterior segment OCT. (Courtesy João Marcelo Lyra, MD, Maceió, Brazil.)

measurements with direct anatomical measurements (postfixation) in postmortem eyes, there was no correlation between the horizontal WTW distance and the AC angle diameter; nor was there correlation between either technique of external measurement and the ciliary sulcus diameter.<sup>26</sup>

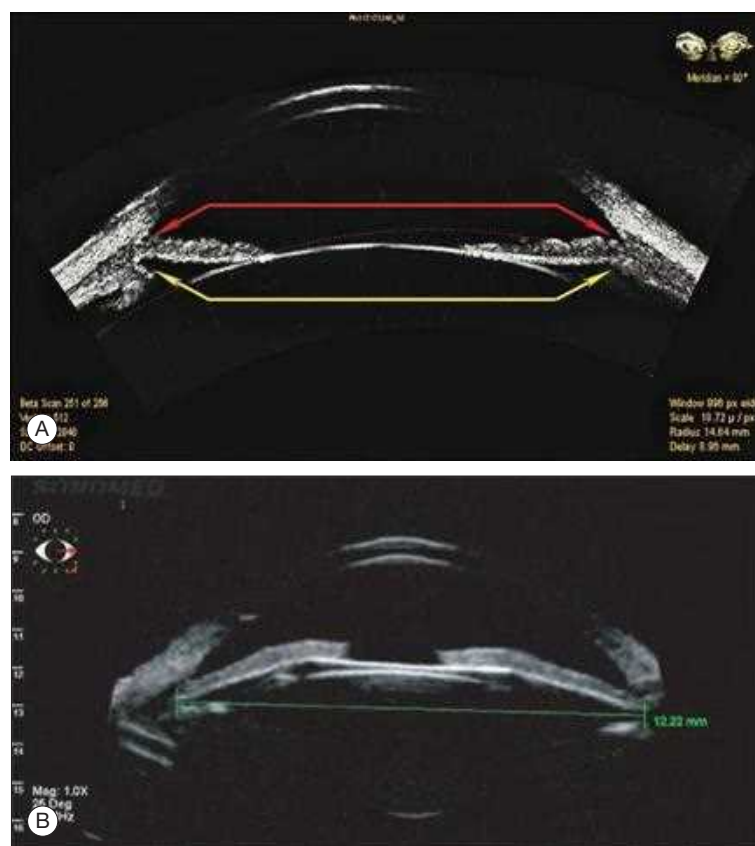
High-frequency ultrasound biomicroscopy (35 to 60 MHz) has been used to directly measure the STS diameter. It was not until recently, however, that more adequate devices for imaging and measuring the anterior segment became available. The wide-angle high-frequency (50 MHz) ultrasound systems (Eye Cubed, Ellex; VuMAX II, Sonomed; Aviso, Quantel Medical; Artemis, Ultralink LLC; among others) (Fig. 3.7.7) currently are the best tools to measure the STS distance. Although the FDA-approved technique for measurement remains WTW, growing evidence demonstrates that direct sulcus measurement using any of these methods is superior and minimizes the risk of incorrect ICL sizing.

Despite there being no consensus in the literature regarding the upper and lower limits of safe vault, the lens manufacturers suggest that an acceptable amount of vaulting of the lens optic over the crystalline lens is  $1.00 \pm 0.5$  corneal thicknesses (approximately 250–750  $\mu\text{m}$ ). The clinical significance of vault outside of the range of safety resides in the risk of specific adverse events, including pupillary block, anterior subcapsular cataract, pigment dispersion, and glaucoma.<sup>23</sup>

## VISUAL OUTCOMES

Phakic IOLs are the most predictable and stable of the refractive methods for preserving the crystalline lens in high myopia. New improved designs and current methods for sizing and power determination are providing increasing safety and efficacy for the correction of severe ametropias.

In high myopia correction, significant postoperative gain of best-corrected visual acuity (BCVA) over the preoperative levels likely occurs as a result of a reduction in the image—the minimization that is present with spectacle correction of high myopia. A loss of BCVA is uncommon. The loss of contrast sensitivity observed after LASIK for high myopia does not occur after phakic IOL.<sup>27,28</sup> In fact, with phakic IOLs an increase in contrast sensitivity occurs in all spatial frequencies compared with preoperative levels with best spectacle correction.<sup>29</sup> Even for moderate myopia (between  $-6.00$  and  $-9.00\text{D}$ ) phakic IOLs provide better CDVA, contrast sensitivity at high spatial frequencies, and higher percentage of eyes gaining lines of CDVA compared with femtosecond laser-assisted LASIK.<sup>30</sup>



**Fig. 3.7.7** (A) Artemis High-Frequency (50 MHz) 3D-Digital Ultrasound Imaging of the Anterior Segment. Red arrows indicate angle-to-angle distance; yellow arrows indicate sulcus-to-sulcus distance. (B) UBM Vumax II (50 MHz transducer) of a myopic ICL in the posterior chamber. Sulcus-to-sulcus measurement: 12.22 mm. STS diameter measurement is important to determine adequate sizing of the phakic IOL.

## ANTERIOR CHAMBER ANGLE-SUPPORTED PHAKIC INTRAOCULAR LENSES

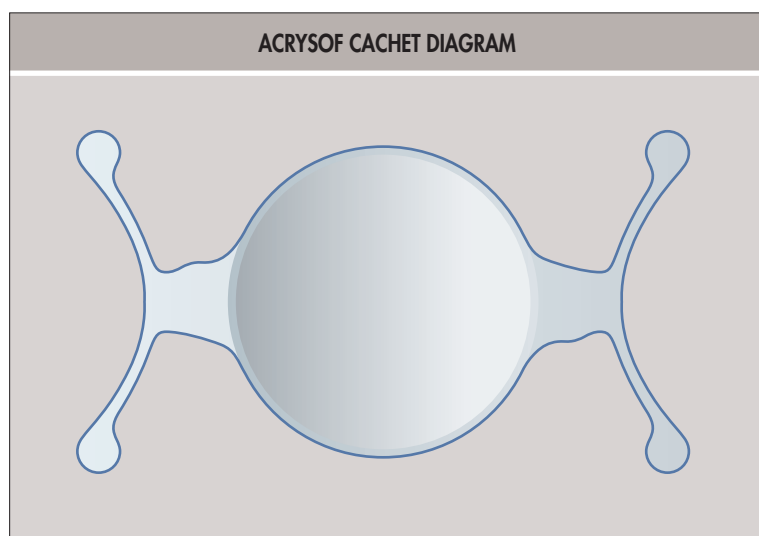
After the development of foldable AC angle-supported phakic IOLs, the rigid PMMA IOLs were almost abandoned, including the NuVita MA20, ZSAL-4 (Morcher GmbH) and Phakic 6 H2 (Ophthalmic Innovations International). Later, due to safety concerns related to endothelial cell loss, the NewLife and Vivarte (both from IOLTech–Zeiss Meditec) (Fig. 3.7.8) and the Icare (Corneal Inc.) were also withdrawn from the market.<sup>31,32</sup>

A few years ago the AcrySof Cachet (Alcon Laboratories, Inc., Fort Worth, TX) phakic lens was approved by the FDA. The Cachet is a single-piece,

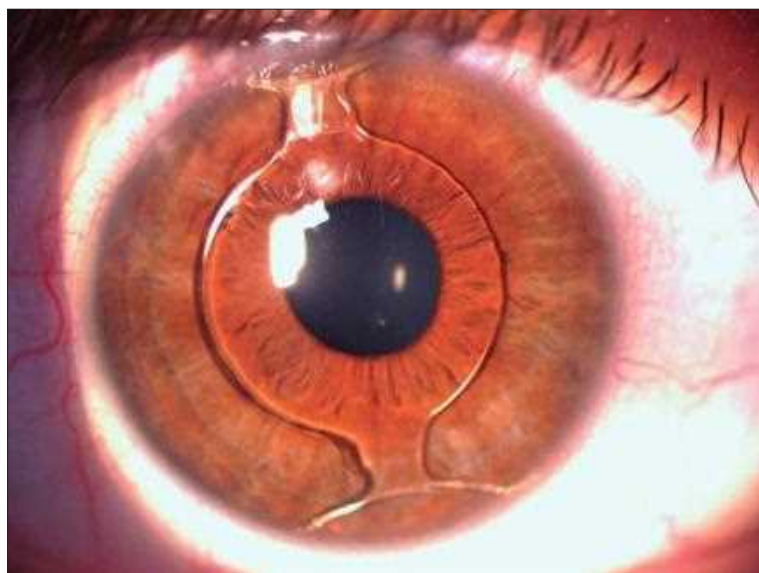


**Fig. 3.7.8** Foldable Hydrophilic Acrylic Angle-Supported Vivarte Lens.





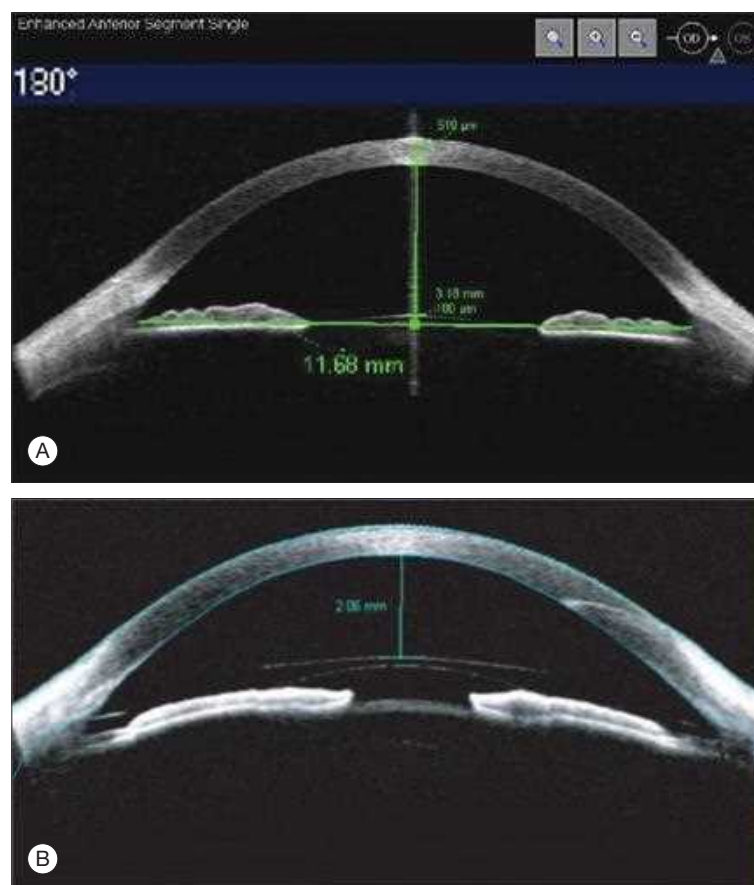
**Fig. 3.7.9 AcrySof Cachet Diagram.** A single-piece, foldable, soft hydrophobic acrylic phakic IOL.



**Fig. 3.7.10 Biomicroscopy Photograph of the AcrySof Cachet Phakic IOL Implant for High Myopic Correction.** (Courtesy Wallace Chamon, MD, São Paulo, Brazil.)

foldable, soft hydrophobic acrylic phakic IOL (Fig. 3.7.9). Four models were available, each with a different overall length. The haptics were designed to allow compression within the angle for IOL stability without creating excessive force that could cause angle tissue damage or pupil ovalization. The vault of the IOL was designed to provide optimal central clearance distance between the IOL and the cornea and the natural crystalline lens (Video 3.7.1) (Figs. 3.7.10 and 3.7.11).<sup>33</sup> The 3-year findings from pooled global studies (United States, Canada, and the European Union) showed favorable refractive results and acceptable safety in patients with moderate to high myopia.<sup>34,35</sup> Recently, however, its distribution was placed on hold due to a significant late-term endothelial cell loss (ECL) in a subset of patients, especially in those with small eyes and patients self-identified to be of Asian race. Data predict that eyes need to be monitored frequently because ~30% of eyes are at risk of early explantation based on the observed ECL rates, and 5% have loss rates higher than 3.9% per year. These rates can accelerate suddenly.

The Kelman Duet (Tēkia, Inc., Irvine, CA) consists of a duet of an independent PMMA tripod haptic and a silicone optic (Fig. 3.7.12). The haptic is implanted first in the AC through a 2.5-mm incision. The optic is then inserted using an injector system. Finally, the optic is fixated in the AC by the optic eyelets and haptic tabs using a Sinsky hook. At 12 months, 17% of eyes had more than 15% ECL.<sup>36</sup> No mid- or long-term data of endothelial cell loss have been reported to date. The Duet is not FDA approved.



**Fig. 3.7.11 Anterior Segment OCT Use in Pre and Postoperative Assessment of a Highly Myopic Eye.** (A) Preoperative measurement of the internal anterior chamber diameter at axis 180 = 11.68 mm. This measurement can be used to determine the total diameter of the phakic implant. (B) Anterior segment OCT in the postoperative assessment of Cachet phakic IOL in a highly myopic eye with angle supported haptics (left and right) and central distance to endothelium: 2.06 mm.

## Complications

### Pupillary Ovalization

Ovalization of the pupil, one of the most prevalent complications of angle-supported phakic IOLs, has a reported incidence of between 7% and 22%.<sup>5,6,9,37-40</sup> Pupillary abnormalities tend to be progressive, being more frequent with longer follow-up visits.<sup>6,9</sup> The most accepted mechanism is related to haptic compression of the angle structure due to an oversized lens causing inflammation of the angle, peripheral synechia formation, and pupillary ovalization. This mechanism was believed to be associated with iris ischemia.<sup>5,41</sup> Iris hypoperfusion was confirmed using indocyanine green angiography (ICGA).<sup>40</sup>

Another associated complication is iris retraction and atrophy<sup>6</sup>; the atrophy usually occurs in the iris sector affected by ovalization. Total sector iris atrophy can occur after progressive pupil ovalization in long-standing cases (Fig. 3.7.13).

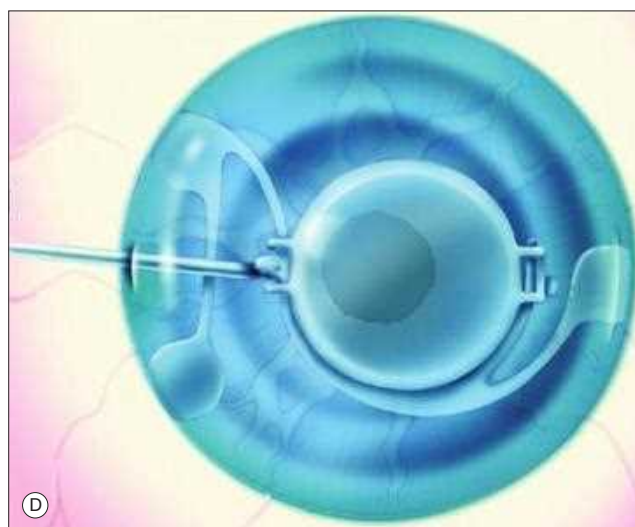
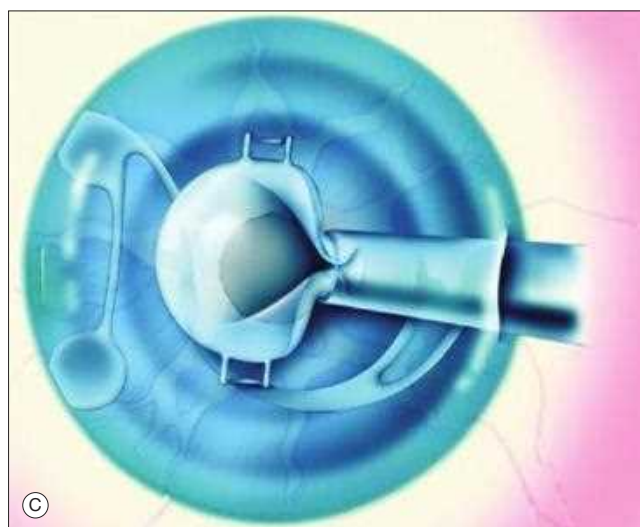
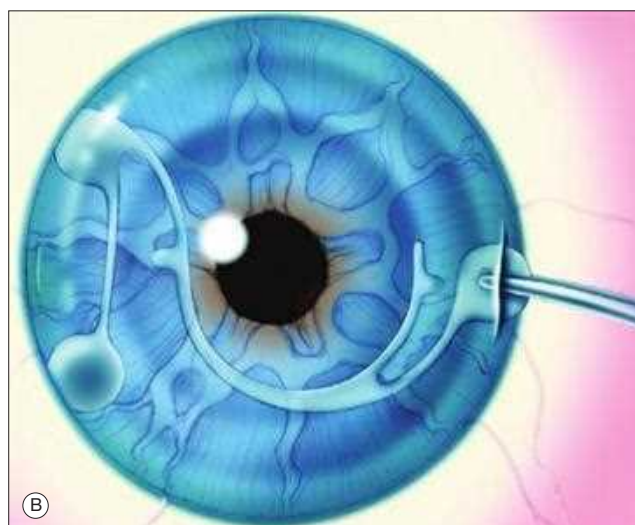
### Endothelial Damage

Endothelial damage was the main reason for recalling several AC phakic IOLs from the market.<sup>42</sup>

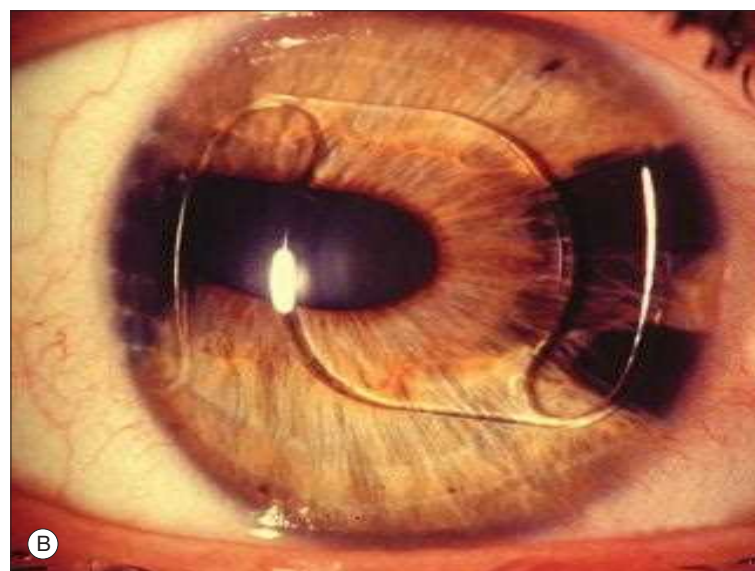
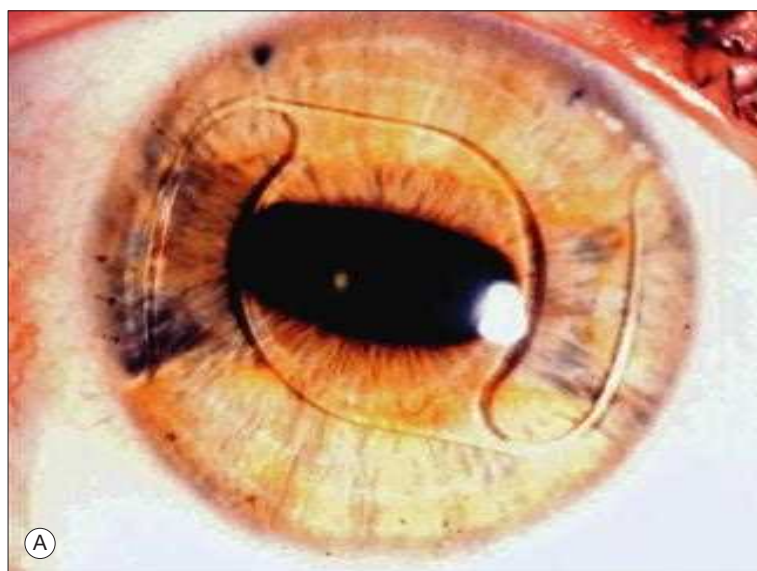
Two different mechanisms have been proposed to explain the ECL: the excessive proximity of the IOL parts to the corneal endothelium, which may intermittently or permanently be in contact with the posterior cornea<sup>43</sup> or the presence of inflammatory cytokines in the aqueous humor produced by trauma to uveal structures.<sup>44</sup> A follow-up study of more than 15 years of an angle-supported phakic intraocular lens model (ZB5M) for high myopia found a median coefficient of ECL of 17.5% with a rate of 0.97% every year, twice the physiological loss. Careful long-term follow-up of each patient with an AC phakic IOL is necessary to identify patients who may need explants of the IOL.

## Elevation of Intraocular Pressure

Elevation of intraocular pressure (IOP) usually occurs transiently during the early postoperative period but may become chronic due to peripheral synechiae, which affects 2%–18% of patients.<sup>3,5,6,37,38</sup> Another risk is



**Fig. 3.7.12** Foldable “two parts” (silicone optic/PMMA haptics) Kelman Duet lens (A). The haptics are implanted initially through a small incision (B), then the optic is injected (C). The optic-haptics are assembled inside the anterior chamber (D).



**Fig. 3.7.13** Pupil ovalization 2 years after implantation of an angle-supported phakic IOL (A). At 5 years, progressive ovalization was observed and the lens was explanted (B). (Courtesy Emir Amin Ghanem, MD, Joinville, Brazil)

acute glaucoma secondary to pupillary block in the absence of adequate iridectomies.

### ***Uveitis***

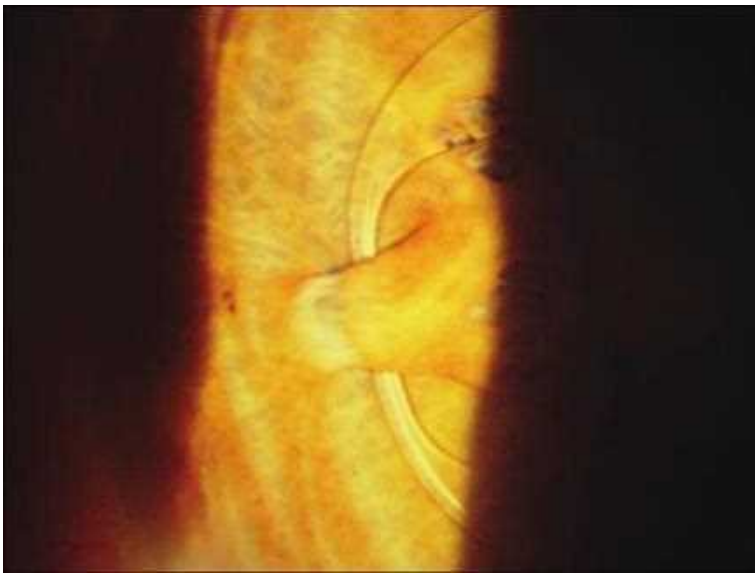
Chronic uveitis can be observed after angle-supported IOLs, with rates from 1% to 5%.<sup>3,5,6,37,38</sup> An oversized lens can be a potential cause, compressing the angle structures and altering the blood–aqueous barrier (BAB) permeability. The chronic inflammation may continue for several years, inducing

pupil ovalization, iris atrophy, and other complications, such as glaucoma, cataract, or anterior synechiae.

### ***Cataract***

Cataract after an AC lens—less common than with posterior chamber IOLs—can still occur, mainly due to chronic uveitis and other complications. A meta-analysis of cataract development after AC phakic IOL implantation found an incidence of 1.29%.<sup>45</sup>





**Fig. 3.7.14 Artisan/Verisyse Lens.** Detail of the midperipheral iris stroma enclavated by the haptic claw.

### IRIS-FIXATED PHAKIC INTRAOCULAR LENSES

The Artisan iris-claw (Ophtec)/Verisyse (Abbott Medical Optics, Inc.) lens is fixated to the anterior iris surface by enclavation of a fold of iris tissue into the two diametrically opposed “claws” of the lens (Fig. 3.7.14). The fixation sites are located in the midperiphery of the iris, which is virtually immobile during pupillary movements. The optic vaults approximately 0.87 mm anterior to the iris, providing good clearance from both the anterior lens capsule and the corneal endothelium. The distance from the optic edge to the endothelium ranges from 1.5 to 2.0 mm, depending on the dioptric power, AC anatomy, and optic diameter.

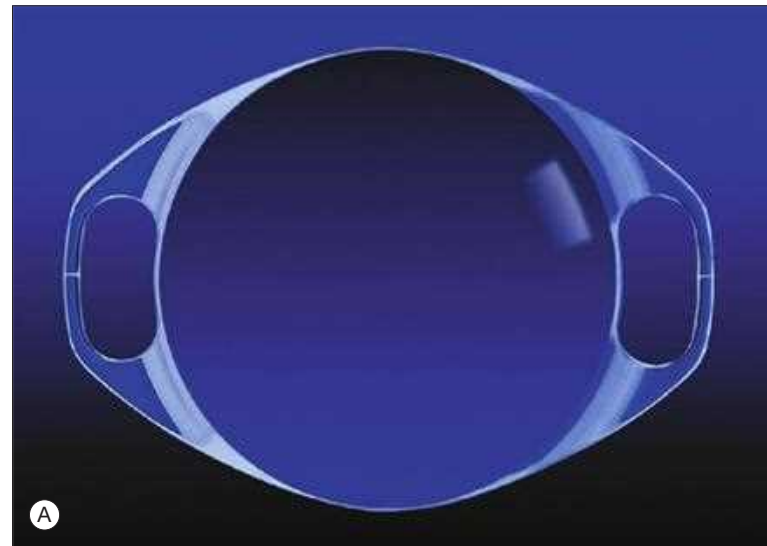
The Artisan/Verisyse has a fixed overall length of 8.5 mm (7.5 mm for pediatric implantations or small eyes), which means a great advantage to the surgeon for not dealing with sizing measurements. Another major advantage of these IOLs is that they can be properly centered over the pupil, even when the pupil is off-center, a relatively common situation among people with high ametropia.<sup>32</sup> Off-center pupils cannot be used as a reference for centration of symmetrical IOLs such as angle-supported and sulcus-fixated IOLs.<sup>32</sup> Additionally, the fixation system inhibits IOL movement,<sup>46</sup> which warrants the correction of astigmatism and may help to correct other vectorial or asymmetrical aberrations in the future.<sup>32</sup> Pupil size in scotopic conditions should be equal or less than body size of IOL + 1.0 mm to reduce the risk of glare and halos (e.g., if the IOL has a body size of 6 mm, the scotopic pupil can be up to 7 mm). A convex, bulging, or volcano shaped iris, usually found in hyperopes, is a contraindication for its implantation. Currently, this lens is mainly used to treat high primary myopia (FDA approved—Models 204 and 206; Fig. 3.7.15),<sup>47</sup> and astigmatism<sup>48–50</sup> in adults. Other indications include:

- Treatment of refractive errors after penetrating keratoplasty.<sup>51–54</sup>
- Treatment of anisometropic amblyopia in children.<sup>55,56</sup>
- Secondary implantation for aphakia correction.<sup>57–59</sup>
- Treatment of refractive errors in patients with keratoconus.<sup>60</sup>
- Correction of progressive high myopia in pseudophakic children<sup>61</sup> and postoperative anisometropia in unilateral cataract patients with bilateral high myopia.<sup>62</sup>

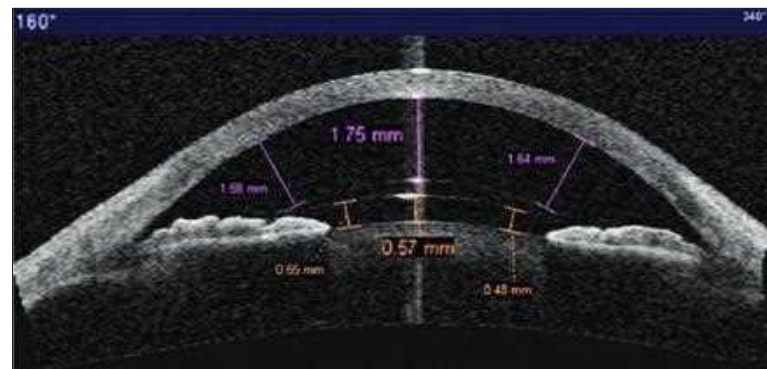
The foldable model (Artiflex/Veriflex, Ophtec) is approved in Europe and is now under clinical investigation for FDA approval. This lens is a convex-concave three-piece phakic IOL with a hydrophobic polysiloxane 6-mm optic and PMMA haptics. The toric model of the Artiflex is also available in Europe.<sup>63</sup>

### Surgical Procedure

Preoperative application of topical pilocarpine for miosis is mandatory to form a protective shield for the natural lens during the insertion and fixation of the iris-claw lens. A constricted pupil facilitates proper centration of the lens. Although a very low risk of pupil-block glaucoma exists (because the vaulted configuration of the Artisan lens ensures a normal aqueous



**Fig. 3.7.15 Artisan/Verisyse Lens.** FDA-approved models (A) 204 (6.0 mm optic) and (B) 206 (5.0 mm optic) for the correction of myopia.



**Fig. 3.7.16 Anterior Segment Optical Coherence Tomography of an Artisan Phakic IOL to Correct High Hyperopia.** The posterior vault is 0.57 mm (distance from the IOL to the lens) and the distance of the anterior surface of the IOL optic to the endothelium (safety distance) at the center is 1.75 mm.

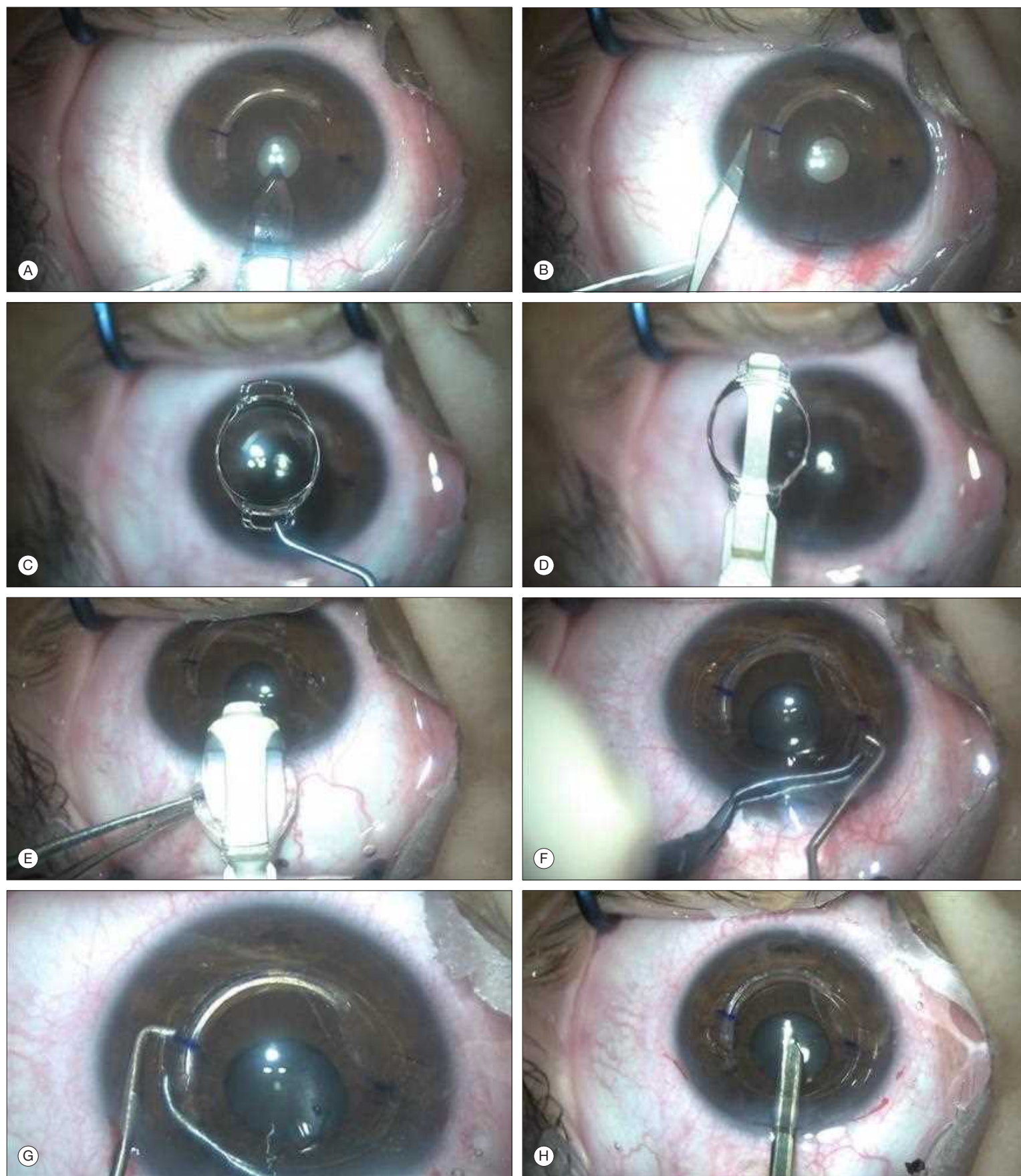
outflow), a peripheral iridectomy during surgery is mandatory. Alternatively, a neodymium:YAG (Nd:YAG) laser can be used preoperatively to create one or two small iridectomies (Videos 3.7.2, 3.7.3, and 3.7.4)

Various incision techniques (e.g., corneal, limbal, or scleral tunnel incision) can be used, usually with peribulbar anesthesia, but topical anesthesia also can be used. Usually a superior limbal or clear-corneal incision is used. Depending on the diameter of the lens used—5.0 mm or 6.0 mm—the incision should be at least 5.2 mm or 6.2 mm, respectively, to avoid difficulties with IOL insertion. The incision is usually located on the steep corneal meridian, minimizing postoperative astigmatism.

The “claw” haptics are fixated to the iris by a process called enclavation, and specially designed bent needles are used. Another option to facilitate

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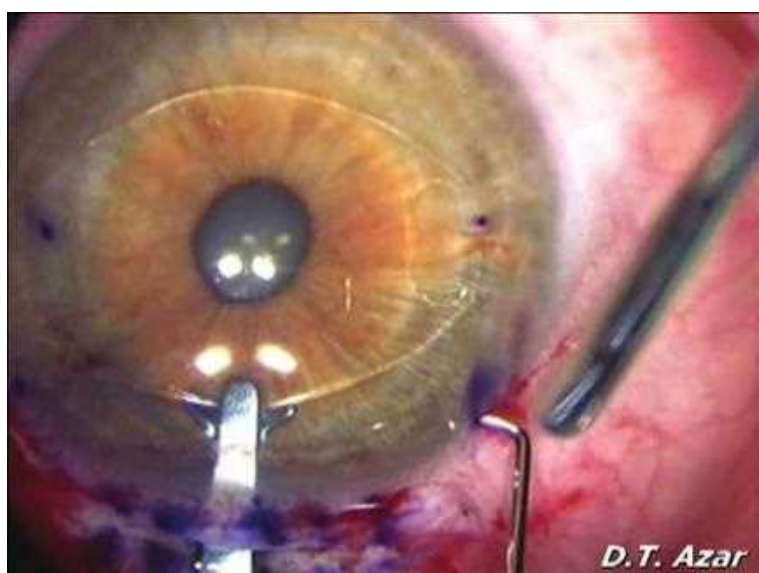


**Fig. 3.7.17 Toric Artiflex Implantation Technique.** (A) A 3-mm clear corneal incision is created. (B) Two paracentesis are created parallel to the limbus, oriented toward the enclavation site. (C) Lens is removed from package and held with special forceps. (D) The Artiflex is mounted in the implantation spatula. (E) The optic edge bends downward during the lens insertion. (F) and (G) Lens is rotated, centered on the pupil and positioned according to the preoperative markings on the cornea (toric model). The superior claw is grasped and the enclavation is performed with the VacuFix. (H) Cohesive viscoelastic material is removed and peripheral iridectomy is performed. Main incision is closed.

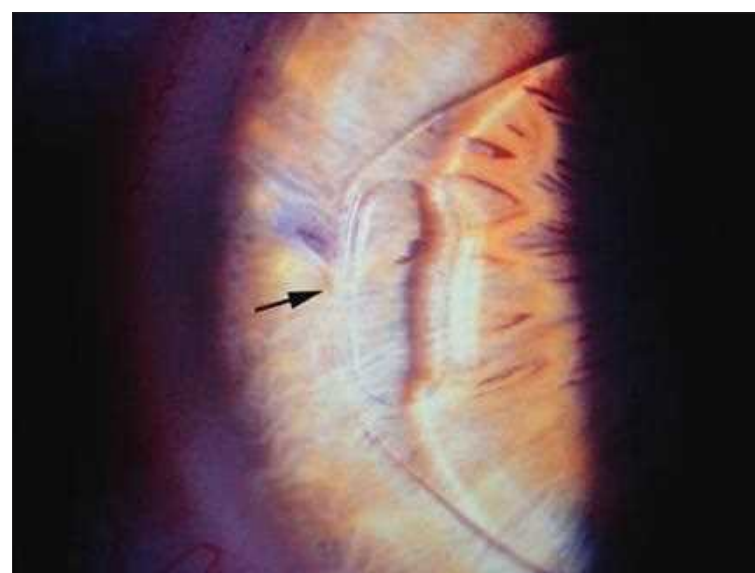
controlled and reproducible enclavation in the exact desired spot is the VacuFix (Ophtec) (Fig. 3.7.17). This is especially important for the toric models, to facilitate cyclotorsion control.

Two 1.0-mm side-port incisions at 10 and 2 o'clock positions are required for enclavation. The lens is implanted vertically through the incision, then

rotated and centered in front of the pupil with the haptics at 3 and 9 o'clock positions. When using toric models, the correct axis of implantation will be calculated preoperatively. Limbal marks at the slit-lamp or iris marks with Nd:YAG should be done in the axis of implantation helping to control cyclotorsion and increasing axis enclavation precision.



**Fig. 3.7.18** Blunt Iris Entrapment Needles Can Be Used to Create a Fold of Midperipheral Iris Tissue Through Vertical Movement of the Needle.



**Fig. 3.7.19** Inadequate Iris Enclavation (arrow) increases the risk of focal iris atrophy, uveitis, and dislocation of the IOL.

The AC is filled with cohesive viscoelastic material, usually high-viscosity sodium hyaluronate injected through one of the puncture incisions to create a deep AC to maintain working space in the AC. If additional viscoelastic material needs to be injected during surgery, care should be taken not to let it slip under the IOL. It should be used as a stabilizing agent that presses the implant onto the iris surface.

Centration and fixation of the IOL are probably the most critical steps of the procedure, and their accuracy influences the postoperative results. The pupil is used as a reference for centration. Fixation is performed by gently creating an iris fold under the claw and then entrapping the iris fold into the claw (Fig. 3.7.18). If adjustment of the lens is needed after fixation, the iris must first be released before the lens is moved. At the end of surgery, it is not unusual to have mild ovalization of the pupil due to the effect of the miotic agent.

The number of stitches depends on the type of incision. Watertight wound closure is of paramount importance to prevent a shallow AC from leading to IOL–endothelial contact in the immediate postoperative period. A small incision will help minimize surgically induced astigmatism and inflammation.

When the foldable Artiflex is used, a small 3.2-mm clear cornea incision may be preferred. A special Artiflex implantation spatula and a lens holder are necessary. The lens should be held by the haptics as the optic is made of polysiloxane and should not be touched during surgery.

The viscoelastic material should be completely removed, preferably with automated irrigation/aspiration system as it may induce an early postoperative IOP rise.

Topical corticosteroids and antibiotics are usually prescribed for 2–4 weeks after surgery. Regular follow-ups are recommended, in particular long-term evaluations of the corneal endothelium. Correct timing of suture removal is critical in reducing residual astigmatism.

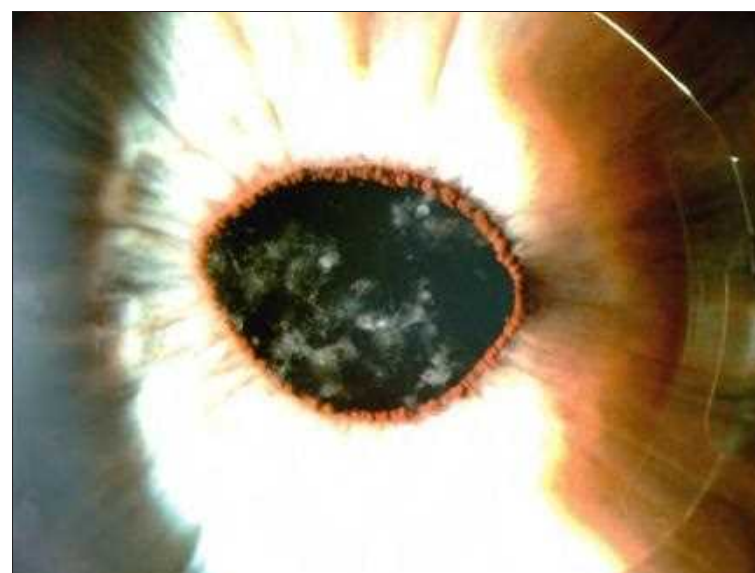
## Complications

### Glare and Halos

The incidence of glare and halos is greater with the 5.0-mm than with the 6.0-mm optic diameter.<sup>64,65</sup> The general incidence has varied from 0 to 8.8%. In the FDA prospective study, as many as 13.5%–18.2% of the patients had glare and halos postoperatively, but approximately 10%–13% had these symptoms preoperatively with an improvement after surgery. Pupils larger than 5.5 mm are at a significantly increased risk for glare and halos.<sup>66</sup>

### Anterior Chamber Inflammation/Pigment Dispersion

Cases of severe iritis are rarely observed after surgery but can occur after repeated traumatic attempts at iris enclavation or occasionally without any predisposing factors.<sup>67,68</sup> Pigment dispersion syndrome has occasionally been observed. A known mechanism is poor fixation/enclavation of the IOL to the iris with subsequent pseudophakodonesis (IOL movement), which may cause chronic inflammation with the need for reintervention for refixation (Fig. 3.7.19). Poor fixation has been observed in as many as



**Fig. 3.7.20** Nonpigmented (cellular) Deposits on the Posterior Surface an Artiflex Lens.

3% of cases.<sup>65</sup> In the FDA trial, iritis was observed in 0.5% of cases and poor fixation in 2.1%.

With the Artiflex, Tehrani et al.<sup>69</sup> observed an increased incidence of pigment dispersion (12.2%), believed to be due to a slight step within the implant in the area of the connection of the foldable silicone optic to the rigid haptic (claw), which may have caused iris pigment abrasion during pupillary movement. Another complication in about 12% of patients is a nonpigment deposition on the polysiloxane optic of the Artiflex lens. Treatment, which is successful in almost all cases, is with topical corticosteroids.<sup>70a</sup> The deposits tend to diminish after the third month and usually disappear after 12 months, even when not treated with corticosteroids. In one of our cases, surface IOL cleaning was needed once topical treatment was not successful (Fig. 3.7.20).<sup>70b</sup> A re-enclavation or even an explantation can be considered if the deposits recur.

### Endothelial Cell Loss

Intraoperative trauma is considered the main cause of early cell loss. Investigators have found an acceptable mean endothelial loss of 2.8%–9.2% 2 years following iris-claw phakic lens implantation,<sup>47,65,69,71,72</sup> which is similar to results of posterior chamber IOL implantation.<sup>73</sup> Menezo et al.<sup>65</sup> noted endothelial cell loss of 13.4% at 4 years, without morphometric changes. The largest cell loss was observed in the first 6 months after surgery.

In the FDA trial, a mean corneal endothelial cell change of 4.8% was observed 3 years after surgery.<sup>66</sup> Artisan phakic IOLs implanted in eyes with AC depths less than 3.2 mm exhibited the greatest cumulative endothelial



cell loss (9%) at 3 years. The FDA panel then contraindicated the use of this lens for patients with an AC depth of less than 3.2 mm. Morral et al.<sup>74</sup> observed that Artisan/Artiflex implantation did not produce significant ECL up to 10 years after surgery compared with corneal refractive surgery and unoperated eyes. Patients should never rub their eyes and never press them against the pillow at night.

### Glaucoma

Postoperative glaucoma after Artisan lens implantation can occur due to residual ophthalmic viscosurgical device in the AC, dispersion of iris pigment during surgery with partial occlusion of the trabecular meshwork, use of topical corticosteroids, and postoperative inflammation.<sup>65,68,72</sup> Temporary ocular hypertension was demonstrated in a prospective study of 100 eyes with Artisan IOL. IOP showed a mean increase of 2.1 mm Hg at 3 months after surgery but a return to preoperative levels by 6 months.<sup>75</sup> In the same study, one lens was explanted due to chronic high IOP at 11 months. In the FDA study, no case of raised IOP requiring treatment was observed.

### Iris Atrophy or Dislocation

Despite successful implantation of an Artisan lens, there is a risk of subsequent IOL dislocation. In the FDA trial, IOL dislocation occurred in five cases (0.8%) at 3 years. IOL dislocation can occur due to iris atrophy at the site of enclavation, usually when a small amount of tissue is entrapped, or due to blunt ocular trauma, as reported previously in two cases<sup>76,77</sup> (Fig. 3.721). Repositioning of the lens may be done with an excellent visual outcome in most cases.

### Cataract

Nuclear cataract (NC) developed in 7 of 231 eyes (3%) with an Artisan lens after 8 years follow-up in one study.<sup>78</sup> Patients older than 40 years of age at implantation of the IOL and axial length greater than 30 mm were factors significantly related to NC formation.<sup>78</sup> A meta-analysis of cataract after iris-fixated phakic IOL implantation found an incidence of 1.11%.<sup>45</sup> In the FDA trial, the cumulative incidence of lens opacity was 4.5% (49/1088 eyes). The majority of these opacities were not visually significant. During the study, four opacities were determined to be visually significant and three required cataract extraction. The authors pointed out that the rate of cataract surgery in the general population over 40 years of age is 1.7%–10.8%.<sup>66</sup>

### Other Complications

Other complications include hyphema,<sup>71</sup> intermittent myopic shift (of 4.00 D),<sup>79</sup> retinal detachment, and giant retinal tears.<sup>71,80,81</sup>

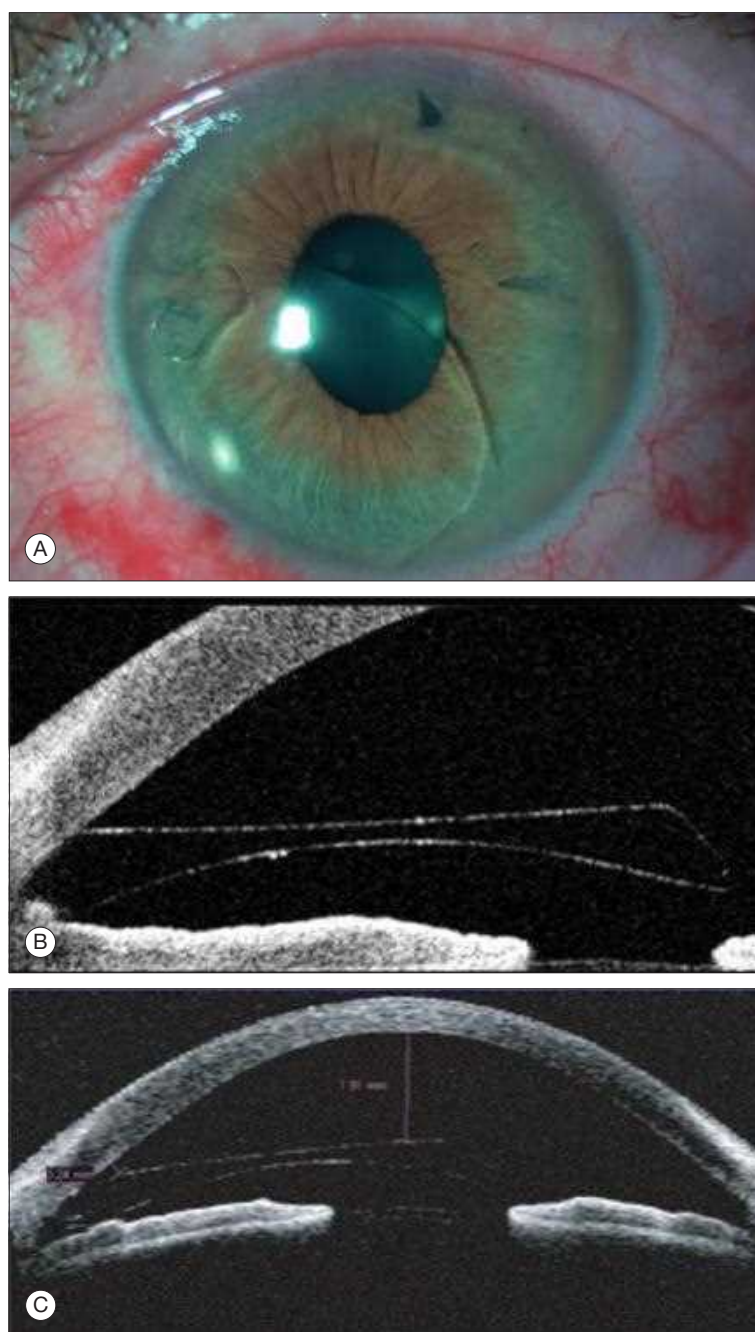
## POSTERIOR CHAMBER PHAKIC INTRAOCULAR LENSES

Since 1986, when Fyodorov first implanted a phakic IOL in the prelenticular space to correct high myopia, several posterior chamber phakic IOLs of his derivation have been developed.<sup>12,82</sup> Results with phakic IOL materials and designs used to date suggest that both biocompatibility with and adequate spacing from sensitive intraocular structures are required for improved safety in all patients. For implantation of a phakic IOL in the prelenticular space, we would ideally desire materials that would allow permeability of nutrients and circulation of aqueous humor and would not cause crystalline lens or zonular trauma.

Until recently, two models of posterior chamber phakic IOLs were available on the market, the phakic refractive lens and the implantable collamer lens. Despite initial promising results with the PRL, it was withdrawn from the market due to safety concerns.

The PRL (IOLTech/CIBA Vision) (see Fig. 3.73), a model based on previous work by Fyodorov et al.,<sup>12,13,24</sup> was a silicone single-piece plate design IOL that had a concave posterior base curve mimicking the anterior curvature of the crystalline lens. Earlier designs of this IOL caused cataract because of mechanical touch, impermeability of nutrients, and stagnation of aqueous flow without the elimination of waste products.<sup>13,14,83</sup> Further improvements in the vaulting reduced the incidence of cataract, but UBM studies documented that the PRL was located on the zonules in most cases.<sup>84</sup> After reports of PRL decentration and dislocation into the vitreous cavity the lens was withdrawn from the market.<sup>85–87</sup>

ICL: In 1993, a posterior chamber phakic IOL made of Collamer (0.2% collagen and 60% hydroxyethyl methacrylate copolymer) was developed.<sup>88–90</sup> The ICL (STAAR Surgical Co.); Fig. 3.722 is designed to be implanted in the posterior chamber supported in the ciliary sulcus.



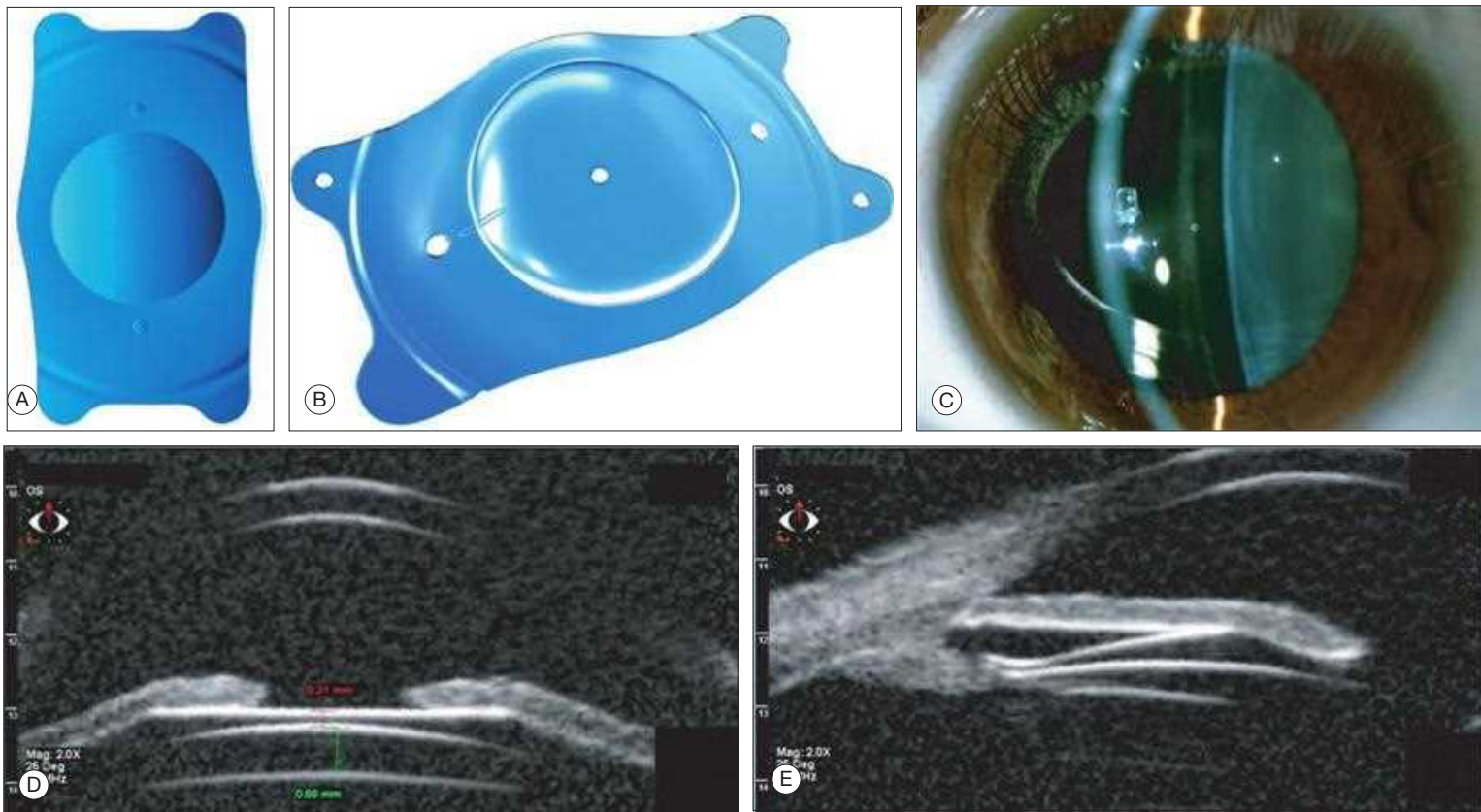
**Fig. 3.721** (A) Artisan Dislocation After Blunt Trauma. Note the avulsion of iris stromal tissue in the site of enclavation. (B) and (C) Anterior segment OCT of a dislocated Artisan intraocular lens. IOL optic touch to endothelium (left in both figures) and correspondent thickening of the cornea (edema).

Collamer is a hydrophilic flexible material with a high biocompatibility and permeability to gas (oxygen) and metabolites.<sup>88</sup> These features and the free space left between the IOL and the crystalline lens, named “vault,” should allow the crystalline to have a normal metabolism and thus avoid the development of cataracts. Yet cataract formation, pigment dispersion, and glaucoma still are the main complications.<sup>91–93</sup> The FDA-approved model of the ICL—the Visian ICL V4 (Fig. 3.722A), a rectangular single-piece IOL, 7 mm wide, with greater vaulting than the V2 and V3 models—has been associated with a decrease in the frequency of lens opacification.<sup>94,95</sup> A newer design, currently available outside the United States, the V4c Visian ICL with Aquaport (Fig. 3.722B), incorporates a 0.36-mm diameter port in the center of the optic. The presence of this port obviates the need for preoperative iridotomies.

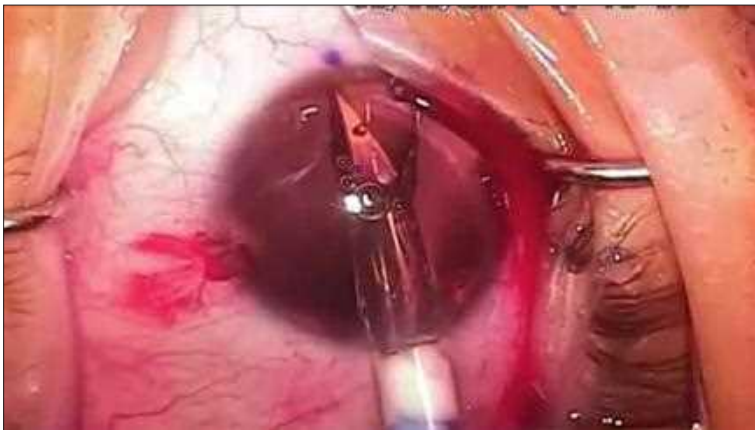
### Surgical Technique

A combination of topical mydriatics (e.g., cyclopentolate 0.75% and phenylephrine 2.5%) is applied three times 30 minutes before surgery to obtain good pupil dilation. For toric cases the 0° and 180° horizontal corneal axis are marked while the patient is sitting upright to control cyclotorsion while





**Fig. 3.7.22** (A) ICL V4 and (B) V4c toric with central Aquaport. (C–E) Myopic ICL. (C) Biomicroscopic slit demonstrating the distance ICL to the crystalline lens. (D) UBM (50 MHz) quantitatively assessing lens vault (distance ICL to lens) = 590 microns; and (E) UBM showing the proximity of the ICL haptic to the ciliary processes and zonulae.



**Fig. 3.7.23** A Posterior Chamber Lens (ICL) Is Inserted Through a Small Incision With an Injector. (Courtesy Glauco R. Mello, MD, Curitiba, Brazil.)



**Fig. 3.7.24** After the Lens Unfolds, the Footplates Are Placed Underneath the Iris.

lying supine. Topical or peribulbar anesthesia are usually preferred. A 2.7- or 3.0-mm temporal clear corneal tunnel, and two paracentesis are created. Following the placement of cohesive viscoelastic, the posterior chamber IOL is introduced into the AC using an injector (**Fig. 3.7.23**) (Video 3.7.5).

While the IOL unfolds, its proper orientation must be checked. Each footplate then is placed one after the other beneath the iris with use of a specially designed, flat, nonpolished manipulator, without placing pressure on the crystalline lens (**Fig. 3.7.24**). The surgeon should avoid contact with the central 6.0 mm of the lens, as any contact might damage the thin lens optic. Except for the newest model (V4c), a small peripheral iridectomy should be performed to prevent pupillary block. Then the viscoelastic material is removed with irrigation–aspiration, and acetylcholine (Miochol) is injected. Corticosteroid–antibiotic eyedrops are prescribed for 4 weeks.

## Complications

### Cataract

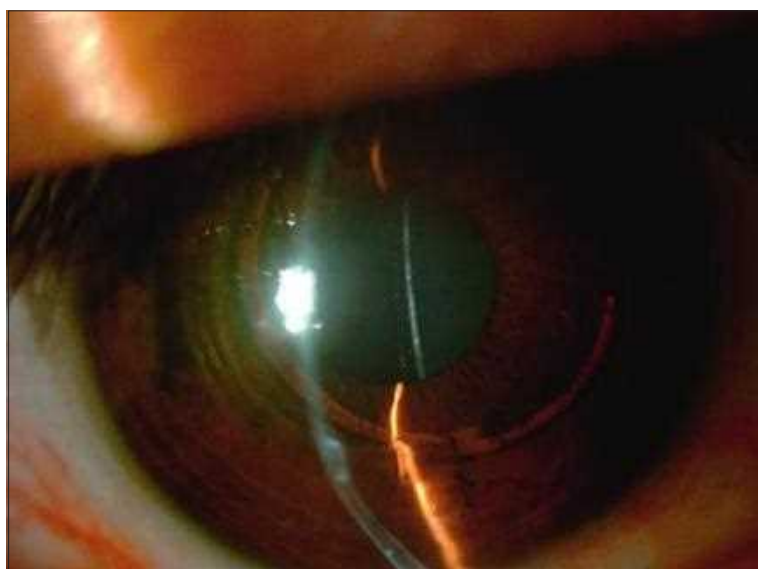
Cataract is the most crucial concern for the future of posterior chamber phakic IOLs (**Fig. 3.7.25**). Cataract may form as a result of trauma to the crystalline lens during the implantation procedure or due to long-term contact between the IOL and the crystalline lens. Metabolic disturbances

induced by the implant also may be partially responsible for cataract formation.

A meta-analysis of cataract development after different posterior chamber phakic IOLs found that 223 of 1210 eyes developed new-onset cataract.<sup>45</sup> Of these, 195 were anterior subcapsular. The overall incidence of cataract formation was 9.6%. In the ICLV4 FDA trial with a mean follow-up of 4.7 years, a cumulative probability estimate of 6%–7% of anterior subcapsular opacities was found more than 7 years after implantation of the Visian ICL.<sup>96</sup>

In a more recent meta-analysis comprising 2592 eyes, the occurrence of cataract formation with the V4 ICL models was 5.2%. Of those, 43.4% were reported within 1 year, 15.4% between 1 and 3 years, and 35.3%  $\geq 3$  years after ICL implantation.<sup>97</sup> In a retrospective review of 133 consecutive eyes implanted with the V4 ICL model, the observed rate of phacoemulsification increased from 4.9% at 5 years to 18.3% at 10 years after ICL implantation, and 13% of eyes developed ocular hypertension that required topical therapy at 10 years. A smaller vault height was associated with the development of lens opacity.<sup>98</sup> Another study with 84 eyes with V4 ICL reported a rate of phacoemulsification of 17% at 10 years.<sup>99</sup>

The treatment of cataract in patients implanted with posterior chamber phakic IOLs is not difficult. Explantation of the ICL is easily performed



**Fig. 3.7.25** Anterior Cortical Cataract 1 Year After ICL-V4 Implantation in a Patient With Previous Intracorneal Ring Segment for Keratoconus. (Courtesy João Marcelo Lyra, MD, Maceio, Brazil).

through the same incision. Phacoemulsification and posterior chamber IOL implantation can be done in a routine fashion.<sup>100</sup>

### ICL Replacement

ICL exchange for insufficient or excessive vault is an uncommon complication. In a cohort of 616 eyes implanted with V4 ICLs sized according to WTW and ACD measurements, 16 eyes (2.6%) had lens replacement.<sup>101</sup> Eight surgeries (50%) were performed because of low vaulting ( $\leq 100 \mu\text{m}$ ) and another 8 (50%) because of too high vaulting ( $\geq 1000 \mu\text{m}$ ). In the US FDA trial using the same sizing methodology, ICL replacement for insufficient or excessive vault was reported in five of 526 eyes (1.0%).<sup>102</sup> In the absence of complications, however, ICL replacement remains a matter of medical judgment. On the other hand, excessive vault in the presence of compromised AC angle function (Fig. 3.7.26) (Video 3.7.6) and insufficient vault in the presence of visually significant cataract are indications for surgical intervention.<sup>23</sup>



See clip:  
3.7.6

### Pigmentary Dispersion and Elevated Intraocular Pressure

Pigmentary dispersion syndrome occurs when the iris is abraded and releases pigments into the aqueous humor. Because of the close position to the iris and ciliary sulcus, the placement of posterior chamber phakic IOLs may increase the risk of pigmentary dispersion<sup>14,24,92</sup> (Fig. 3.7.27). Pigmentary reaction has been described with rates between 0% and 15.5% with posterior chamber phakic IOLs and is frequently associated with elevated IOP. Sanders et al.<sup>102</sup> reported two eyes out of 526 (0.4%) with increased IOP requiring treatment at 3 years postoperative. Guber et al.<sup>98</sup> reported that at 10 years, 12 eyes (12.9%) had developed ocular hypertension that required topical medication, which raises some concern about the long term.

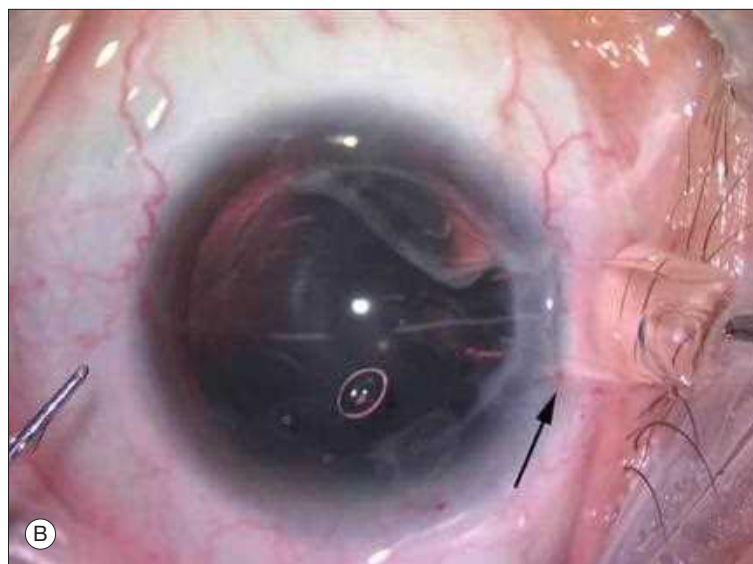
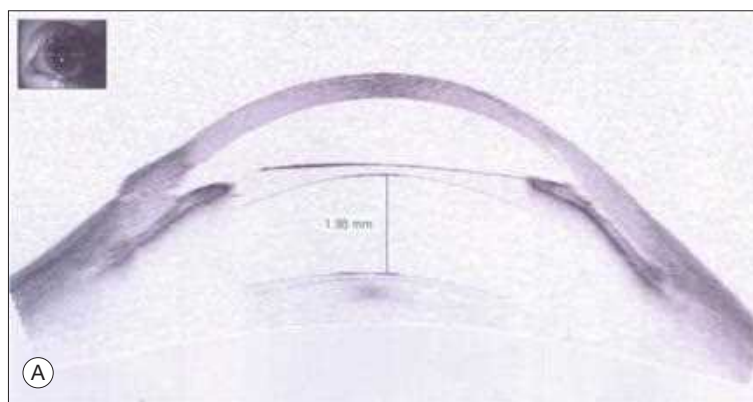
### Endothelial Cell Damage

Although endothelial cell loss is a major concern with AC IOLs, it is not such an important problem with posterior chamber phakic IOLs. In the ICL FDA trial, cumulative cell loss over the first three postoperative years was 8.4%–9.7%, depending on the method of analysis.<sup>94</sup> Most loss occurred in the first year and is considered to be due to surgical trauma.

### BIOPTICS

Zaldivar et al.<sup>104</sup> introduced the term “bioptics” in the late 1990s to describe the combination of phakic IOL implantation followed by LASIK in patients with extreme myopia, high levels of astigmatism, and in patients whose lens power availability was a problem. The concept of first implanting a phakic IOL to reduce the amount of myopia and then fine-tuning the residual correction with LASIK has gained appeal.

When an AC phakic IOL combined with LASIK is planned, the corneal flap can be created just before the insertion of the lens. Then, usually after 1 month, the flap is lifted for laser correction of the residual ametropia.



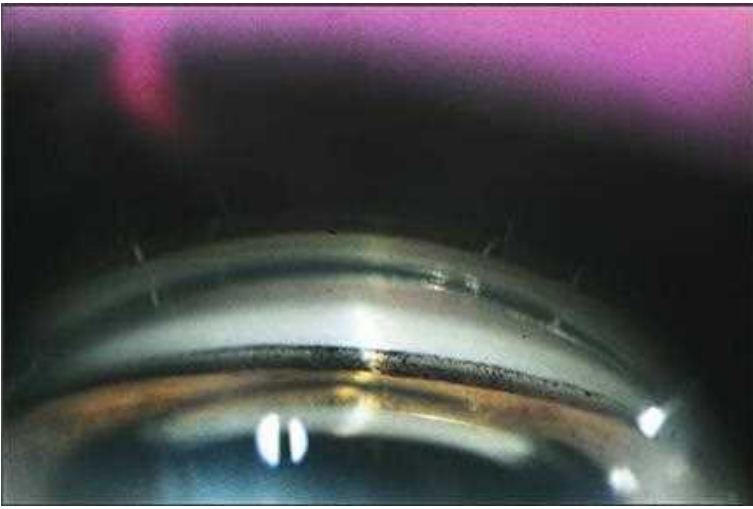
**Fig. 3.7.26** (A) Anterior chamber angle closure and excessive vault after ICL V4 implantation in a patient with high myopic astigmatism after previous deep anterior lamellar keratoplasty. (B) The ICL was replaced for a smaller size through a microincision (arrow). (C) After replacement, a normal vaulting was observed. (Courtesy Walton Nosé, MD, PhD, São Paulo, Brazil.)

This two-step technique was called adjustable refractive surgery (ARS) by Guell.<sup>105</sup> The rationale for performing the flap first is to avoid any possibility of contact between the endothelium and the IOL during the suction and cut for the LASIK procedure. Most authors believe that the corneal flap can be created despite the presence of an AC phakic IOL. The combination of phakic IOLs and LASIK is a safe, effective, predictable, and stable procedure for the correction of high myopia and hyperopia.

### CONCLUSION

The field of phakic IOLs has greatly progressed in recent years. The increased knowledge on anterior segment anatomy and the availability of better imaging technologies along with improved IOL designs and materials and surgical techniques have led to higher success rates with these lenses. Compared with corneal refractive surgery, phakic IOLs compete favorably for the correction of high ametropias with increasing predictability, efficacy, safety, and quality of vision.





**Fig. 3.7.27 Pigmentary Deposits Are Seen in the Angle in an Eye With a Posterior Chamber Phakic Intraocular Lens.** (From Arné JL, Hoang-Xuan T. Posterior chamber phakic IOL. In: Azar DT, editor. IOLs in cataract and refractive surgery. Philadelphia: WB Saunders; 2001. p. 267–72.)

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# Astigmatic Keratotomy: The Transition from Diamond Blades to Femtosecond Lasers

3.8

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## Definitions:

- Astigmatic keratotomy (AK) is an incisional procedure in which a diamond blade or a femtosecond laser is used for the correction of astigmatism.
- Radial keratotomy (RK) is a procedure in which radial incisions are used to correct myopic spherical refractive error. The lower predictability and higher complication rates of RK relative to laser refractive surgery have reduced its utility for the correction of myopia.

## Key Features

- The effect of incisional keratotomy is influenced by corneal wound healing and patient age.
- For astigmatic keratotomy, the surgeon must screen surgical candidates for myopic or planospherical equivalents.
- The axis of astigmatism is important for the placement of AK incisions. Sound clinical judgment is needed when disparity occurs between corneal topography and clinical refraction.
- Complications of incisional keratotomy may be reduced by adequate marking of the visual axis, adequate corneal incision shape and depth, and avoidance of corneal perforations.
- Postoperative complications include progressive hyperopia, progressive wound gaping, induced astigmatism, and contact lens intolerance.
- Femtosecond laser arcuate keratotomy (femtosecond AK) is an effective alternative to AK. Laser arcuate resection (LAR) is an effective alternative to manual wedge resection for high postkeratoplasty astigmatism.

## HISTORICAL REVIEW

### Incisional Keratotomy

The diamond knife, although still in use today, is being replaced in many centers by the femtosecond laser with its ultrashort pulses capable of chiseling precise incisions on the cornea. Femtosecond lasers have garnered acclaim in terms of generating corneal incisions with greater precision, accuracy, safety, predictability, and reproducibility.

Incisional keratotomy now is mainly limited to astigmatic keratotomy at the time of cataract surgery and, rarely, to two-incision radial keratotomy (RK) for patients with low-grade myopic astigmatism who are not good candidates for laser in situ keratomileusis (LASIK) and photorefractive keratectomy (PRK).

Several options are available today for femtosecond laser AK: femtosecond laser astigmatic keratotomy (femtosecond AK) and intrastromal astigmatic keratotomy (ISAK). Methods for astigmatism correction can be performed alone or in combination with other procedures such as cataract surgery. Further, the correction can be done for natural or surgery-induced astigmatism such as postkeratoplasty astigmatism.

## SURGICAL TECHNIQUES FOR ASTIGMATIC AND RADIAL KERATOTOMY

The surgical techniques for AK and RK<sup>1-4</sup> (rarely used today) have many common aspects. AK remains a surgical option for correcting high astigmatism (e.g., postkeratoplasty astigmatism) that is beyond excimer laser correction or for the correction of smaller degrees of astigmatism in patients undergoing cataract surgery. Femtosecond AK has increased the predictability and improved the safety of AK.<sup>5,6,7</sup> Although limbal relaxing incisions have become popular as well, they do not have the tensile strength of Descemet's membrane, which fortifies a corneal incision.

## Preoperative Considerations

### Patient Selection

In selecting patients for AK, the surgeon must screen surgical candidates for myopic or planospherical equivalents. AK does not, as a general rule, benefit patients who have hyperopic astigmatism in which the spherical equivalents are relatively unaffected or associated with a further hyperopic shift.

Ideal candidates for AK, in addition to having a myopic or planospherical equivalent, have no keratoconus, are intolerant of contact lenses, and experience meridional magnification and distorted peripheral vision with high-cylinder spectacles.

### Visual Axis Determination and Marking

The use of scanning slit topography or Scheimpflug-based topography along with clinical refraction will help confirm the positioning of the planned AK incisions. Modern topographers provide an estimate of pachymetry at the location of the intended AK incision sites.<sup>8,9</sup>

A corneal light reflex used to guide procedure centration serves only to approximate the physiological visual axis location, because a coaxially aligned light reflex corresponds to the center of the corneal optical system and not the true visual axis. Studies have demonstrated this site to be associated most closely with the physiological visual axis.<sup>10</sup>

For marking of the visual axis, the administration of a drop of fluid over the corneal apex may enhance an otherwise dull corneal light reflex. A Sinskey hook is used to indent gently the epithelium that overlies the visual axis. If the epithelial indentation is not visualized readily, a Weck cell may be applied to the central epithelium, which enhances the central epithelial mark.

Treatment alignment is important for successful correction of astigmatism. The results of vector analysis have indicated that treatment decentration by 5°, 15°, and 30° corresponds to losses of the flattening effect by 1.5%, 13.4%, and 50%, respectively. Moreover, complete loss of the flattening effect is seen with treatment misalignment of 45°.<sup>11</sup>

### Intraoperative Corneal Pachymetry

The paracentral corneal thickness (1.5 mm from the visual center, at the 3-mm central clear zone) is measured at both the temporal site and the thinnest paracentral site, as previously established by pachymetry at the screening examination. Most often, this thinnest paracentral site coincides with the paracentral temporal (or inferotemporal) site as the region closest to the anatomical corneal center. If the two sites do not coincide,



the diamond blade is set to 100% of the thinner of the two intraoperatively measured sites using a calibration microscope.

## Incision Technique

Astigmatic incisions, either arcuate or tangential, produce maximal flattening in the meridian of the incision when they are placed within 2.5–3.5 mm of the visual axis, which also is within the 5–7 mm optical zone. Incisions made closer than the 5-mm optical zone cause visual disturbances. Incisions beyond 7 mm (such as limbal relaxing incisions [LRIs]) have a diminished effect on central corneal flattening.

When arcuate incisions are lengthened, increasingly greater degrees of astigmatic correction are provided, up to an arc length of 90°. Beyond an arc length of 90°, no reliable additional flattening occurs. Stacking multiple rows of astigmatic incisions is neither productive nor advised. Incisions carried out at progressively smaller optical zones may result in global corneal flattening. Such incisions may be associated with increased incidence of irregular astigmatism.

### Diamond Blade–Assisted AK

The diamond blade–assisted AK procedure is a manual process that requires marking the optical zone of the desired incision, marking the steep axis of astigmatism according to the appropriate arc length, and then determining the corneal thickness at the optical zone with ultrasound pachymetry before inserting the blade into the cornea to make the incision. A sterilized diamond knife blade then is mounted onto the sterile mounting block of the calibration microscope with the knife footplates set to zero and the diamond either extended to 550 mm or set at the thinnest paracentral screening pachymetric reading. Once real-time, intraoperative ultrasonic pachymetry is obtained, the diamond-tip extension is adjusted to the newly selected level. In this way, a minor adjustment is generally all that is needed, and it can be carried out in only a few seconds. When LRIs are being applied during cataract surgery, a preset blade is often used without the need for precalibration.<sup>12,13</sup>

Although this AK procedure has the potential to reduce high degrees of astigmatism, the postoperative outcomes are often accompanied by complications such as wound gape, perforation, skin lesions, epithelial inclusion, higher order aberrations, and poor predictability. LRIs have become popular as well, but the tensile strength of Descemet's membrane that strengthens a corneal incision is absent in laser arcuate resection (LAR).

### Full Penetrating Femtosecond AK

Femtosecond AK corneal surgery creates arcuate incisions to flatten the cornea. AK incisions are generally placed in the steep corneal meridian and result in flattening of the steep meridian (often associated with a compensatory steepening “coupling” effect of the orthogonal flat meridian). A coupling ratio is defined as the ratio of the values of the flattening of the steep meridian and the steepening of the orthogonal flat meridian after placement of AK incisions.<sup>14</sup> A coupling ratio equal to 1 indicates an unchanged spherical equivalent (SE) after the procedure due to equal flattening and steepening of the two meridians. A coupling ratio less than 1 indicates a SE shift toward myopia, and conversely, a coupling ratio greater than 1 indicates a SE shift toward hyperopia. Corneal topography or tomography, along with refraction, are performed in planning the femtosecond AK incisions.<sup>15</sup> Nomograms are then used to determine the arc length and the optical zone to achieve the desired astigmatism correction.

Although prior nomograms existed, developing their own nomogram based on a series of cases was important for each surgeon as demonstrated by the different surgery results of the femtosecond procedure experienced by some surgeons compared with the manual AK technique. Donnenfeld and Nichamin LRI nomograms were most commonly used as the baseline for the laser nomograms. Some surgeons altered both the blade nomogram and the laser's power output to come up with an effective approach for using the IntraLase laser. The modified Lindstrom nomogram is the most widely implemented nomogram for planning femtosecond AK incisions. Usually, when using the modified Lindstrom nomogram, surgeons recommend adding 0.05 diopters (D) to the planned astigmatism correction per year for patients less than 30 years old and subtracting 0.02 D per year for patients over 30 years old. Additional nomograms have been developed for femtosecond AK as well.

When femtosecond laser incisions are made, a series of spherical spots are created adjacent to each other tightly so that the final effect is similar to a wide-open incision made using the traditional diamond blade. Alternatively, this process can be adjusted by altering the laser energy and the spot size. Lowering the laser energy creates a weaker shot, making the

spot sizes smaller. This way the spots never really connect, which reduces the effectiveness of the femtosecond laser–created AK incision compared with those created using the diamond blade. However, the incision is made tighter, ensuring that it does not open immediately. The laser pulses are typically placed around 3  $\mu$ m on both the spot and layer separations.

### Femtosecond Intrastromal Astigmatic Keratotomy (ISAK)

Intrastromal incision is conceptually different from a manual LRI or full penetration astigmatic incision in that there is no breakage of Bowman's layer during the procedure. Compared with penetrating AK incisions, the optical zone is made a little smaller and the arc angle is made a little longer in ISAK.<sup>16</sup> The complete intrastromal nature of the incision allows the healing of the realigned stroma without wound gaping or epithelial plug formation. To ensure proper alignment, limbal marks can be made with a sterile pen placed at the 3 o'clock and 9 o'clock positions at the slit lamp just before the procedure. The incision details such as the depth, optical zone, and arc length can be preprogrammed into the femtosecond laser post limbal marking, after which the procedure can be carried out in a very similar manner to LASIK flap creation with the femtosecond laser. Patients with mixed astigmatism with a plano spherical equivalent will best benefit from the ISAK procedure, because the AK incisions are neutral in relation to myopia or hyperopia.<sup>17</sup> Thus, ISAK is a great additional potential option available for femtosecond laser users, especially for astigmatism ranging from 0.50 to 2.75 D of cylinder.

The variables in performing ISAK incisions are arc length on the nomograms and the surgical platform. As for femtosecond AK, Donnenfeld, Nichamin LRI, and modified Lindstrom nomograms are used as starting points for performing ISAK. However, additional nomograms have been determined for ISAK incisions combined with other procedures such as phacoemulsification.<sup>18</sup> The surgeons suggest an incision depth of 80% or 90%.

ISAK confers a unique advantage to the process of astigmatism correction by virtue of its intrastromal nature. The intrastromal incisions can be titrated easily by opening of the incision, and they can be performed easily in a minor procedure room or right at the slit lamp.<sup>17</sup> It is easiest to open the incision if the anterior edge of the incision is left just under the Bowman's layer.

### Wedge Resection Using Laser Arcuate Resection (LAR)

LAR is a standardized technique in which intersecting arcuate cuts are used to perform a wedge resection for the correction of high astigmatism through corneal steepening. The arcuate wedges to be excised are placed in the flat meridian. A simple formula is used to estimate the relative size and location of the arcuate cuts based on the radii of curvature and desired wedge width to be resected. The feasibility of the procedure was established in porcine corneas before treatment of a patient with 20.00 D of postkeratoplasty astigmatism.<sup>13</sup> The astigmatism was reversed (Fig. 3.8.1), and suture removal resulted in a 14.5 D reduction of astigmatism. LAR can be an effective alternative to manual wedge resection, allowing easier, more controlled, and more precise excision of tissue in width, length, and depth.<sup>13</sup>

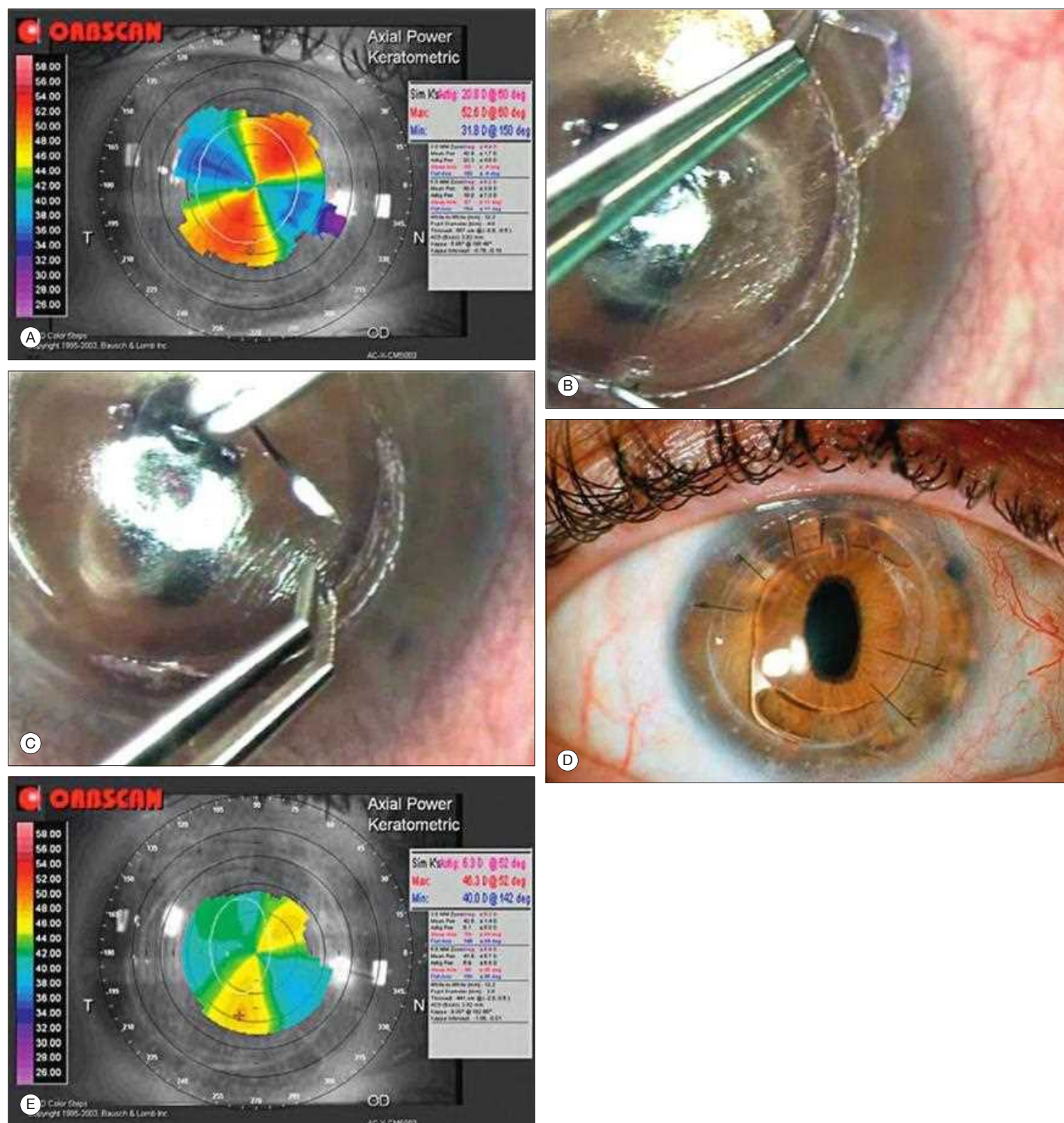
## Surgical Protocol

When AK is planned, careful attention to quantitative keratography (corneal topography) may be valuable, because paired incisions based on either the standard keratometer measurements or the refraction alone may be inaccurate. If a manifest refraction fails to yield the patient's potential acuity, irregular astigmatism may be present, and a topographical analysis is useful.

The visual axis is determined first, followed by selection of the appropriate optical zone, incision number, and length, as directed by the nomogram.

### Axis of Astigmatism

When disparity occurs between corneal topography and clinical refraction, the surgeon needs sound clinical judgment on a case-by-case basis. In such circumstances, if topographical analysis demonstrates orthogonal astigmatism, the surgeon may proceed according to the manifest refraction, as this provides the physiological combined (lenticular plus corneal) astigmatism. Alternatively, in cases of nonorthogonal astigmatism (when the two steep hemimeridians differ by any angle other than 180°), if the spherocylindrical reconstruction of the topographical pattern is consistent with the refraction, the incisions are placed as indicated by the topographical map.



**Fig. 3.8.1** (A) Preoperative corneal topography of the right eye demonstrated 20.0 D of post-PKP astigmatism. (B) Intraoperative view during wedge tissue removal (0.5 mm width) after LAR. The tissue was easily peeled off the wound. (C) Single 10–0 nylon sutures were placed. (D) Biomicroscopy appearance 1 month following LAR. (E) At 4 months, the corneal topography showed a decrease in topographical astigmatism to 6.3 D. (Reproduced with permission from Ghanem RC, Azar DT. Femtosecond-laser arcuate wedge-shaped resection to correct high residual astigmatism after penetrating keratoplasty. *J Cataract Refract Surg* 2006;32:1415–19.)

Once the desired axis of astigmatic correction has been determined, this needs to be translated onto the cornea. Because the astigmatic axis is defined so carefully with the patient in an upright position without sedation or a lid speculum, one must not estimate the surgical axis intraoperatively with the patient in a supine position or sedated or with a lid speculum in place. Cyclotorsional rotation of the globe may occur and introduce significant error.

For control, with the patient seated at the slit lamp, epithelial marks are placed on either the vertical or horizontal axis. Using the slit beam for centration and with the contralateral eye covered, the patient fixates straight ahead first on the slit-lamp light source. Fixation on the slit-lamp filament

at eye level and from head-on provides a virtual image of the light filament, which falls at the center of the corneal optical system and closely approximates the visual axis. The epithelium is abraded at the outer margins along the long axis of the beam using a Sinskey hook.

After true 90° or 180° is marked precisely at the slit lamp, the true visual axis is determined in the operating room under the operating microscope. With the 90° (or 180°) position determined precisely (reference axis), any desired axis may be marked using an axis marker and a surgical marking pen.

After appropriate marking of the astigmatic axis, pachymetry is carried out at the selected optical zone over the incision sites. The diamond blade



is set at 100% of the measurement at the thinner of the two sites. With the globe fixated, the corneal marks are incised.

The use of guarded diamond knife blades is advisable. The conjunctiva is grasped close to the limbus, where it fuses with Tenon's capsule and enables stable fixation; this region also is anesthetized more deeply than are the posterior conjunctiva and sclera.

The surgeon needs patience when secondary enhancements to AK are planned and performed. AK incisions require more time to stabilize than do radial incisions, so enhancement should be deferred for a minimum of 6 weeks after the primary procedure. A computerized videokeratography system is indispensable when the enhancement of an AK procedure is carried out. Caution is advised in treating overcorrected AK patients. If the resultant refractive error is one of hyperopic astigmatism, the original incisions may be reopened, the fibrous plug removed, and the wound margins approximated using a 10–0 nylon suture. Likewise, if an astigmatic incision is placed incorrectly in the flat axis, the wound margins are approximated using 10–0 nylon suture. Alternatively, if the residual refractive error is myopic astigmatism, further astigmatic incisions may be placed in the newly defined, steep hemimeridian. Such incisions are shorter than otherwise indicated, because the cornea has now demonstrated an excessive response to the initial incisions and could respond in like fashion to any further astigmatic incisions.

## Postoperative Protocol

At the termination of the procedure, diclofenac sodium, mild corticosteroid, and anti-infective agent drops (such as tobramycin, ciprofloxacin, ofloxacin, or norfloxacin) can be given. The diclofenac drops are discontinued on postoperative day 2 to avoid masking early keratitis and to minimize the risk of a toxic response.

## OUTCOME COMPARISON FOR VARIOUS ASTIGMATISM CORRECTION METHODS

In 2008, Harissi-Dagher and Azar<sup>5</sup> first reported the outcomes of high astigmatism correction in postkeratoplasty patients treated with femtosecond laser–assisted paired arcuate keratotomies. The report included two patients whose outcome measures included best-corrected visual acuity (BCVA), refraction, keratometry, and topography findings. The patients' BCVA improved from 20/100 and 20/200 to 20/30 and 20/60, respectively, without any postprocedure complications such as microperforations, graft rejection, or graft failure.

Newer versions of femtosecond laser platforms utilize both static and real-time optical coherence tomography (OCT) imaging systems to provide better accuracy and precision for the determination of planned AK incisions. LenSx is an example of a new generation femtosecond laser platform that has a video microscope and OCT integrated to facilitate visualization of detailed corneal structures in real time. Significant successes in the reduction of high residual astigmatism have been reported with this AK technique because of the production of precise and reproducible incisional cuts with proper depth, length, and curvature. Some examples of such success include astigmatism reduction rates of 36% by Kumar et al.,<sup>19</sup> 47% by Buzzonetti et al.,<sup>20</sup> 54% by Cleary et al.,<sup>21</sup> 55% by Hoffart et al.,<sup>6</sup> and 65.5% and 89.42% by Viswanathan et al.<sup>15</sup>

The efficacy of the astigmatic incisions has been shown to be dependent on the depth and length of the incisions, the optical zone, and the age and gender of the patient. These reports have been made based on studies on both live patients and on cadaver eyes. Incisions can be arcuate or beveled, full penetrating or intrastromal. Clearly et al.<sup>21</sup> performed paired femtosecond AK incisions at a bevel angle of 135° at a depth of 65%–75%, and with arc length of 60°–90°. The outcomes of these beveled incisions were compared with a case of perpendicular femtosecond AK incision. They reported an astigmatism reduction rate of 54%, which is comparable or better than those achieved with vertical incisions at similar depths. The major advantage observed from the beveled incision technique compared with the regular perpendicular incision technique was the lack of wound gaping.

## COMPLICATIONS AND MANAGEMENT OF ASTIGMATISM CORRECTION METHODS

The complications associated with incisional keratotomy may be categorized into those that are self-limited side effects, those that occur

### BOX 3.8.1 Potential Complications of Astigmatic and Radial Keratotomy

#### Self-Limited

- Halo effect
- Starburst effect
- Diurnal visual fluctuation
- Early regression

#### Intraoperative

- Marking
  - inaccurate visual axis marking
- Incisions
  - incision invading optical zone
  - incision beyond clear cornea
  - intersecting incisions
- Perforations
  - corneal perforation
  - lens capsule perforation
- Associated with retrobulbar anesthetic
  - optic nerve damage
  - globe penetration/retinal detachment
- Miscellaneous
  - diamond blade chip

#### Postoperative

- Non-sight-threatening complications related to refractive changes
  - undercorrection
  - overcorrection
  - regression
  - progression
  - induced irregular astigmatism
- Miscellaneous non-sight-threatening complications
  - contact lens intolerance
  - epithelial basement membrane disorders
  - epithelial inclusion cysts
  - foreign particles within grooves
  - epithelial iron lines
  - diminished corneal strength
  - endothelial cell loss
- Sight-threatening complications
  - stromal melting
  - infectious keratitis
- Therapy-related
  - Pharmacological
    - drug toxicity
  - Chronic corticosteroid use
    - cataracts
    - glaucoma
  - Contact lens wear
    - keratitis
    - neovascularization
    - late progression of effect
  - Retrobulbar injection
    - optic atrophy
    - globe penetration/retinal detachment

intraoperatively, those that occur postoperatively, and those that are associated with adjunctive therapy (Box 3.8.1).

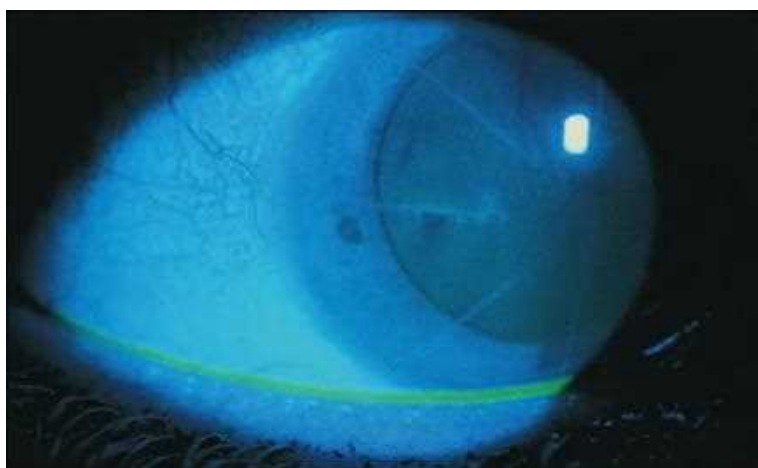
A number of potential complications may develop intraoperatively as a result of deviations from prescribed surgical protocols or faulty surgical technique. Such complications can generally be avoided by diligent training, literature review, detailed preparation, and adherence to proper surgical protocols. In the unusual event that a complication does occur, sound judgment generally can remedy the problem.

## Complications Related to Corneal Incisions

### Incision Beyond Clear Cornea

Extension of incisions beyond the clear cornea onto the corneoscleral limbus or onto limbal vascular arcades must be avoided to prevent subsequent vascular ingrowth. Incisions that invade the limbus may render the patient intolerant to subsequent contact lens use because of the associated vascularization of the incision grooves. Fibrovascular ingrowth may result





**Fig. 3.8.2 Corneal Perforation.** The risk of corneal perforation has been minimized greatly through recent developments (see text). The horizontal slit shows mild leakage of fluorescein.

in corneal destabilization over time, with large diurnal fluctuation and progression of refractive effect.

### Optical Zone Invasion

Optical zone invasion as a result of spontaneous patient eye movement or lack of surgical control represents one of the more worrisome potential complications of centripetal incisions. Patient education or globe fixation may reduce—but not entirely eliminate—the potential for optical zone invasion. The combined (Genesis) incision technique was designed to address this and other potential complications. Because the uphill margin of the blade cuts only along its distal portion, the diamond cannot produce deep incisions outside the previously incised groove. Once the central zone has been reached and intentionally slightly undermined, continued pressure must not be applied against the optical zone as the diamond is lifted from the groove.

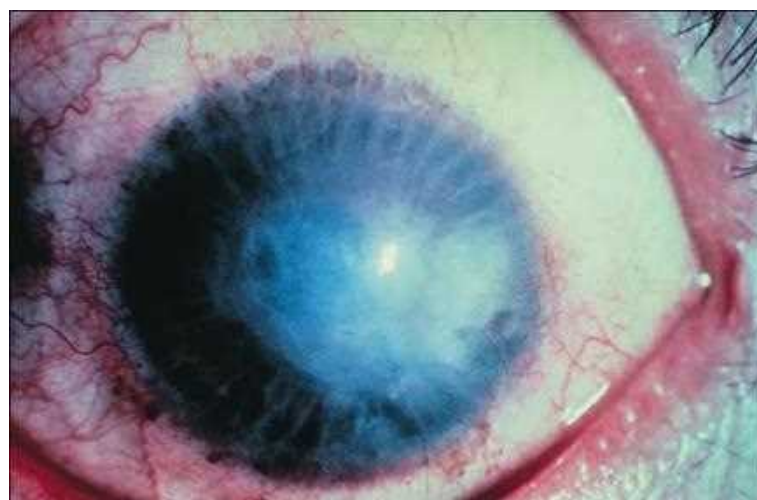
### Complications Related to Corneal Perforations

The risk of corneal perforation (Fig. 3.8.2) has been reduced with the advent of screening and real-time pachymetry, the availability of microscopes for precise diamond knife calibration, and the adherence to protocols suggesting incision of the thinnest corneal zones first and the use of diamonds not set at substantially more than 100% of paracentral pachymetry. The use of the femtosecond laser for AK reduces the complications related to corneal perforations, although it does not eliminate them entirely. The best way to prevent the development of a self-sealing perforation into a more serious perforation is to operate on a relatively dry field so that any leakage of aqueous humor is detected readily.

Early recognition of a self-sealing perforation, by operating on a relatively dry field (no tear pooling within the cul-de-sac), prevents its extension into a nonsealing perforation. Patients who have self-sealing perforations are managed using cycloplegia (for dilatation and prevention of iris adherence to the self-sealing perforation site), topical aqueous suppressants such as beta-blockers, a loading dose of topical antibiotics such as polymyxin and ofloxacin every 5 minutes for three doses, and an ocular shield over the eye. The eye must not be patched, as this compresses the corneal apex, bows open the incisions, and retards healing. The use of collagen shields is not recommended. Incision of the thinnest quadrant first greatly reduces the risk of a self-sealing perforation, as the cornea continues to thin throughout the procedure. If the diamond penetrates the globe on the first incision or on the centrifugally directed component of any incision, the operation may be terminated and completed at a later time, with repeated pachymetry and diamond calibration. The surgeon cannot determine intraoperatively the degree to which the diamond has been overextended or whether pathological corneal thinning exists.

In the event of a nonsealing perforation, it is prudent to place a single (or multiple) interrupted 10-0 or 11-0 nylon suture to seal the wound and prevent any of the sequelae of hypotony or of an open wound.

Early detection of the corneal perforation is important. When a perforation occurs, air bubbles, indicating the invasion of endothelium and/or epithelium integrity, can typically be observed in the anterior chamber.<sup>22</sup> Care should be taken because sometimes the perforation can go undetected, which may lead to postoperative corneal infection and/or endophthalmitis.



**Fig. 3.8.3 Fibrovascular Tracks.** The postoperative development of fibrovascular tracks within incision grooves is most often associated with chronic irritation or hypoxia.

## Postoperative Complications

### Progressive Hyperopia

Risk factors associated with postoperative progressive hyperopia include multiple enhancement procedures, peripheral redeepening procedures, lack of preoperative cycloplegic refraction (latent hyperopia), postoperative contact lens wear, and postoperative ocular massage. The surgeon may wish to consider these factors when patient management strategies are determined.

### Induced Astigmatism

Induced regular or irregular astigmatism may occur if fewer incisions are placed, if the incisions are placed asymmetrically about the visual axis or are of variable depth, or if the optical zone is decentered with respect to the visual axis. The great majority of these refractive aberrations are self-limited and spontaneously improve within the first 6 postoperative weeks. Thus wait until the refraction and surface topography have stabilized before placing additional incisions.

### Contact Lens Intolerance

Newly designed rigid, gas-permeable lenses that have peripheral curves to match the patient's preoperative parameters are recommended to overcome postoperative lens intolerance. The risk of lens-associated corneal vascularization is reduced by a shorter incision that does not extend to the limbus. The fibrovascular tracks within the incision sites are associated most often with chronic irritation and hypoxia from subsequent soft contact lens wear (Fig. 3.8.3). To diminish the risk of this complication, RK incisions are stopped approximately 1 mm short of the limbus. Chronic contact lens wear may provide a direct compressive effect, with associated wound stretching and progressive hyperopia.

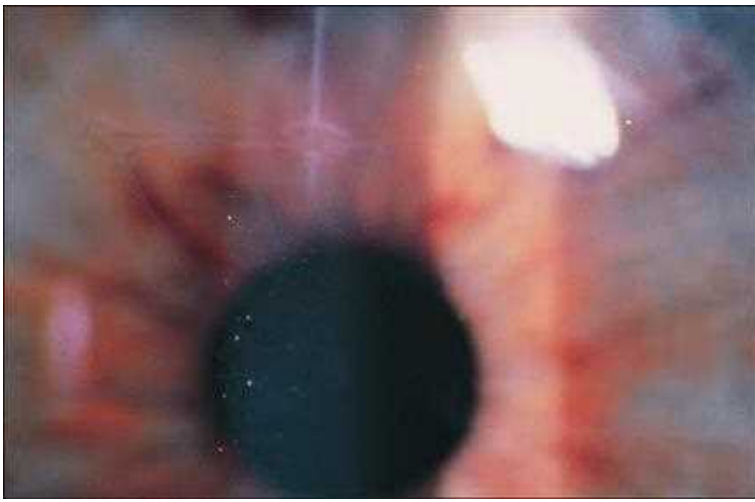
### Stromal Melting

Stromal melting often develops in patients who have crossed incisions. Thus this complication can be prevented by taking great care to avoid crossed incisions during surgery. Corneal stromal melt is also associated with patients who have rheumatoid arthritis or other collagen vascular diseases and concomitant severe keratoconjunctivitis sicca with diffuse punctate epitheliopathy (Fig. 3.8.4). Patients affected by such advanced disease are not viable candidates for incisional keratotomies. For patients who have significantly diminished tear production, it may be necessary to perform punctal occlusion before considering incisional keratotomy.

### Infectious Keratitis

Although its incidence is lower than that observed in contact lens wearers, this disorder generally develops in the perioperative period, although delayed cases in association with contact lens wear have been reported. Indeed, the only two cases of keratitis reported in the PERK study<sup>23</sup> occurred in association with postoperative contact lens wear.

Intensive, broad-spectrum antibiotic therapy is instituted. An aggressive protocol may include fortified cefazolin (50 mg/mL), fortified tobramycin (14 mg/mL), and fourth-generation fluoroquinolone—gatifloxacin on an hourly basis, with rotation every 20 minutes, while waiting for culture



**Fig. 3.8.4 Chronic Stromal Melting.** Serious complications as a result of chronic stromal melting may occur in the setting of crossed incisions.

results. A combination of 0.4 mL cefazolin (250 mg/mL) and 0.4 mL tobramycin (40 mg/mL) mixed with 0.1 mL lidocaine 2% may be administered further as a subconjunctival injection to the affected quadrant on a daily basis until culture results are available.

## CONCLUSIONS

The use of incisional keratotomy has declined over the past decade as laser vision correction has gained popularity (due to superior predictability). RK was the most common form of surgical correction of myopia from the 1970s through the early 1990s. It was an important milestone in the history of refractive surgery. In the early 1990s, at the 10-year follow-up of the PERK study, concerns arose about the lack of predictability and stability of RK. There were no identifying risk factors to predict those at risk for the hyperopic shift and the diurnal change in refraction. This is in contrast to the safety, efficacy, and predictability of excimer laser ablation. Incisional keratotomy continues to be an important surgical method for correcting high astigmatism, which, for example, may occur iatrogenically

after penetrating keratoplasty or for the correction of smaller degrees of astigmatism within the framework of cataract surgery. The use of the femtosecond laser to create AK incisions has increased the applicability of AK to correct high and asymmetrical astigmatism, singly or in conjunction with other procedures, although the combined therapy outcomes need to be explored further.

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# Intrastromal Corneal Ring Segments and Corneal Cross-Linking

3.9

Claudia E. Perez-Straziota, Marcony R. Santhiago, J. Bradley Randleman

## Definitions:

- Corneal cross-linking (CXL) is a procedure combining corneal saturation with riboflavin and exposure to UV light to increase the amount of links between collagen fibers in the corneal stroma, thereby increasing its tensile strength.
- Intracorneal ring segments (ICRS) are semi circularly shaped polymethyl methacrylate (PMMA) segments that are inserted into the paracentral region of the anterior corneal stroma to flatten the center of the cornea and induce a hyperopic shift.
- CXL is used to halt progression of corneal ectasias, whereas ICRS are used in patients with moderate to advanced stable keratoconus to counterbalance the myopic shift induced by corneal steepening.

## Key Features

- Preoperative evaluation and topographical assessment is necessary to select the appropriate ICRS size and positioning.
- The flattening effect of ICRS can be potentiated by the combination with cross-linking.
- Careful selection of patients for combined ICRS and CXL is imperative to increase the chances of success and reduce the risk of postoperative complications.
- There is currently no consensus regarding timing of combined procedures. Inserting the ICRS before CXL may optimize the impact of ring segment insertion, whereas CXL alone may be sufficient to halt progression and improve corneal shape, thereby obviating the need for a combined procedure.

## INTRODUCTION

For the majority of patients seeking refractive surgery, the best, most effective treatment will be laser ablation as highlighted in the previous chapters. However, for patients with ectatic corneal disease, ICRS and CXL play a prominent role in halting disease progression and improving acuity.

## INTRACORNEAL RING SEGMENTS

Intracorneal ring segments add volume peripherally by changing the arc length of the anterior corneal curvature and redistributing the posterior corneal tissue.<sup>1</sup> This shortens the posterior lamellae and flattens the cornea centrally, correcting myopia.<sup>2,3</sup>

Intracorneal ring segments received European Conformité Européenne certification in 1996 and US Food and Drug Administration (FDA) approval in 1999. However, the initial enthusiasm for the correction of myopia faded due to a limited range of correction, less predictability, induced astigmatism, and slower visual recovery.

The idea of using intrastromal rings in the treatment of keratoconus was proposed in 2000 by Colin et al.<sup>4</sup> Since then their use has evolved into an important therapeutic intervention in corneal ectatic diseases.<sup>4,5,6</sup> Intacs received FDA approval for the use in the treatment of keratoconus in 2004 for rings 0.25–0.35 mm and in 2010 for 0.4–0.45 mm.

In patients with ectatic disease, ICRS induce morphological changes by flattening the steepest meridian and decreasing the cone location magnitude index (CLMI) and the mean curvature in the 2-mm area over the cone. They do not induce significant changes in biomechanical corneal

parameters such as corneal hysteresis and corneal resistance factor, and in younger patients ICRS outcomes have regressed in long-term follow-up,<sup>7</sup> suggesting the underlying biomechanical failure in keratoconus has been left untreated.

## Corneal Cross-Linking (CXL)

In 1998, Spoerl et al. published their findings after collagen cross-linking of porcine corneas, establishing riboflavin as a safe and effective component of the treatment.<sup>8</sup> The first clinical results after CXL in human keratoconic corneas were published in 2003.<sup>9</sup> In the photochemical reaction, riboflavin acts as a photosensitizer that absorbs UV-A energy and excites into a triplet state. This triplet can undergo an aerobic (type 2) or anaerobic (type 1) reaction, both of which create oxygen species that induce covalent bonds between collagen molecules and between proteoglycans and collagen. The depth of this effect is thought to be seen in the demarcation line on optical coherence tomography (OCT) images of post-cross-linking corneas, usually at 300–350  $\mu\text{m}$  of depth.<sup>10</sup> Long-term follow-up of cross-linked corneas has demonstrated that in contrast to ICRS, CXL affects the biomechanical properties of the cornea and halts the progression of the disease with only mild and refractive changes.

## CXL Plus

The lack of significant refractive impact of CXL stimulated the development of treatment protocols combining CXL with a variety of techniques (CXL Plus), including phakic intraocular lens (IOL) implantation and selective excimer laser ablation and CXL combined with ICRS.<sup>11–15</sup>

The rationale behind the combination of ICRS and CXL seems to be the symbiosis that occurs when combining the mechanical and refractive changes induced by the segments with the biomechanical changes induced by CXL and their benefits in halting disease progression.

## SURGICAL PROCEDURE: ICRS

### Patient Selection

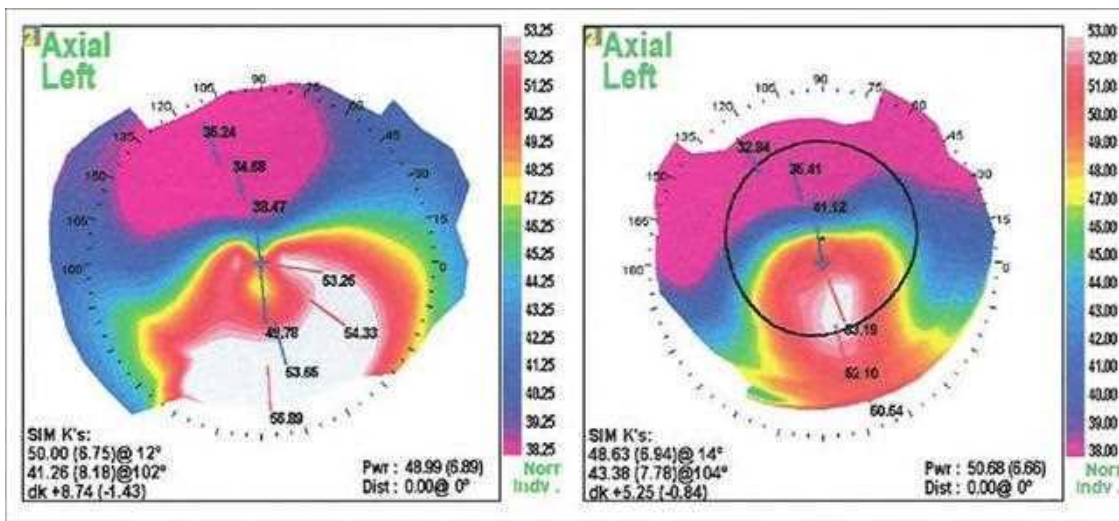
The primary indication for ICRS implantation in ectatic patients include moderate to advanced stages of disease, with clear corneas and unsatisfactory corrected near visual acuity (CDVA) or contact lens intolerance,<sup>16</sup> steepest keratometry less than 58 diopters (D), no corneal scarring or opacities, and at least 450  $\mu\text{m}$  thickness at the 7-mm diameter where the segments are to be placed.<sup>17</sup> The flattening effect of ICRS becomes more robust in advanced stages of ectasia.

### Preoperative Considerations

Preoperative refraction, aberrometry, and corneal topography are important factors to consider in surgical planning. Topographical features are relevant in the selection of the segments and their location in asymmetrical corneas, with thicker and longer segments placed in the area just below the cone. Single versus paired segment implantation appear to be equivalent in terms of refractive results,<sup>18</sup> and the decision should be made on a case-by-case basis using the manufacturer's ICRS nomograms.

### ICRS Selection

There are currently three main types of ICRS: **Intacs** (Addition Technology, Sunnyvale, CA), with a hexagonal transverse shape, and **Intacs SK**, with



**Fig. 3.9.1 Topographical Flattening After Intacs Segment Placement.**  
 Note the reduction in size and maximal steepness in the right image (after segment implantation) compared with the left image (before segment implantation).

an oval cross-section shape; **Ferrara**, with triangular shape, and **Keratings** (both from Mediphacos, Belo Horizonte, Brazil), with almost identical design to Ferrara rings, but different arc lengths and internal diameters. Intacs are the only FDA-approved ICRS for the reduction or elimination of myopia and astigmatism in normal patients or those with keratoconus and are available in 0.25, 0.30, and 0.35 mm. The 0.4-mm Intacs and the Ferrara rings are available only in European countries and South America. The effect of the implantation of an ICRS correlates directly to its thickness and inversely to its distance from the visual axis, or *optical zone*, with thicker implants and smaller optical zones resulting in greater flattening effect and reduction of coma-like aberrations.<sup>1,19,20</sup>

### Single Versus Paired ICRS

In cases of peripheral steepening, where the main issue is irregular astigmatism, implanting a single segment may provide better results than two segments, whereas in central cones, where the high myopic refractive error is the main issue, two segments or a longer continuous segment with a simple nomogram using keratometry readings only are a better alternatives because they target a larger change in spherical equivalent.<sup>21–24</sup>

### ICRS Surgical Technique

Intrastromal corneal ring segments are placed within the peripheral stroma at approximately two-thirds of the stromal depth, outside the central optical zone, to reshape the anterior corneal surface while maintaining the positive asphericity of the cornea.<sup>25–32</sup>

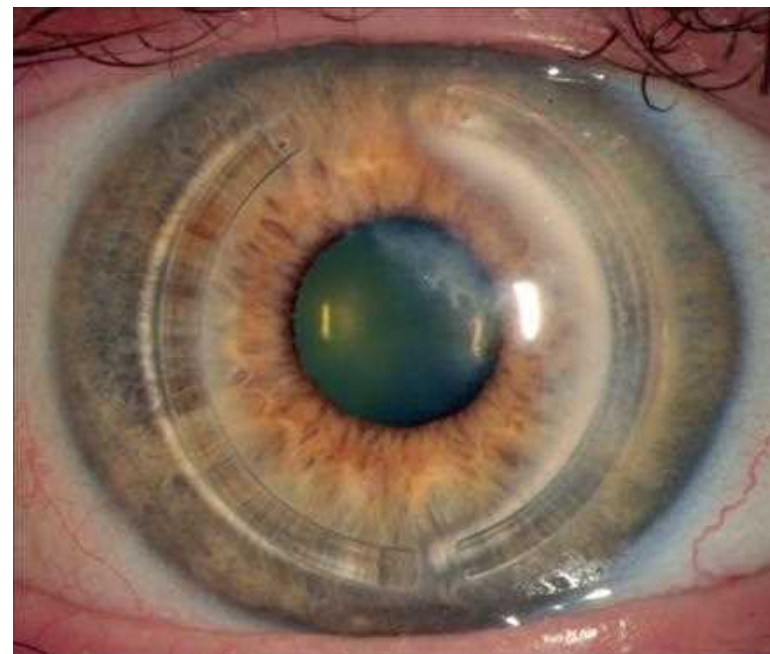
There are no significant differences in refractive outcomes of ICRS between femtosecond laser and manual spreader. When using femtosecond laser, the efficacy in creation of an intrastromal channels can be affected by previous cross-linking treatment, perhaps due to changes in the optical quality of the anterior stroma that interfere with laser tracking. Therefore even though femtosecond laser is associated with fewer complications compared with the mechanical spreader,<sup>33</sup> manual dissection of the channels may be considered in patients that have been previously cross-linked.

After channel formation, the segments are introduced with forceps into the channels. In their final position, the segments should be located 3 mm apart superiorly. Once the segments have been inserted, each segment has a small positioning hole at the superior end to aid with surgical manipulation for proper positioning, after which the incision site is hydrated and closed with 10–0 nylon sutures.<sup>25</sup>

### Clinical Outcomes

ICRS flatten the cornea permanently, but the major shifts in refraction and topographical findings after ICRS implantation usually occur in the first 6 months of postoperative period<sup>34</sup> with some fluctuations during the first month (Fig. 3.9.1). Even though late postoperative variations probably occur due to intrinsic biomechanical changes in those with unstable disease, the difference in CDVA and keratometry between month 6 and month 36 is not significant.

The results of ICRS in patients with corneal ectasia are encouraging, especially in decreasing astigmatism and improving topographical



**Fig. 3.9.2 Late-Onset Corneal Haze After Intracorneal Ring Segment Implantation.**

abnormalities, with reported significant changes in spherical equivalent (SE), (average 4.0 D reduction in SE), manifest astigmatic error and UCVA, with the most significant improvement in the first 6<sup>4</sup> and 9 months.<sup>5,6</sup>

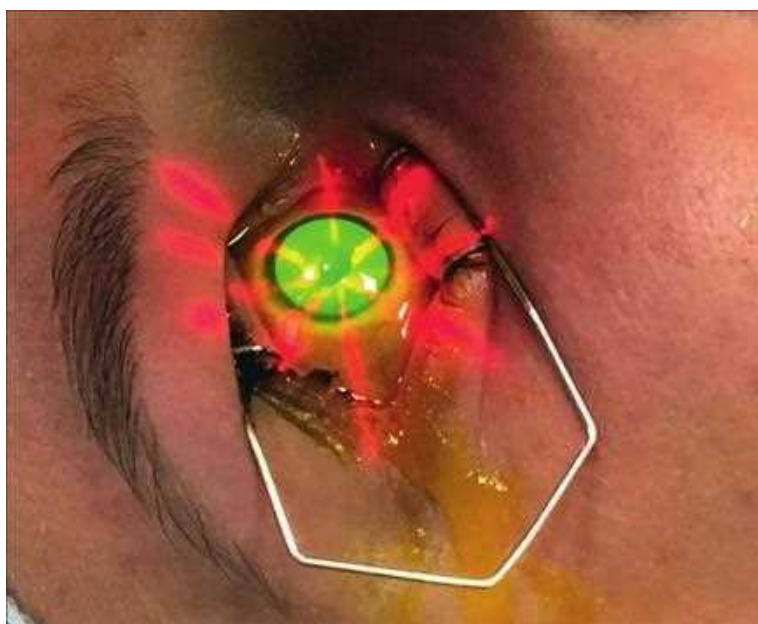
### Postoperative Complications

The overall reported adverse event rate after ICRS is 1.1% including infectious keratitis (0.2%), shallow placement (0.2%), loss of two lines of best spectacle-corrected visual acuity (BSCVA) (0.2%), and anterior chamber perforation during initial and exchange procedures (0.4%).<sup>35,36</sup> Reduced central corneal sensation can occur up to 6 months after surgery and can persist up to 12 months in 5.5% of cases. Some patients experience difficulty with night vision (4.4%), blurry vision (2.9%), diplopia (1.6%), or glare and halos (1.3%),<sup>35</sup> which accounts for an explantation rate of 8.7%, mostly due to glare, halos, and difficulty with night vision as well as dissatisfaction with refractive results. Late onset corneal haze is another potential complication (Fig. 3.9.2).

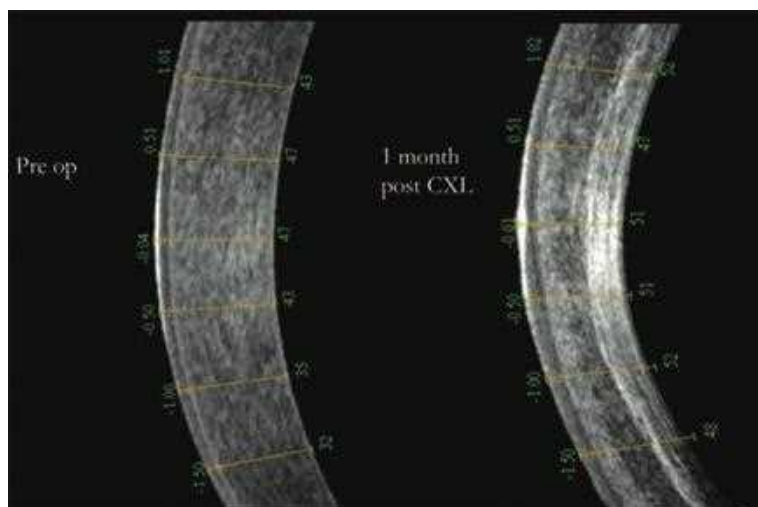
### SURGICAL PROCEDURE: CXL

The procedure for CXL involves three essential steps: epithelial removal (9 mm debridement), riboflavin saturation of the corneal stroma, and stromal irradiation with UV-A light (Fig. 3.9.3). These elements can be combined in varying intensities and times. For CXL, after complete UVA irradiation, a bandage soft contact lens is typically placed and left in place until complete epithelialization is achieved.





**Fig. 3.9.3 Corneal Cross-Linking Procedure.** After riboflavin saturation, the cornea is exposed to UV-A light. The red lines are guidance beams to ensure proper treatment centration.



**Fig. 3.9.4 Corneal Demarcation Line Following CXL With the Standard Protocol.** Note the prominent demarcation line at approximately 300  $\mu\text{m}$  depth.

The **standard protocol** delivers 3  $\text{mW}/\text{cm}^2$  of energy for 30 minutes for a total energy dose (fluence) of 5.4  $\text{J}/\text{cm}^2$ , resulting in up to 70% increase in cornea rigidity compared with controls using porcine and human cadaver eyes.<sup>8,37</sup> **Accelerated protocols**, still with a total dose of 5.4  $\text{J}/\text{cm}^2$ , have been derived from the Bunson–Roscoe law of reciprocity of photochemistry, which states that the photochemical effect of ultraviolet light is proportional to the total amount of energy delivered and should be equivalent for equivalent total doses regardless of the relative irradiation time and intensity for each protocol.<sup>38</sup> These accelerated protocols have been evaluated with mixed results.

The demarcation line, evident after cross-linking with the standard protocol (Fig. 3.9.4) and typically approximately 300  $\mu\text{m}$  deep, is thought to represent the depth of cross-linking treatment and thereby serves as a surrogate of biomechanical impact.<sup>39–44</sup> In accelerated protocols and iontophoresis CXL, the demarcation line is less dense, less uniform, and demonstrably present in fewer cases.<sup>40,45,46</sup> Recently a modified accelerated protocol of 9  $\text{mW}/\text{cm}^2$  for 14 minutes has been proposed by Kymionis and colleagues with no difference in the demarcation line compared with standard CXL protocol.<sup>44</sup>

**Transepithelial (epi on) CXL** has also been reported, but while corneal confocal microscopy alterations are similar in the subbasal nerve plexus and anterior stromal keratocytes between standard and accelerated (30  $\text{mW}/\text{cm}^2$  for 3 minutes) protocols, no changes are seen after transepithelial approaches.<sup>47</sup> Effective riboflavin concentration seems to be

achieved only when corneal epithelium is removed.<sup>48</sup> To date, long-term clinical results of transepithelial CXL have failed to find equivalency with the standard protocol.

## CXL CLINICAL OUTCOMES

Results from the first US-based prospective clinical trial for cross-linking demonstrated improvement in visual acuity and reduction in Kmax in patients with ectatic disease either LASIK induced or from keratoconus, with greater flattening in keratoconus compared with post-LASIK ectasia patients.<sup>49</sup> These changes continued over time, resulting in progressive improvement of uncorrected and corrected distance visual acuities and reduction in higher order aberrations up to 4 years postprocedure, which do not necessarily correlate with the topographical changes observed.<sup>50</sup> Failure to halt progression has been seen in approximately 2%–4% of eyes treated, with up to 2% of eyes losing lines of Snellen visual acuity.<sup>51</sup> These failures were initially associated with older age (beyond 35 years old), thinner corneas (<400  $\mu\text{m}$ ), preoperative CDVA better than 20/25, and Kmax >58.00 D. These risk factors were not confirmed in prospective trials.

## Postoperative Complications

UV light can have deleterious effects *within* the corneal stroma. Standard epi-off riboflavin/UVA treatments trigger a temporary UVA dose-dependent keratocyte apoptosis response approximately at 300  $\mu\text{m}$  deep that typically resolves with nerve regeneration and stromal keratocyte repopulation 4–6 weeks after the procedure. Endothelial damage is possible, but avoidable by maintaining a safe stromal thickness of 400  $\mu\text{m}$  during treatment. Monitoring corneal thickness throughout the procedure with use of iso-osmolar riboflavin solution to minimize stromal thinning along with use of hypo-osmolar riboflavin solutions to temporarily thicken the cornea all reduce the risk of endothelial cell damage in patients with thinner corneas.

The corneal wound-healing process after epithelial removal increases the risk of delayed re-epithelialization, sterile and infectious stromal infiltrates, corneal haze, and scarring. Matrix metalloproteinases (MMPs)-mediated activation of keratolysis, caused by nonsteroidal anti-inflammatory drugs (NSAIDs), also can induce corneal melting. For this reason the use of NSAIDs in the early postprocedure period after CXL is controversial. The disruption of corneal epithelium also increases the risk of infectious keratitis. CXL may lead to the reactivation of herpes simplex keratitis. Sterile stromal infiltrates rarely occur; these usually are asymptomatic and not visually significant. Persistent stromal haze correlated with advanced keratoconus (steeper keratometric values and/or thinner corneas) and older age (beyond 35 years old) at the time of treatment can become visually significant and affect final outcomes after CXL.

## COMBINING ICRS WITH CXL

Due to potential optical changes in the corneal stroma after CXL that could interfere with laser tracking, inserting the ICRS *before* CXL when using the femtosecond laser appears optimal. Refractive outcomes appear better when ICRS are implanted before cross-linking, possibly due to reduced mechanical effect from ICRS after CXL, but some concerns remain about the impact of CXL on the PMMA material of the ICRS.

Timing of treatment is undetermined, with some advocating for waiting 3–6 months between treatments, while others advocate for implantation of ICRS with intrastromal injection of riboflavin through the ring channels, followed immediately by CXL treatment.<sup>52</sup> Comparative studies are warranted to determine whether simultaneous treatments are superior to sequential treatments.

## CONCLUSIONS

Epithelium-off CXL using the standard protocol has been proven to effectively flatten the steepest regions of the cornea in patients with progressive ectatic disease, halting the progression of disease, reducing the need for corneal transplantation, and improving visual acuity and quality of life. ICRS also play a role in management of ectatic corneal disease, with surgical techniques advancements resulting from the advent of the femtosecond laser. The preservation of the prolate cornea and the reversibility of the procedure are major advantages of ICRS implants, and their mechanical effect can have a symbiotic effect with CXL.



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# Surgical Correction of Presbyopia

Veronica Vargas Fragoso, Jorge L. Alió

3.10

**Definition:** Presbyopia is an age-related condition that enables the patient to perform near visual tasks due to the decay of accommodation.

Key Features

- Presbyopia starts affecting people around 40 years of age.
- Its surgical correction may be performed at the cornea, lens, or sclera.
- Corneal procedures like monovision have good visual outcomes, but some stereopsis may be lost.
- Multifocal intraocular lenses (IOLs) have a high rate of spectacle independence, but the appearance of glare and halos are an important drawback.
- Not all commercially available accommodative IOLs have proved to really restore accommodation.
- Surgical correction of presbyopia with the restoration of accommodation is still a challenge for all refractive surgeons.

INTRODUCTION

Presbyopia is an age-related condition characterized by the loss of accommodation, enabling the patient not to perform near visual tasks, decreasing the quality of life.<sup>1</sup>

Its correction remains a challenge for the refractive surgeons; although many procedures to restore near vision are available, not all of them really restore accommodation (with the exception of some accommodative IOLs).

Accommodation is the change of power of the crystalline lens that allows us to change the point of focus from far to near.

During accommodation, there is a contraction of the ciliary muscle, which releases the zonular tension, allowing the anterior and posterior surfaces of the lens to increase in curvature, increasing the optical power of the lens (Helmholtz theory).

This is accompanied by the accommodative triad: accommodation, convergence, and miosis,<sup>2</sup> and there is also an increase in negative aberration of the eye.

Most of the presbyopia treatments induce pseudo-accommodation, which improves near vision through multifocality or increasing the depth of field, not by a change of the optical power of the eye sustained by the active action of the ciliary body.<sup>2</sup>

Presbyopia can be corrected at the cornea, lens, or sclera or treated with topical medication; all therapeutic options come with pros and cons.

In this chapter, we will discuss all of the current treatment options for presbyopia correction.

PRESBYOPIA CORRECTION AT THE CORNEAL LEVEL

Correction at the cornea can be achieved by monovision, presby-LASIK, and corneal inlays.

Monovision

Correction with monovision was first described in 1958 by Westsmith with contact lenses wearers.<sup>3,4</sup>

It can be achieved through contact lenses, LASIK, or pseudo-phakia.

In monovision, an intended anisometropia is induced in order to provide near and distance vision. Usually, the nondominant eye is corrected for near vision and the dominant eye for far vision. This is because

TABLE 3.10.1 Advantages and Disadvantages of LASIK Monovision

Advantages	Disadvantages
Good far and near outcomes	Reduction of stereopsis
Reversible	Slight reduction in contrast sensitivity
Easy to perform surgically	Not all patients are good candidates
	Asthenopia

monovision depends on interocular blur suppression, and an assumption exists that it is easier to suppress blur in the nondominant eye.<sup>4,5</sup> However, pseudo-phakic crossed monovision (nondominant eye is corrected for far and the dominant eye for near vision) has had similar outcomes to conventional monovision.<sup>3,4</sup>

There is a correlation between the degree of anisometropia and the improvement of near and intermediate distance acuity; the greater the anisometropia, the better the near visual outcome.<sup>6</sup> At the same time, the greater the anisometropia, the greater the loss of stereopsis.<sup>6,7</sup> Also, an increased time for neuroadaptation is required,<sup>7</sup> and a major risk for monofixation syndrome (loss of foveal fusion which manifests as a facultative absolute scotoma in the fovea of the nonfixating eye) exists.<sup>8</sup> Thus, the anisometropia should not be more than 1.5 diopters (D) because it has been reported for good spectacle independence in patients with mini-monovision, in which the target for the nondominant eye is -1.00 to -1.25 D and that for the dominant eye is plano.<sup>9</sup> In this way, stereopsis is maintained.

Patient selection is important as in every other surgical procedure, and monovision is generally contraindicated for the following patients: airplane pilots,<sup>3,10</sup> truck or taxi drivers,<sup>6,10</sup> and patients with strong ocular dominance,<sup>3,11,12</sup> strabismus,<sup>3,12</sup> or exophoria of more than 10.0 Δ.<sup>3,4,6,10</sup>

Good near and distance outcomes have been reported for LASIK monovision. Spectacles for night driving were used in only 16.2% of patients, and there was a slight decrease in contrast sensitivity and stereopsis<sup>13</sup> (Table 3.10.1).

Pseudo-phakic monovision has a success rate of approximately 80%,<sup>12,14</sup> and the advantage over multifocal IOLs is the lower cost.<sup>14</sup> Although the rate of spectacle independence is higher with multifocal IOLs, they induce more dysphotopsia.<sup>15a</sup>

Monovision is one of the most popular presbyopia treatments among refractive surgeons; it also offers the possibility of reversal in case of patient dissatisfaction. LASIK monovision is ideal for presbyopic patients over 40 years of age, and in pseudo-phakic monovision for patients with cataract in whom a multifocal or accommodative IOL is contraindicated.

Presby-LASIK

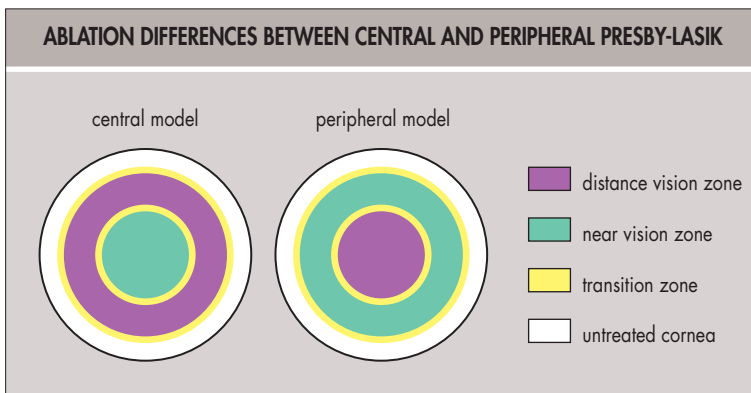
Presby-LASIK is a surgical technique that employs the principles of LASIK to create a multifocal corneal surface.

There are three main types of multifocal corneal excimer laser profiles: (1) multifocal transition profile (no longer in use because it induced significant levels of vertical coma), (2) central presby-LASIK, and (3) peripheral presby-LASIK (Fig. 3.10.1). The principles of each algorithm are based on the dioptric power of refractive error and presbyopia correction calculation, corneal asphericity quotient (Q-value), and changes in higher-order spherical aberrations or optical and transition zone manipulation.

Central Presby-LASIK

This technique was first described by Ruiz in 1996.<sup>15b</sup> It creates a hyper-positive area for the near vision at the center, and the periphery is left for far vision.





**Fig. 3.10.1 Ablation Differences Between Central and Peripheral Presby-LASIK.** In the peripheral model, the center of the cornea is modified for distance vision; in the central model, the center of the cornea is modified for near vision.

It is pupil dependent, and an advantage is that it can be performed at the center of the cornea in myopic and hyperopic profiles as well as in emmetropes with minimal corneal excision. Adequate centration is crucial for having a controllable result.

Its main limitation is the lack of adequate alignment among the line of sight, the central pupil, and the corneal vertex, which leads to the induction of coma aberrations.

These are the platforms available for central presby-LASIK:

- **AMO VISX** hyperopia-presbyopia multifocal approach steepens the central zone to improve near vision and the peripheral zone for distance vision. It is for hyperopic patients with astigmatism up to +4.00 D and -2.00 D.
- **SUPRACOR** (Technolas Perfect Vision GmbH, Munich, Germany) is an aberration-optimized presbyopic algorithm. The SUPRACOR creates a hyperpositive area in the central 3.0 mm zone, and the treatment targets 0.50 D of myopia in both eyes.<sup>16</sup> It treats hyperopic presbyopia and minimizes the aberrations normally induced during treatment.
- **PresbyMAX** (SCHWIND eye-tech-solutions GmbH, Kleinostheim, Germany, Dr Jorge Alió's trademark) is based on the creation of a biaspheric multifocal corneal surface with a central hyperpositive area to achieve +0.75 to +2.50 D of near vision correction, surrounded by an area in which the ablation is calculated to correct the distance refractive error.<sup>17,18</sup> It can be performed in hyperopes and myopes.
- In **peripheral presby-LASIK**, the center of the cornea is left for distance and the periphery is ablated in a way that a negative peripheral asphericity is created to increase the depth of field.

However, when positive spherical aberration is present, if the pupil becomes miotic, the refraction of the eye experiences a shift toward positive spherical values.

One of its disadvantages is that when it is used in association with myopic correction, it is necessary to remove a significant amount of corneal tissue. This is why it is mainly done in hyperopes. It also requires an efficient excimer laser beam profile that can compensate for the loss of energy that happens while the peripheral cornea is ablated. This is one of the main difficulties in targeting specifically high negative asphericity values with this technique. A relatively flatter central cornea and more highly curved corneal midperiphery were described by Avalos (PARM technique), and a proprietary peripheral presby-LASIK algorithm was described and patented by Tamayo.

## Laser Blended Vision

This technique combines a low degree of asphericity and micromonovision in the near eye to achieve good near and distance vision.<sup>19</sup> A sphericity between -0.58 and -0.70 is created to increase the depth of field.

Reinstein et al.<sup>19</sup> reported good visual outcomes with this technique, achieving binocular visual acuity of 20/20 at distance and J3 at near in 99% of patients. These hybrid techniques combine the best features of the multifocal cornea and monovision, achieving good visual outcomes.

The rates of spectacle independence with central presby-LASIK vary from 72%<sup>20</sup> to 93%.<sup>16</sup> A loss of corrected distance visual acuity (CDVA) of at least one line has been reported with central<sup>16,21-25</sup> and peripheral<sup>26-28</sup> presby-LASIK.

The main disadvantage of presby-LASIK is the lack of long-term results (beyond 3-year outcomes), and having a multifocal cornea can be a limitation for further multifocal IOL implantation.

## Intracorneal Inlays

### Historical Background

In 1964 Barraquer developed keratophakia, a lamellar refractive procedure in which an alloplastic lenticule is placed at the interface of the free corneal cap and the stromal bed.<sup>29a</sup> The difficulty of the surgical procedure and the unpredictability of the refractive results meant that few surgeons adopted keratophakia.<sup>29b</sup>

Early corneal implants were made of polymethylmethacrylate or polysulfone, and although they corrected the refractive error, they produced corneal necrosis and implant extrusion.<sup>30</sup> Nowadays, the material used in corneal inlays allow sufficient nutrient flow; a very important feature because interruption of the nutrient flow can cause loss of transparency, corneal thinning, epithelial and stromal decompensation, and melting.<sup>31</sup> The permeability of the hydrogel material used in the inlays is similar to that of the corneal stroma, allowing to some extent the exchange of nutrients<sup>32,33</sup> such as glucose and oxygen.

Corneal inlays have several advantages: There is no need to remove corneal tissue, the surgical technique is relatively easy and minimally invasive, and the inlays are all removable.<sup>9,34,35</sup>

There are three types of corneal inlays<sup>9,34</sup>:

- **Corneal reshaping inlays**  
They enhance near and intermediate vision through a multifocal effect. There's a reshape of the anterior curvature of the cornea (hyperprolate region of increased power).<sup>34,35</sup>
- **Refractive inlays**  
An alteration of the refractive index occurs with a bifocal optic.<sup>34</sup>
- **Small aperture inlays**  
There is an improvement of depth of focus.<sup>34</sup>

The inlays are implanted in the nondominant eye within a corneal pocket made by a femtosecond laser or under a stromal flap (the pocket is preferred because it might decrease the incidence of dry eye).<sup>31</sup> The depth depends on the inlay.<sup>35</sup> Inlays that alter the curvature of the cornea are implanted more superficially; inlays with small aperture or those that have a different index of refraction are implanted deeper to avoid changes in the cornea curvature and to allow a proper diffusion of nutrients in the corneal stroma.<sup>31</sup> The inlays must be centered on the first Purkinje reflex.

There are currently four corneal inlays available on the market:

- **KAMRA Vision** (AcuFocus Inc., Irvine, CA, USA). Small aperture inlay.
- **Raindrop** (ReVision Optics Inc., Lake Forest, CA, USA). Corneal reshaping inlay.
- **Flexivue Microlens** (Presbia Cooperatief U.A., Amsterdam, the Netherlands). Refractive inlay.
- **Icolens** (Neoptics AG, Hünenberg, Switzerland). Refractive inlay.

## Corneal Reshaping Inlay

### Raindrop

Formerly known as the PresbyLens or Vue + lens (ReVision Optics, Lake Forest, CA, USA), it's made of biocompatible hydrogel material and 80% water. It has a thickness of 10  $\mu$ m at the periphery and 32  $\mu$ m at the center; the diameter is 2 mm (Fig. 3.10.2).<sup>30</sup> The inlay is permeable, allowing the passage of nutrients and oxygen.<sup>9,34-36</sup> It reshapes the anterior central corneal surface, creating a hyperprolate region, resulting in a multifocal cornea.<sup>36</sup> It has no refractive power.<sup>34,35</sup>

It should be placed in the nondominant eye at a minimum depth of 150  $\mu$ m with a residual stromal bed thickness of 300  $\mu$ m and has to be aligned over the center of the light-constricted pupil.<sup>35-37</sup> The central corneal thickness of the eye should be 500  $\mu$ m or thicker. After the inlay is positioned over the center of the pupil, it has to dry for 30 seconds before the flap is repositioned.<sup>37</sup>

Barragan et al.<sup>30</sup> reported the results of a 1-year follow up using the Raindrop inlay in emmetropic presbyopes. In their study, 100% of eyes achieved an uncorrected near visual acuity (UNVA) of 0.2 logMAR or better in the operative eye, and binocularly, 100% of patients achieved an UNVA of 0.18 logMAR or better. No eye lost two or more lines of corrected distance visual acuity (CDVA) or corrected near visual acuity (CNVA).

Yoo et al.<sup>38</sup> measured the corneal and optical aberrations in 22 emmetropic presbyopes with a mean addition power of  $+1.97 \pm 0.30$  D. All



**Fig. 3.10.2** Raindrop corneal inlay.

patients gained monocular and binocular UNVA. For a 4-mm pupil size, significant increases occurred in total root mean square (RMS), coma-like RMS, and spherical-like RMS. Overall, 82% of the patients were satisfied or very satisfied with their near vision, and 13.6% reported that they needed glasses for near vision more often after surgery than before surgery. Moreover, 37% of patients reported glare. They concluded that the procedure can induce higher-order aberrations (HOA) but had moderate effects on the entire optical system.

In a study by Alió et al.,<sup>33</sup> increases in spherical aberrations, coma, and total HOA were reported with the implantation of hydrogel inlays.

Whitman et al.<sup>39</sup> reported the clinical outcomes with the Raindrop inlay in patients with emmetropic presbyopia. In total, 340 patients completed a 1-year follow-up, and on average, they had an improvement in UNVA of five lines and in uncorrected intermediate visual acuity (UIVA) of 2.5 lines. However, the uncorrected distance visual acuity (UDVA) decreased by 1.2 lines. Contrast sensitivity loss occurred at the highest spatial frequencies with no loss of binocularly. Eighteen inlays were replaced because of decentration, and 11 were explanted (five patients were dissatisfied with their vision, two had inlay misalignment, two had epithelial ingrowth, one had visual symptoms associated with decreased visual acuity, and 1 had recurrent central corneal haze that failed to respond to topical treatment).

### Refractive Inlays

#### Presbia Flexivue Microlens

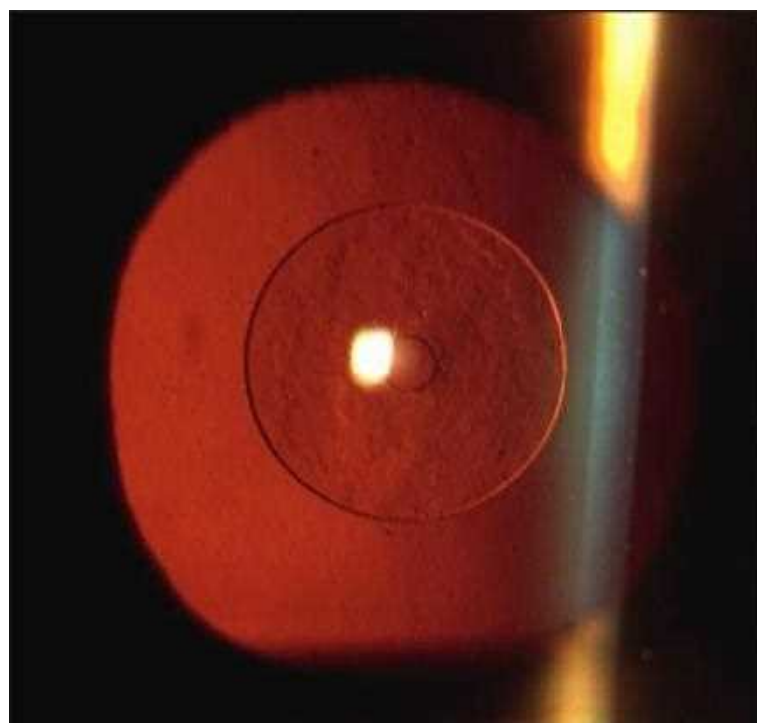
The Presbia Flexivue Microlens, a transparent hydrophilic concave-convex disc made of a clear copolymer of hydroxyethylmethacrylate and methylmethacrylate with an ultraviolet blocker.<sup>31,36,40</sup> It has a diameter of 3.2 mm and a thickness of 15–20  $\mu\text{m}$ , depending on the additional power. The central 1.8 mm diameter of the disc is plano in power, and the peripheral zone has an add power, ranging from +1.25 D–3.00 D in 0.25-D increments. At the center, there is an opening of 0.15 mm that facilitates the transfer of nutrients and oxygen through the cornea (Fig. 3.10.3).<sup>31,34–36,40</sup> It has a refractive power of 1.4583 and a light transmission of 95% at a wavelength above 410 nm.<sup>36,40</sup>

During distance vision, light rays pass through the central zone of the inlay that does not have refractive power (plano), so they will be sharply focused on the retina. Light rays that pass through the refractive peripheral zone will focus in front of the retina.

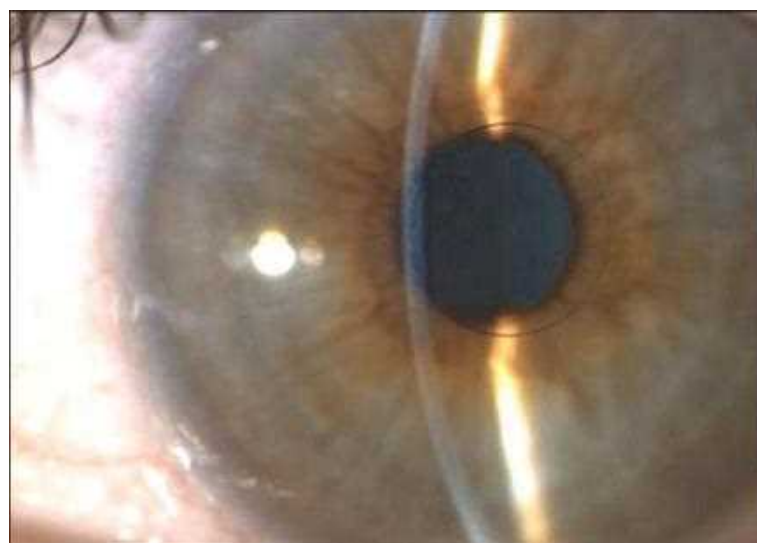
During near vision, rays passing through the central zone of the inlay will focus behind the retina, and those passing through the peripheral refractive zone of the inlay will be focused on the retina.<sup>31,40</sup> The rays passing through the peripheral clear cornea will be blocked by the pupil.<sup>40</sup>

It is implanted in the nondominant eye. The corneal pocket is within a depth of 280–300  $\mu\text{m}$ <sup>34,36,40</sup> and is centered over the patient's visual axis based on the first Purkinje reflex. The corneal inlay power is calculated by decreasing the preoperative CNVA manifest refraction SE by 0.25 D.<sup>31</sup>

Limnopoulou et al.<sup>40</sup> reported in their 1-year follow-up study a UNVA of 20/32 or better in 75% of operated eyes; the UDVA decreased significantly in the operated eye from 20/20 to 20/50, but binocular UDVA was not significantly altered. HOA increased and contrast sensitivity decreased in the operated eye. They included 47 emmetropic presbyopes between 45 and 60 years old. No removals of the inlay and no intra- or postoperative complications occurred.



**Fig. 3.10.3 Flexivue Inlay.** (Image from Malandrini A, Martone G, Menabuoni L. Bifocal refractive corneal inlay implantation to improve near vision in emmetropic presbyopic patients. *J Cataract Refract Surg* 2015;41:1962–72.)



**Fig. 3.10.4 Icolens Inlay.** (Image taken from Bailly C, Kohnen T, O'Keefe M. Preloaded refractive-addition corneal inlay to compensate for presbyopia implanted using a femtosecond laser: one-year visual outcomes and safety. *J Cataract Refract Surg* 2014;40:1341–8.)

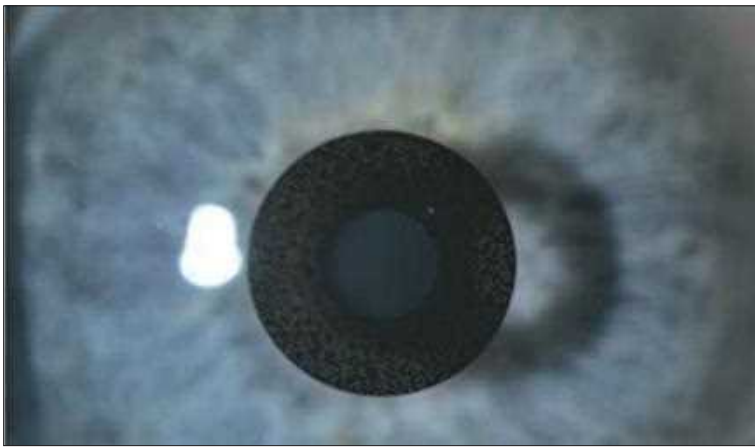
Malandrini et al.<sup>31</sup> performed a 36-month follow-up study in 26 eyes, and the mean preoperative UNVA and UDVA were 0.76 logMAR and 0.00 logMAR, respectively, compared with 0.10 logMAR and 0.15 logMAR, postoperatively. Overall, 62% of the eyes lost more than 1 line of UDVA, and 19% lost more than two lines of UDVA. Also, 8% of the eyes lost more than 1 line of CDVA at 36 months. The mean spherical aberration increased after surgery. Explantation was performed in six eyes because of reduced UDVA, halos, and glare; 6 months after explantation, the CDVA in all cases had returned to preoperative levels.

#### Icolens (Neoptics AG)

This corneal inlay is made of a copolymer of hydroxyethyl methacrylate and methyl methacrylate. It has a bifocal design with a peripheral positive refractive zone for near vision and a central zone for distance vision.<sup>41</sup> It has a diameter of 3 mm, a peripheral thickness of 15  $\mu\text{m}$ , and a central 0.15 mm hole for nutrient flow (Fig. 3.10.4).<sup>35,41</sup>

Bailly et al.<sup>41</sup> reported the results of the Icolens 12 months after implantation. The inlay was implanted in the nondominant eye of emmetropic





**Fig. 3.10.5 KAMRA Inlay in a Light-Colored Eye.** (Image taken from Abbouda A, Javaloy J, Alió JL. Confocal microscopy evaluation of the corneal response following AcuFocus KAMRA inlay implantation. *J Refract Surg* 2014;30:172–8.)

**TABLE 3.10.2 Inlay Characteristics**

Characteristic	ACI7000 (First One)	ACI7000T	ACI7000PDT (Latest)
Thickness	10 $\mu\text{m}$	5 $\mu\text{m}$	5 $\mu\text{m}$
Holes	1600	1600	8400
Diameter	25 $\mu\text{m}$	25 $\mu\text{m}$	5–11 $\mu\text{m}$

patients through a corneal pocket created by femtosecond laser at a depth of 290  $\mu\text{m}$ ; 52 patients were included. The UNVA improved from N18/N24 preoperatively to N8 postoperatively, with 100% of patients having N16 or better, and nine patients having N5 or better. The mean UDVA in the surgical eye worsened significantly from 0.05 $\pm$ 0.12 logMAR preoperatively to 0.22 $\pm$ 0.15 logMAR postoperatively. There was a loss of CDVA, with 77% of the patients losing more than one line (they believe this was secondary to a neuro-optical phenomenon related to the implant). Seven inlays were removed because of inadequate centration, three secondary to ambiguous ocular dominance, and one because the patient had unrealistic expectation, for a total of 11 inlays removed.

### Small Aperture Inlays KAMRA

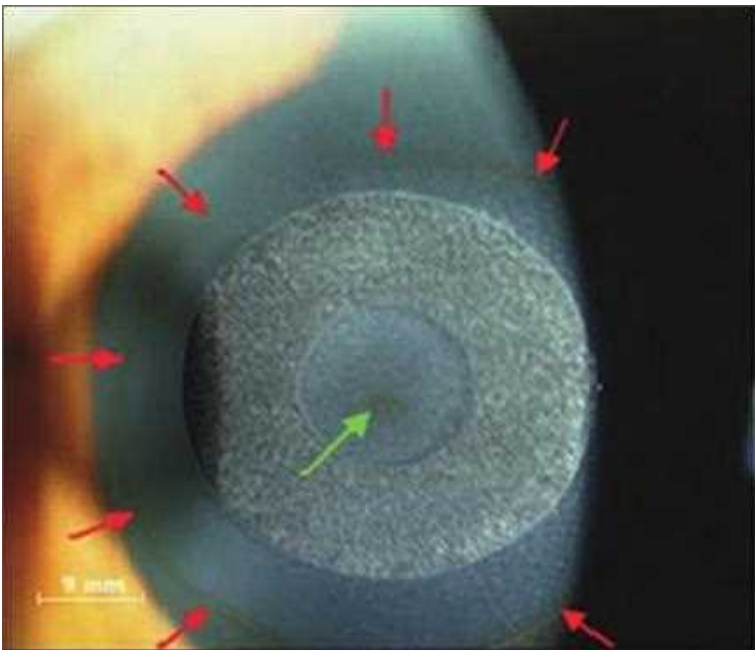
The KAMRA inlay (AcuFocus Inc., Irvine, CA, USA) is the most widely used corneal inlay,<sup>35</sup> with nearly 20,000 inlays implanted worldwide.<sup>9,36</sup> It is made of polyvinylidene fluoride. The latest design (ACI 7000PDT) has a 3.8-mm diameter with a central 1.6-mm aperture and a thickness of 5  $\mu\text{m}$ . It has 8400 microperforations ranging in diameter from 5 to 11  $\mu\text{m}$  to allow nutritional flow through the cornea.<sup>9,34–36,42</sup> It also has nanoparticles of carbon, which<sup>43,44</sup> has a light transmission of 5%.<sup>43</sup> Because it is an opaque inlay, it may be visible in light-colored eyes (Fig. 3.10.5).<sup>9</sup>

The KAMRA inlay improves near vision by increasing the depth of focus<sup>35,36</sup> through the principle of small aperture optics. It is implanted in the nondominant eye in a lamellar pocket that is 200–220  $\mu\text{m}$ . Its implantation does not cause scotomas in the visual field.<sup>34</sup> It allows a normal visualization of the central and peripheral fundus and a good quality of central and peripheral imaging and optical coherence tomography (OCT) scans.<sup>45</sup> However, annular shadows visible on the GDx VCC scans have been reported.<sup>46</sup>

The inlay has evolved over the years, with the same artificial aperture of 3.8-mm outer diameter and 1.6-mm inner diameter. Table 3.10.2 describes the inlay characteristics.

Tomita et al.<sup>43</sup> evaluated the outcomes of KAMRA inlay implantation and simultaneous LASIK in hyperopic, myopic, and emmetropic patients. With a 6-month follow-up, they concluded that the procedure was safe and improved distance and near visual acuity. However, postoperative symptoms like halos, glare, and night-vision disturbances were observed.

Igras et al.<sup>47</sup> reported a 1-year follow-up of combined LASIK and KAMRA inlay implantation. Of 132 patients evaluated, 85% were hypermetropic, 11% emmetropic, and 4% myopic. By 12 months, 97% of patients had J3 or better UNVA. Also, 6.3% of patients lost one line of CDVA in the implanted eye, and none lost two or more lines compared with their preoperative VA. Two inlays were explanted, one due to poor night vision and one secondary to persistent hyperopic shift and corneal haze. They concluded that a significant improvement occurred in near visual acuity



**Fig. 3.10.6 Iron Deposits in the Periphery on the Inlay (Red Arrows) and in the Center of the Inlay (Green Arrow).** (Image taken from Dexl AK, Ruckhofer J, Riha W, et al. Central and peripheral corneal iron deposits after implantation of a small-aperture corneal inlay for correction of presbyopia. *J Refract Surg* 2011;27:876–80.)

with a slight compromise in uncorrected monocular distance visual acuity in the implanted eye without a binocular effect on the UDVA.

Seyeddain et al.<sup>46</sup> performed a 3-year follow-up with 32 emmetropic presbyopic patients and reported that although there were significant gains in UNVA and UIVA, 28.3% of patients lost one line of CDVA.

Dexl et al.<sup>48</sup> described iron corneal deposits after implantation of the AcuFocus corneal inlay (ACI 7000) in 18 eyes (56%), but these deposits did not have any influence on distance, near, uncorrected, or corrected visual acuity (Fig. 3.10.6).

Alió et al.<sup>42</sup> reported that after removal of the KAMRA inlay, the topography and aberrometry were not permanently affected, and more than 60% of the patients had a CNVA, CDVA, UNVA, and UDVA similar to their preoperative values. The study involved 10 eyes and had a follow-up of 6 months after the inlay removal. The reason for removal in eight eyes was subjective dissatisfaction with visual symptoms (glare, starburst, blurry vision, and halos). One case was related to an inadvertent thin flap, and the other was related to insufficient near vision.

Abbouda et al.<sup>49</sup> analyzed the corneal tissue appearance 6 months after KAMRA inlay implantation by confocal microscopy; the study included 12 eyes in which one of three models of the KAMRA inlay had been implanted. The epithelial layers appeared normal in all patients. A low grade of keratocyte activation was found in all patients. Few patients had an elevated number of activated keratocytes, and they had a reduction in UNVA (needed reading glasses), CNVA, and CDVA. The UDVA was not affected. Subbasal nerve plexus was detected in 10 patients, and the branch pattern was found in eight patients. Four patients had the inlay explanted, the main reason being subjective dissatisfaction with visual symptoms and poor vision. All of them had a donut appearance at the slit-lamp examination. None of the patients had refractive postoperative changes. They concluded that the corneal tolerance to the inlay is good and that it modifies the normal structure of the corneal layer without associated complications.

Keratocyte activation is an important variable for the refractive outcome after KAMRA inlay implantation; flap thickness depth, low laser energy cut, and topical corticosteroid treatment are helpful to avoid it.

Lin et al.<sup>50</sup> compared the contrast sensitivity before and after implantation of the KAMRA inlay in 507 patients. They reported that postoperatively contrast sensitivity was mildly reduced monocularly but not binocularly, and that it remained within the normative ranges.

This inlay can be implanted also in patients with previous cataract surgery who have a monofocal IOL, as reported by Huseynova et al.<sup>51</sup> They implanted the KAMRA inlay in 13 pseudo-phakic patients with a monofocal IOL. Four patients had LASIK at the time of the inlay implantation. There was no change in mean UDVA after the inlay implantation, and the mean UNVA improved by five lines. Three eyes lost two lines, and one eye lost one line of UDVA. Two eyes lost two lines, and one eye lost one line of CDVA (Table 3.10.3, Table 3.10.4, Fig. 3.10.7).



## Presbyopic IOLs

Correction of presbyopia with premium IOLs has been the best option, because they provide good distance and near visual outcomes and spectacle independence. However, perfection has not been achieved with these IOLs, which can be divided in two main groups, multifocal IOLs and accommodative IOLs.

### Multifocal IOLs

The perfect multifocal IOL must provide excellent near, intermediate, and distance visual acuity; should not produce photic phenomena; and should be pupil independent. The design has to be aspherical and able to be implanted through a small incision to allow the performance of micro incision cataract surgery (<2 mm). Sadly, there is no single multifocal IOL that can provide all these factors at the same time.

The aim of these IOLs is to provide patients with spectacle independence for both near and distance vision through the division of the incoming light into two or more foci<sup>52–55</sup> independently of capsular mechanics and ciliary body function.<sup>56</sup>

Multifocal IOLs can be divided based on their design as rotationally symmetrical IOLs (which can be further divided as: diffractive, refractive, or a combined design) and rotationally asymmetrical IOLs (also called varifocal IOLs).<sup>53–57</sup>

### Rotationally Symmetrical

**Diffractive IOLs.** These IOLs have in them surface rings that form a discontinued optical density, so when the light particles encounter these rings, it is directed toward two focal points (near and distance; light changes direction and slows down when encountering an edge of discontinuity [principle of diffraction])<sup>53,55,58</sup> or three foci (near, intermediate, and distance) in case of the trifocal IOLs.<sup>53</sup>

Diffractive IOLs can be categorized as apodized and nonapodized. The term *apodization* is derived from the Greek words for “cutting off the feet.”<sup>58</sup> The apodized IOLs have a gradual decrease in diffractive step heights from the center to the periphery<sup>55,58</sup> to create a smooth transition of light between the focal points. Under myopic conditions (when the pupil is on mydriasis), the light is more focused to the distant point.<sup>55</sup>

These are the most commonly implanted multifocal IOLs.<sup>59</sup>

The steps on the nonapodized IOLs have a uniform height from the center to the periphery, so the light is equally distributed in both focal points independently of the pupil size.<sup>55</sup>

The extended range of vision IOLs is also diffractive, and they provide near vision by the correction of achromatic and spherical aberrations.<sup>60</sup>

**Refractive IOLs.** These IOLs have concentric zones of different dioptric power to achieve multifocality. They are pupil dependent and may be affected by decentration.

TABLE 3.10.3 Advantages and Disadvantages of Corneal Inlays

Advantages	Disadvantages
Minimally invasive	Patient must tolerate monovision
Reversible	Decrease in distance visual acuity
No need to remove corneal tissue	Decrease in contrast sensitivity
No need for a cataract	Presence of halos
Quick recovery	Corneal topography changes in the long term
Doesn't affect visual field testing	Induction of higher-order aberrations
Can be combined with other refractive procedures	Corneal haze in long term
Normal visualization of central and peripheral fundus	Inlay centration is crucial
	Dry eye

### Rotationally Asymmetrical IOLs (Varifocal)

These are characterized by an inferior segmental near add.<sup>57</sup> The IOL has a larger section for distance vision and a smaller reading segment, with only one transition zone. The near add varies from +1.5 D to +3.00 D, depending on the patient's visual needs.<sup>61</sup>

### Patient Selection Criteria

Adequate patient selection is the most important part in implanting a multifocal IOL. We must know the patient's visual expectations and make sure that we can fulfill them by selection of the correct IOL, because depending on the IOL design, the patient can have better near or intermediate distance vision. Also, patients' expectations have to be realistic, and we have to inform them of the visual side effects that they may experience with the multifocal IOLs (glare, halos) and that a process of neuroadaptation exists that takes a couple of months.

The correct IOL power calculation is crucial, and emmetropia should be the target. It has been reported<sup>62</sup> that the cause of 20% of cases of multifocal IOL explantation is incorrect IOL power.

Astigmatism correction is mandatory for a good performance of the multifocal IOL. Patients with irregular astigmatism are not good candidates for a multifocal IOL<sup>63</sup> because its correction is not easy or predictable.

Patients with corneal abnormalities like central scars and Fuchs' dystrophy are not suitable candidates for multifocal IOL implantation.<sup>63</sup>

Because many of the multifocal IOLs are pupil dependent, an adequate function before and after surgery is needed. Therefore, if a patient has a very small pupil diameter that needs surgical manipulation, the surgeon should be very careful to not damage the iris sphincter. Patients with larger pupils may experience glare and halos after multifocal IOL implantation.<sup>63</sup> Identification of zonular weakness during surgery is very important, as decentration or tilt of the multifocal IOL can have a detrimental effect on the visual acuity. This can be prevented by the implantation of a capsular tension ring.<sup>63,64</sup>

Any macular alteration must be recognized before implantation of a multifocal IOL, especially if the patient has these predisposing factors:

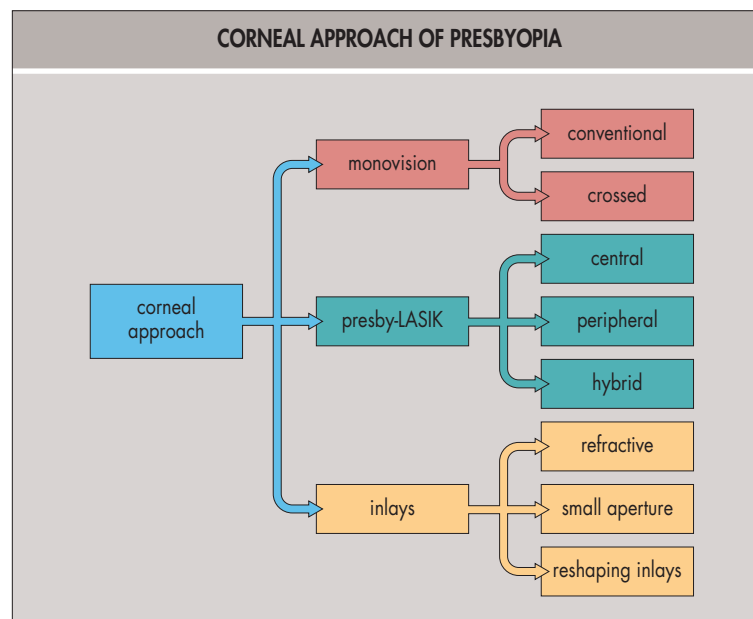


Fig. 3.10.7 Corneal Approach of Presbyopia.

TABLE 3.10.4 Corneal Inlays

Inlay	Material	Type of Inlay	Measurements	Mechanism of Action
Raindrop	Biocompatible hydrogel 80% water	Corneal reshaping inlay	Thickness of 10 $\mu$ m at the periphery and 32 $\mu$ m at the center Diameter: 2 mm	Reshapes the anterior corneal, creating a hyperprolate region $\rightarrow$ multifocal cornea
Flexivue	Clear copolymer of hydroxyethylmethacrylate and methylmethacrylate with an ultraviolet blocker	Refractive inlay	Thickness: 15–20 $\mu$ m Diameter: 3 mm	The central 1.8 mm diameter of the disc is plano in power (for distance vision), and the peripheral zone has an add power ranging from +1.25 D–3.0 D in 0.25 D increments (for near vision)
Icolens	Copolymer of hydroxyethyl methacrylate and methyl methacrylate	Refractive inlay	Thickness: 15 $\mu$ m Diameter: 3 mm	Bifocal design Central zone for distance and peripheral positive refractive zone for near
KAMRA	Polyvinylidene fluoride, nanoparticles of carbon	Small aperture inlay	Thickness: 5 $\mu$ m Diameter: 3.8 mm	Increases the depth of focus through the principle of small aperture optics



**Fig. 3.10.8 AcrySof Restor SN6AD3.** (Image from Alió J, Pikkel J. Multifocal intraocular lenses. The art and the practice. 1st ed. Editorial Springer; Switzerland 2014.)

male gender, former or current smoker, and history of heart disease.<sup>65</sup> A macular disease is a relative contraindication for the implantation of a multifocal IOL<sup>65</sup> because these patients have a reduced contrast sensibility that can be worsened by a multifocal IOL. Thus the macula should be evaluated with either a macular function test or OCT.

Retinal diseases like Stargardt and retinitis pigmentosa are absolute contraindications for multifocal IOL implantation. Other diseases like diabetic retinopathy, macular degeneration, and epiretinal membranes have a decreased contrast sensitivity that may be worsened by the multifocal IOL.<sup>63</sup> Glaucoma is a relative contraindication for the use of multifocal IOLs. If the patient has an early glaucoma or controlled ocular hypertension, a multifocal IOL can be implanted, but IOL implantation should be avoided in patients with progressive and advanced glaucoma.<sup>66</sup>

There are many multifocal IOLs available on the market; we will discuss the most popular ones.

**AcrySof Restor SN6AD3 (Alcon Laboratories, Inc.)**

Apodized diffractive and refractive technologies

Type: One-piece multifocal IOL

Material: hydrophobic acrylic

Filter: UV and blue light

Pupil dependent: No

Optic diameter: 6 mm

Overall diameter: 13 mm

Refractive index: 1.47

Power range: +6.00 to +34.00 D

Near addition at lens plane: +4.00 D

Incision size: >2.2 mm

The central 3.5 mm of the optic zone has 12 concentric steps of gradually decreasing (1.3–1.2) step heights. Surrounding this apodized region is the refractive area that directs light to a distance focal point for large pupil diameters.<sup>67</sup>

In bright light with constricted pupils, the lens sends light energy to near and distant focal points; in low light with dilated pupils, the apodized diffractive lens sends a greater amount of energy to distance vision to minimize visual disturbances (Fig. 3.10.8).<sup>68</sup>

**Lentis Mplus LS-313 (Oculentis GmbH)**

Type: one piece, refractive rotationally asymmetrical multifocal IOL (varifocal)

Material: HydroSmart acrylate copolymer with hydrophobic surface

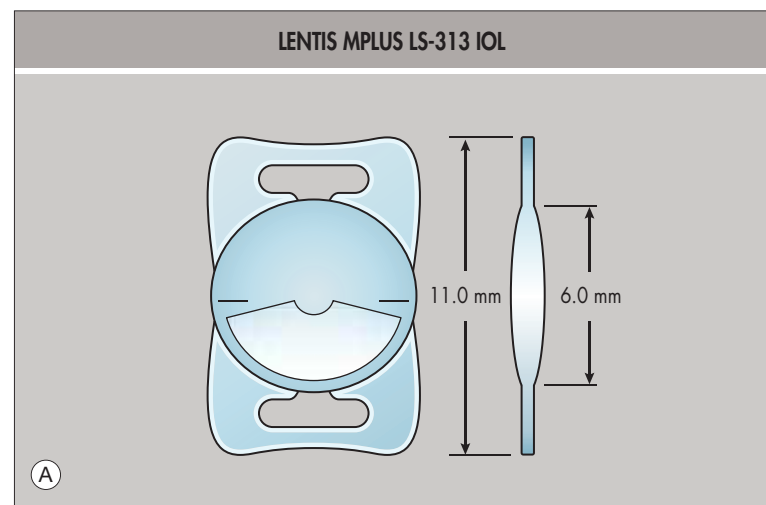
Optic diameter: 6.0 mm

Overall diameter: 11.0 mm

Refractive index: 1.46

Addition at IOL plane: +3.00 D

Addition at spectacle plane: +2.5 D



**Fig. 3.10.9 Lentis Mplus LS-313 IOL.** (Image on the left from Alió J, Pikkel J. Multifocal intraocular lenses. The art and the practice. 1st ed. Editorial Springer; Switzerland 2014. Image on the right from <http://www.device.com.au/shop/oculentis/>.)

Diopter range: Mplus: +15.00 D to +25.00 D in 0.5 D steps, Mplus X: –10.00 D to +1.00 D in 1.0 D steps, and from +0.00 D to +36.00 D in 0.5 D steps

Incision size: 2.6 mm

360° continuous square optic and haptic edge (Fig. 3.10.9)

Pupil-independent IOL

The design has an inferior surface-embedded segment with the optical power required for near vision and seamless transitions between the near and far zones.

Light in the near vision zone is refracted to the near focus, and the rest is refracted to the far focus.<sup>59</sup>

Light hitting the transition area of the embedded sector is reflected away from the optical axis to prevent superposition of interference or diffraction.<sup>57,59</sup>

The position of the near segment does not have a detrimental effect on the visual performance,<sup>69</sup> although the manufacturer recommends an inferior placement.

**Symfony (Abbott Medical Optics, Inc.)**

Type: diffractive nonapodized achromatic

Material: UV-blocking hydrophobic acrylic

Optic diameter: 6 mm

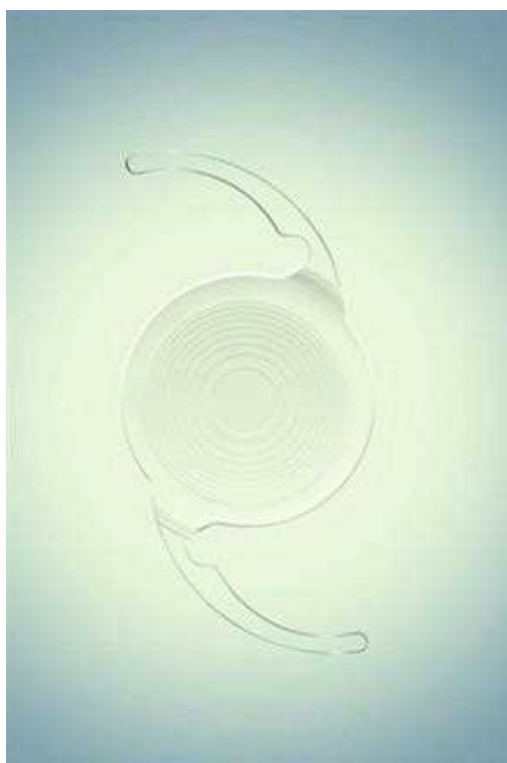
Overall diameter: 13 mm

Power range: +5.00 D to +34.00 D in 0.50 D increments

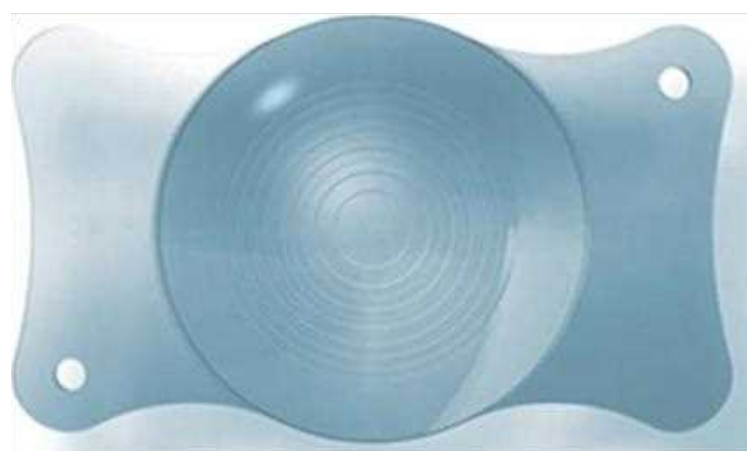
Refractive index: 1.47

It has a biconvex wavefront-designed anterior aspherical surface and a posterior achromatic diffractive surface (Fig. 3.10.10).

This IOL elongates the focus and corrects the corneal chromatic and spherical aberration using an achromatic technology also known as “extended range of vision.”<sup>60,70</sup>



**Fig. 3.10.10 TECNIS Symphony IOL.** (Image from <http://eyewiretoday.com/news.asp?t=474>.)



**Fig. 3.10.11 AT LISA Tri 839 mp IOL.** (Image from Alió J, Pikkell J. Multifocal intraocular lenses. The art and the practice. 1st ed. Editorial Springer; Switzerland 2014.)



**Fig. 3.10.12 FineVision Micro F IOL.** (Image from Alió J, Pikkell J. Multifocal intraocular lenses. The art and the practice. 1st ed. Editorial Springer; Switzerland 2014.)

The chromatic aberrations have a detrimental effect on vision because they reduce contrast vision and induce blur.<sup>71</sup>

The improvement of both aberrations increases the retinal image quality with a better tolerance of decentration and without sacrificing the depth of field.<sup>72</sup>

It provides better near, intermediate, and distance vision than aspherical monofocal IOLs, and in contrast to multifocal IOLs, it does not induce aberrations to extend the depth of focus.<sup>60</sup>

Because it provides an elongated focal area rather than various focal points, halos are not as common as with the multifocal IOLs. In fact, one study<sup>70</sup> reported that 90% of patients in whom a Symphony IOL was implanted reported no or mild halos or photic phenomena, and the visual results were better than those obtained with a rotationally asymmetrical multifocal IOL or an apodized diffractive IOL.

#### **AT LISA tri 839 MP (Carl Zeiss Meditec AG)**

Type: one-piece trifocal diffractive aspherical IOL

Material: hydrophilic acrylic 25% with hydrophobic surface

Optic diameter: 6 mm

Overall diameter: 11 mm

Power range: from plano to +32.00 D in 0.5 D increments

Near addition at the IOL plane: +3.33 D for near vision, +1.66 D for intermediate vision

Incision size: 1.8 mm.

Asphericity:  $-0.18 \mu\text{m}$ .

The central 4.34 mm of the IOL optic is the trifocal zone, and the peripheral bifocal zone is from 4.34 to 6 mm with diffractive rings covering the entire optic diameter (Fig. 3.10.11).<sup>73</sup>

#### **Fine Vision Micro F (Physiol)**

Type: one-piece trifocal

Optic: diffractive anterior surface, aspherical posterior surface

Material: 25% hydrophilic acrylic

Optic diameter: 6.15 mm

Overall diameter: 10.75 mm

Power range: +10.00 D to +35.00 D in 0.5 D increments

Near addition at spectacle plane: +1.75 D intermediate vision, +3.5 D near vision

Incision size:  $>1.8 \text{ mm}$

Asphericity:  $-0.11 \mu\text{m}$

Pupil-dependent IOL

The anterior surface of the IOL is convoluted. By the varying of the height of the diffractive step, the amounts of light distributed to the near,

intermediate, and distant foci are adjusted according to the pupil aperture. The IOL distributes 43% of light energy to far vision, 28% to near vision, and 15% to intermediate vision for a 3-mm pupil, and the remaining light energy is lost (Fig. 3.10.12).<sup>74</sup>

#### **Panoptix (Alcon)**

Type: one piece, aspherical

Material: hydrophobic, ultraviolet- and blue light-filtering acrylate/methacrylate copolymer

Optic diameter: 6.0 mm

Overall diameter: 13.0 mm

It has a 4.5-mm diffractive area in the center with 15 diffractive zones and an outer refractive rim (Fig. 3.10.13).

Light distribution is 25% to near (40 cm), 25% to intermediate (60 cm), and 50% to distance vision.

There is a more physiological transition from different distances because of an advanced optical technology, so the light from the first focal point is diffracted to the distance focus. This helps to create a fourth focal point at 1.20 m, making this IOL a quadra-focal IOL, although it acts as a trifocal IOL.<sup>75</sup>

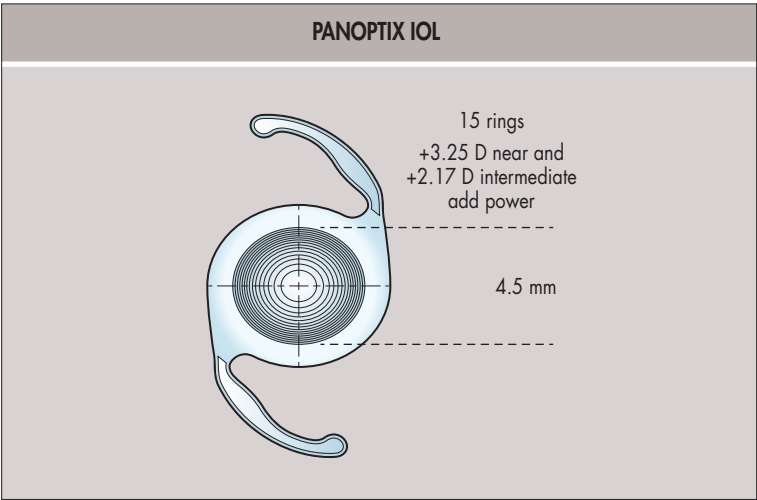
Based on laboratory simulations, the performances in image quality, photic phenomena, and resolution are equivalent between the Panoptix IOL and the AT LISA tri 839MP and FineVision Micro F trifocal IOL.<sup>76</sup>

#### **Clinical Outcomes and Quality of Life**

Carballo-Alvarez et al.<sup>74</sup> evaluated visual outcomes 3 months after bilateral implantation of the FineVision trifocal IOL. They reported adequate near, intermediate, and far vision, with satisfactory contrast sensitivity and no significant photic phenomena.

A comparison between the FineVision trifocal and the Restor IOL reported similar refractive outcomes, reading speeds, and patient





**Fig. 3.10.13 Panoptix IOL.** (Image from Kohnen T. First implantation of a diffractive quadrafoveal (trifocal) intraocular lens. *J Cataract Refract Surg* 2015;41:2330–2.)

satisfaction, although the intermediate distance in the defocus curve was better in the trifocal IOL group. Spectacle independence was achieved in 80% of the patients with the trifocal IOL and in 50% of the patients with the bifocal IOL.<sup>77</sup>

Similar outcomes were reported by a study comparing the Restor IOL with the AT LISA tri. The latter gave better intermediate visual acuity, whereas near and distance visual acuity were good with both IOLs. The Quality of Vision questionnaire showed similar visual disturbances between the two groups.<sup>78</sup>

A comparison of the visual outcomes and intraocular optical quality between the Lentis Mplus and the Restor IOL reported that the UNVA and distance-corrected near visual acuity (DCNVA) were better with the Lentis Mplus, although this IOL significantly induced HOA. The intermediate VA and the photopic contrast sensitivity were better with the Restor IOL.<sup>59</sup>

Patient satisfaction with multifocal and toric multifocal IOLs is very good, ranging from 93% to 95%.<sup>53</sup>

### Complications

The most common visual symptoms of multifocal IOLs are glare and halos.<sup>52,53,79</sup> These phenomena are secondary to the light division into two or more foci that happens with a multifocal IOL; the light in the out-of-focus image reduces the contrast of the in-focus image.<sup>52</sup>

Other symptoms include starbursts, shadows, and negative and positive dysphotopsia.<sup>53</sup> A decrease in contrast sensitivity has been reported also.<sup>52,53</sup> Multifocal aspherical IOLs have been developed to improve these visual phenomena. A meta-analysis compared the visual outcomes between aspherical and spherical multifocal IOLs, and aspherical multifocal IOLs achieved better image quality than spherical multifocal IOLs and also had less spherical aberrations.<sup>52</sup>

Although no multifocal IOL design exists without night vision disturbances, patients may adapt to them in a 6-month period<sup>53</sup> through a process of neuroadaptation,<sup>63</sup> which is faster with fully diffractive IOLs because the pupil does not affect the visual outcome.<sup>74</sup>

Posterior capsule opacification is the most common complication after cataract surgery. A study<sup>73</sup> compared the ND:YAG capsulotomy rates after the implantation of the FineVision Micro F and AT LISA tri 839MP trifocal IOLs, and the ND:YAG capsulotomy rate was significantly higher with the AT LISA tri 839MP IOL, although both IOLs had the same incidence of posterior cystoid macular edema.

It is important to note that not every patient is going to adapt to the multifocality and visual side effects, and some may want an IOL exchange (photopic phenomena and waxy vision can only be treated by IOL exchange). Kamiya et al.<sup>62</sup> reported the reasons for multifocal IOL explantation. The principal reason, accounting for 36% of all cases, was decreased contrast sensitivity; of these, 34% was for photopic phenomenon, 32% for unknown origin, including neuroadaptation failure, 20% for incorrect IOL power, 14% for preoperative excessive expectation, 4% IOL decentration, and 4% for anisometropia. It is important to note that 70% of the eyes from which the multifocal IOL was explanted had an UDVA of 20/20 or better, which means that the side effects of multifocal IOLs can be really disturbing for the patient (Table 3.10.5). See Table 3.10.6 for a review on Multifocal IOLs.

**TABLE 3.10.5 Multifocal Intraocular Lens Complications**

#### Complications Following Multifocal IOL Surgery

IOL decentration
IOL tilt
Inadequate pupil size
Residual refractive error
Posterior capsule opacification
Photopic phenomena and contrast sensitivity
Dry eye

### Accommodating IOLs

Accommodating IOLs have been designed to mimic physiological accommodation and avoid the optical side effects of multifocal IOLs.

IOLs proposed to restore accommodation have initially been designed to do so by enabling a forward movement of the optic component during an accommodation effort.<sup>80</sup>

These IOLs employ one of three basic approaches to restore accommodation:

1. Change in axial position
  - Single optic
    - The accommodative effect is dependent on IOL power,<sup>81</sup> so it provides limited near vision.<sup>82</sup>
      - Crystalens
      - Tetraflex
      - 1CU
  - Dual optic
    - They consist of a mobile front optic and a stationary rear optic that are interconnected with spring-type haptics.<sup>83</sup>
      - Synchrony
2. Change in shape or curvature
  - FluidVision
  - NuLens
3. Change in refractive index or power
  - Lumina

For the newest accommodating IOLs, researchers have found the sulcus instead of the capsular bag to be the ideal place to provide a real accommodative outcome. Capsular contraction has shown to be a major problem for accommodating IOLs implanted in the capsular bag. An asymmetrical capsular contraction causes the plate haptics to vault in opposite directions (Z-syndrome, Fig. 3.10.14),<sup>84</sup> inducing astigmatism, even >1 D of lenticular astigmatism.<sup>85</sup> Although this capsular contraction can be treated by an Nd:YAG laser capsulotomy, some patients may need an IOL exchange.<sup>85,86</sup>

Here we review some of the most popular and recently introduced accommodating IOLs:

#### 1) IOLs With Change in Axial Position, Single Optic

##### *Crystalens HD (Bauch & Lomb)*

This IOL was designed by Dr J. Stuart Cumming<sup>80</sup> and was the first accommodating IOL approved by the FDA.

Type: biconvex single-optic

Material: biocompatible third generation silicone (Biosil)

Refractive index: 1.428

Two sizes are available depending on the required power: 12.0 mm (HD520) for 10.00–16.50 D and 11.5 mm (HD500) for 17.00–33.00 D.

The center is biphase to increase the depth of focus, so it provides better near and intermediate focus.

It has a double mechanism to improve near visual: (1) axial movement of the optic and (2) variation of the radius of curvature of the anterior surface (Fig. 3.10.15).<sup>87</sup>

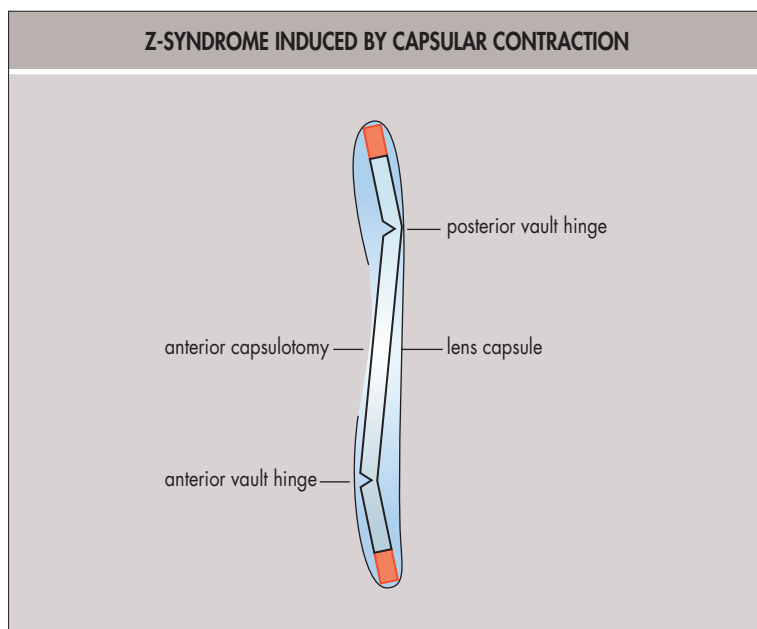
Alió<sup>87</sup> compared the visual acuity outcomes and ocular optical quality between the Crystalens HD and a monofocal IOL (Acri.Smart 48S). The UNVA was significantly better in the accommodating IOL group, but no significant difference in CNVA occurred between the two groups. Also there was no difference in the intraocular aberrometric coefficient.

A study comparing the visual outcomes between the Crystalens HD and the Lentis M-Plus<sup>88</sup> showed the latter achieved better DCNVA, and no significant differences occurred in postoperative UNVA or CNVA between the groups. The near add was reduced significantly after surgery in both groups, with a lower near-add power in the Lentis M-Plus group. Regarding optical quality, a significantly larger amount of IOL tilt existed in the Lentis M-Plus group, but the difference in mean ocular HOA was not statistically significant. The Crystalens HD had significantly better contrast

TABLE 3.10.6 Review of Multifocal IOLs

IOL Name*	Manufacturer	Near Addition (D)	Pupil Independent (Yes/No)	Aspheric (Yes/No)
Refractive (concentric rings)				
Array (SA40N)	Abbott Medical Optics	+3.50	No	No
M-flex (580F, 630F)	Rayner Ltd.	+3.00, +4.00	No	Yes
M-flex T (588F, 638F) (toric)	Rayner Ltd.	+3.00, +4.00	No	Yes
PA154N	Allergan	+3.50	No	No
PY-60MV	Hoya	+3.00	No	No
TrueVista 68STUV	Storz	+4.00	No	No
ReZoom (NXG1)	Abbott Medical Optics	+3.50	No	No
SFX MV1	Hoya	+2.25	No	No
UV360M4-07	Ioptex Research, Inc.	+4.00	No	No
Refractive (sector shaped)				
LENTIS Mplus (LS-312 MF15)	Oculentis GmbH	+1.50	Yes	Yes
LENTIS Mplus (LS-312 MF30, LS-313 MF30)	Oculentis GmbH	+3.00	Yes	Yes
LENTIS Mplus (LU-313 MF30)	Oculentis GmbH	+3.00	Yes	Yes
LENTIS Mplus toric (LU-313 MF30T)	Oculentis GmbH	+3.00	Yes	Yes
LENTIS Mplus X (LS-313 MF30)	Oculentis GmbH	+3.00	Yes	Yes
SBL-3	Lenstec	+3.00	Yes	Yes
Diffractive				
Acri.Twin (733D, 737D)	Acri.Tech/Carl Zeiss Meditec	+4.00	Yes	Yes
AcriviaReviol (BB MF 613, BB MFM 611)	VSY Biotechnology	+3.75	Yes	Yes
CeeOn 811E	Pharmacia	+4.00	Yes	No
Diffractiva-aA	Dr. Schmidt	+3.50	Yes	No
OptiVis	Aaren Scientific	+2.80	No	Yes
Tecnis (ZM900, ZM001, ZMA00, ZMB00)	Abbott Medical Optics	+4.00	Yes	Yes
Tecnis ZMT (toric)	Abbott Medical Optics	+4.00	Yes	Yes
Diffractive, trifocal				
FineVision	Physiol	+1.75, +3.50	No	Yes
AT Lisa tri 839MP	Carl Zeiss Meditec	+1.66, +3.33	Yes	No
Hybrid refractive diffractive				
AT Lisa (801, 802, 809M) former	Carl Zeiss Meditec	+3.75	Yes	Yes
Acri.Lisa (376D, 536D, 366D)				
AT Lisa toric (909M) former	Carl Zeiss Meditec	+3.75	Yes	Yes
Acri.Lisa (466TD) (toric)				
ReSTOR (SA60D3, SN60D3, MN60D3)	Alcon Laboratories	+4.00	No	Yes
ReSTOR (SN6AD1, SN6AD2, SN6AD3)	Alcon Laboratories	+3.00, +2.50, +4.00	No	Yes
ReSTOR (SNDIT2/3/4/5) (toric)	Alcon Laboratories	+3.00	No	Yes

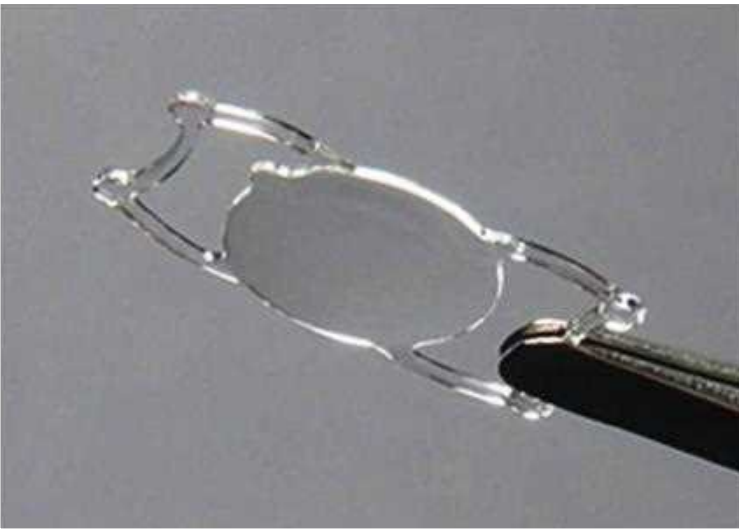
\*Intraocular lens names are listed as spelled by the manufacturer and not per journal style.



**Fig. 3.10.14 Z-Syndrome Induced by Capsular Contraction.** (Image from Page TP, Whitman J. A stepwise approach for the management of capsular contraction syndrome in hinge-based accommodative intraocular lenses. Clin Ophthalmol 2016;10:1039–46.)



**Fig. 3.10.15 Crystalens IOL.** (Image from Alió JL, Plaza-Puche AB, Montalbán R, Javaloy J. Visual outcomes with a single-optic accommodating intraocular lens and a low-addition-power rotational asymmetric multifocal intraocular lens. J Cataract Refract Surg 2012;38:978–85.)



**Fig. 3.10.16 Tetraflex IOL.** (Image from Wolffsohn JS1, Davies LN, Gupta N, et al. Mechanism of action of the tetraflex accommodative intraocular lens. *J Refract Surg* 2010;26:858–62.)

sensitivity results under photopic conditions at all spatial frequencies. They concluded that both IOLs had limitations in providing complete near-vision outcomes.

With ray-tracing aberrometry, it was shown that the Crystalens accommodative power was lower than 0.4 D.<sup>89</sup>

Commercially available: Yes

#### 1CU (Human Optics AG)

Type: one-piece biconvex

Material: hydrophilic acrylic

Optic diameter: 5.5 mm

Total diameter: 9.8 mm

Mechanism of action: anterior movement of the optic; four haptics for the transduction of the ciliary muscle contraction

Saiki et al.<sup>90</sup> performed a 4-year follow-up of patients who received the 1CU IOL and reported that the amplitude of accommodation was not enough to provide good near vision. One possibility for the lack of accommodation is the contraction of the capsule.

Not commercially available; it has been discontinued

#### Tetraflex (Lenstec Inc)

Type: one-piece IOL

Material: hydroxyethylmethacrylate (HEMA)

Optic diameter: 5.75 mm

Overall diameter: 11.5 mm

Refractive index: 1.46

Incision size: 2.5–3.0 mm

Mechanism of action: Increase in HOA with accommodative effort<sup>91</sup> rather than forward movement within the capsular bag as was the original proposed action (Fig. 3.10.16).

Commercially available: Yes, although the results have been contradictory.

### 2) IOLs With Change in Axial Position, Dual Optic

#### Synchrony (Visiogen Inc.)

Type: one-piece dual optic

Material: silicone

Power range: +16.00 D to +28.00 D in 0.5 D steps

The anterior IOL component has a high plus power beyond that required to produce emmetropia, and the posterior component has a minus power to return the eye to emmetropia. A bridge with a spring function connects the two components. Once the IOL is in the capsular bag, the tension of the bag compresses the optics. This leads to strain energy in the haptics that is released when there is an attempt to accommodate (Fig. 3.10.17).<sup>82,92</sup>

A comparison of the visual and ocular performances between the Crystalens HD and the Synchrony IOL was made by Alió et al.<sup>82</sup> No statistically significant differences occurred in UDVA, CDVA, and near or intermediate visual outcomes between the two IOLs. Reading acuity and reading speed were similar in both groups. Contrast sensitivity was significantly better in patients who received the Synchrony IOL. HOA were higher in the Crystalens HD group. Both IOLs had limitations in providing adequate near visual outcomes.



**Fig. 3.10.17 Synchrony IOL.** (Image from Bohórquez V, Alarcon R. Long-term reading performance in patients with bilateral dual-optic accommodating intraocular lenses. *J Cataract Refract Surg* 2010;36:1880–6.)

Bohórquez et al.<sup>92</sup> evaluated reading ability at 1 and 2 years after the implantation of the Synchrony IOL. The reading speed, mean reading acuity, and mean critical print size were significantly better by 2 years postoperatively. They concluded that these results were a consequence of true accommodation, although the reasons for the improved reading skills at 2 years postoperatively were not fully clear.

Commercially available: No, it has been discontinued

### 3) IOLs With Change in Shape or Curvature

**FluidVision (Powervision, Inc).** This IOL has an overall diameter of 10.0 mm and an optic diameter of 6.0 mm. It is made of acrylic material; the haptics and interior of the optic are filled with silicone oil. During accommodation, the silicon oil is pushed into the optic through fluid channels that connect the haptics to the optic. This inflates the lens, which increases the dioptric power for near vision.<sup>93a</sup> When the eye focuses at far, fluid flows from the optic body back into the haptics, flattening the lens and decreasing the dioptric power.

In a pilot study, Roux reported a subjective accommodation of 2.5 D.<sup>93b</sup> The lens is implanted through a 4-mm incision; the results of this study have not been published yet.

Commercially available: No, still in trials.

**Nulens (DynaCurve).** This IOL consists of polymethyl methacrylate (PMMA) haptics, a PMMA anterior reference plane that provides distance vision correction, a small chamber that contains a solid silicone gel, and a posterior piston with an aperture in the center (Fig. 3.10.18).

Mechanism of action: The piston is pressed, making the flexible gel bulge and resulting in an increase or decrease in IOL optical power.

It is inserted at the sulcus and must be implanted through a limbal incision of 9 mm.

It can provide up to 10.00 D of accommodation, improving near visual acuity without compromising DVA.<sup>94</sup>

Commercially available: No

### 4) IOL With Change in Refractive Index or Power

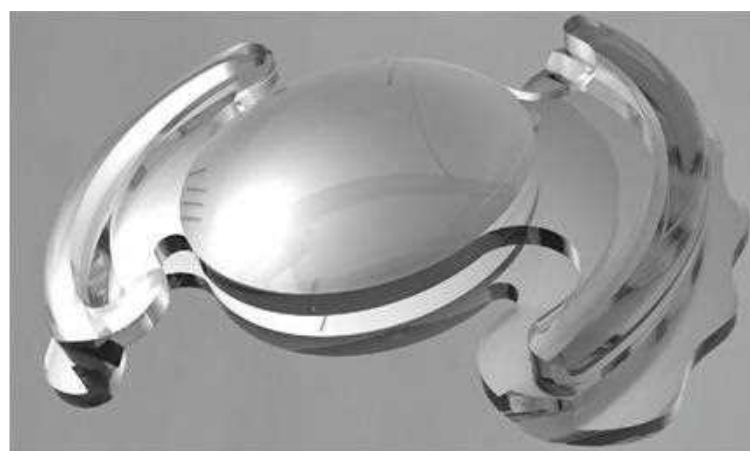
**Lumina (Akkolens).** This IOL consists of two optical elements, each having an elastic U-shaped loop with a spring function, and nonelastic connections to the main body of the lens (Fig. 3.10.19).

The optics are aspherical. The anterior one has a power of 5.0 D, and the power of the posterior one depends on the required correction of the eye (10–25 D).

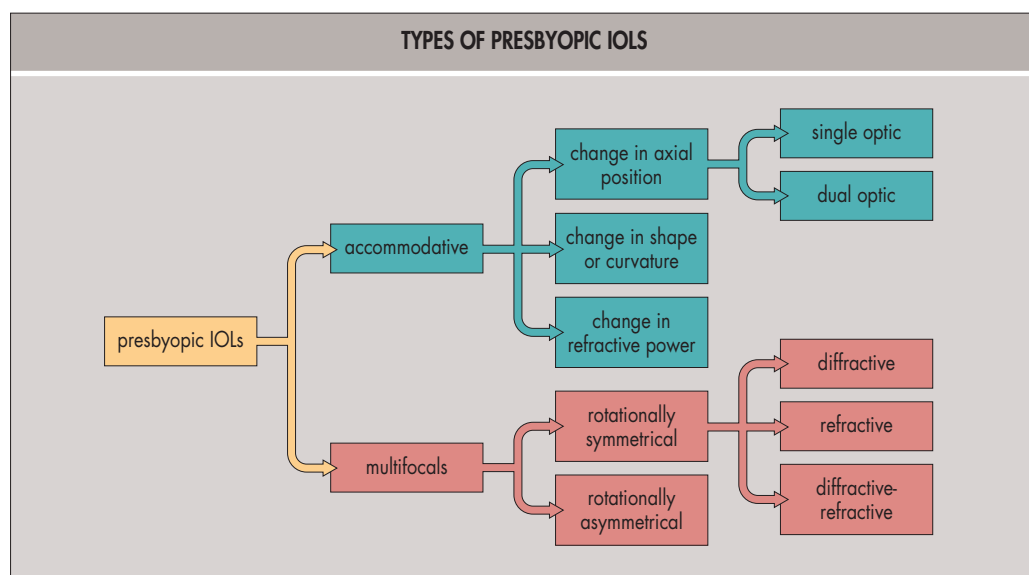




**Fig. 3.10.18 Nulens IOL in the Human Eye.** (Image from Alió JL, Ben-nun J, Rodríguez-Prats JL, et al. Visual and accommodative outcomes 1 year after implantation of an accommodating intraocular lens based on a new concept. *J Cataract Refract Surg* 2009;35:1671–8.)



**Fig. 3.10.19 Lumina IOL.** (Image from Alió JL, Simonov A, Plaza-Puche AB, et al. Visual outcomes and accommodative response of the Lumina accommodative intraocular lens. *Am J Ophthalmol* 2016;164:37–48.)



**Fig. 3.10.20 Types of Presbyopic IOLs.**

It must be implanted at the sulcus, and its size is customized based on the sulcus to sulcus diameter, as measured by OCT at the 12 o'clock meridian.

During accommodation, the IOL is compressed by the contraction of the ciliary muscle, and the optics move in opposite directions, increasing the optical power of the lens. When the muscle relaxes, the springs force the elements back to their original state, decreasing the optical power.

It has been proven through subjective and objective methods that the Lumina IOL improves near, intermediate, and far vision without affecting contrast sensitivity and with an accommodative power between 1.5 and 6.0 D.<sup>95</sup>

**Comments.** The long-term effectiveness of accommodating IOL implantation for presbyopia treatment still has to be demonstrated (Fig. 3.10.20).

### Other Treatments

#### Scleral Expansion Bands

This treatment is based on Schachar's theory of accommodation, which states that presbyopia is secondary to an increase in the lens diameter, which causes a reduction in the space between the lens and the ciliary body such that upon contraction the zonules can no longer exert their effect on the lens due to a loss of tension.<sup>96</sup>

The Refocus Group is conducting a phase III study of a new scleral implant surgery. Four PMMA segments are inserted in scleral tunnels at a depth of 400  $\mu$ m, 4 mm from the limbus to restore accommodation. Preliminary reports indicate good uncorrected near and intermediate

vision without compromise of distance vision. Primary outcomes are still pending.<sup>97</sup>

### Topical Treatment

This is an emerging topic that is under clinical evaluation; the mechanism of action is through ciliary body stimulation, miosis, and lens softening.

### FOV Tears

A topical treatment is available for the correction of near vision, with scientific evidence reporting a gain of two to three lines of UCVA. The ophthalmic solution contains pilocarpine, phenylephrine, polyethylene glycol, nepafenac, pheniramine, and naphazoline, and this combination stimulates the contraction of the ciliary body and maintains a physiological pupil diameter. FOV tears are commercially available in some Latin American countries.<sup>98</sup>

### Liquid Vision

This is a combination of aceclidine (parasympathomimetic) and tropicamide. Its mechanism of action is through a pinhole effect. The pilot study reported a gain of more than three lines of near vision. It is being tested in a phase IIb trial.<sup>99</sup>

### EV06 (Encore Vision)

An increment of the lens elasticity may be achieved by topical treatment with lipoic acid choline ester 1.5% (EV06, Encore Vision), which reduces the lens protein disulfides.

The lens disulfide bonds that form between the crystalline proteins are broken down because of the dihydrolipoic acid (a reduced active agent of lipoic acid), thus increasing the lens elasticity. A phase I/II study has shown good outcomes.<sup>100</sup>

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# Corneal Anatomy, Physiology, and Wound Healing

## 4.1

Ayad A. Farjo, Matthew V. Brumm, H. Kaz Soong, Christopher T. Hood

**Definition:** The cornea represents the transparent anterior wall of the globe.

### Key Features

- The cornea, including the tear film, is the major refractive surface of the eye.
- It provides structural integrity for the anterior part of the eye.
- It is a key barrier against infection.

### INTRODUCTION

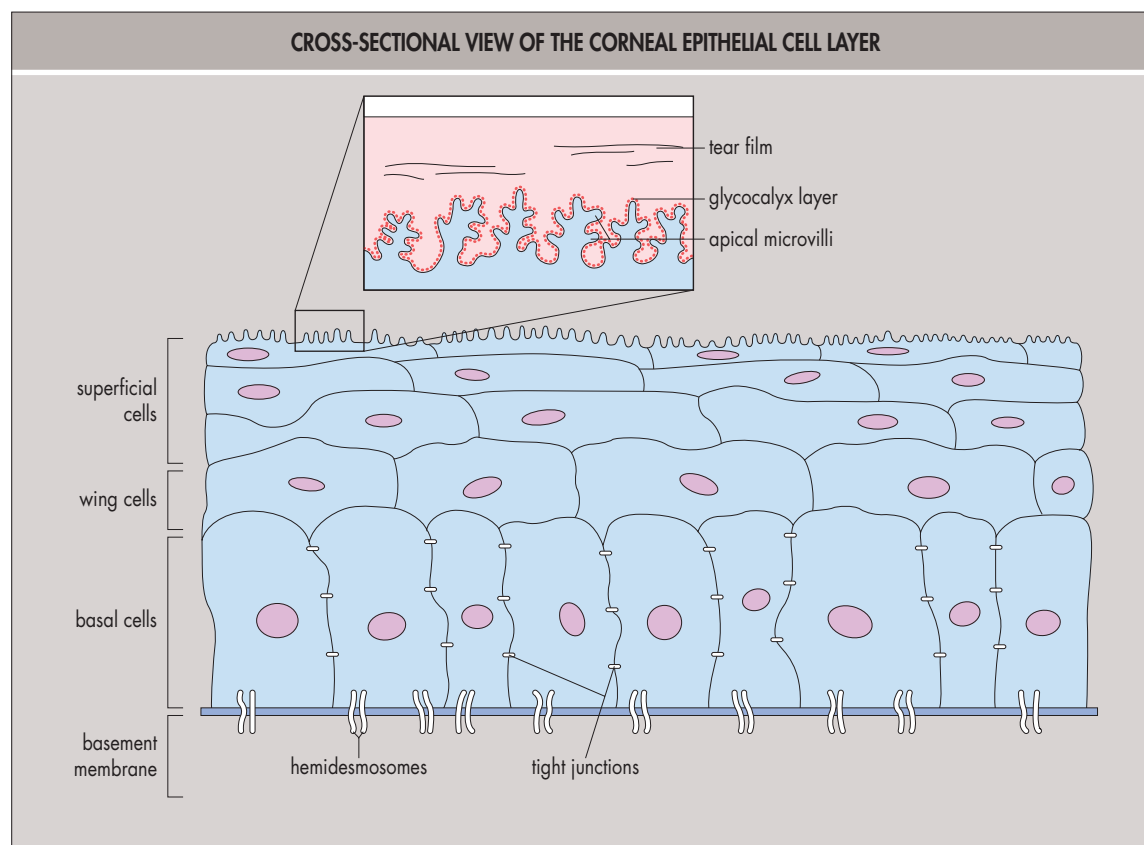
A healthy cornea, together with the overlying tear film, is necessary to provide a proper anterior refractive surface and to protect the eye against infection and structural damage to the deeper components of the eye. The average adult cornea is 11.5–12 mm<sup>1</sup> in horizontal diameter and about 1 mm smaller in vertical diameter. The anterior refractive power is +43.00 to +43.50 diopters (D). The shape of the cornea is prolate, being steeper centrally and flatter peripherally, which creates an aspherical optical system.

### Embryology, Anatomy, and Physiology of the Cornea

#### Epithelium

The corneal epithelium is derived from surface ectoderm at approximately 5–6 weeks of gestation. It is composed of nonkeratinized, nonsecretory, stratified squamous epithelium (Fig. 4.1.1), which is four- to six-cell-layers thick (40–50  $\mu\text{m}$ ). The epithelium is covered with a tear film of 7  $\mu\text{m}$  thickness, which is optically important in masking microirregularities of the anterior epithelial surface. The tear–air interface, together with the underlying cornea, provides roughly two thirds of the total refractive power of the eye. The mucinous portion of tears, which forms the undercoat of the tear film and is produced by the conjunctival goblet cells, interacts closely with the corneal epithelial cell glycocalyx to allow hydrophilic spreading of the tear film with each blink of the eyelid. The tear film also helps protect the corneal surface from microbial invasion and from chemical, toxic, or foreign body damage. Thus, the ocular surface tear film and the corneal epithelium share an intimate mutual relationship, both anatomically and physiologically.

Corneal epithelial cells undergo orderly involution, apoptosis, and desquamation. Complete turnover of corneal epithelial cells occurs in about 7–10 days,<sup>2</sup> with the deeper cells eventually replacing the desquamating superficial cells in an apically directed fashion. The most superficial cells of the corneal epithelium form an average of two to three layers of flat,



**Fig. 4.1.1** Cross-sectional view of the corneal epithelial cell layer.

polygonal cells. Extensive apical microvilli and microplicae characterize the cell membranes of the superficial cells, which, in turn, are covered by a fine, closely apposed, charged glycocalyx layer. The apical membrane projections increase the surface area of contact and adherence between the tear film's mucinous undercoat and the cell membrane. Laterally, adjacent superficial cells are joined by barrier tight-junctional complexes, which restrict entry of tears into the intercellular spaces. Thus a healthy epithelial surface repels dyes, such as fluorescein and rose bengal.

Beneath the superficial cell layer are the suprabasal or wing cells, so named for their cross-sectional alar shapes. This layer is about two to three cells deep and consists of cells that are less flat than the overlying superficial cells but possess similar tight, lateral, intercellular junctions. Beneath the wing cells are the basal cells, the deepest cellular layer of the corneal epithelium. The basal cell layer is composed of a single-cell layer of columnar epithelium approximately 20  $\mu\text{m}$  tall. Besides the stem cells and transient amplifying cells, basal cells are the only corneal epithelial cells capable of mitosis.<sup>3,4</sup> They are the source of both wing and superficial cells and possess lateral intercellular junctions characterized by gap junctions and zonulae adherens. The basal cells are attached to the underlying basement membrane by an extensive basal hemi-desmosomal system. This attachment is of pivotal importance in preventing the detachment of the multilayer epithelial sheet from the cornea. Abnormalities in this bonding system may result clinically in either recurrent corneal erosion syndromes or in persistent, nonhealing epithelial defects.

The basement membrane is composed of an extracellular matrix material secreted by the basal cells. Following destruction of the basement membrane, about 6 weeks are required for it to reconstitute and heal. The epithelial bond to the underlying, newly laid basement membrane tends to be unstable and weak during this period. The epithelium also adheres relatively poorly to bare stroma or Bowman's layer. Under ordinary conditions, type IV collagen and laminin are the major components of the basement membrane; however, fibronectin production increases to high levels during acute epithelial injury. The basement membrane, approximately 0.05  $\mu\text{m}$  in thickness, adheres to the underlying Bowman's membrane through a poorly understood mechanism that involves the anchoring fibrils and plaques.<sup>5</sup>

Epithelial stem cells—undifferentiated pluripotent cells that serve as an important source of new corneal epithelium—have been localized to the limbal basal epithelium. As the cells migrate to the central cornea, they differentiate into transient amplifying cells (cells capable of multiple but limited cellular division) and basal cells. The corneal epithelial cell layer mass appears to be the complex resultant of three phenomena. According to the “X, Y, Z hypothesis,” X is the proliferation of basal epithelial cells, Y is the centripetal mass movement of peripheral epithelial cells, and Z is the cell loss resulting from death and desquamation.<sup>6</sup> These three phenomena probably are not totally independent of each other but, rather, are controlled by a complex interactive feedback mechanism that maintains the status quo, vis-à-vis cell density, cell distribution and polarity, and cell layer thickness. These cytodynamics are likely to be responsible for the striking verticillate (vortex or whorl-like) biochemical deposition patterns seen in Fabry's disease (Fig. 4.1.2) and drug deposition keratopathies (e.g., from chloroquine and amiodarone). Langerhans' cells, immunologically

active dendritic macrophages derived from bone marrow and capable of antigen processing, are present in the peripheral corneal epithelium near the limbus. Under certain conditions (e.g., corneal graft rejection or injury), these cells are found among the central corneal epithelial cells. Human lymphocyte antigens are expressed by these corneal Langerhans' cells. Langerhans' cells have been detected in the epithelial basal cell layer and in Bowman's membrane in pathological inflammatory conditions, such as Thygeson's superficial punctate keratitis. After treatment with topical corticosteroids, these cells are no longer detectable by laser confocal microscopy.<sup>7</sup>

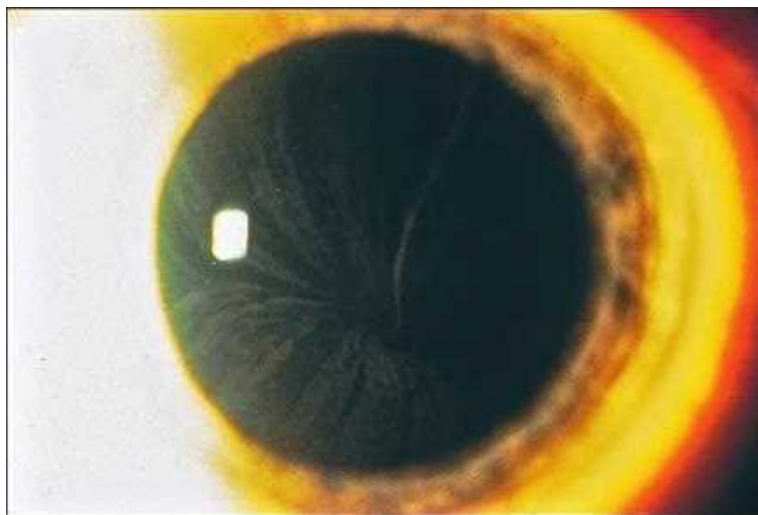
### Stroma

In week 7 of gestation, after the establishment of the primitive endothelium, a second wave of neural crest cells forms the early corneal stroma. Akin to the dermis of the skin, the corneal stroma provides important structural integrity and comprises roughly 90% of the corneal thickness. The stroma differs from other collagenous structures in its transparency and biomechanical properties. These functional properties result from the precise organization of stromal fibers and extracellular matrix, and the relatively dehydrated state of the corneal stroma.<sup>7-11</sup> The fibers are aligned in a parallel fashion within each lamella, and arranged at angles relative to fibers in adjacent lamellae.<sup>12,13</sup> This network reduces forward light scatter and contributes to the mechanical strength of the cornea. The peripheral stroma is thicker than the central stroma and the collagen fibrils may change direction to run circumferentially as they approach the limbus.<sup>13,14</sup> Bowman's membrane is the acellular condensate of the most anterior portion of the stroma.

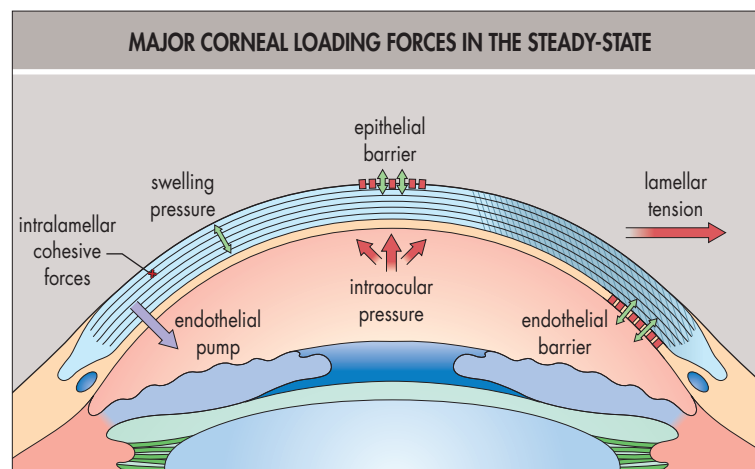
The stromal collagen fibrils, which provide the major tensile strength to the cornea, are composed mostly of type I collagen, but require a heterodimeric complex with type V collagen to obtain their unique and narrow diameter.<sup>15-17</sup> They are surrounded by specialized proteoglycans, consisting of keratan sulfate or chondroitin sulfate/dermatan sulfate side chains, which help regulate hydration and structural properties. Keratocytes, the major cell type of the stroma, comprise approximately 10% of the stroma by volume and are involved in maintaining the extracellular matrix environment.<sup>18,19</sup> More keratocytes are situated in the anterior stroma than in the posterior stroma.<sup>20</sup> Morphological differences between the anterior and posterior stromal keratocytes, such as fenestrations, have been identified.<sup>21</sup> Corneal “crystallins,” representing 25%–30% of soluble protein in keratocytes, appear to be responsible for reducing backscatter of light from the keratocytes and maintaining corneal transparency.<sup>22</sup>

Dua et al. have proposed unique biomechanical properties of the most posterior 6–15 microns of the stroma (pre-Descemet's layer [PDL]<sup>23,24</sup>). These five to eight lamellae of compact collagen appear distinct on electron microscopy and may be of relevance as a plane of cleavage in keratoplasty. The electron microscopic details of this membrane were first illustrated in 1972 by Fine and Yanoff.<sup>25</sup>

Corneal shape and curvature are governed by the intrinsic biomechanical structure and extrinsic environment (Fig. 4.1.3). Anterior corneal stromal rigidity in particular appears to be important in maintaining the corneal curvature.<sup>26</sup> Organizational differences in the collagen bundles of the anterior stroma may contribute to a tighter cohesive strength in this



**Fig. 4.1.2** Whorl-like deposition keratopathy in corneal epithelium seen in Fabry's disease.



**Fig. 4.1.3** Major corneal loading forces in the steady state. (Illustration courtesy William J. Dupps, MD, PhD.)



area and may explain why the anterior curvature resists change to stromal hydration much more compared with the posterior stroma, which tends to develop folds more easily. Corneal nerves and sensation are derived from the nasociliary branch of the first (ophthalmic) division of the trigeminal nerve. In the superficial cornea, the nerves enter the stroma radially in thick trunks forming plexiform arrangements, which eventually perforate Bowman's membrane to provide a rich plexus beneath the basal epithelial layer.<sup>27</sup> The fibers appear to directly communicate with keratocytes and epithelial cells<sup>28</sup> and may play an important role in corneal homeostasis.

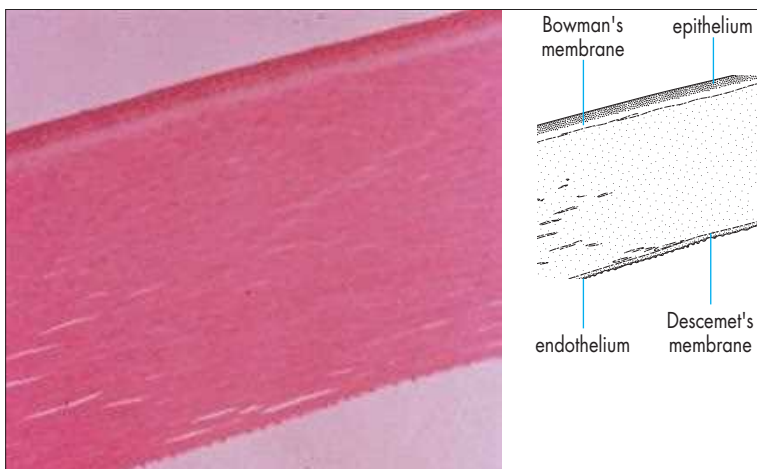
### Endothelium

In early embryogenesis, the posterior cornea is lined with a neural crest-derived<sup>29</sup> monolayer of orderly arranged cuboidal cells.<sup>30</sup> By the 78-mm stage, the cells become flattened and tightly abut one another. At this stage, immediately anterior to the flattened layer is a discontinuous, homogeneous acellular layer, which in time becomes Descemet's membrane.<sup>31</sup> By the 120-mm and 165-mm stages of development, the endothelial monolayer is uniform in thickness, spans the entire posterior corneal surface, and fuses with the cells of the trabecular meshwork.<sup>31</sup> Similarly, Descemet's membrane becomes continuous and uniform, fusing peripherally with the trabecular beams.<sup>31</sup> The fusion site, known as Schwalbe's line, is a gonioscopic landmark that defines the end of Descemet's membrane and the start of the trabecular meshwork. At birth, the endothelium is approximately 10  $\mu\text{m}$  thick.<sup>32</sup>

The intact human endothelium is a monolayer, which appears as a honeycomb-like mosaic when viewed "en face" (Fig. 4.1.4). The individual cells continue to flatten over time and stabilize at about 4  $\mu\text{m}$  in thickness in adulthood (Fig. 4.1.5).<sup>33</sup> The posterior surface of the endothelium is devoid of villi, except in certain pathological conditions, in which it may develop epithelioid characteristics. Adjacent cells share extensive lateral interdigitations and possess gap and tight junctions along their lateral borders. The lateral membranes contain a high density of sodium ( $\text{Na}^+$ ), potassium ( $\text{K}^+$ )-adenosine triphosphatase (ATPase) pump sites.<sup>34</sup> The basal surface of the endothelium contains numerous hemi-desmosomes that promote adhesion to Descemet's membrane. Endothelial cells contain numerous mitochondria and a prominent Golgi apparatus, and continuously secrete



**Fig. 4.1.4 Specular Photomicrograph of Normal Endothelium.** Note the dark, well-defined cell borders, the regular hexagonal array, and the uniform cell size. (Bar = 50  $\mu\text{m}$ .)



**Fig. 4.1.5 Light Micrograph of Normal Endothelium ( $\times 100$ ).** Note the single-cell endothelial layer with a Descemet's membrane of uniform thickness (epithelial surface at top of figure). (Courtesy Dr David Barsky.)

Descemet's membrane throughout life, beginning in utero at the week 8 stage. The anterior portion of Descemet's membrane formed in utero has a distinctive banded appearance when viewed by electron microscopy, but Descemet's membrane produced after birth is unbanded and has an amorphous ultrastructural texture. This membrane is approximately 3  $\mu\text{m}$  thick at birth, but thickens to 10  $\mu\text{m}$  with age. Endothelial cell density and topography continue to change throughout life. From the second to eighth decades of life, the cell density declines from approximately 3000–4000 cells/ $\text{mm}^2$  to around 2600 cells/ $\text{mm}^2$ , and the percentage of hexagonal cells declines from about 75% to around 60%.<sup>35</sup> The central endothelial cell density decreases at an average rate of 0.3% per year in normal corneas.<sup>36</sup>

As a result of endothelial activity, the stroma is maintained in a relatively deturgesced state (78% water content).<sup>37</sup> One hypothesis is that this endothelial activity is mediated by a pump-leak process; net fluid egress from the corneal stroma follows movement down an osmotic gradient from a relatively hypo-osmotic stroma toward a relatively hypertonic aqueous humor. This passive bulk fluid movement requires no energy. The energy-requiring processes are the intracellular and membrane-bound ion transport systems, which generate the osmotic gradient. The two most important ion transport systems are the membrane-bound  $\text{Na}^+$ ,  $\text{K}^+$ -ATPase sites and the intracellular carbonic anhydrase pathway.<sup>38</sup> Activity in both these pathways produces a net flux from stroma to aqueous humor. The barrier portion of the endothelium is unique in that it is permeable to some degree, permitting the ion flux necessary to establish the osmotic gradient.<sup>31,33</sup>

Little in vivo mitotic potential exists within the normal endothelium but may come into play in pathological situations. Although the exact minimum number of cells per millimeter squared required to maintain corneal deturgescence is not known, corneas with central cell counts below 500 cells/ $\text{mm}^2$  may be at risk for development of corneal edema. Endothelial cell morphology (size and shape) appears to correlate with pump function. An increase in cell size (polymegathism) and an increase in variation of cell shape (pleomorphism) correlate to reduced ability of the endothelial cells to deturgesce the cornea.<sup>39,40</sup>

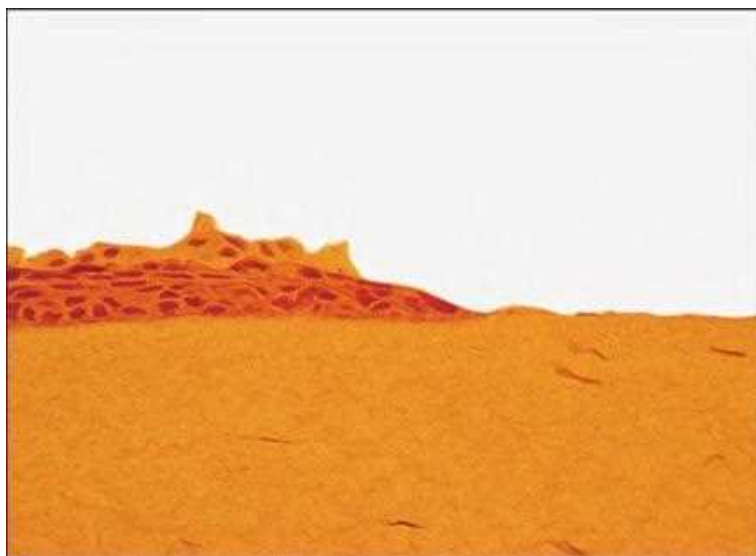
In vivo assessment of endothelial function relies on measurements of corneal thickness or on clinical morphological studies of the endothelial monolayer with specular microscopy. Measurement of the corneal thickness (pachymetry) indirectly reflects endothelial function. The average central corneal thickness is around 0.5 mm and gradually increases toward the periphery to around 0.7 mm. Normally, as a diurnal variation, corneas tend to be slightly thicker just after the person awakes in the morning. This increase in thickness is the consequence of diminished evaporation of water from underneath the closed eyelids, and the result of reduced nocturnal metabolic activity of the endothelium. Such overnight corneal swelling is more exaggerated in persons with unhealthy endothelium, causing blurred vision in the morning, but it gradually resolves later during the day.

### Endothelial Responses to Stress

Mild endothelial stress may result in cell size and shape changes, whereas greater stress may result in cell loss as well as irreversible alterations in the endothelial cytoskeleton.<sup>41</sup> Sources of stress may include metabolic disorders (hypoxia or hyperglycemia), toxins (drugs or their preservatives), injury (trauma or surgery), or alterations in pH or osmolarity. For example, contact lenses cause a hypoxic stress of varying degree to the endothelium.<sup>42</sup> Over time, this may result in alteration of the morphology, microanatomy, and possibly the function of the endothelium.<sup>43,44</sup> Hyperglycemia is another common metabolic stress that may produce changes in the endothelium. When compared with age-matched controls, the corneal endothelium in patients with type 1 and type 2 diabetes has a lower mean cell density and greater pleomorphism and polymegathism.<sup>45,46</sup>

Tissue manipulation, fluid flow in the anterior chamber, and intracameral pharmacological agents introduced during anterior segment surgery may cause damage to the endothelium.<sup>47,48</sup> Ophthalmic viscoelastic materials (composed of hydroxypropyl methylcellulose, chondroitin sulfate, or sodium hyaluronate) provide significant protection against intraoperative trauma to the endothelium.<sup>49,50</sup>

Glaucoma has been associated with endothelial cell loss. Compared with age-matched controls, significantly lower endothelial cell counts were noted in patients with glaucoma and ocular hypertension in one study.<sup>51</sup> Cell counts were inversely proportional to the mean intraocular pressure in the glaucoma and ocular hypertension groups. Mechanisms of cell loss may include direct damage from intraocular pressure, congenital alterations of endothelium in glaucoma, and drug toxicity.<sup>52</sup>



**Fig. 4.1.6** Light Micrograph That Shows the Leading Edge of Migrating Rat Corneal Epithelium as It Tapers to a Layer of One-Cell Thickness. As the epithelial defect is rapidly covered by migrating cells, it is initially coated with a thin, rarefied cell population prior to onset of mitotic activity (hematoxylin & eosin).

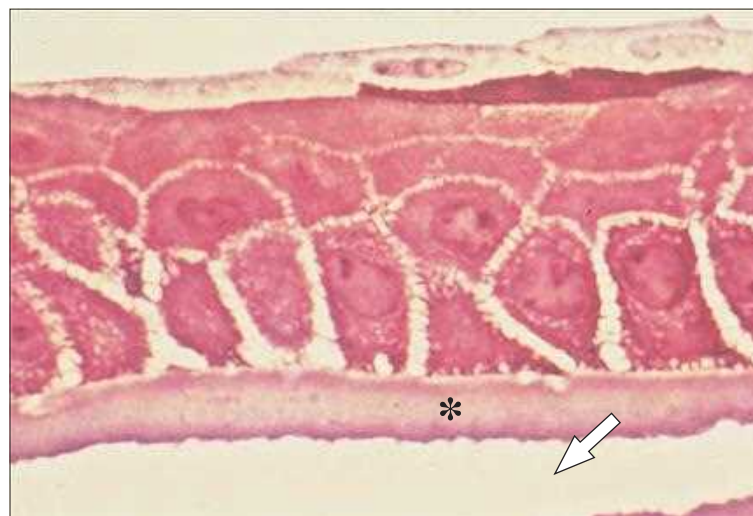
## CORNEAL WOUND HEALING

### Epithelial Injury

Within minutes after a small corneal epithelial wound, cells at the edge of the abrasion begin to cover the defect as rapidly as possible by a combination of cell migration and cell spreading. A longer delay of up to 4–5 hours is seen in larger defects. This lag phase is necessary for the preparatory cellular changes of an anatomical, physiological, and biochemical nature to occur before rapid cell movement. Various cell membrane extensions, such as lamellipodia, filopodia, and ruffles, develop at the leading edge of the wound. Anchoring hemi-desmosomes disappear from the basal cells. This early nonmitotic wound coverage phase is remarkable for its speed; the cells have been measured to migrate at a rate of 60–80  $\mu\text{m}/\text{h}$  (Fig. 4.1.6).<sup>53</sup> The migrating sheet of epithelial cells is attached most firmly to the underlying substrate at the leading margin. The relatively firmer adhesion at the leading margin suggests that the epithelial sheet movement may have “front-wheel drive,” with the less well-anchored cells behind the leading margin being pulled forward, possibly by intracellular contractile mechanisms that involve actin.<sup>54</sup> Fibronectin, a ubiquitous extracellular matrix protein present in plasma and in fresh wounds, is thought to be one of the key elements in the mediation of cell-to-substrate adhesion and cell migration. Present on the extracellular side of adhesion plaques, it is thought to mediate the linkage between the vinculin–talin–integrin complex and the substrate during epithelial migration after a wound has occurred. Laminin, a less ubiquitous extracellular matrix protein, is thought to serve a similar function.

At 24–30 hours after medium-sized epithelial injuries, mitosis or cell proliferation begins and restores the rarefied epithelial cell population. After large epithelial injuries, significant increases in cellular division occur as late as 96 hours.<sup>55</sup> Only the basal cells, transient amplifying cells, and the limbal stem cells partake in this reconstitutive mitosis.<sup>3,4</sup> The corneal epithelial stem cells, which reside at the limbus in the Pallisades of Vogt, cannot be regenerated after injury.<sup>56,57</sup> Limbal stem cell deficiency is an increasingly recognized cause of nonhealing epithelial defects. The extracellular matrix, in addition to other environmental signals, such as cytokines and growth factors, likely plays a central role in regulating epithelial stem cell commitment, corneal differentiation, and participation in corneal wound healing.<sup>58</sup> In laboratory and clinical trials, agents known to influence epithelial migration, mitosis, apoptosis, adhesion, and differentiation have been studied as possible therapeutic agents to enhance corneal epithelial healing, including growth factors, fibronectin, and retinoids. Primarily mitogenic agents and growth factors also stimulate production of extracellular matrix components to enhance cell-to-substrate adhesion. Bowman’s layer does not regenerate following injury.

Various pathological conditions may delay or prevent the normal corneal epithelial healing process. These include the following: damage to the cellular substrate (caused by herpetic or other infectious disease, diabetes mellitus, chemical burns, or basement membrane injuries and/



**Fig. 4.1.7** Recurrent Erosion in a Diabetic Cornea. Note the abnormally thick basement membrane (asterisk) and the intralamellar split within (arrow) (hematoxylin & eosin).

or dystrophies), ocular surface inflammation or atopic disease, medication, dry eyes, neurotrophic and exposure keratopathies, conjunctival disease (e.g., mucous membrane pemphigoid, radiation keratoconjunctivitis, and Stevens–Johnson syndrome), extensive damage to the limbal stem cells, and eyelid abnormalities.

In neurotrophic corneas, it is possible that interruption of corneal innervation results in depletion of growth factors and substance P, a neurogenic chemical known to regulate corneal physiological functions.<sup>59</sup> Diabetic corneas may manifest as abnormally thickened and easily delaminated basement membranes (Fig. 4.1.7), perhaps akin to basement membrane abnormalities elsewhere, as in the ciliary epithelium and the renal glomeruli.<sup>52</sup> A combination of pharmacological interruption of corneal nerve function and damage to the epithelial cells and substrate may cause persistent epithelial defects associated with topical anesthetic abuse.<sup>60,61</sup> Evidence also implicates matrix metalloproteinase-9 (gelatinase B) as a factor that may impact epithelial healing and/or desquamation.<sup>62,63</sup>

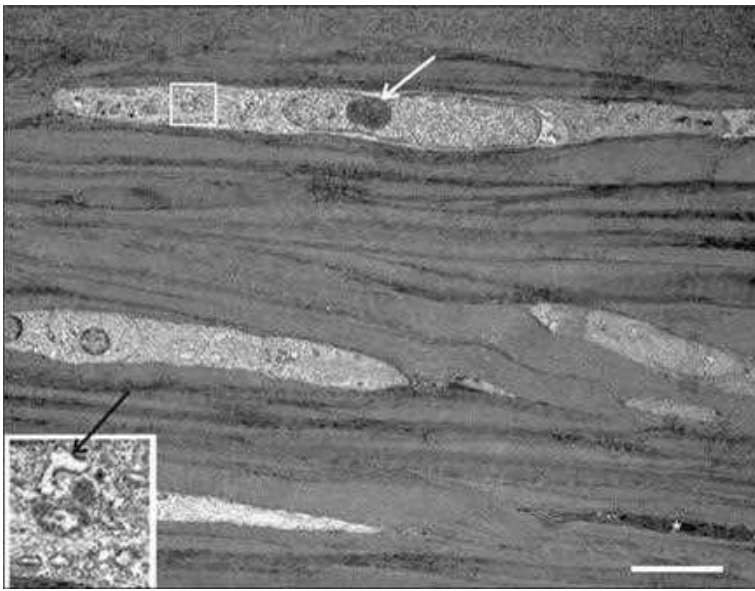
### Stromal Injury

Similar to skin, stromal wound healing consists of repair, regeneration, and remodeling,<sup>15</sup> involving a complex interplay of cytokines, growth factors, and chemokines.<sup>64</sup> Importantly, stromal repair differs from dermatological healing in that it occurs avascularly and ideally maintains corneal clarity. The reparative cascade begins with activation of stromal keratocytes (Fig. 4.1.8), which enlarge in size within the first 6 hours after injury and migrate into the injured area within 24 hours, becoming more fibroblast-like in appearance and behavior.<sup>65</sup> Activation of the keratocytes may be triggered by epithelial factors,<sup>65</sup> and regeneration of a fully functional epithelial basement membrane appears to have a critical role in the maintenance of corneal stromal transparency after mild injuries and recovery of transparency when opacity is generated after severe injuries.<sup>67</sup> The reparative cascade that follows typically results in corneal opacity in the affected area. The keratocytes within the area of injury undergo apoptosis, peaking 4 hours after the initial insult.<sup>66</sup> Apoptosis appears to modulate the wound healing response by influencing the activation of adjacent keratocytes.

Within 1–2 weeks, myofibroblasts with contractile properties enter the area under the epithelium and become involved in the remodeling of the stroma, with increased expression of matrix metalloproteinases.<sup>15,68</sup> These cells may be responsible for the “haze” seen after corneal injury or surgery.<sup>70</sup> The remodeling process sometimes can continue over a prolonged period of several years and may eventually restore corneal clarity in the affected area. Certain corneal surgeries, such as laser in situ keratomileusis, may cause a progressive loss of keratocytes over time through an as yet unclear mechanism.<sup>69</sup>

### Endothelial Injury

Nonpenetrating puncture injuries of the anterior cornea that do not directly involve the endothelium (e.g., those that occur when the cornea is struck by small, high-velocity particles) may cause concentric lesions of



**Fig. 4.1.8** Transmission electron micrograph of the corneal stroma. Activated keratocytes with dilated endoplasmic reticulum (*inset: black arrow*) and prominent nucleoli (*white arrow*) 1 week after keratoplasty. Bowman's layer is at the upper border of the micrograph. A normal keratocyte (*asterisk*), noticeably smaller than the activated cells, is visible above the scale bar. (Bar = 5.0  $\mu\text{m}$ .) (Reproduced with permission from Ohno K, Mitooka K, Nelson LR, et al. Keratocyte activation and apoptosis in transplanted human corneas in a xenograft model. *Invest Ophthalmol Vis Sci* 2002;43:1025–31.)

the endothelium arising from rapid focal distortion of the cell layer. Buckling of the endothelial layer also can result from excessive corneal bending in large-incision surgeries and/or from lens fragments striking the endothelium during cataract surgery and may occasionally produce snail-track lesions, clinically seen as serpentine, grayish lines on the endothelium. The damaged cells are rapidly replaced by enlargement of the surrounding cells and their centripetal migration into the injured region. Clinically, by slit-lamp biomicroscopy, these endothelial lesions disappear 1–3 days after injury. With more severe trauma, the underlying Descemet's membrane

may even be torn or ruptured, as in forceps delivery injuries and in corneal hydrops in keratoconus. When injured, Descemet's membrane curls in toward the stroma and surrounding endothelial cells slide in to cover the defect and produce new Descemet's membrane.<sup>72</sup> Although normal endothelium does not appear to replicate in vivo, recent evidence suggests that endothelial cells retain a degree of latent proliferative potential even into adulthood.<sup>71</sup> Recently, rho-kinase inhibitors have demonstrated potential in treating endothelial damage, with evidence of accelerated endothelial cell spread in rabbit models and clearing of corneal edema in small human trials.<sup>73</sup>

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Anterior Segment Imaging Modalities

Anam Akhlaq, Paula Kataguir, Ricardo Nosé, Nicolas J. Pondelis, Pedram Hamrah

4.2

**Definition:** Anterior segment (AS) imaging allows topographic, anatomical, and cellular visualization of ocular tissues.

Key Features

- Anterior segment optical coherence tomography is essential in pre- and postoperative evaluation for lamellar corneal transplantations, refractive surgery, and ectasia-related disorders. It may be utilized for the diagnosis and management of ocular surface neoplasia.
- Ultrasound biomicroscopy is a valuable tool for the assessment of anterior segment tumors and corneal opacities.
- Specular microscopy is useful in evaluation of the corneal endothelium, in Fuchs’ endothelial corneal dystrophy and for preoperative planning of anterior segment surgery.
- In vivo confocal microscopy has a high sensitivity and specificity for detection of *Acanthamoeba* and fungal keratitis. It can be utilized in the evaluation of corneal nerve and inflammatory changes in the cornea for dry eye disease, neuropathic corneal pain, neurotrophic keratopathy, and related conditions. It also has utility in visualization of *Demodex* mites in the eyelids.
- Topography and wavefront imaging are critical in the evaluation and management of refractive surgery, cataract surgery, corneal transplantations, astigmatism, and corneal ectasia.
- Meibography can be used to assess structural abnormalities of meibomian glands in dry eye disease and related disorders.

INTRODUCTION

Advances in anterior segment (AS) imaging over the past decade have revolutionized clinical care by allowing topographical, anatomical, and cellular visualization of tissues. The choice of imaging modalities used depends on the tissue to be visualized and the suspected pathology. AS optical

coherence tomography (AS-OCT), for example, can be used to visualize anatomical structures anterior to the iris, and the structures behind the iris are best seen with ultrasound biomicroscopy (UBM). In vivo confocal microscopy (IVCM) provides layer-by-layer images of the entire cornea at a cellular level, whereas specular microscopy can best assess the corneal endothelium. Corneal topography and wavefront imaging can visualize topography-related abnormalities. Finally, meibography demonstrates meibomian gland (MG) abnormalities that are difficult to discern with slit-lamp biomicroscopy. The detailed principles, functions, and clinical applications of AS imaging modalities are discussed below.

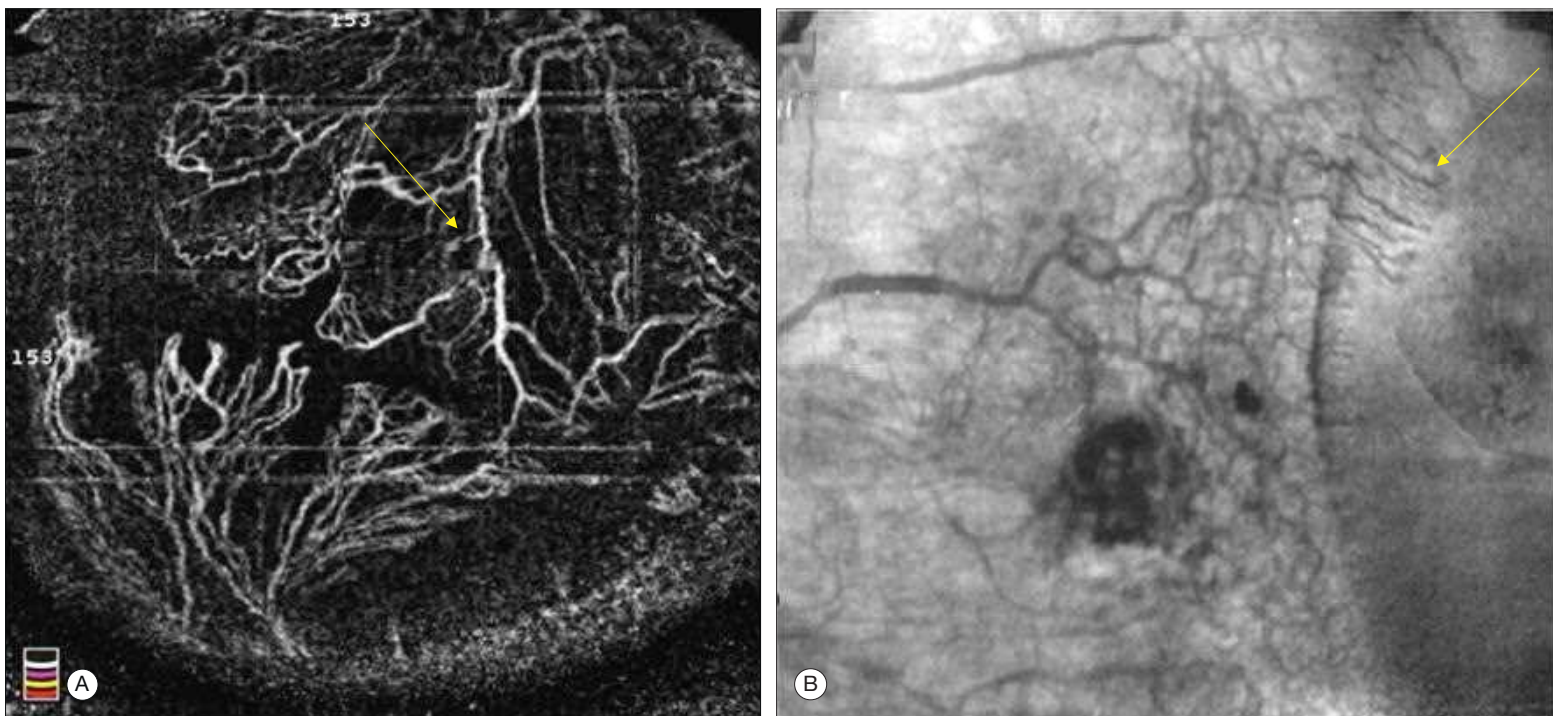
ANTERIOR SEGMENT OPTICAL COHERENCE TOMOGRAPHY

AS-OCT is a noninvasive, noncontact imaging device that allows cross-sectional, anatomical imaging of the eye,<sup>1</sup> with the use of an interference pattern of reflected light,<sup>2-4</sup> and relies on images reconstructed from cross-sectional scans (A-scans). Since the advent of original time domain (TD) OCT, the technology has rapidly evolved with the development of the higher resolution Fourier domain (FD-OCT) (5-μm FD-OCT versus 18-μm TD-OCT resolution), and faster speed of A-scans (26,000 scans/sec FD-OCT versus 2,000 scans/sec TD-OCT), resulting in fewer motion artifacts and the capability to obtain three-dimensional images of ocular tissues. The more recent spectral domain (SD, 5 μm) and swept-source (SS, up to 2.6 μm) OCTs provide even higher-resolution images (SD, 5 μm and SS, up to 2.6 μm) and higher speed of A-scans (about 50,000 scans/sec SD-OCT versus 100,000 scans/sec SS-OCT).<sup>3</sup> Although TD AS-OCT has deeper penetration due to longer wavelength, the SD-OCT and SS-OCT have better signal-to-noise ratio and allow for more structural detail.<sup>5</sup> A comparison summary of the types of AS-OCT devices is provided in Table 4.2.1.

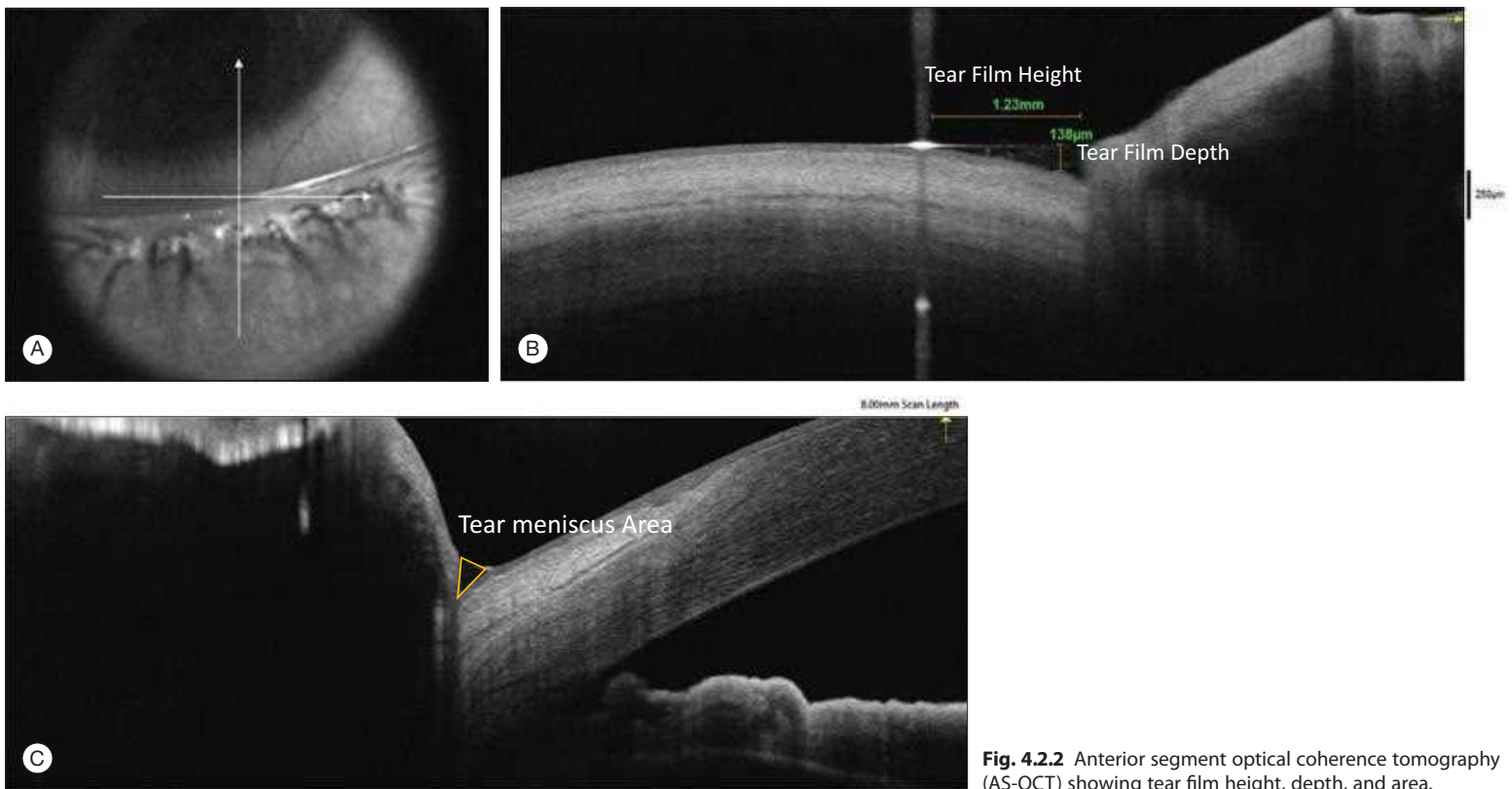
Application of the “en face” technique provides a layer-by-layer horizontal sectioning of the tissue. These sections allow for identification of microstructural information throughout the scanned area that is not available with standard AS-OCT scans. Moreover, AS-OCT angiography (OCTA), which has recently been described, allows for visualization and quantification of vessel density in the cornea, iris, and sclera (Fig. 4.2.1).<sup>6</sup>

TABLE 4.2.1 Anterior Segment Optical Coherence Tomography (OCT) Operating Systems

Types	Time-Domain OCT (TD-OCT)		Fourier-Domain OCT (FD-OCT)									
			Spectral-Domain OCT (SD-OCT)							Swept-Source OCT (SS-OCT)		
Subtypes/ Examples	Visante	Heidelberg Slit-Lamp OCT	RTVue	iVue	Avanti XR	Cirrus	Spectralis	Envisu_C Class	3D-OCT	Casia	Triton	Plex Elite 9000
Manufacturer	Carl Zeiss Meditec, Dublin, CA	Heidelberg Engineering, Heidelberg, Germany	Optovue Inc., Fremont, CA	Optovue Inc., Fremont, CA	Optovue Inc., Fremont, CA	Carl Zeiss Meditec, Dublin, CA	Heidelberg Engineering	Bioptigen, Bioptigen Inc., Research Triangle Park, NC	Topcon Medical Systems, Oakland, NJ	Tomey, Nagoya, Japan	Topcon Medical Systems, Oakland, NJ	Carl Zeiss Meditec, Dublin, CA
Light source	Beam		Broadband light sources (Spectrometer)							Swept-source laser		
Wavelength (nm)	1310	1310	840	840	840	840	820	1310	850	1310	1050	1060
Depth (mm)	6	7	2–2.3	2–2.3	3	2	1.9	1.6–2.4	3–6	6	12	3
Resolution (μm) (axial × transverse)	18 × 60	25 × 20-100	5 × 15	5 × 15	3-5 × 15-25	5 × 15	3.9 × 14	2.4-7.5	6 × 20	10 × 30	2.6 × 20	5.5 × 20
Imaging speed (A-scans/sec)	2,000	200	26,000	26,000	70,000	27,000- 68,000	40,000	32,000	50,000	30,000	100,000	100,000
Image size (mm)	6 × 16	15 × 7	13 × 9	13 × 9	12 × 9	-	-	20 × 2.5	12 × 9	16 × 16	16 × 16	12 × 12



**Fig. 4.2.1** (A) Optical coherence tomography angiography (OCTA) image showing vessels in the cornea (arrow). (B) En face OCT image showing corneal neovascularization (arrow).



**Fig. 4.2.2** Anterior segment optical coherence tomography (AS-OCT) showing tear film height, depth, and area.

## Clinical Applications

### Tear Film Evaluation

Tear meniscus height, depth, area, radius of curvature, and volume can be measured using AS-OCT (Fig. 4.2.2).<sup>1</sup> Thus, AS-OCT is a valuable noninvasive tool for the evaluation of the tear film abnormalities.

### Refractive Surgery and Ectasia-Related Disorders

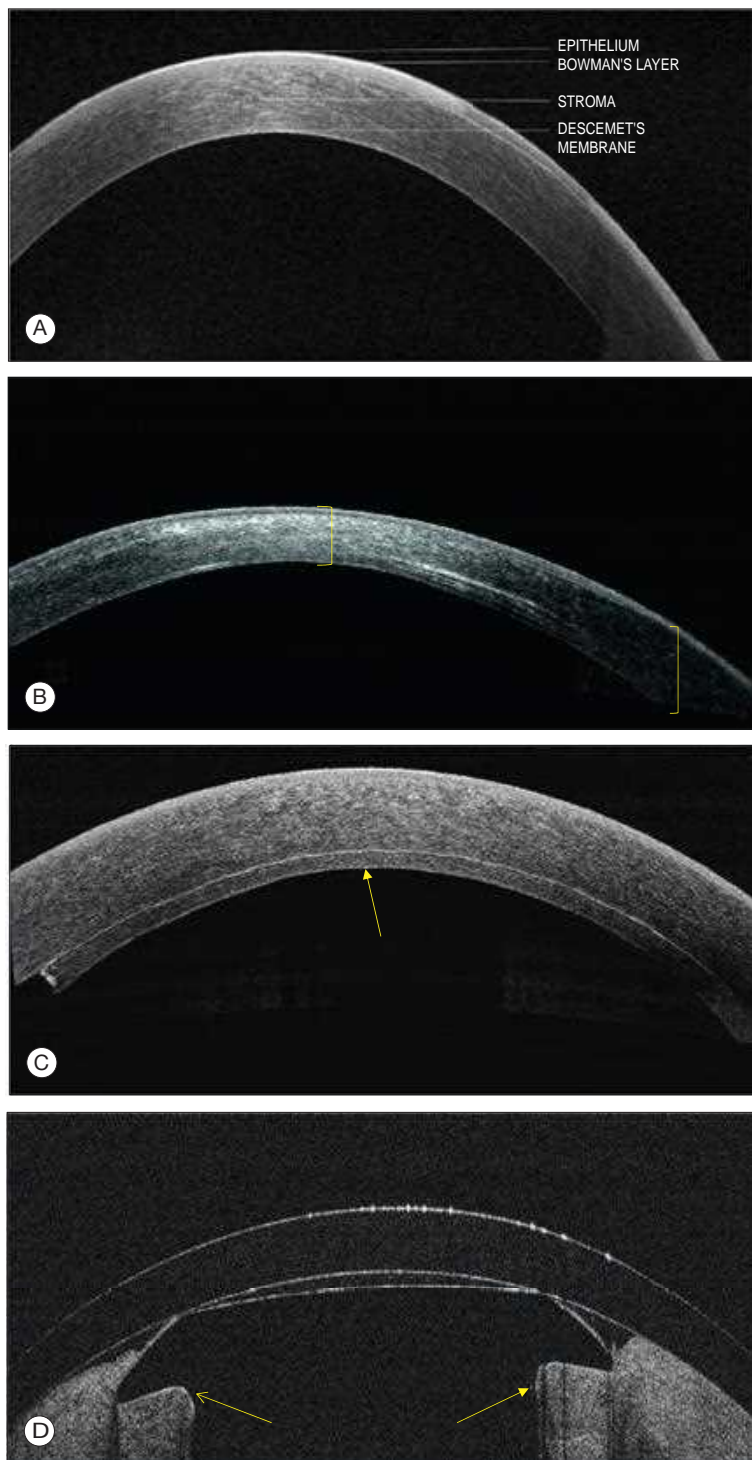
AS-OCT scans of the healthy corneas show corneal layers as seen in Fig. 4.2.3, A, and allow for the evaluation of flap thickness and stromal bed after refractive surgery.<sup>1</sup> Thus AS-OCT measurements of preoperative corneal thickness and postoperative residual stroma thickness may help in risk stratification of patients by an ectasia scoring system.<sup>17</sup> Similarly, corneal thinning can be measured by using AS-OCT for screening,

risk-assessment, and diagnosis of patients with ectasia-related disorders by assessment of area and range of thinning (see Fig. 4.2.3B).<sup>1,8</sup> Postoperative AS-OCT can further be used to monitor complications, such as interface fluid or haze, and flap dislocation.<sup>1</sup> Patients with prior refractive correction, who require cataract surgery may benefit from additional data obtained using AS-OCT for the latest biometry formulas to improve surgical outcomes.<sup>1</sup>

### Penetrating and Endothelial Keratoplasty-Related Procedures

AS-OCT can provide valuable information both intraoperatively and postoperatively for penetrating corneal grafts and endothelial keratoplasty detachment. Endothelial grafts can be visualized on AS-OCT for



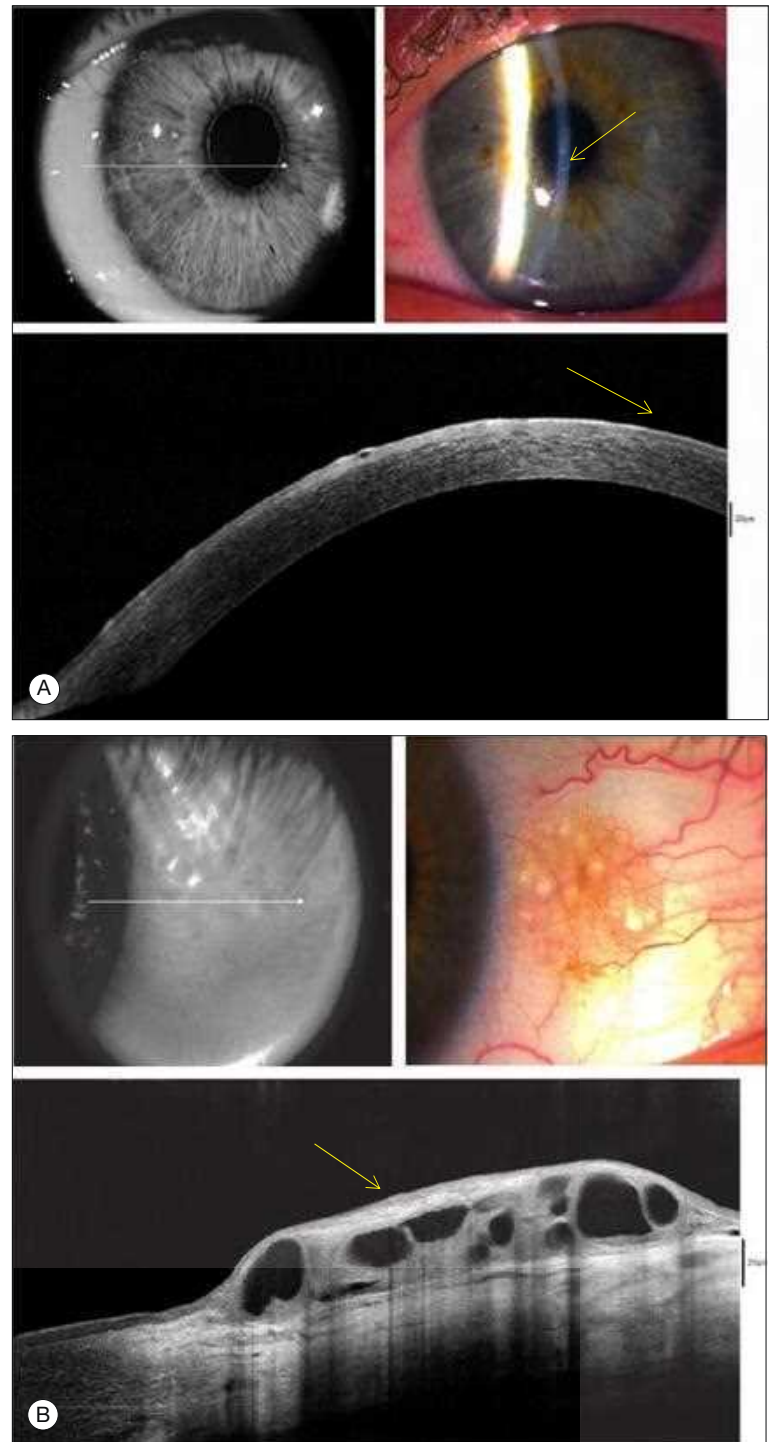


**Fig. 4.2.3** An anterior segment optical coherence tomography (AS-OCT) image of (A) normal cornea; (B) keratoconus, seen as central corneal thinning, identified with markings; (C) endothelial corneal graft, shown with yellow arrow; and (D) corneal keratoprosthesis; arrows show posterior side of the front plate of the keratoprosthesis.

orientation, position and interface fluid intraoperatively, and for detachment postoperatively using warning signs, such as interface fluid and poor margins.<sup>9,10</sup> Intraoperative AS-OCT can assess dissection depth in deep anterior lamellar keratoplasty (DALK) and identify graft orientation and the need for repositioning for Descemet's membrane endothelial keratoplasty (DMEK) and Descemet's membrane stripping automated endothelial keratoplasty (DSAEK).<sup>10</sup> Postoperative graft adherence/detachment status in DMEK and DSAEK also may be seen (Fig. 4.2.3C).<sup>1,9</sup> Moreover, keratoprosthesis (KPro) offers a useful alternative for patients with severe corneal pathology, (Fig. 4.2.3D), identifying corneal thinning and melting under the front plate.<sup>9</sup>

### Ocular Surface Tumors

Although conjunctival and corneal tumors can be observed clinically by using slit-lamp biomicroscopy, their exact location, depth, extent, and



**Fig. 4.2.4** Anterior segment optical coherence tomography (AS-OCT) showing (A) conjunctival tumor extending to the corneal epithelium; the lesion is seen as hyperreflective epithelium; (B) conjunctival nevus; lesion shows cystic spaces on AS-OCT.

anatomic relationship to surrounding structures can be assessed further by using AS-OCT (Fig. 4.2.4).<sup>8,11</sup> AS-OCT can complement UBM in imaging and is superior to UBM for imaging ocular surface tumors.<sup>11,12</sup> For example, squamous cell neoplasia presents as a localized area of hyperreflective thickened epithelium with an abrupt transition between the normal and thickened area; a lymphoma manifests as a hyporefective, homogeneous subepithelial mass; a melanoma presents as a hyperreflective subepithelial mass; and nevi present with cysts in a subepithelial mass.<sup>11,12</sup>

### Cataract Surgery and Intraocular Lens Implantation

Pre- and postoperative AS-OCT imaging helps assess the anterior chamber (AC) in evaluation of phakic intraocular lenses.<sup>1</sup> Preoperative AS-OCT can determine the AC angle, width, and lens rise, whereas postoperative AS-OCT can evaluate surgical wounds and assess for complications, including angle-closure glaucoma and corneal decompensation.<sup>1</sup> Further, as detailed above, AS-OCT may aid in biometry in patients who have previously undergone LASIK surgery.

TABLE 4.2.2 Types of Commercially Available Specular Microscopes	
Contact Specular Microscopes	Noncontact Specular Microscopes
CL-1000xz (HAI Labs Inc., Lexington, MA)	CL-1000nc (HAI Labs Inc., Lexington, MA)
	CELLCHEK Series (Konan Medical USA, Inc., Irvine, CA)
	CellCheck D (eyebank) (Konan Medical USA, Inc., Irvine, CA)
	CEM-530 (Nidek Fremont, CA)
	EM-3000 (Tomey, Inc., Phoenix, AZ)
	SP-1P (TopCon Medical, Inc., Tokyo, Japan)

Keratitis

Keratitis may be diagnosed clinically, but the areas of necrosis and infiltration may be better assessed by using AS-OCT, particularly in opaque corneas. Because AS-OCT allows for quantitative measurement of corneal thickness, it serves as an additional aide in detection and treatment of keratitis and corneal ulcers.<sup>1</sup> Localization of stromal necrosis and radial hyperreflective stromal bands in *Acanthamoeba* keratitis can further be translated for rapid diagnosis and reduction of perforation rates as a result of earlier intervention.<sup>1,13</sup>

Miscellaneous Uses

AS-OCT has several other applications, such as grading of cells in anterior uveitis and visualization of intracorneal implants.<sup>1</sup> Further, it is useful in screening corneas from eye banks for corneal abnormalities, such as prior LASIK surgery.

Limitations

AS-OCT has limited ability to visualize structures posterior to iris as a result of pigmentation, whereas UBM is more useful clinically.

SPECULAR MICROSCOPY

Specular microscopy allows for imaging and analysis of the corneal endothelium. It works on the basic principle of light reflection using a mirror: the angle of incidence is equal to that of reflection. As light passes through a media with higher index of refraction, most of it is reflected; this reflected light is captured by a detection lens. The endothelial cells can be imaged because their refractive index is greater than that of the aqueous humor. The light source can be a stationary or moving slit or spot; wider slit allows greater field, but reduced contrast and resolution.<sup>14</sup> Specular microscopy can be contact or noncontact and automated or manual, or both.<sup>15</sup> The types of specular microscopes are shown in Table 4.2.2.

Specular microscopy provides pachymetric measurements and endothelial cell analysis (density and morphology), including endothelial cell density, mean cell area, coefficient of variation (standard deviation divided by mean area of cells), and percentage of hexagonality or pleomorphism (percentage of cells with variation from normal hexagonal shape). Coefficient of variation and pleomorphism are the more sensitive indicators of endothelial dysfunction and stress, as even at low endothelial density (<500 cells/mm<sup>2</sup>) the endothelial function may remain uncompromised.<sup>15</sup>

The fixed-frame method allows for cell quantification within a fixed area (Fig. 4.2.5A), and the variable-frame method allows the observer to make an accurate boundary around the edges of the cells.<sup>15,16</sup> In contrast, the center method requires the centers of contiguous cells to be marked manually, hence peripheral cells are not counted as they do not have adjoining cells. Moreover, the center-flex method requires delineating the boundary of an area, followed by marking of cell centers.

Clinical Applications

The normal corneal endothelium comprises hexagonal and similar size cells (see Fig. 4.2.5A).<sup>17</sup> The cell density decreases with aging (0.5% per year). Examples of cell abnormalities include guttae (excrecences of the Descemet’s membrane).<sup>16</sup> Contact lens wear can cause transient or chronic changes to the endothelial cell morphology.<sup>16</sup>

Corneal Dystrophies

Specular microscopy is a valuable tool to diagnose different endothelial disorders, such as Fuchs’ endothelial corneal dystrophy (FECD), posterior polymorphous dystrophy (PPMD), or iridocorneal endothelial (ICE)

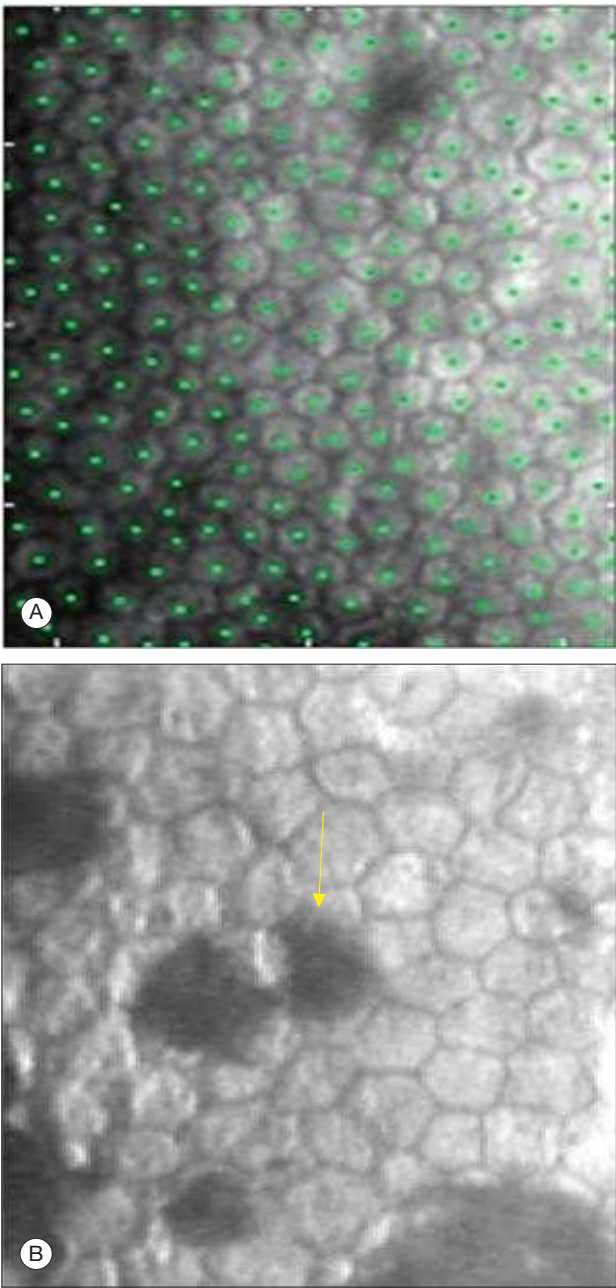


Fig. 4.2.5 Specular microscopy image of (A) normal endothelium quantified using fixed-frame method; (B) endothelium with Fuchs’ endothelial corneal dystrophy; note the presence of guttae (arrow) and dysmorphic cells.

syndrome.<sup>18,19</sup> In FECD, the mosaic endothelium presents dark areas (guttae) (see Fig. 4.2.5B).<sup>20</sup> Bilateral involvement, with donut-shaped vesicles and clearly defined black rings anterior to the cells may be seen in PPMD; whereas in ICE syndrome, many pentagonal cells are seen with intracellular dark areas.<sup>19</sup> In advanced ICE disease, a “reversal appearance” occurs with black areas and white margins.

Intraocular Surgery Evaluation

Permanent corneal edema occurs at low epithelial cell density (300–700 cells/mm<sup>2</sup>) or presence of other morphological abnormalities (coefficient of variation >40% or <50% hexagonal cells). Loss of cells with ocular surgery is estimated to be between 0 and 30%; preoperative assessment of the patients’ endothelium to assess cell density may reduce postoperative complications.

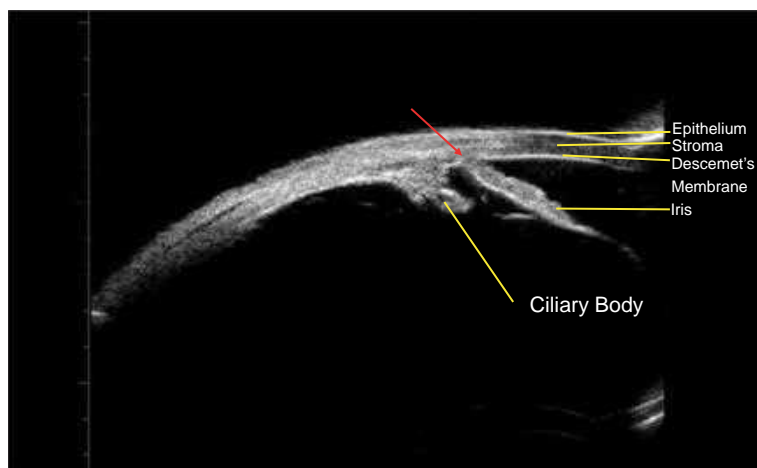
Donor Cornea Evaluation

Specular microscopy is particularly important in assessment of donor corneas to assess for sufficient endothelial cell density and donor quality.<sup>21</sup>

Limitations

One of the limitations of specular microscopy is that it is difficult to image endothelial cells through edematous or opaque corneas. In these cases, confocal microscopy provides superior image quality.





**Fig. 4.2.6** Ultrasound biomicroscopy image of a patient with anterior synechiae (red arrow).

## ULTRASOUND BIOMICROSCOPY

UBM uses high frequency (20–100 MHz) ultrasound waves and is useful for the evaluation of deeper structures in the eye and in opaque corneas.<sup>14</sup> Echoes from tissues at different depths are recorded at different time intervals and can be used to construct the image. In general, higher frequency waves have lesser penetration, and lower frequency waves have lower penetration. Most UBMs in use today have scan rate of 35–50 MHz, giving an axial resolution of 42  $\mu$ m, and a depth of 4–5 mm.<sup>11,22</sup>

## Clinical Applications

Using UBM, surface epithelium, Bowman's layer, and Descemet's membrane can be identified as reflective structures, while the endothelium cannot be identified. As a result of penetration of sound through the pigmented epithelium, UBM can visualize the structures posterior to the iris, which is not possible with an AS-OCT. Hence, posterior chamber structures, including lens zonules, ciliary body, and anterior choroid, can be visualized (Fig. 4.2.6).<sup>22</sup>

### Ocular Masses

Although no imaging technique can replace histopathological examination, UBM has shown utility in the diagnosis of anterior segment tumors. Solid tumors can be identified and the extent of involvement seen.<sup>11</sup> UBM has shown superiority over AS-OCT in image quality and assessment of tumor margins and posterior surface of both pigmented and nonpigmented tumors. For evaluation of anterior surface tumor, conjunctival nevi, and anatomical relationships, AS-OCT may be superior. However, posterior shadowing with AS-OCT is not seen with UBM.<sup>11</sup> Dermoid tumors of the limbus appear as hyperreflective masses, whereas pigmented conjunctival nevi present with cysts.<sup>11</sup> For solid tumors and conjunctival melanomas, UBM can assess the margins and depth.<sup>11,22</sup>

### Glaucoma

The corneoscleral junction can be seen as a line of reflectivity change between the sclera (highly reflective) and cornea; the corneal spur is 1 mm posterior to corneoscleral junction. Hence, it can be used to assess the anterior chamber (AC) (angle, depth, and angle opening distance [AOD]), iris (thickness, distance from ciliary process, contact lens, or zonules), ciliary sulcus (diameter and distance of process from trabecular meshwork), and other angles (trabecular–iris angle, iris–lens angle, and iridocorneal angle).<sup>23,24</sup> The scleral spur may be identified manually for improved accuracy. In glaucoma evaluation, UBM has shown promise in evaluation of mechanisms underlying glaucoma, such as acute angle closure caused by pupillary block (bowed iris causing angle blockade), plateau iris (AC shallower than in controls, but deeper than in patients with pupillary block), ciliary effusion syndrome, lens dislocation/subluxation, and ciliary body masses (cyst or tumor). Postoperatively, UBM is highly useful especially if clinical examination cannot differentiate between pupillary block and malignant glaucoma. As UBM can assess anatomical relationships, it can also be used to evaluate anatomical changes with diseases.

**TABLE 4.2.3** Commercially Available Meibography Devices

Topcon slit-lamp microscope (Topcon Cooperation, Tokyo, Japan)
EyeTop Topographer (Costruzione Strumenti Oftalmici, Florence, Italy)
Sirius Scheimpflug Camera and Cobra Fundus Camera (bon Optic Vertriebs GmbH, Lübeck, Germany)
Oculus Keratograph 5M (Oculus, Wetzlar, Germany)
Lipiview II (TearScience, Morrisville, North Carolina, USA)
LipiScan™ with Dynamic Meibomian Imaging™ (TearScience, Morrisville, North Carolina, USA)

**TABLE 4.2.4** Grading Systems to Assess Meibomian Gland Dysfunction

Characteristics	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Gland dropout	None	33%	34%–66%	>66%	-
Partial glands	None	<25% of image	25%–75% of image	>75% of image	-
Loss of total meibomian gland area	None	<1/3	1/3–2/3	>2/3	-
Area of loss	0%	25%	25%–50%	51%–75%	75%

## Ocular Trauma

Because ocular trauma can present with opaque corneas or hyphema, UBM is an especially useful modality to evaluate damage to the internal structures of the eye. It can evaluate nonmetallic foreign bodies less than 1 mm that may be missed even by computed tomography (CT). Iridodiolysis can be caused with blunt trauma and is viewed as a detached iris by using UBM. A cyclodialysis cleft may be missed with gonioscopy, but a cleft that separates the ciliary body and scleral spur are evident on UBM; reattachment of ciliary body after cyclodialysis has been observed by using UBM. Because the intraocular lens vault can be seen, traumatic cataract, lens displacement, subluxation, rupture of lens capsule, and zonular damage may be seen.

## Limitations

UBM needs contact with the globe, hence patients have better tolerance to its application with topical anesthesia. It has a limited depth of penetration behind the anterior vitreous and has a limited field of view. Further, it has a relatively poor interobserver reproducibility in the assessment of AC angle, iris dimensions, and ciliary sulcus diameter.

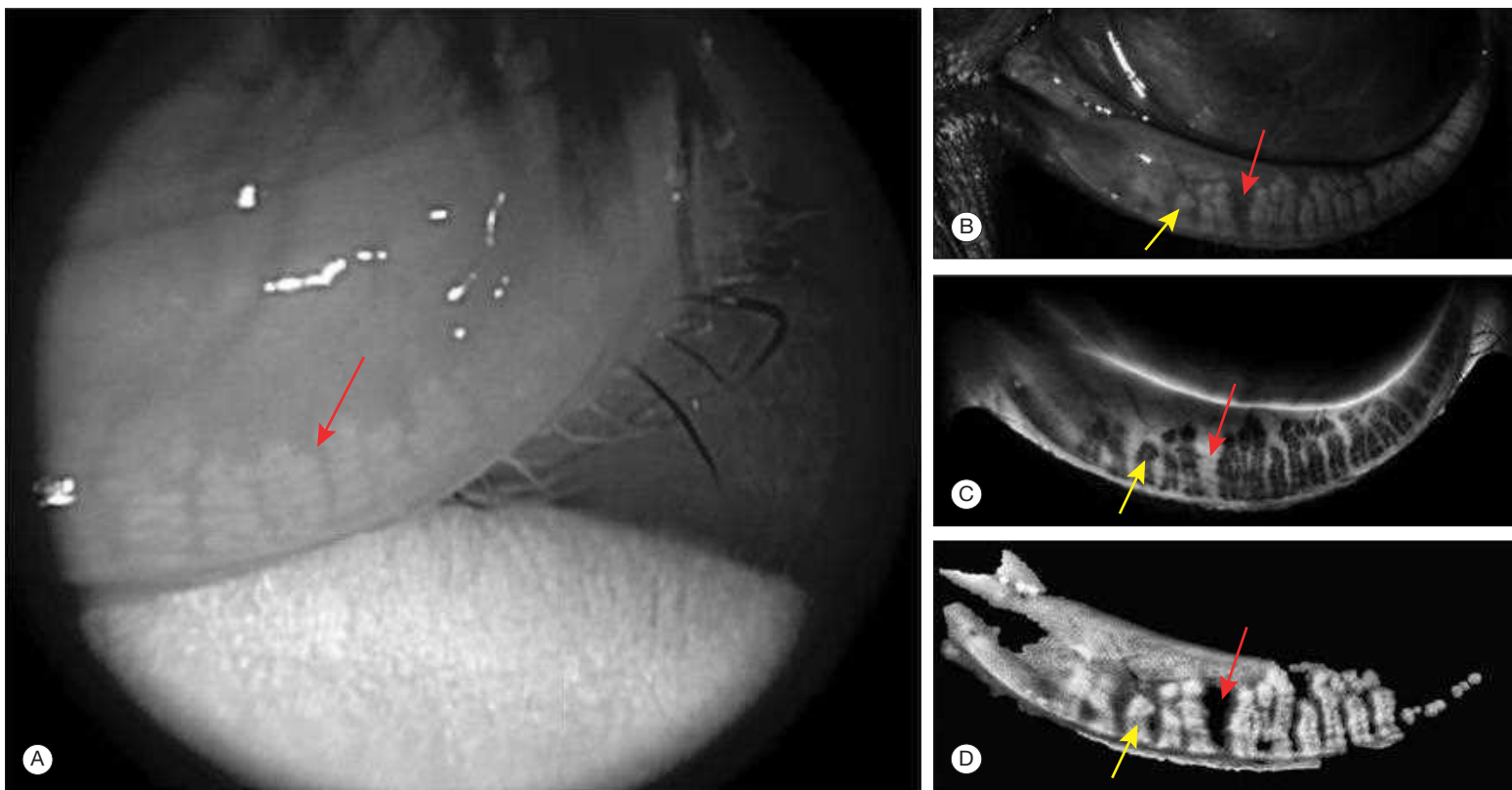
## MEIBOGRAPHY

Meibography comprises various in vivo techniques that can study the structure of meibomian glands (MGs) and their abnormalities.<sup>25,26</sup> Traditionally, using white light and an infrared camera, meibography has evolved over time to employ infrared or near-infrared spectrum of light (wavelength 650–700 nm) and a camera with filter for infrared light or infrared-sensitive film for photography or videography. Infrared light may not be visible to the naked eye but provides high-resolution images.<sup>25,26</sup> Meibography may be employed using transillumination (contact), direct illumination (noncontact), interferometry, or by AS-OCT. In contact meibography, transilluminated MGs are seen after a fiberoptic light probe touches the palpebral surface of an everted eyelid. In noncontact meibography, the infrared light probe does not touch the lid, and a camera is used to visualize glands. This technique is more tolerable for patients because of its noncontact nature and now has been employed in various slit-lamps and other imaging devices.<sup>25–27</sup> The technique of using an AS-OCT device to view MGs is termed OCT meibography.<sup>25</sup> Ocular surface interferometers use white light, which produces a color interference pattern when it strikes the lipid–aqueous interface. This interference is quantified to assess MG structure and lipid layer thickness (LLT), as well as blink dynamics as measures of MG function.<sup>28</sup> A list of some commercially available meibography devices is given in Table 4.2.3.

## Clinical Applications

Normal MGs appear as hyperilluminated acini clusters that are surrounded by hyperilluminated ducts, adjacent to orifices and hypoilluminated areas between the MGs. The noncontact technique shows a similar image, but the contrast is inverted.<sup>29</sup> There are several classification systems in literature to assess MGs (Table 4.2.4).<sup>25</sup> These include systems based on the





**Fig. 4.2.7** (A) Meibography with anterior segment optical coherence tomography (AS-OCT) showing dysfunctional meibomian glands (MGs) (red arrow); glands are shortened, wider and do not reach the lid margin; (B–D) Lipscan images in dynamic illumination mode, adaptive transillumination mode, and dual mode, respectively; images show loss of glands (red arrows) and shortened glands that do not reach the lid margins (yellow arrows).

number of glands, percentage of partial glands, and percentage area of gland dropout (Fig. 4.2.7).<sup>27,30</sup>

### Meibomian Gland Dysfunction

The most commonly studied disease that causes an alteration of MG morphology is meibomian gland dysfunction (MGD). Viewing the MGs can help differentiate the aqueous-deficient subtype of dry eye disease (DED) from the evaporative type related to MGD. MGD can be seen on meibography as a decrease in acinar density and wall homogeneity and an increase in acinar and duct diameter.<sup>25</sup> MG dropout of the lower lid is a highly effective parameter to measure MGD as it correlates with the acinar histological findings.<sup>31,32</sup>

### Limitations

In contact meibography, patient tolerability is lower compared with non-contact meibography; topical anesthesia may need to be employed in contact meibography.

## IN VIVO CONFOCAL MICROSCOPY

IVCM allows for real-time, layer-by-layer, and near-histological resolution cellular imaging in four dimensions.<sup>33</sup> The principle of IVCM is confocality: By utilizing a white or laser light and pinhole, light is focused at a point, and reflected scattered light is deflected through a second confocal aperture.<sup>34,35</sup> Because of different indices of refraction of the various structures, different types of light scatter differently. Size, orientation, and surface of structures may influence light scatter; rough surfaces scatter beam broadly, and vice versa.<sup>35</sup> Through slicing of a tissue in various focal planes, various layers can be visualized, a concept known as “optical slicing.”<sup>34</sup> The types of IVCMs in use are discussed in Table 4.2.5. Cellular details of the cornea magnified up to 800-fold, including epithelial cells, keratocytes, endothelial cells, corneal nerves, and immune and inflammatory cells, including dendritic cells, can be viewed by laser IVCM.<sup>33,34</sup>

## Clinical Applications

### Dry Eye Disease and Neuropathic Corneal Pain

Changes from normal architecture can be seen in several corneal disorders using IVCM. With DED, epithelial and stromal changes may be viewed as

**TABLE 4.2.5** Comparison of the Types of In Vivo Confocal Microscopes

Types	HRT III with Rostock Cornea Module (Heidelberg Engineering)	Confoscan 4 (Nidek, Inc.)
Light source	670 nm laser beam	Variable slit
Objective magnification	× 63	× 40
Numerical aperture	0.95	0.75
Axial (z-axis) resolution	1 μm	26 μm
Image size	400 μm × 400 μm	460 μm × 345 μm
Stability	Applanation device provides stability	Noncontact objective lens; less stable while changing focal planes
Ease of use	Needs manual adjustment to change focal plane after 80 μm, or requires add-on joystick	User-friendly (automatic alignment and scanning)

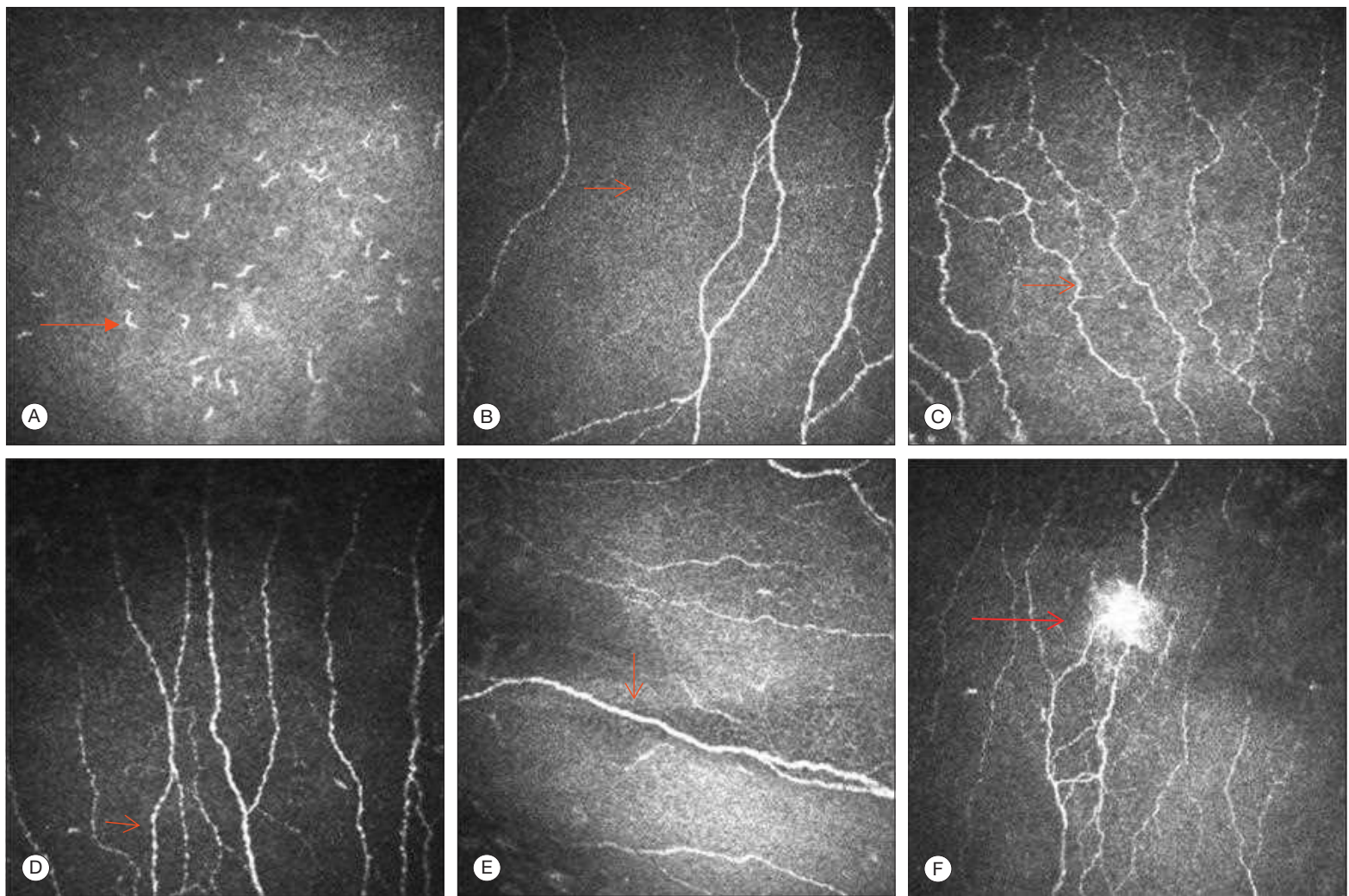
a decrease in density of superficial and basal epithelial cells and keratocytes. Inflammation associated with DED may present with activated keratocytes (identified by increased nuclear reflectivity) and with an increase in density and activation of dendritic cells (Fig. 4.2.8A).<sup>36,37</sup> A decrease in length, number, and density of nerve fibers in subbasal nerve plexus and an increase in width, tortuosity, reflectivity, and beading can be seen in patients with DED and neuropathic corneal pain (NCP) (Fig. 4.2.8B–F).<sup>33,36</sup> Abnormal nerve regeneration with presence of microneuromas may be seen in patients with NCP.<sup>33</sup>

### Infectious Keratitis and Demodex

IVCM is a useful noninvasive tool to support the identification of various infectious agents. *Acanthamoeba* cysts and trophozoites can be visualized directly as bright reflective areas (Fig. 4.2.9A).<sup>38</sup> Filaments of *Fusarium solani*, *Aspergillus*, and *Candida* and bacterial keratitis caused by microsporidia and *Borrelia*, as well as mites, such as *Demodex*, can also be distinguished (see Fig. 4.2.9B,C).<sup>38,39</sup> Moreover, a decrease in subbasal nerve density can be observed in patients with herpetic diseases.<sup>33</sup>

### Corneal Deposits and Corneal Dystrophies

Corneal deposits, such as in amiodarone-induced keratopathy, present with bright intracellular inclusions on IVCM, whereas long, atypical and



**Fig. 4.2.8** In vivo confocal microscopy (IVCM) showing changes in the subepithelial layer (A); arrow represents dendritic cells associated with inflammation in the basal epithelium. Image of subbasal plexus showing (B) loss of nerves (*arrow*) in dry eye disease; (C) tortuosity (*arrow*); (D) nerve beading (*arrow*); (E) nerve hyperreflectivity (*arrow*) in a patient with DED; (F) microneuromas (*arrow*) in a patient with neuropathic corneal pain.

centripetal epithelial cells are seen in wave-like epitheliopathy. Different types of corneal dystrophies, although diagnosed clinically, can be assessed by IVCM, and examples are given below.<sup>40,41</sup> Epithelial basement membrane dystrophy presents with hyperreflective linear tissue and cysts in the epithelium, distorted basal epithelial cells, and abnormal subbasal nerve plexus.<sup>40</sup> Patients with Meesman's dystrophy have dark areas of the basal epithelium with bright spots and a distorted subbasal nerve plexus.<sup>40</sup> Among stromal dystrophies, lattice dystrophy is visualized as linear, branching, and ill-defined hyperreflective filaments, whereas bright round, irregular or trapezoid deposits are seen with granular dystrophy.<sup>42</sup> Among stromal dystrophies, needle-shaped hyperreflective intrastromal crystalline material are seen in Schnyder's crystalline corneal dystrophy (see Fig. 4.2.9D).<sup>43</sup> Among endothelial dystrophies, FECD presents with guttae, thick Descemet's membrane, and hyperreflective pleomorphic endothelium.<sup>40</sup>

## Limitations

IVCM has a limited field of view; several nonlapping images or image reconstruction are needed.

## TOPOGRAPHY AND TOMOGRAPHY

Corneal topography is a method of visualizing the corneal surface, and tomography involves measuring the entire corneal shape. The standard corneal topographer consists of three components: a Placido disc made up of multiple circles that can be projected onto the corneal surface, a video camera capable of capturing the reflected image of these rings, and a computer with software to digitize the resultant captured images.<sup>44</sup> The digitized image is broken down to individual points around each circle. The distance of every point is measured from the center of the Placido disc image (Fig. 4.2.10). Point-source color topographer can use color LED targets and give accurate readings with reconstruction of every single

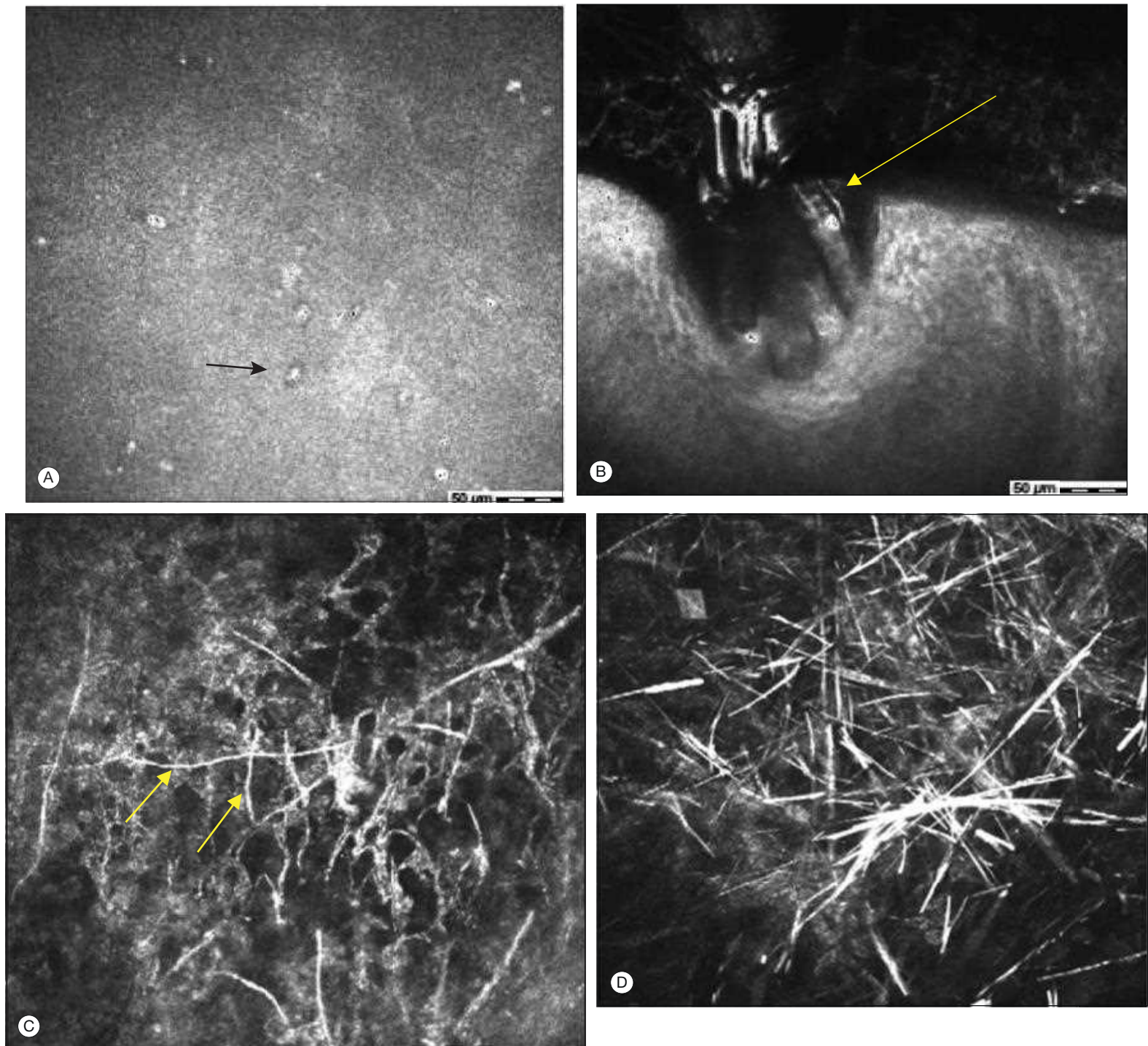
point. Slit-scanning tomography utilizes a slit beam to visualize both the anterior and posterior corneal surfaces to assess corneal shape and thickness. Corneal power and curvature of the posterior cornea are not accurate with this technique; in addition, the power for the anterior cornea is less sensitive than that by Placido disc. Scheimpflug tomography is another technique that has a high depth of focus. Both anterior and posterior cornea, AC, and lens can be visualized. Like slit-scanning techniques, curvature differences are difficult to detect. Types of commercially available hybrid (combination) devices are given in Table 4.2.6. The resulting data are displayed as a corneal curvature maps, consisting of colors corresponding to corneal power and curvature. Steep contours are displayed as warm colors (e.g., red), whereas flat contours correspond to cool colors (e.g., green, blue). Other maps generated include refractive maps (calculate true corneal power), elevation maps (show elevation/depression at both anterior and posterior cornea in comparison to a computer-generated best-fit line; anterior surface is scaled to 10  $\mu$ m and posterior to 20  $\mu$ m), and pachymetry maps (reveal corneal thickness). When interpreting maps, it is important to be cognizant of the scale used. A standard way to present the power of the corneal surface is with the axial power map solution by using a scale whose fixed range (+30.00 to +65.50 D) is broad enough to encompass most variations in corneal curvature and whose standard contour interval (+1.50 D) will highlight only topographic features of clinical significance.<sup>45</sup> Corneal topography powers displayed are best viewed as estimates and should not be routinely used in planning cataract surgery for intraocular lens calculations.<sup>46</sup> Peripheral corneal power estimates are less precise than central measurements.

## Clinical Applications

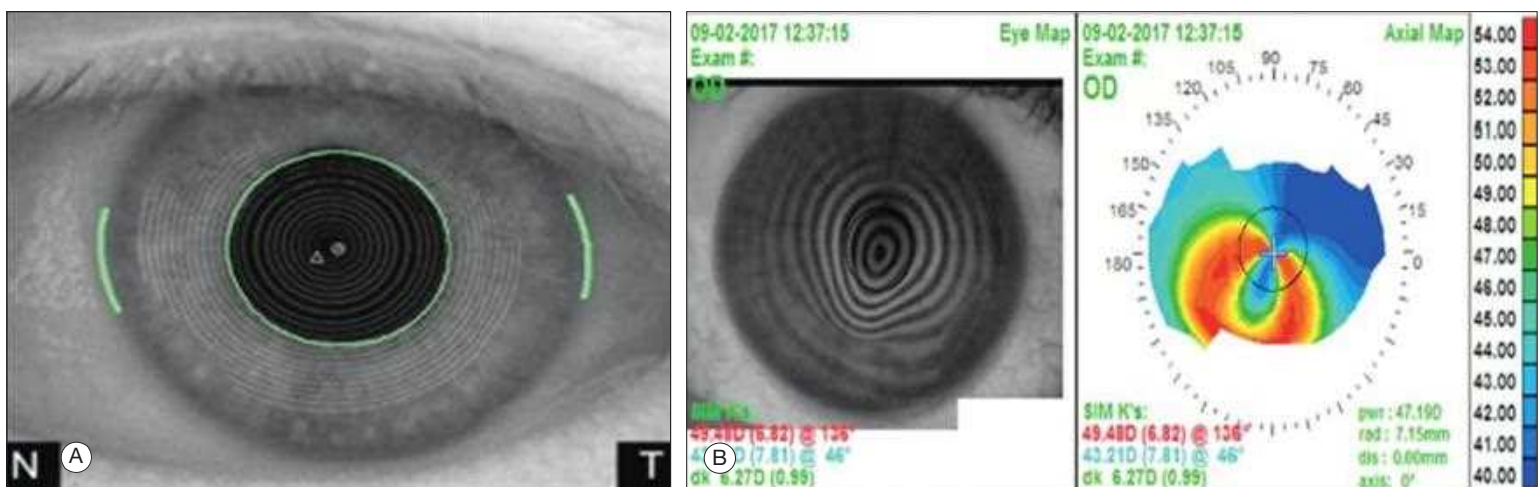
### Refractive Surgery

Corneal topography is used primarily as a screening tool to evaluate prospective refractive surgical candidates and as a diagnostic aid in evaluating



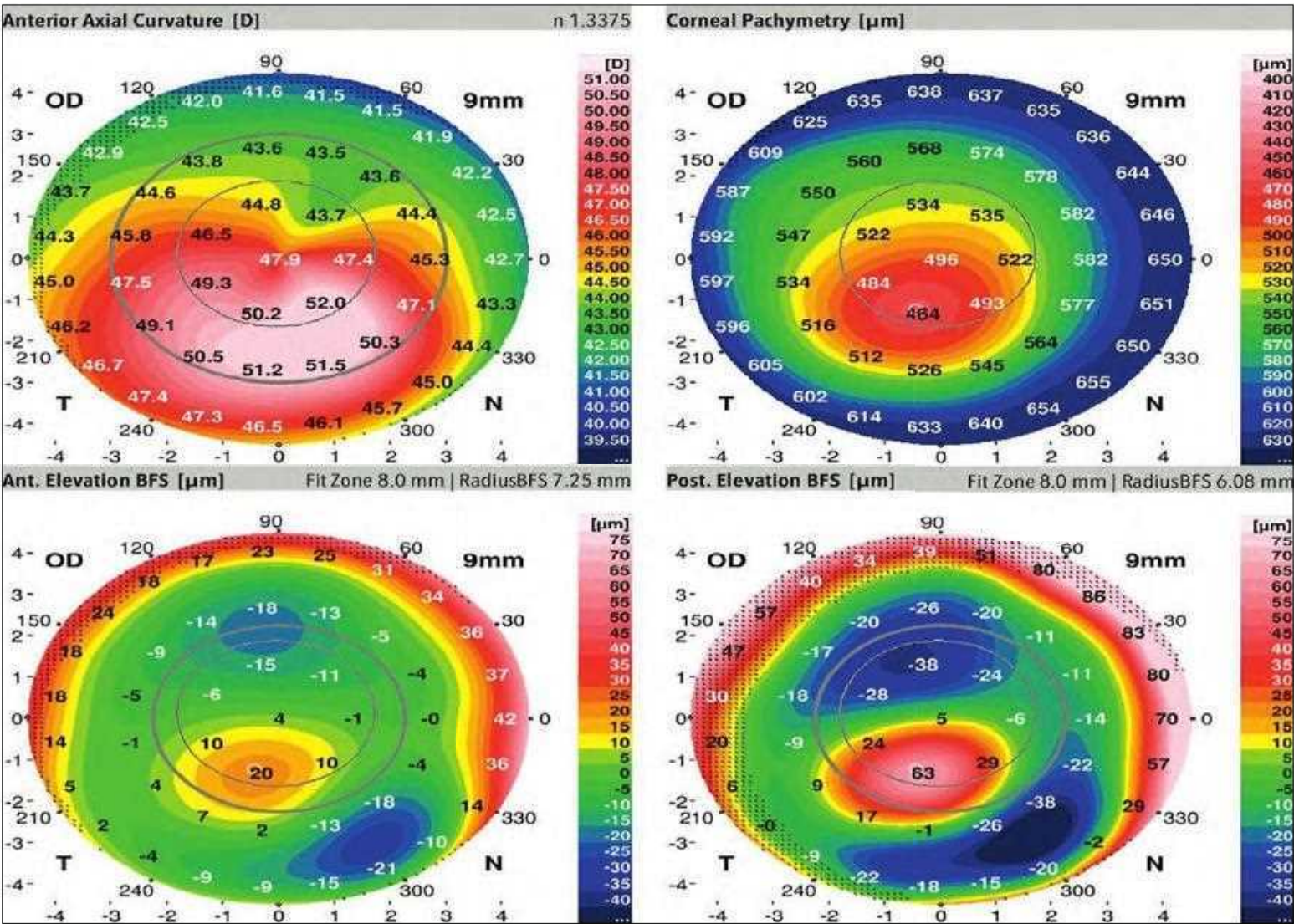


**Fig. 4.2.9** In vivo confocal microscopy (IVCM) images showing (A) *Acanthamoeba* cysts; shown with arrow, visualized as a result of a darker double wall outside the cyst; (B) *Demodex*, visualized in follicles, shown with arrow; (C) fungal filaments in the stroma, shown with arrows; (D) Schnyder's dystrophy; needle-shaped hyperreflective intrastromal crystalline material is seen.



**Fig. 4.2.10** A classic Placido disc mapped (A) in an individual with normal topography; (B) in a cornea with pellucid marginal degeneration, shows ring widening inferiorly.





**Fig. 4.2.11** Topography maps (by Galilei) of a patient with keratoconus; inferior thinning of the anterior curvature (red area) in axial map correlates with lower pachymetry and anterior and posterior elevation.

TABLE 4.2.6 A Comparison of the Types of Topography Devices				
Device	Orbscan	Pentacam	Galilei	Visante Omni
Manufacturer	Bausch & Lomb, Rochester, NY	Oculus, Inc., Wetzlar, Germany	Ziemer Ophthalmic Systems AG, Port, Switzerland	Carl Zeiss Meditec AG, Dublin, CA
System	Placido disc and slit scanning hybrid	Scheimpflug camera (50 images with 180° rotation in 2 seconds)	Dual (vertical and horizontal) Scheimpflug camera Placido hybrid	AS-OCT device (Visante) that attaches to a Placido disc device (Atlas)
Source of illumination	White light	475 nm Blue, UV free, LED	470 nm Blue, UV free, LED	1310 nm superluminescent LED
Type of system	Noncontact	Noncontact	Noncontact	Noncontact
Image size (mm)	–	5.6 × 4.5	7.4 × 7.4	10 × 3
Number of images/scan	40	25–100	15–60	512
Number of points/scan	9000–23,000	>25,000	>122,000	2048
Time of scan (sec)	1.5	2	1–2	

patients with poor vision following refractive surgery. Irregular corneas with steepening are poor candidates for refractive surgery as they are at high risk for postoperative ectasia.<sup>44,47</sup> In eyes with a history of refractive surgery, intraocular lens calculations using regular algorithms are inaccurate; topography data can help understand the new anterior–posterior corneal surface ratio.

### Ectasia-Related Disorders

Keratoconus and contact lens use are the most common causes of irregular corneas in the screening population. Steep (i.e., red) areas isolated in the inferior cornea suggest keratoconus. Many topographers come equipped with programs to alert the clinician when a diagnosis of keratoconus is likely (Fig. 4.2.11). Postoperative patients with poor vision should undergo

topography; for example, irregular ablation profiles, and decentered laser ablations can be assessed with these devices (Fig. 4.2.12).<sup>44,48</sup>

### Astigmatism

Another area where videokeratography plays an important role is the evaluation of patients with significant astigmatism.<sup>49</sup> In the past, only the anterior cornea was measured to evaluate astigmatism, but more recently, the contribution of posterior cornea has been highlighted. Topographic images can be helpful in assessing impact of conjunctival lesions, including pterygia and Salzmann’s nodular degeneration, as well as planning interventions, such as astigmatic keratotomy, limbal relaxing incisions, or removal of tight sutures after keratoplasty.<sup>50</sup> Three-dimensional images can be used to assess corneal and lens densitometry, a measure of light backscatter.

## WAVEFRONT ANALYSIS

Wavefront analysis examines the interaction of light with the optical system of an eye, giving a snapshot of the entire optical system.<sup>51</sup> With a perfect optical system, a point source of light emanating from the back of the eye creates a locus of points, with the same optical path length and in the same temporal phase, that exit the pupillary plane in the form of a flat sheet called an *unaberrated wavefront*. With imperfections in the cornea or lens, optical aberrations are created, causing the wavefront to exit as bent

or curved sheets of light. Wavefront aberration is calculated as the difference between the actual wavefront and an ideal wavefront.

Hartmann–Shack devices employ microlenslet arrays to characterize the surface of wavefronts: if the wavefront is flat, it will form a perfect lattice of points corresponding to the axis of each lenslet; if the wavefront is aberrated, it will result in a displaced spot on the grid (Fig. 4.2.13). The displacement in location, from the ideal, represents a measure of the shape of the wavefront. The complex shapes can be analyzed by deconstruction using Zernike's and Fourier's polynomial equations and basic shapes (Fig. 4.2.14).<sup>51</sup>

Wavefront maps are displayed as two-dimensional maps: green indicates minimal distortion, blue characterizes myopic wavefronts, and red represents hyperopic wavefront errors (Fig. 4.2.15A). The root mean square value quantifies the wavefront error and compares it to normal: values approaching 1  $\mu\text{m}$  for individual aberrations are considered abnormal.

## Clinical Applications

### Refractive Surgery

Wavefront technology has utility in refractive errors, especially in laser ablation for spherocylindrical errors. Traditional lasers can induce spherical aberrations; custom laser treatment that incorporates a wavefront-designed algorithm helps limit this and improves night vision (as aberrations are more pronounced with wider pupil) (see Fig. 4.2.15B).<sup>52</sup>

### Limitations

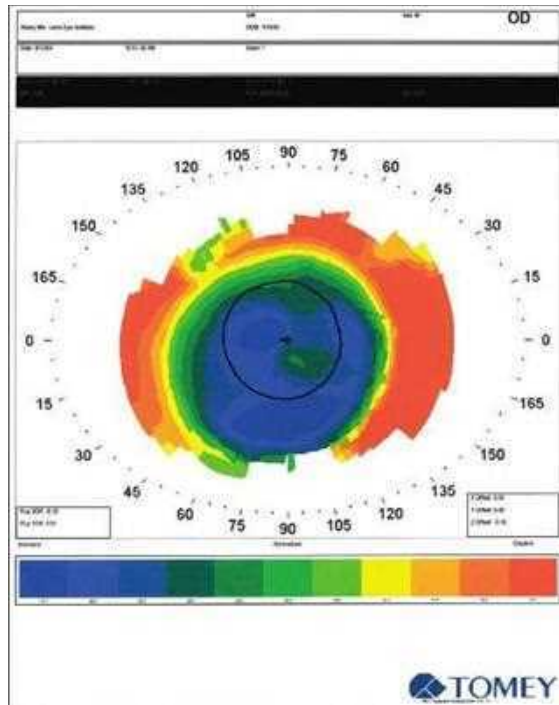
Wavefront may be affected by pupil size, vitreous or lens opacities, and the quality of the tear film. Hence, it may not be accurate in some conditions, such as DED. Additionally, the resolution of a wavefront is much lower than that of topography.

## SUMMARY

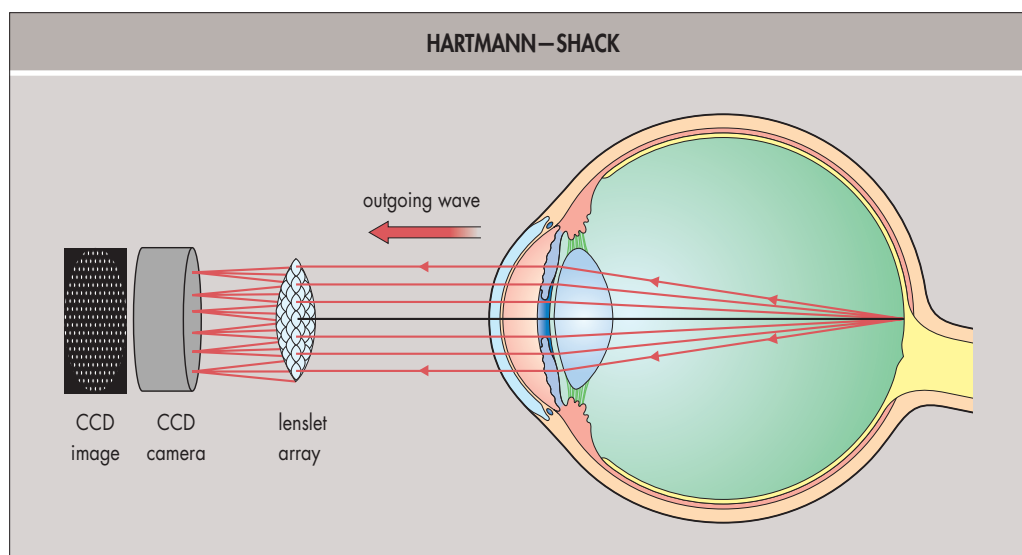
The above-mentioned modalities have clinical utility in various diseases. The choice of modality depends on the clinical experience of the physician and the area to be visualized.

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**Conflict of Interest:** Dr. Hamrah is consultant for Heidelberg Engineering, Allergan, Eyegate Pharmaceuticals, and Dompe Pharmaceuticals.

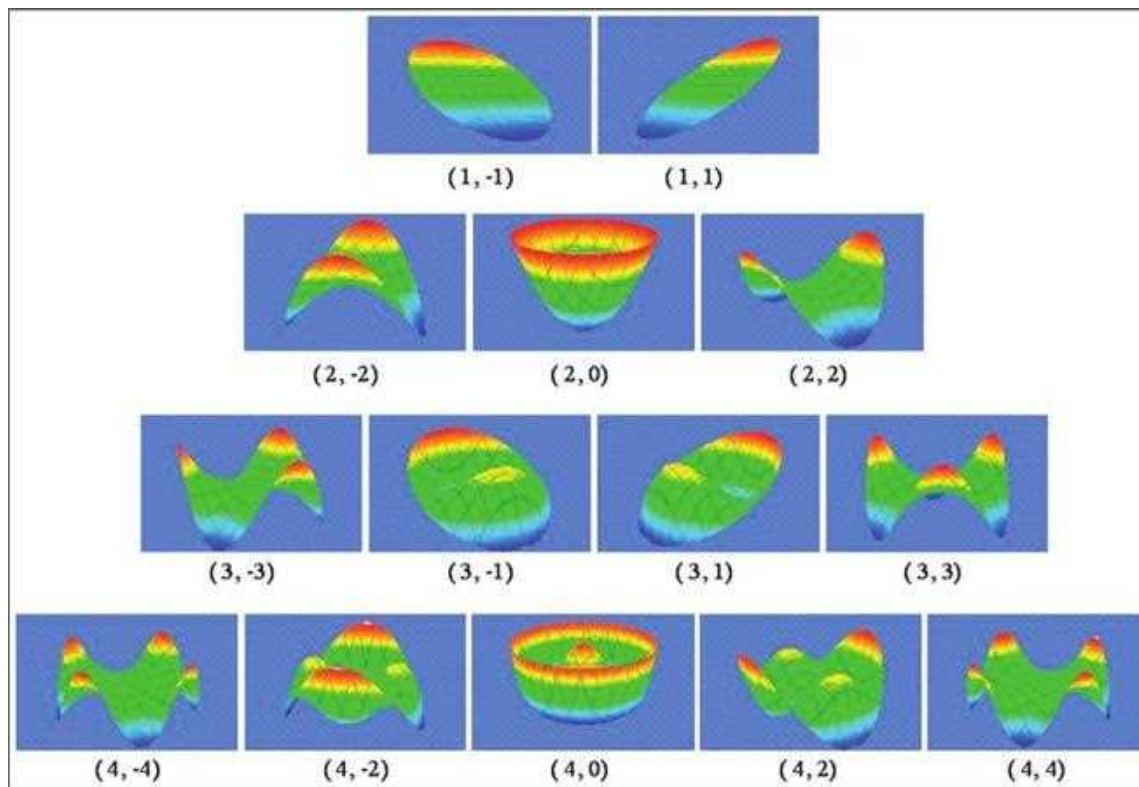


**Fig. 4.2.12** Decentered laser ablation pattern. Blue area represents laser-induced corneal flattening and the pupil is outlined with a black circle. Patients with decentered ablations may have poor vision and night vision problems such as glare or ghosting of images.

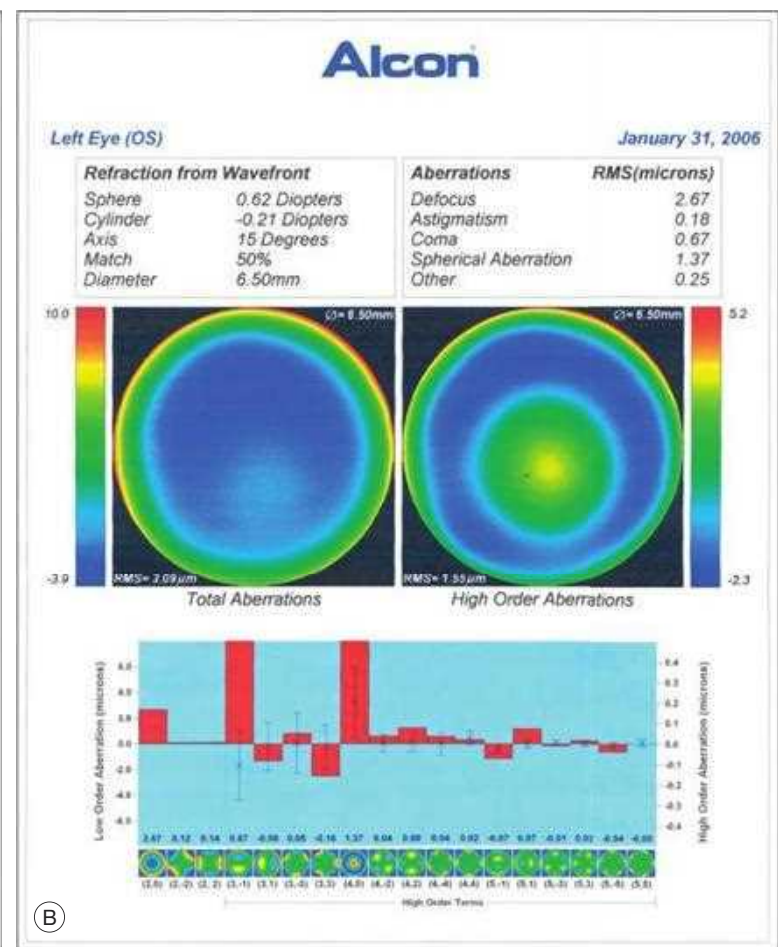
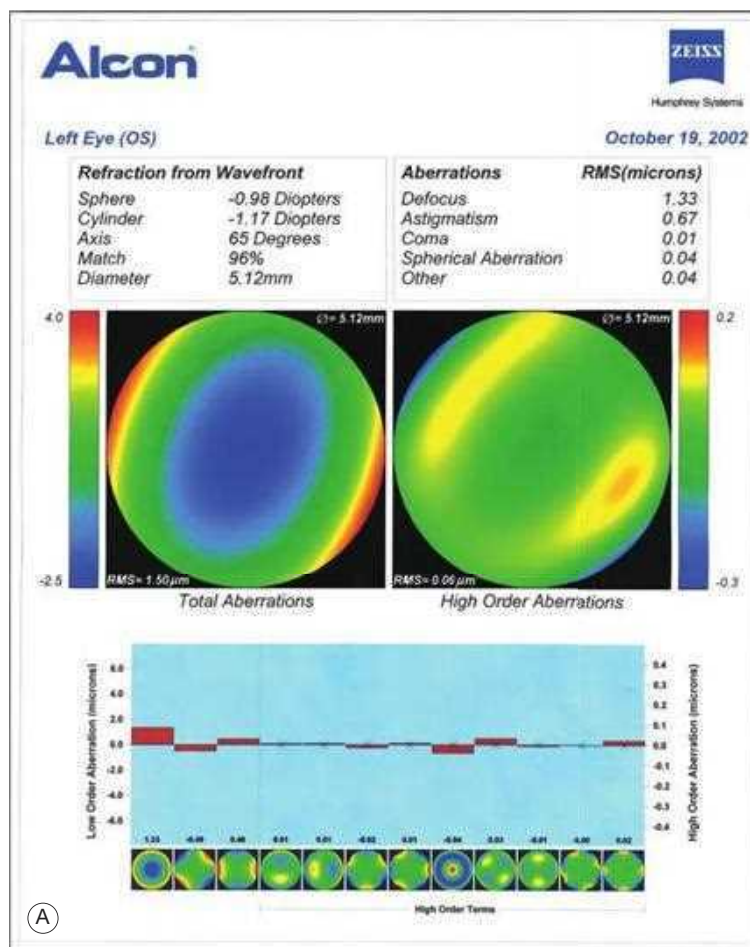


**Fig. 4.2.13** Schematic of Hartmann–Shack device used to capture wavefront data. (Courtesy AMO VISX.)





**Fig. 4.2.14** The fundamental Zernike's shapes. Complex wavefront maps can be deconstructed to determine the individual contribution of these shapes. Spherical aberration is a fourth-order term and is represented by the central figure in row 4. Coma is a third-order term and is represented by the two central figures in row 3.



**Fig. 4.2.15** (A) Normal wavefront map. The left side of the map shows total aberrations including nearsightedness and astigmatism. The right side represents higher-order optical aberrations only. (B) Wavefront map of a patient with post-LASIK night vision problems. The patient complaints are most likely caused by spherical aberration.



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# Congenital Corneal Anomalies

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## 4.3

**Definition:** Developmental abnormalities of the cornea present at birth.

### Key Features

- Inherited or sporadic but not acquired.
- Generally involve dysgeneses of anterior segment mesenchyme.
- Frequent association with iris, angle, and lens anomalies.

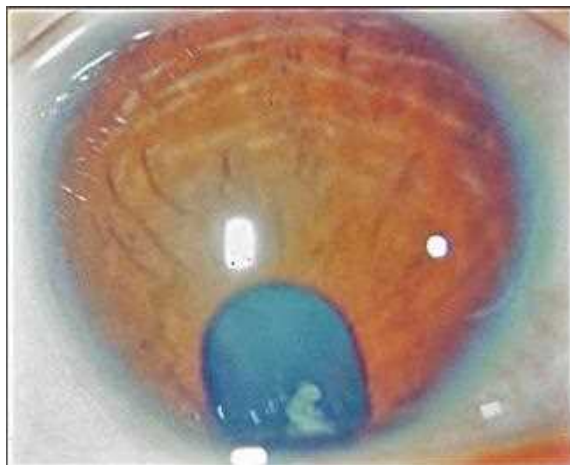
## INTRODUCTION

Developmental corneal anomalies are evident at birth, consequent to genetic, teratogenic, or idiopathic causes. During gestational week 5, as the lens vesicle separates from the surface ectoderm, the neural crest mesenchyme migrates between the surface ectoderm and the optic cup.<sup>1</sup> The first wave of mesenchyme becomes the corneal endothelium and trabecular meshwork, the second becomes corneal keratocytes, and the third becomes the anterior iris stroma. Aberrations in this process result in the anomalies of corneal size, shape, and clarity, most commonly posterior polymorphous dystrophy, Peters' anomaly, congenital glaucoma, and sclerocornea. Although pediatric keratoplasty is a challenging and complex procedure, recent series with a 40-month mean follow-up reported up to 78% graft success.<sup>2</sup> However, medical therapy remains the predominant management (52.7%) of such eyes.<sup>3</sup>

## SIZE AND SHAPE ANOMALIES

### Microcornea

The normal horizontal corneal diameter is 9.5–10 mm at birth increasing to 10–12.5 mm by adulthood. An adult cornea that is less than 10 mm horizontally is considered microcornea<sup>4</sup> and may occur in conjunction with microphthalmos, often associated with colobomas of the iris, retina, choroid, and even optic nerve (Fig. 4.3.1).<sup>5–11</sup> In contrast, nanophthalmos is a small functional eye that retains normal internal organization and proportion.



**Fig. 4.3.1**  
**Colobomatous Microphthalmos.**  
The cornea is reduced in diameter but clear and the inferior iris coloboma is typical.

### Epidemiology, Pathogenesis, and Ocular Manifestations

Most cases are sporadic, although autosomal recessive and autosomal dominant pedigrees have been reported.<sup>12</sup> In microcornea, because the remainder of the eye is normal in size, lens development may cause angle-closure glaucoma. Microphthalmos in association with dermal aplasia and sclerocornea is termed *MIDAS (microphthalmia, dermal aplasia, and sclerocornea) syndrome* (caused by deletion in Xp22).<sup>13,14</sup> An autosomal dominant variant of microcornea plus other anterior segment anomalies has been described.<sup>15</sup> Microcornea also occurs in conjunction with numerous other anomalies, including the “micro-” syndrome of microcornea, congenital cataract, mental retardation, retinal dystrophy, optic atrophy, hypogenitalism, and microcephaly.<sup>5,16,17</sup> It is also associated with fetal alcohol syndrome.<sup>18</sup>

### Treatment

Treatment involves spectacle correction for high hyperopia resulting from flat anterior corneal curvature. Other associations, such as cataract and glaucoma, are managed independently.

## Megalocornea

### Epidemiology, Pathogenesis, and Ocular Manifestations

Megalocornea with bilateral anterior segment enlargement is defined as horizontal corneal diameter of greater than 12 mm at birth or greater than 13 mm after age 2 years (Fig. 4.3.2). Most commonly associated with mutations in the *CHRD* (Xq23) gene, which encodes ventropin,<sup>19–21</sup> defective growth of the optic cup is hypothesized to leave larger space for the development of the cornea. Congenital megalocornea with childhood secondary glaucoma from spherophakia and/or ectopia lentis is a distinct condition caused by recessive *LTBP2* (14q24) mutations that must to be distinguished from buphthalmos—enlargement of the entire globe secondary to primary congenital/infantile glaucoma.<sup>22</sup>

A number of variants have been described, and of those, the autosomal dominant form without other ocular abnormalities is the least common. X-linked recessive megalocornea is more frequent and is associated with iris transillumination, pigment dispersion, lens subluxation, arcus, and central crocodile shagreen.<sup>23,24</sup> Endothelial cell density is normal, and this confirms that the enlargement does not arise from corneal stretching, and corneal clarity and thickness usually are normal.<sup>25</sup> The genetic locus for X-linked megalocornea resides in the Xq21–q22.6 region. Megalocornea has been associated with congenital miosis,<sup>26</sup> ectopia lentis, ectopia pupillae, mental retardation, congenital Marfan's syndrome, albinism, and Neuhauser's syndrome.<sup>20,27</sup> Further distinction, however, is required from megalophthalmos, a probably autosomal recessive condition, comprising an enlarged cornea in an overall enlarged eye without glaucoma, also resulting in increased axial length (often >30 mm), juvenile cataract, and high myopia.<sup>28</sup>

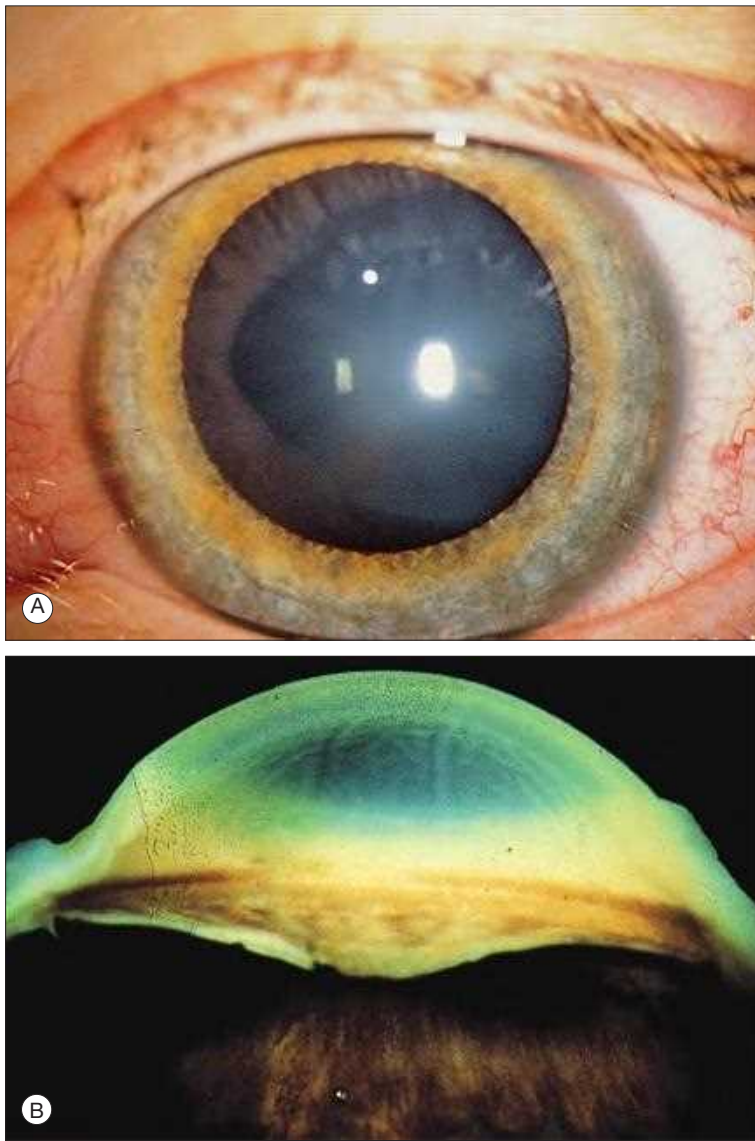
### Treatment

Treatment is not necessary apart for spectacle correction for myopic refractive error and for somewhat challenging cataract surgery in a much enlarged anterior segment.<sup>29</sup>

## Corneal Absence

Developmental absence of the cornea does not occur in isolation, rather as a concomitant of severe dysgenesis of the anterior segment or the entire eye. Anophthalmos—total or subtotal absence of the entire eye—is consequent to, for example, extreme developmental disorders.<sup>30–32</sup> Cryptophthalmos involves partial or complete failure of eyelid formation, corneal dermoids, and either a hypoplastic anterior segment or a rudimentary cyst-like globe





**Fig. 4.3.2 Megalocornea.** (A) The cornea is clear but enlarged to 14 mm diameter bilaterally. (B) Gross examination of postmortem specimen discloses normal cornea of large diameter and heavily pigmented trabecular meshwork probably consequent to iris pigment dispersion. (B, Courtesy Dr. M. Yanoff.)

with absence of anterior segment. Cryptophthalmos associated with systemic anomalies, such as syndactyly and genitourinary defects, is known as *Fraser's syndrome*, an autosomal recessive trait.<sup>33</sup> Pseudo-cryptophthalmos occurs when the lids fail to separate, but the underlying globe is intact.

### Congenital Anterior Staphyloma

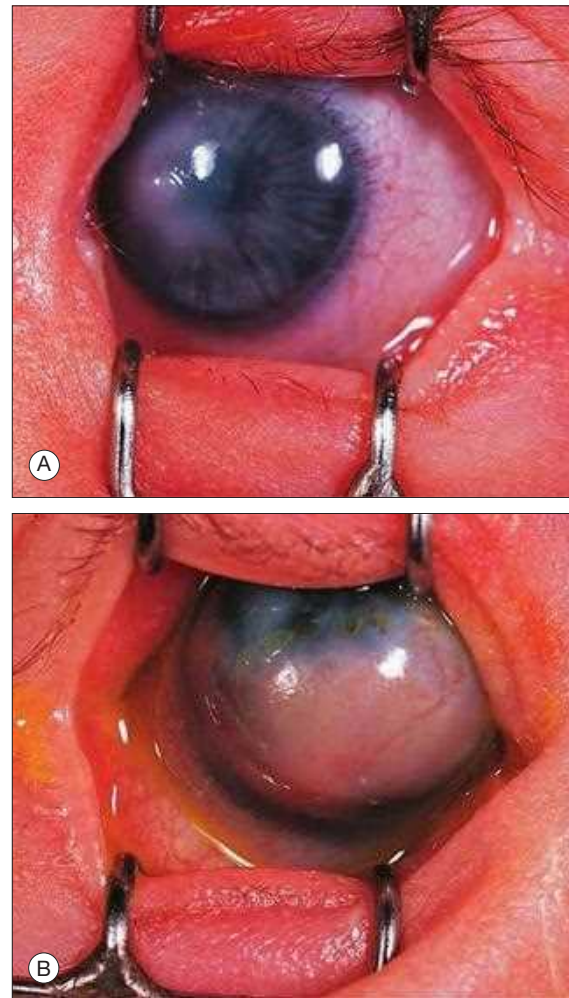
Keratoglobus (see Chapter 4.18) is not congenital, but a more extreme corneal ectasia may be present at birth as part of congenital anterior staphyloma, often also in concert with severe variants of Peters' anomaly (Fig. 4.3.3). This anomaly is usually unilateral and frequently also presents with iris developmental defects. Anterior staphyloma may occur consequent to inflammatory or infectious corneal thinning in utero.

### ANOMALIES OF CORNEAL CLARITY

Depending on the affected wave(s) of neural crest mesenchyme migration, various corneal, angle and/or iris structures are compromised (Table 4.3.1).

#### Anterior Embryotoxon

Anterior embryotoxon represents a congenitally apparent widening of the superior limbal transition from sclera to cornea. The term also describes arcus juvenilis, an appearance similar to arcus senilis but present at birth. Although often sporadic, autosomal dominant and autosomal recessive pedigrees have been described.



**Fig. 4.3.3 Mesenchymal Dysgenesis of the Anterior Segment.** (A) Typical Peters' anomaly type I with central corneal opacity. (B) Congenital anterior staphyloma includes features of Peters' anomaly plus extreme corneal ectasia and thinning.

**TABLE 4.3.1 Relationship of Embryonic Neural Crest Migratory "Waves" to Various Anomalies**

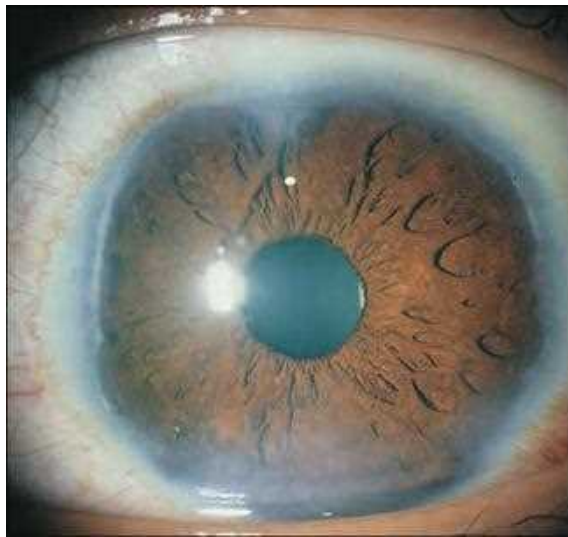
Anomaly	Mesenchymal Wave Abnormality		
	1st	2nd	3rd
Posterior embryotoxon	x		
Axenfeld-Rieger syndrome	x		x
Peters' anomaly	x		x
Posterior keratoconus	x		
Sclerocornea		x	

### Posterior Embryotoxon

Posterior embryotoxon is highly prevalent, occurring in perhaps 24% of a random population.<sup>34</sup> It comprises thickening and anterior displacement of Schwalbe's line, most readily apparent in the temporal cornea (Fig. 4.3.4). The term *toxon*, derived from the Greek word for "bow," in reference to the crescent of Schwalbe's line, when present alone has no functional significance.

### Corneal Keloids

Keloids are white, glistening, protuberant lesions that involve all or part of the cornea. Although usually resulting from trauma or ocular inflammation, they may be evident at birth. Histopathologically comprising an irregular array of collagen, fibroblasts, and capillaries within the corneal stroma, they sometimes progress and may be associated with oculodigital disorders, such as Lowe's syndrome.<sup>35</sup> In otherwise healthy eyes, keratoplasty is appropriate.<sup>36,37</sup> For lesions where growth causes discomfort, corneal dissection with a conjunctival flap may halt progression.



**Fig. 4.3.4**  
**Posterior Embryotoxon.**  
Anteriorly displaced Schwalbe's line is evident nasally, superiorly and temporally.

## Dermoids

Dermoids are choristomas, defined as benign growths of tissue not normally present at a given location, and in the cornea they typically develop at the inferotemporal limbus where fusion of optic cup fissure occurs. At times they may involve larger areas of the cornea, the entire limbus, the entire cornea, or the interior of the eye. They usually are round, domed, pink to white to yellow in color and may have hair or, in the lipodermoid variant, globules of lipid. Depending on size, they constitute a minor cosmetic concern but may induce astigmatism or even consequent amblyopia, in which case surgical excision is indicated as also for larger lesions of anatomical and cosmetic concern. Limbal dermoids may be associated with other malformations, commonly Goldenhar's syndrome, comprising lid colobomas, hemi-facial microsomia, preauricular skin tags, and other ear anomalies (Fig. 4.3.5). Other mandibular and other facial anomalies may be concomitant and may be part of trisomy 8 mosaicism.<sup>38</sup>

Histopathology confirms the presence of skin-like collagen with skin adnexal appendages, which include hair follicles, sweat and sebaceous glands, and fat. When indicated, surgical treatment usually consists of simple superficial lamellar dissection, although the depth of the lesion, on rare occasions, requires focal lamellar keratoplasty.<sup>39</sup> Although infrequent, dermoids may involve the full thickness of the eye wall; ultrasound biomicroscopy<sup>40</sup> is useful to avoid surgical surprises. Rare spontaneous partial regression has been reported.<sup>41</sup>

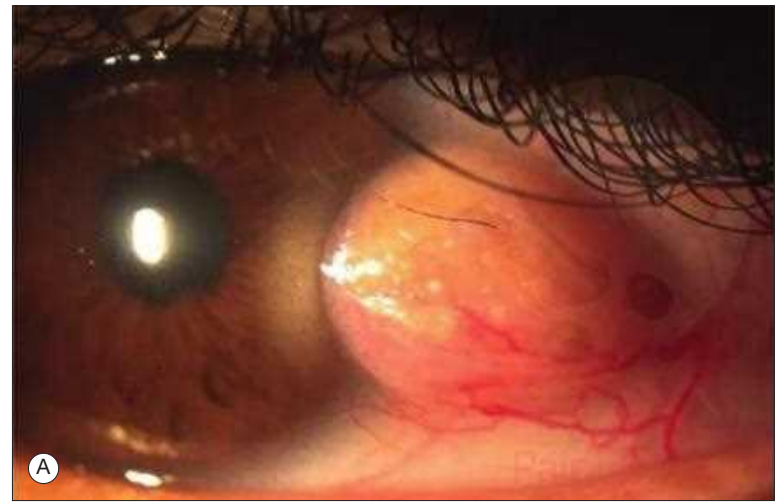
## Axenfeld's Anomaly and Rieger's Syndrome

Axenfeld's anomaly comprises bilateral posterior embryotoxon often associated with iris strands adherent to Schwalbe's line (Fig. 4.3.6). Rieger's syndrome includes Axenfeld's anomaly plus iris atrophy, corectopia, and polycoria. Dental anomalies and a flattened midface and nasal bridge are common with the Axenfeld–Rieger syndrome (Fig. 4.3.7). Thus in describing this spectrum, the term *anomaly* refers to the localized anatomical changes, whereas the term *syndrome* describes more widespread ocular and systemic findings. Glaucoma occurs in about half the patients with Axenfeld–Rieger syndrome.<sup>42</sup> Seemingly, Axenfeld's anomaly and Rieger's syndrome arise from retention of neural crest remnants and primordial endothelium on the iris and chamber angle.<sup>43</sup> Defects in the *PITX2* and *FOXC1* gene on chromosome 4q25 and in the *FKHL7* gene on 6p25, as well as other defects, have been found in different patients with Axenfeld–Rieger syndrome.<sup>44,45</sup> Differential diagnosis includes iridocorneal endothelial syndrome (which is acquired and usually unilateral), posterior polymorphous dystrophy with iridocorneal adhesions, and iridogoniodysgenesis syndrome.<sup>46,47</sup>

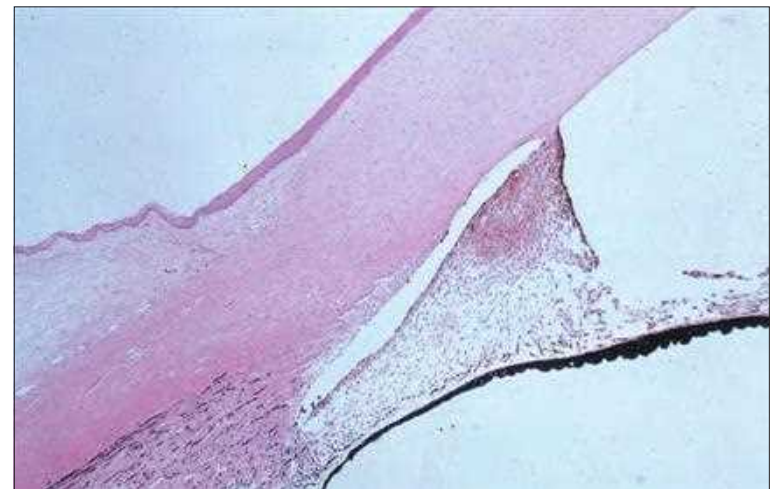
## Peters' Anomaly

### Ocular Manifestations

Peters' anomaly comprises another mesenchymal dysgenesis condition, with most cases being sporadic but also exhibiting recessive and occasional dominant inheritance. In 80% of cases, the condition is bilateral. The manifestations are variable, with the classic type I consisting of a central



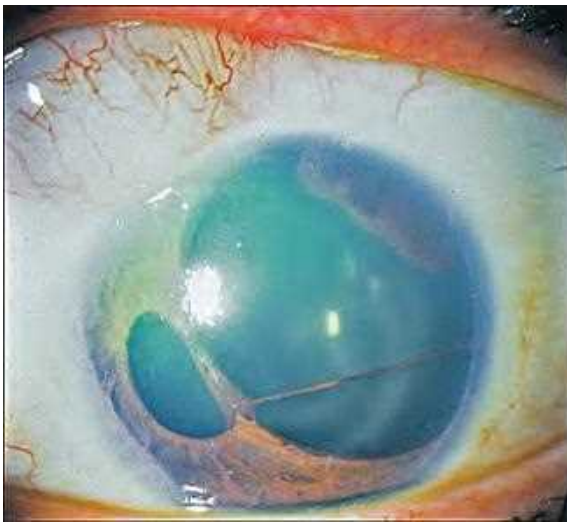
**Fig. 4.3.5** **Goldenhar's Syndrome.** Limbal dermoid (A) associated with preauricular skin tags, and ear anomalies (B).



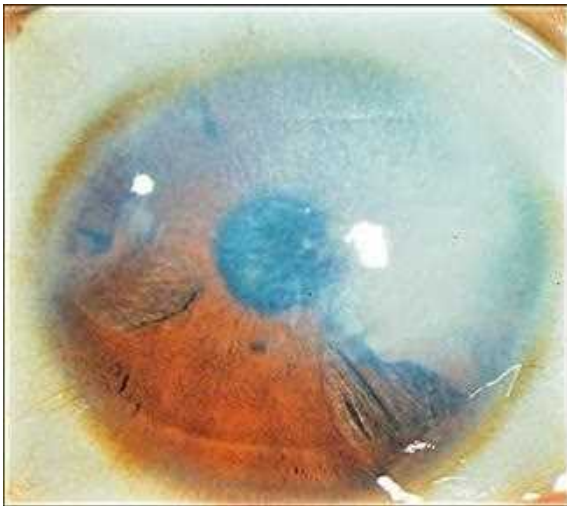
**Fig. 4.3.6** **Axenfeld's Anomaly.** Histological section shows an iris process attached to the anteriorly displaced Schwalbe's ring (posterior embryotoxon). (Courtesy Dr. R. Y. Foos.)

corneal stromal opacity and iris strands arising from the collarette and attaching to the periphery of the opacity. Initially, a central endothelium and Descemet's membrane defect results in marked corneal edema (see Fig. 4.3.3); with time, however, the endothelium can regenerate centrally, and the edema may regress.<sup>48–50</sup> So-called posterior keratoconus and the internal ulcer of von Hippel may be considered as Peters' anomaly without iris adhesions. A type II variant has been characterized with lens adherence to the posterior cornea and/or cataract. Type I usually is unilateral, whereas type II is frequently bilateral. Other associated ocular anomalies (Fig. 4.3.8) most frequently include glaucoma in greater than 50% cases but also include microcornea, cornea plana, sclerocornea, chorioretinal





**Fig. 4.3.7 Axenfeld–Rieger Syndrome.** Polycoria with glaucoma bilaterally in a patient with dental and facial anomalies.



**Fig. 4.3.8 Mesenchymal Dysgenesis of the Anterior Segment.** This infant combines features of Peters' anomaly type II plus peripheral sclerocornea and bilateral glaucoma.

coloboma, iris coloboma, angle and iris dysgenesis, persistent hyperplastic primary vitreous, microphthalmos, optic nerve hypoplasia, and foveal hypoplasia.<sup>51</sup>

### Systemic Associations

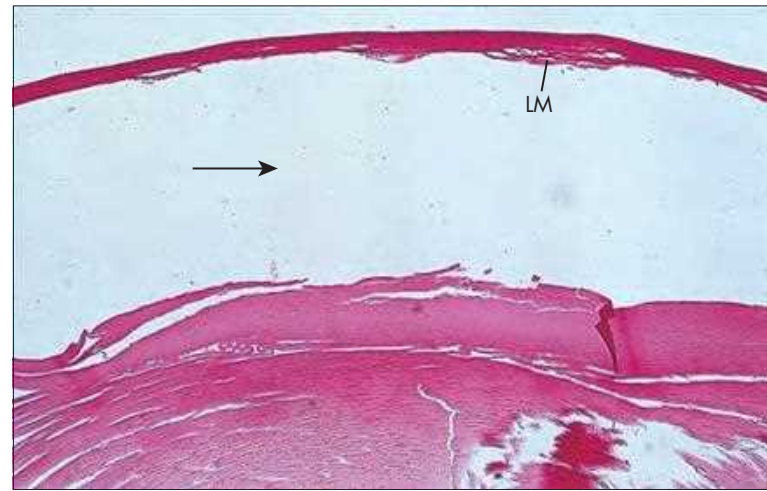
Systemic associations include short stature, facial dysmorphism, developmental delay, and delayed skeletal maturation, constituting the autosomal recessive Krause–Kivlin syndrome. Peters' plus syndrome consists of ocular Peters' anomaly as well as syndactyly, genitourinary anomalies, brachycephaly, central nervous system anomalies, cardiac disease, or deafness.<sup>52–54</sup> Peters' anomaly may be part of fetal alcohol syndrome.<sup>55</sup> Mutations at the PAX 6 locus on chromosome 11p13 in few patients with Peters' anomaly<sup>56,57</sup> are of interest because this gene appears to be important in embryogenesis regulation and also is abnormal in aniridia and autosomal dominant keratitis.<sup>58</sup> Mutations in the *CYP11B1* gene might be causative in Peters' anomaly<sup>59</sup> because this and other gene defects (e.g., Axenfeld–Rieger syndrome, 4q25) have been implicated in ocular development as well as glaucoma.<sup>60</sup>

### Pathology

The pathology of Peters' anomaly shows absence of central Descemet's membrane and endothelium (Fig. 4.3.9), which may undergo repair over time. Other features include residual fibrosis in the opacified stroma and central absence of Bowman's layer.

### Treatment and Outcome

Primary therapy includes treatment of glaucoma, if present. Penetrating keratoplasty is clearly appropriate when corneal opacification is bilateral.



**Fig. 4.3.9 Peters' Anomaly.** Histopathological section demonstrates lens material (LM) attached to the posterior cornea. Centrally, the endothelium, Descemet's membrane, and Bowman's layer are not present. Large space (arrow) is fixation shrinkage artifact. (Courtesy Dr. M. Yanoff.)

Questioning whether keratoplasty for funicular Peters' anomaly is effective, a recent study of 14 such cases<sup>61</sup> disclosed 11 patients (78.6%) had clear grafts at 30 months' follow-up, with 10 gaining seemingly useful vision. For eyes with localized central opacity and clear midperiphery, optical iridectomy can afford a far more simplified and visually effective course. Of increasing importance to surgical decision making is the use of spectral domain–optical coherence tomography (SD-OCT) to facilitate anterior segment microstructural resolution in these complex and variable situations.<sup>62</sup> For children at high risk for keratoplasty failure, the Boston keratoprosthesis has become an alternative<sup>51</sup> because despite the challenges of long-term management, useful vision may result.<sup>63,64</sup>

### Sclerocornea

Sclerocornea defines a nonprogressive, noninflammatory scleral-like clouding of the cornea, which may be peripheral or diffuse (see Fig. 4.3.8). Resulting from defective second wave mesenchyme migration, it can cause corneal flattening or cornea plana because of limbal involvement. Sclerocornea additionally may be associated with other entities in the spectrum of anterior segment developmental defects (see Table 4.3.1), such as Peters' anomaly (see Fig. 4.3.9). Glaucoma is common, as are other systemic and ocular anomalies, as previously discussed. Inheritance may be autosomal dominant, recessive, or X-linked, although most cases are sporadic and usually bilateral. Once glaucoma has been controlled, penetrating keratoplasty or perhaps the Boston keratoprosthesis is appropriate, although outcomes usually are poor because of glaucoma and/or optic nerve anomalies.

### Congenital Hereditary Endothelial Dystrophy and Congenital Stromal Corneal Dystrophy

These two inherited corneal dystrophies are manifest at birth and, as such, comprise congenital corneal anomalies.

Congenital hereditary endothelial dystrophy appears as diffuse bilateral corneal edema in the absence of elevated intraocular pressure. Although initially held to have both autosomal dominant and recessive forms, recent evidence localizes the genetic defect to 20p13, responsible for sodium borate transport, and the recent International Committee for Classification of Corneal Diseases report<sup>65</sup> recognizes only autosomal recessive inheritance. The often-profound corneal edema results from a primary dysgenesis of the corneal endothelium with concomitant Descemet's layer changes and is appropriately considered a mesenchymal dysgenesis disorder. Rarely is intraocular pressure elevated. The results of keratoplasty generally are favorable.

Congenital stromal corneal dystrophy is a rare autosomal dominant condition resultant from a genetic defect at 12q21.33 producing abnormality of decorin.<sup>65</sup> Clinically diffuse corneal clouding results from myriad flake-like, whitish stromal opacities. Visual loss is variable, and when uncommonly indicated, keratoplasty may be successful.



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# Blepharitis

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## 4.4

**Definitions:** *Blepharitis* is a general term describing inflammation of the eyelids, whereas *marginal blepharitis* is inflammation of the eyelid margin, which can be subdivided into anterior and posterior blepharitis.

*Anterior blepharitis* involves inflammation of the lid margin anterior to the gray line and concentrated around the eyelashes and hair follicles. It may be accompanied by squamous debris, scurfs, and collarettes around the lashes. *Posterior blepharitis* involves inflammation posterior to the gray line, which may have various causes, including meibomian gland dysfunction (MGD) and conjunctivitis.

*MGD* is defined as a chronic, diffuse abnormality of the MGs, commonly characterized by terminal duct obstruction and/or qualitative/quantitative changes in glandular secretion. It may result in alteration of the tear film, symptoms of eye irritation, clinically apparent inflammation, and ocular surface disease.<sup>1</sup>

### Key Features

- Chronic burning, irritation, foreign body sensation, epiphora.
- Inflammatory changes of the eyelid including thickening, erythema, hyperkeratinization, vascularization, telangiectasia, or notching.
- Presence of scurf, collarettes, and sleeves along lashes.
- Minimal meibomian gland secretion with pressure or abnormal meibum, which is turbid, foamy, or granular in appearance.

### Associated Features

- Tylosis (thickening and distortion of the lid margin).
- Poliosis (loss of lash pigmentation).
- Punctal misdirection and/or scarring.
- Conjunctival hyperemia.
- Perilimbal superficial corneal neovascularization.
- Catarrhal infiltrates.
- Acne rosacea.

## INTRODUCTION

*Blepharitis*, first described by Elschnig in 1908,<sup>2</sup> poses a significant challenge for the clinician because of its chronic nature and availability of diverse treatment options but minimal scientific evidence for their efficacy.

Nonetheless, given the prevalence of blepharitis, its association with dry eye disease (DED), and its effect on quality of life, better understanding and management of this condition is essential for reducing ocular discomfort and improving the patient's quality of life.<sup>1</sup>

## EPIDEMIOLOGY

MGD is one of the most common disorders encountered by eyecare providers. MGD is now considered the leading cause of evaporative dry eye.<sup>1</sup>

The prevalence of MGD varies considerably in published studies, from 3.5% to almost 70%.<sup>1,3-7</sup>

This striking difference is partly attributed to inconsistent diagnostic criteria among countries and to varying age distribution between study groups.<sup>1,7</sup> The prevalence of MGD is affected by age, with older patients at increased risk of developing MGD.

## PATHOGENESIS

The pathophysiology of blepharitis involves a complex interaction of various factors, including abnormal lid-margin secretions, lid-margin organisms, and a dysfunctional precorneal tear film. Several classification systems exist for blepharitis.<sup>2,8-10</sup> It can be anatomically subdivided into anterior blepharitis (Fig. 4.4.1) and posterior blepharitis. Alternatively, blepharitis can be classified according to the presenting clinical features into staphylococcal, seborrheic, mixed staphylococcal and seborrheic, and MGD (Fig. 4.4.2).

The lid inflammation characteristic of blepharitis is most often caused by a combination of anterior and posterior factors of varying degrees. In most types of blepharitis, some MG involvement occurs.<sup>11</sup> MGs are tubuloacinar, holocrine glands that produce and secrete meibum, an oily substance that produces the lipid layer of the precorneal tear film.<sup>12</sup> Embedded in the tarsal plates, normally 30–40 MGs occur in the upper lid and 20–30 glands in the lower lid. Each MG consists of a main duct surrounded by grape-like acinar clusters. These ducts open into the lid margin just anterior to the mucocutaneous junction, delivering meibum to the tear film.



Fig. 4.4.1 Anterior blepharitis.



Fig. 4.4.2 Meibomian gland dysfunction.



MGD is defined as a chronic, diffuse abnormality of MGs, commonly characterized by terminal duct obstruction and/or qualitative/quantitative changes in the glandular secretion.<sup>9</sup> Alterations in the composition of the meibomian secretions occur in patients with chronic blepharitis.<sup>12-14</sup> Alteration in nonpolar lipids raises the melting point of the meibum, leading to thickening of the meibum and stagnation. Decreased amounts of polar lipids result in uneven spreading of tears,<sup>15</sup> likely leading to instability of the tear film and hyperosmolarity, increased bacterial growth, evaporative dry eye, and ocular surface inflammation, including keratinization, scarring, and retraction of the gland orifices, thus further exacerbating MGD. Several factors can aggravate MGD, such as increasing age, contact lens wear, and hormonal imbalance.<sup>10,11,14</sup>

Several bacteria, fungi (*Pitysporum*), and parasites (*Demodex*) also have been implicated. The most common organisms isolated from patients with chronic blepharitis include *Staphylococcus epidermidis*, *Propionibacterium acnes*, corynebacteria, and *Staphylococcus aureus*.<sup>16</sup> *S. epidermidis* and *S. aureus* produce lipolytic enzymes, such as triglyceride lipase, cholesterol esterase, and wax esterase, which hydrolyze wax and sterol esters with the release of highly irritating free fatty acids, resulting in the disruption of the tear film integrity.<sup>12</sup> In seborrheic blepharitis, the increased amount of low viscosity meibum favors the growth of bacteria and leads to inflammation of the lids.<sup>14</sup> Acne rosacea is a relatively common chronic skin disease characterized by persistent erythema, telangiectasis, papules, pustules, and sebaceous gland hypertrophy, predominantly affecting the forehead, cheeks, and nose. Although the pathogenesis is still unclear, studies suggest that it is primarily caused by an altered innate immune response in those with a genetic predisposition. Certain reactive oxygen species and infectious agents, such as *Demodex folliculorum* and *Helicobacter pylori* also have been implicated.<sup>17</sup>

## OCULAR MANIFESTATIONS

Typical symptoms of blepharitis include redness, itching, burning, crusting along the lid margin, loss of lashes, stickiness of lashes, and tearing. Furthermore, as MGD has been suggested to be the leading cause of DED,<sup>1</sup> presenting symptoms, such as dryness, ocular irritation, and fluctuating vision, may indicate the need for the clinician to examine the lid margin. These symptoms are chronic, usually waxing and waning, and may be exacerbated by some environmental factors, such as wind, smoke, dust, cosmetic products, and so on. Symptoms usually are bilateral but may be asymmetrical. The presence of predominantly unilateral symptomatology should alert the clinician to consider other diagnoses, such as sebaceous cell carcinoma, which may masquerade as chronic unilateral blepharitis.

External examination using slit-lamp biomicroscopy is essential in establishing diagnosis and determining the type of blepharitis. Staphylococcal anterior blepharitis is more common in the younger population and has a female preponderance. Findings include vascularization and erythema of the lid margin, telangiectasia, eyelid edema, loss or misdirection of lashes, collarettes around the base of the lashes, and crusting or hyperkeratosis. Chronic findings of ulceration, punctal misdirection, and scar formation may be seen. There can be signs of corneal involvement in severe cases, presenting with phlyctenulosis, corneal neovascularization, thinning, or marginal ulceration. Seborrheic blepharitis is more common in the older age group. It presents with *scurf*s, which is a term used to refer to the scales, oily debris, and greasy material that collects along the lash shaft as a result of hypersecretion from MGs.<sup>18</sup> In blepharitis associated with *Demodex* sp. infestation, the most commonly seen finding is coating of the lash with cylindrical dandruff-like material (sleeves).<sup>19</sup>

Clinical signs of MGD may include rounding, thickening, and irregularity of the eyelid margin; changes in the lid vascularity and presence of telangiectasia; pouting, plugging, and narrowing of the gland orifices; reduction in volume and number of glands secreting liquid; and changes in gland secretion quality, clarity, and viscosity with greater pressure required to express secretions.<sup>19,20</sup> "Non-obvious MGD" is a common form of obstructive MGD that shows no obvious signs of inflammation, hypersecretion, or purulent secretion of the glands but may become more apparent with pressure on the lid as the meibum orifices are examined.<sup>21</sup> In chronic MGD, there may be cicatricial changes along the lid margin, and the mucocutaneous junction may migrate anterior to the MG line.<sup>22</sup> Subtle signs, such as the frothy quality of the tear meniscus, and decreased Schirmer's scores and tear breakup time (TBUT), may be found. Other ocular conditions, such as recurrent chalazia, trichiasis, and keratoconjunctivitis sicca, may be seen. External examination of the face and skin may reveal associated dermatological problems, such as seborrheic dermatitis, atopy, herpes zoster ophthalmicus, and acne rosacea. In ocular

rosacea, dilated and telangiectatic vessels at the lid margin and interpalpebral hyperemia may be seen.

## DIAGNOSIS AND ANCILLARY TESTING

Blepharitis is mainly a clinical diagnosis. However, ancillary testing may be considered in those who have chronic disease or are unresponsive to therapy, to monitor treatment effect, and for research purposes.

Culture samples taken from the eyelid margins may grow the typical bacteria associated with blepharitis, as well as viruses, such as herpes simplex, herpes zoster, and molluscum contagiosum. Microscopic examination of the epilated lashes may show *Demodex* eggs, and adult mites.<sup>18</sup>

MG secretion can be analyzed by its quality and expressibility. This can be done by digital pressure or with the use of a device that applies a standard pressure that is equivalent to the pressure exerted on the lids during a normal blink.<sup>23</sup> This device targets a standard area of one third of the total number of glands (8–10 glands). Expressibility is graded according to the number of glands that express fluid; decreased expressibility indicates disease. Although it sounds simple, marked variability exists among individuals, and hence a definite cutoff between normal and abnormal cannot be defined. Moreover, the location of the glands along the lid margin influences their expressibility. It was found that nasal glands tend to express most actively, followed by central glands, and then temporal glands.<sup>24</sup> The quality of glandular secretion can be evaluated in terms of appearance. It can be classified as clear, cloudy opaque, viscous, or toothpaste-like by using various grading schemes.<sup>21,25</sup>

More recently, interferometry has been developed to measure the lipid layer of tears. The patient's eye is illuminated with light directed at the corneal surface; light passes through the tear film and is reflected into a camera, forming an interference pattern called an *interferogram*. The interferometer measures the lipid layer thickness of a defined area of tear film and captures the blink profile during a designated time interval. A positive correlation between tear film lipid layer thickness and expressible MGs suggests that a low lipid layer thickness indicates a high probability of MGD.<sup>26</sup>

Changes in MG morphology and gland dropout can be assessed using meiboscopy. This is done with transillumination through the skin and observing the glandular silhouette through the everted mucosal side. Photodocumentation of the same is called *meibography*.<sup>18</sup> The disadvantage of the transillumination method is that it may be tedious and time consuming. Noncontact meibography applies the same principle but is easier and more rapid than transillumination. It uses an infrared transmitting filter attached to a slit lamp and video camera.<sup>27</sup> Photographs are taken, and MG morphology and dropout are then analyzed. Recent advancements to the technology now include mobile, handheld, pen-shaped systems with an infrared light-emitting diode fixed to the camera, which enables capturing of videos and images that are comparable in quality with previous meibography systems. It is convenient and applicable for examination of MGs in patients of all ages.<sup>28</sup>

Keratography permits visual assessment of the topography of the corneal surface, allowing for an analysis of tear film stability by comparing the irregularities in recorded images. In addition to evaluating TBUT, keratography can examine MGs, tear meniscus height, and lipid layer.<sup>29</sup>

In vivo laser scanning confocal microscopy is a contact technique can be used to examine the microstructure of MG acinar units and measure their size.<sup>30</sup>

## TREATMENT

The goal of all the treatments of MGD is to improve the flow of meibomian gland secretions, thus achieving normal tear film stability.<sup>31</sup>

Treatment strategies aiming at improving the quality of the meibum include a combination of lid hygiene, management of MGD, reducing bacterial colonization of the lids, suppression of inflammation, and restoring tear quality.<sup>32</sup> It is crucial to educate patients about the chronic, recurrent nature of the disease and the need for long-term intervention. Despite the availability of diverse treatment options, very few treatments have been extensively evaluated for safety and efficacy in randomized controlled trials, and most are typically not approved by the U.S. Food and Drug Administration (FDA) for use in blepharitis specifically. Treatment recommendations are largely dependent on clinical experience and published case reports.

Lid hygiene, the mainstay of treatment for blepharitis, consists of warm compresses, lid massage, lid scrubs, and avoidance of excessive eye makeup. Treatment with warm compresses involves the placement of a

warm washcloth on closed lids daily for 5–10 minutes. The goals of heat therapy are to soften and loosen encrustations, liquefy the solidified and stagnant secretions, and to dilate ducts. This is followed by lid massage. The eyelid is held taut at the outer corner with one hand while the index finger of the other hand sweeps from the inner corner of the lid toward the ear while applying pressure. This is repeated several times to express the MG contents, which have melted during the warm compresses step. Cleansing with lid scrubs is usually done once or twice daily initially. Commercially available scrubs or a cotton-tipped applicator soaked with a weak solution of baby shampoo can be used to rub along the lid margin to remove deposits and the abnormal oily secretions from the lids. Patients should be instructed to avoid excessive scrubbing and massage because these actions can lead to ocular irritation.

Besides self-care, therapeutic MG expression as an in-office procedure performed by the clinician can help relieve MGD by using probes and/or mechanical pressure to open and express meibum. Intraductal MG probing is a relatively nontraumatic method that utilizes small stainless steel probes to open the MG orifices, and this may mechanically open and dilate the natural orifices and ducts of the MGs.

Participants currently are being recruited for a randomized, double-blind trial investigating the efficacy of intraductal MG probing compared with a sham procedure in patients with refractory MGD.<sup>33</sup> However, therapeutic expression may be painful to the patient.<sup>34</sup> The BlephEx device, a less invasive method of microexfoliation of the lid margins, utilizes a rapidly rotating microspoon to remove lid debris and microbial biofilm from the lid margins.<sup>35</sup> Recently, a new thermopulsation device has been developed, and it allows heat to be applied to the palpebral surfaces of the lids directly over the MGs while simultaneously applying graded pulsatile pressure to the outer eyelid surfaces, thereby gently expressing MGs during heating. The automated treatment device has two main components: a lid warmer and an eye cup. The lid warmer resembles a large oval scleral lens designed to rest on the bulbar conjunctiva and vault the cornea. The eye cup contains an inflatable air bladder that massages the eyelids to express MGs in the upper and lower eyelids simultaneously.<sup>36</sup>

Topical antibiotics are added when underlying bacterial infection is suspected. Bacitracin and erythromycin ophthalmic ointments are effective agents for anterior blepharitis. Generally, ointments are applied directly to the lid margins to avoid toxicity to the ocular surface. Fluoroquinolone eyedrops have minimal ocular toxicity and have a wide coverage of organisms. Topical fusidic acid has shown efficacy in patients with ocular rosacea blepharitis. Although not yet approved by the FDA, topical metronidazole gel 0.75%–1% also may be effective when used on the lid margin for treatment of ocular rosacea.<sup>32</sup> Systemic antibiotics, such as cloxacillin, may be added for treatment of persistent or recurrent staphylococcal blepharitis. Oral tetracyclines are commonly used in the management of rosacea and MGD. They are mainly used for their anti-inflammatory and lipid-regulating properties, rather than for their antimicrobial effects. They decrease the production of bacterial lipases, thus reducing the concentration of free fatty acids and their deleterious effects on lipid composition.<sup>37</sup> They exert anti-inflammatory effects resulting from inhibition of matrix metalloproteinases, cytokines, lymphocyte and neutrophil activation, and chemotaxis. They also have antiangiogenic and antiapoptotic properties.<sup>38</sup> They usually are used in doses ranging from 250 mg once to four times a day (tetracycline and oxytetracycline) to 50–100 mg once or twice a day (doxycycline and minocycline). Low doses of doxycycline 20 mg may be used when long-term therapy is required. A 40 mg/day slow-release dose of doxycycline is approved for treatment of rosacea and is used by some clinicians. Tetracycline use is limited by its common side effects, which include sun sensitivity and gastrointestinal upset and known contraindications for use in pregnant women and children. Oral macrolide antibiotics, such as erythromycin and azithromycin, are safer and also have immunomodulatory and anti-inflammatory effects similar to those of tetracyclines. Recently, the use of a topical azithromycin (1%) was suggested as an effective treatment of posterior blepharitis, with a significant improvement in MG secretion quality, eyelid redness, tear quality, and overall symptomatic relief, but results from studies regarding efficacy are mixed.<sup>39</sup>

In cases with more severe lid margin inflammation, a short-term course of topical corticosteroids or antibiotic–corticosteroid combinations may be utilized. Long-term use of corticosteroids is limited by serious side effects, such as cataracts, glaucoma, and infection. Topical immunomodulators, such as cyclosporine A 0.05%, a calcineurin inhibitor, have been shown to be beneficial in the treatment of MGD in conjunction with rosacea and/or DED, with a significant improvement in lid margin inflammation and signs of DED.<sup>40</sup> Nearly all suggested treatments have not received FDA approval for use in lid disease.

As change in tear composition and tear film stability may be a key contributor to lid margin inflammation, supplementation of the tear film may improve both MGD and DED. Treatment options include tears, gels, ointments, environmental control, and moisture goggles. A newer class of tear substitutes involving the use of lipid-containing eyedrops, liposomal sprays, emulsion-type eyedrops, and ointments that may be more effective than saline-based artificial tears in DED associated with MGD.<sup>41,42</sup> Dietary supplementation with omega-3 fatty acids has been shown to be effective in improving signs and symptoms of DED and MGD by reducing ocular surface inflammation and improving the lipid composition of meibum.<sup>11</sup>

Several additional methods of treatment exist that have been found to be helpful when used in conjunction with the core interventions mentioned above. Antiseborrheic shampoos, such as those containing selenium sulfide or tar, may be helpful when seborrheic dermatitis is significant. Weekly lid scrubs with 50% tea tree oil and daily lid scrubs with tea tree shampoo are effective in eradicating *Demodex* infestation of the lids but can be irritating to the ocular surface.<sup>43</sup> As MGD may be related to androgen deficiency or receptor dysfunction, topical androgens are being evaluated as a possible therapeutic option for patients with MGD.<sup>44</sup>

A growing interest exists in the role of blepharitis, especially MGD, in understanding and treating ocular surface disease, especially DED. However, to date, there is still limited understanding of what findings are clinically pathological and associated with signs and symptoms of ocular disease and what treatments would most benefit patients. Current research is addressing environmental, dietary, pharmacological, and surgical interventions to better understand blepharitis and to optimize the treatment of this chronic ocular condition.

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# Herpes Zoster Ophthalmicus

Majid Moshirfar, Gene Kim, Brian D. Walker, Orry C. Birdsong

# 4.5

**Definition:** Infection of varicella (chickenpox) in the ophthalmic division of the trigeminal dermatome most frequently affecting the nasociliary branch.

## Key Features

- Herpes zoster ophthalmicus can affect any of the ocular or adnexal tissues.
- Treatment with antivirals promotes healing of rashes and prevents ocular complications.

## Associated Features

- Postherpetic neuralgia.

## EPIDEMIOLOGY AND PATHOGENESIS

Herpes zoster (zoster, shingles) is a neurocutaneous disease caused by human herpes virus 3 (HHV-3), the same virus that causes varicella (chickenpox). It is a member of the herpes virus family (Herpesviridae) and exclusively infects human or simian cells. Varicella zoster virus (VZV) is the smallest of the alphaherpes viruses and has very stable linear double-stranded DNA. It has an icosahedral capsid and lipid envelope, which contains glycoproteins for cell entry.<sup>1</sup>

Herpes zoster has the highest incidence of any neurological disease, with an annual occurrence of approximately 1 million cases in the United States.<sup>2</sup> The lifetime risk is about 30%, and 50% of those living until 85 years of age will be affected.<sup>2-5</sup> The reported incidence varies from 3.2 to 4.2 per 1000 individuals per year. Increased risk of developing zoster is associated with older age (incidence of 10 per 1000 individuals over 80 years) and immunosuppression.<sup>6</sup>

In temperate climates, primary infection with this virus usually occurs before age 10 years, manifesting clinically as chickenpox (varicella). The virus then establishes a latent state in the sensory ganglia. In circumstances of diminished virus-specific and cell-mediated immunity, the virus may reactivate and spread to the corresponding dermatome along a spinal or cranial nerve to generate the characteristic unilateral vesicular exanthem. The accompanying inflammation of the sensory nerve and skin damage are purportedly responsible for the acute pain.<sup>7,8</sup>

Physical trauma and surgery have been correlated with the development of zoster.<sup>9-12</sup> Other reported triggers include tuberculosis, syphilis, radiation therapy, and corticosteroids.<sup>13</sup>

The epidemiology of zoster ultimately is dependent on the transmission and spread of VZV in a population. The spread of primary varicella (chickenpox) infection is of primary importance, but latent and reactivated infections play an important role in maintaining VZV infections within a population. Latently infected older adults and immunosuppressed patients are important reservoirs of the virus, as these groups are more likely to experience reactivation. When zoster does occur, the virus can be transmitted to a seronegative individual during the vesicular phase of the rash and cause a primary varicella infection. A zoster exposure with a seropositive, latently infected individual may result in a subclinical reinfection and boost humoral and cellular VZV immunity but is unlikely to cause acute varicella or herpes zoster.<sup>14</sup> Herpes zoster may develop in immunocompetent patients who harbor the latent virus and who are re-exposed to it by contact with someone who has active varicella or zoster infection (primary, spontaneous, or infectious zoster).<sup>13,15,16</sup>

## Ophthalmic Herpes Zoster

The frequency of herpes zoster ophthalmicus (HZO) is second only to thoracic dermatomal occurrence, with up to 250 000 cases occurring yearly in the United States.<sup>4,17</sup> Of these, 50%–70% suffer visual morbidity with severity increasing in the 5th–8th decades of life.<sup>4,17</sup> The virus most commonly establishes latency in the trigeminal sensory ganglion and reactivates in 10%–25% of the population.<sup>17</sup> The ophthalmic division of the trigeminal nerve is affected 20 times more frequently than the maxillary or mandibular divisions.<sup>18</sup> Ocular involvement occurs in more than 70% of patients with zoster of the first (ophthalmic) division of the trigeminal nerve. Nasociliary branch involvement with skin lesions located on the inner corner of the eye, tip of the nose (Hutchinson's sign), and root or side of the nose is predictive (50%–85%) of ocular involvement and is strongly prognostic for ocular inflammation and corneal sensory denervation.<sup>13,19</sup> The eye may be seriously affected in up to 50% of cases in the absence of Hutchinson's sign.<sup>20</sup>

HZO usually begins with a prodrome of influenza-like illness, which is characterized by fatigue, malaise, nausea, and mild fever; this is accompanied by progressive pain and skin hyperesthesia, which is characterized by a burning painful area along a specific dermatome, followed by a diffuse erythematous or maculopapular rash that appears 3–5 days later. These eruptions can progress to form clusters of papules and clear vesicles and evolve through stages of pustulation, vesiculation, and crusting. Patients with deeper involvement of the dermis may develop permanent scars with loss of normal pigmentation. Rarely, herpes zoster may manifest with ophthalmic symptoms in the absence of cutaneous eruptions.<sup>8,21</sup>

## CLINICAL MANIFESTATIONS

HZO may affect all ocular and adnexal tissues and manifest with a diverse array of signs and symptoms. Ocular or extraocular involvement may occur at the time of the cutaneous eruptions or years later.

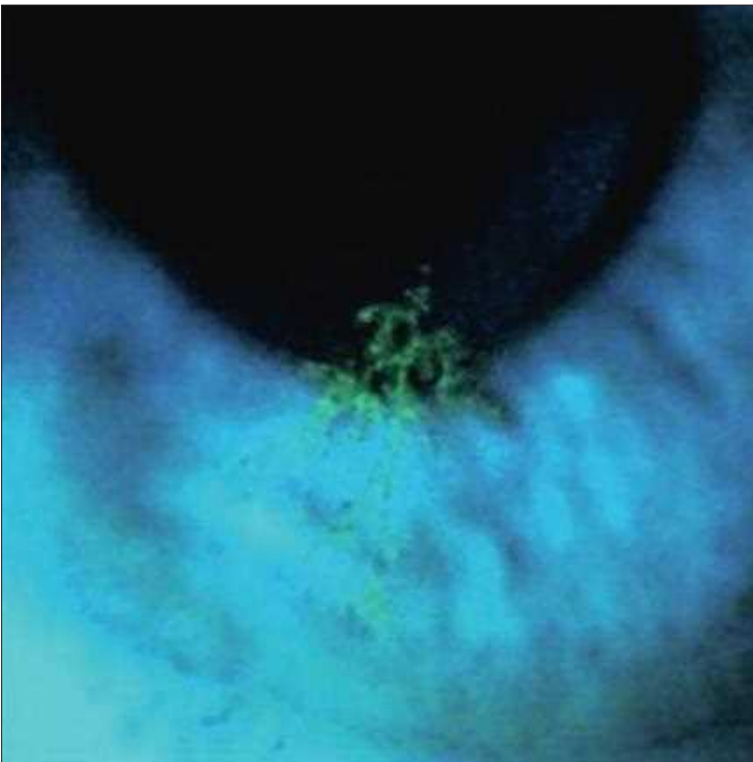
The skin of the forehead and upper eyelid is commonly affected and strictly obeys the midline with involvement of the ophthalmic division of the trigeminal nerve (Fig. 4.5.1). Zoster involves the deep dermis, in contrast to herpes simplex, which is limited to the epidermis. Deep involvement may cause numerous lid complications, such as scarring, entropion, and ectropion. Conjunctival findings include hyperemia, petechial hemorrhages, papillary or follicular reaction, or, rarely, pseudo-membrane. Episcleritis and scleritis are common and tend to progress toward the limbus, causing vasculitis and sterile corneal infiltrates.<sup>22</sup>

Corneal pathology tends to result from three pathophysiological mechanisms: (1) active viral infection; (2) immune-mediated inflammation; and (3) chronic neurotrophic keratopathy. Active viral infections tend to affect the epithelium, leading to punctate epithelial keratitis and pseudo-dendrites (Fig. 4.5.2). Pseudo-dendrites are typically smaller than typical dendrites, and lack terminal end-bulb formations. Immune-mediated stromal keratitis can take multiple forms. Nummular keratitis is the earliest finding of corneal stromal involvement and presents during the second week of the disease in 25%–30% of patients.<sup>22</sup> It is characterized by multiple, fine, granular, coin-shaped infiltrates in the anterior stroma and may cause permanent scarring. Chronic interstitial keratitis may lead to deep corneal neovascularization and lipid keratopathy. Disciform keratitis is a deep stromal infiltrate that develops 3–4 months after the acute phase, characterized by a central disc-shaped area of diffuse corneal edema that results from endotheliitis and anterior chamber inflammation. Perilimbal vasculitis from immune-complex deposition can lead to sterile, peripheral, anterior cornea stromal infiltrates.

Active zoster infections travel through branches of the ophthalmic division of the cranial nerve.<sup>6</sup> Each reactivation damages the corneal nerves



**Fig. 4.5.1** Herpes zoster ophthalmicus involving the V1 distribution.



**Fig. 4.5.2** Peripheral corneal epithelial pseudo-dendrites in a patient with a history of herpes zoster ophthalmicus. (Courtesy Hu AY, et al. Late varicella-zoster virus dendriform keratitis in patients with histories of herpes zoster ophthalmicus. *Am J Ophthalmol* 2010;149:214–20 e3.)

causing progressive neurotrophic keratopathy. Late-stage HZO gives the picture of chronic epitheliopathy with filamentary keratitis and anterior stromal scars from a compromised ocular surface. The risk of secondary bacterial infection may be high in this setting.<sup>20</sup>

HZO can cause nongranulomatous or granulomatous iridocyclitis (anterior uveitis) with keratic precipitates. It often has a chronic course, necessitating topical corticosteroids for control. Specific signs include elevated intraocular pressure from trabeculitis and sectoral, vasoocclusive iris atrophy. Glaucoma from HZO is often multifactorial. An early cause is from trabeculitis that resolves with corticosteroids, but chronic

inflammation leads to pupillary seclusion, chronic angle-closure glaucoma, and, possibly, corticosteroid-response glaucoma.

Posterior segment manifestations of HZO include retinal perivascularitis, ischemic optic neuropathy, and forms of necrotizing retinopathy. These complications are uncommon but vision threatening. Two forms of retinitis are worth noting: acute retinal necrosis (ARN), which tends to occur mainly in immunocompetent patients, and progressive outer retinal necrosis (PORN), which occurs mainly in immunocompromised patients. ARN tends to present with severe ocular inflammation, whereas PORN appears less inflamed but has a much faster and vision-threatening clinical course.<sup>22</sup> PORN is characterized by multifocal, deep retinal lesions that rapidly progress to confluence with minimal or no intraocular inflammation, an absence of vascular inflammation, and perivenular clearing of retinal opacification.<sup>20</sup>

External ocular motor palsies frequently occur in acute HZO. Infections may affect the third, fourth, and sixth cranial nerves. These complications are thought to be from vasculitis within the orbital apex and frequently resolve within a year.

## Postherpetic Neuralgia

Pain that continues following rash healing has been termed *postherpetic neuralgia* (PHN). Pain in HZO has three phases: (1) acute pain—first 30 days during and after rash onset; (2) subacute herpetic neuralgia—between 30 and 120 days; and (3) PHN when greater than 120 days.<sup>23,24</sup>

PHN can occur in any patient with HZO; however, it usually is not seen in patients less than 50 years of age, and its frequency increases until age 70 years. It afflicts about one half of all patients with herpes zoster who are older than 70 years and appears to be more severe in older patients.<sup>13</sup> The pain may occasionally be so extreme and persistent that some patients consider suicide.<sup>13</sup> Risk factors for PHN include greater acute pain severity,<sup>24,25</sup> greater rash severity,<sup>26,27</sup> and presence of a painful prodrome preceding the rash.<sup>28</sup> Additional risk factors for PHN include older age and female gender.<sup>23</sup>

## HERPES ZOSTER OPHTHALMICUS IN ACQUIRED IMMUNE DEFICIENCY SYNDROME

HZO is an important early clinical marker for acquired immunodeficiency syndrome (AIDS), especially in high-risk younger patients.<sup>29–31</sup> Immunocompromised patients have a higher incidence, greater severity, and more prolonged course of ocular involvement, as well as PHN, compared with immunocompetent patients with HZO.<sup>32</sup> All nonpregnant, young patients with HZO should be tested for human immunodeficiency virus (HIV). PORN is reported with increasing frequency in patients with AIDS. Following cytomegalovirus retinopathy, PORN is the second most frequent opportunistic retinal infection in patients with AIDS in North America.<sup>33</sup>

## DIAGNOSIS

The diagnosis of herpes zoster disease generally is based on clinical findings, although in recent decades, the clinical manifestations and spread of VZV have shifted. This change may confound clinical impressions (e.g., HSV lesions may appear to be zosteriform and be difficult to differentiate from zoster). Differential diagnosis includes eczema herpeticum, eczema vaccinatum, impetigo contagiosum, enterovirus-associated exanthema, contact dermatitis, drug eruptions, and insect bites.

Cytological examination of cutaneous vesicular scrapings reveals multiple eosinophilic intranuclear inclusions (Lipschutz's bodies) and multinucleated giant cells (Tzanck's preparation). Specimens (cutaneous vesicular scraping or conjunctival swab) must be transported to the laboratory as quickly as possible under low temperature conditions (4 °C).<sup>33</sup> Immune electron microscopy techniques using specific peroxidase-labeled monoclonal antibodies against specific virus antigens can directly detect VZV.<sup>34</sup> VZV-DNA can be obtained via anterior chamber paracentesis or vitreous tap and analyzed using real-time polymerase chain reaction.<sup>35</sup> Fluorescent antibody techniques, cytospin direct immunofluorescence staining, and rapid direct immunofluorescence assays (SimulFluor direct fluorescent antibody) are additional methods for detecting VZV.<sup>36</sup>

Serological tests to detect herpes zoster antibodies are of limited use because cross-reactivation between VZV and HSV can occur. Following zoster infection, a booster of IgG is detected for 2 weeks and then falls to lower levels and could persist at that level for years.<sup>37</sup>

## MANAGEMENT

HZO is treated with oral antivirals: acyclovir, famciclovir, or valacyclovir. Acyclovir (800 mg, five times daily for 7–10 days), reduces viral shedding and the chance of systemic dissemination, and reduces the incidence and severity of ocular complications, particularly if used within 72 hours of onset of symptoms.<sup>38,39</sup> Acyclovir also can shorten the duration of pain if taken within the first 3 days of onset of symptoms.<sup>40,41</sup> Intravenous acyclovir is recommended in immunocompromised patients.<sup>38,42</sup>

Famciclovir (500 mg, three times daily for 7 days) is a prodrug of penciclovir and has a much higher bioavailability (77%) compared with acyclovir (18%). It has been shown to be well tolerated and safe with similar efficacy to acyclovir.<sup>43</sup>

Valacyclovir (1000 mg three times daily for 7 days) is the L-valine ester of acyclovir and has higher bioavailability (80%) compared with acyclovir (18%). It has similar activity to acyclovir in the prevention of the sequelae of herpes zoster and has been shown to be as effective in preventing ocular complications of HZO. Comparative analysis also has shown that tolerability of the two drugs was similar.<sup>44</sup> Valacyclovir has been shown to significantly accelerate the resolution of pain compared with acyclovir.<sup>45</sup> Comparisons between valacyclovir and famciclovir treatment in HZO have not shown significant difference in resolution of pain or rash.<sup>46</sup>

Of note, acute renal failure rarely has been reported with these medications, especially intravenous administration.<sup>47,48</sup> As a result, kidney function should be monitored closely and renal dosing guidelines followed when appropriate. Dosing for children should be executed with reference to appropriate dosing guidelines. Acyclovir and valacyclovir are thought to be safe for use during pregnancy.<sup>49</sup>

### Management of Ocular Manifestation

Palliative therapy, including Burow's solution, cool compresses, mechanical cleansing of the involved skin, and topical antibiotic ointment without corticosteroid, are helpful in treating skin lesions.

Oral acyclovir has been shown to be effective for the punctate, pseudo-dendritic, and delayed corneal mucous plaque forms of herpes zoster epithelial keratitis.<sup>40,41</sup> Debridement may be helpful.

Neurotrophic keratitis or epithelial defects associated with herpes zoster keratitis may be treated with nonpreserved artificial tears, eye ointments, punctal occlusion, pressure patching, or therapeutic soft contact lenses. If these measures are unsuccessful, tarsorrhaphy, conjunctival flap, or autologous conjunctival transplantation should be considered. Studies have shown that good results can be achieved with corneal transplantation in patients with a history of HZO.<sup>50</sup>

Topical corticosteroids are useful in the management of sclerokeratitis, keratouveitis, interstitial keratitis, anterior stromal infiltrates, and disciform keratitis.<sup>22</sup> Corticosteroids generally should not be used in cases of exposure or neurotrophic keratitis because of the possibility of keratolysis.<sup>22</sup> Topical cycloplegics prevent ciliary spasm associated with herpes zoster inflammatory disease. Aqueous suppressants and topical corticosteroids should be used to treat HZO glaucoma. Herpes zoster vitritis, vitreous hemorrhage, and vitreous debris may respond to topical, periocular, or systemic corticosteroids. Herpes zoster infections affecting the cranial nerves are best treated with a combination of systemic corticosteroids and intravenous acyclovir. Retinitis (ARN and PORN) is best treated with a combination of intravitreal injections and valacyclovir.<sup>51</sup>

### Postherpetic Neuralgia

Postherpetic neuralgia is challenging to control and may be treated with analgesics, tricyclic antidepressants (nortriptyline, amitriptyline, desipramine, clomipramine), and anticonvulsants (carbamazepine and phenytoin), often in combination. Newer medications (e.g., gabapentin—ranging from 300 mg three times daily to 1200 mg three times daily; and pregabalin) are more effective than tricyclic antidepressants against treating allodynia, another subtype of neuralgia.<sup>52</sup> Capsaicin cream (0.025%) is effective when applied to the involved skin three to four times daily, although 2

weeks of treatment is often required for pain relief.<sup>53</sup> PHN may be severe, intractable, and permanent, with some patients requiring psychiatric and pain clinic care, and occasionally trigeminal rhizotomy or stellate ganglion block may occur.<sup>54</sup>

Findings of a meta-analysis reveal that famciclovir and valacyclovir significantly reduce the duration but not the incidence of PHN. Studies have shown corticosteroids to have no beneficial effect in the treatment of PHN.<sup>55,56</sup> Amitriptyline for 90 days reduced the incidence of pain at 6 months. Finally, a single trial of percutaneous electrical nerve stimulation (PENS) in 50 patients reported decrease in pain incidence at 3 and 6 months compared with famciclovir.<sup>57</sup>

## PREVENTION

The varicella vaccine is available in two formulations which are both given subcutaneously: Varivax (Merck) and Zostavax (Merck). The former prevents primary varicella infections in infants, and the latter prevents reactivation of zoster in adults. Both utilize live attenuated virus. Differences in administration are that Zostavax is only administered once and has 14 times the concentration of Varivax, which is given twice.<sup>58</sup>

Studies have shown that Zostavax reduces the incidence of zoster by 50%, PHN by 60%, and HZO by 49% and that it reduces the severity of illness in those with reactivation of the virus.<sup>59,60</sup> The efficacy of all three vaccine measures has been shown to decrease as time after vaccination increases.<sup>61</sup> The most common adverse effect is pain and erythema at the injection site with equivalent rates of adverse events of 1.4% for the vaccine and placebo group.<sup>62</sup> The vaccinated group, however, did have a higher rate of serious adverse events. Case reports in the literature describe exacerbation of chronic HZO, exacerbation of uveitis, new-onset retinitis in immunocompromised patients, and dermatological and disseminated disease after Zostavax administration in patients with a history of HZO.<sup>58,63–71</sup> Despite these reports and possible risks, a history of HZO is currently not a contraindication to the vaccination.

The Centers for Disease Control and Prevention and the Advisory Committee on Immunization Practices recommend that the zoster vaccine be administered to adults age 60 years and above for the prevention of herpes zoster, including those who have already had a case of zoster.

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# Conjunctivitis: Infectious and Noninfectious

# 4.6

Jonathan B. Rubenstein, Tatyana Spector

**Definition:** Conjunctivitis is infectious or non-infectious inflammation of the mucous membrane lining eye wall and inner lids.

### Key Features

- Infectious causes may be bacterial, fungal parasitis, or viral.
- Infectious conjunctivitis can be classified by duration of symptoms.
- The diagnosis is usually made clinically. If the diagnosis is not readily apparent, laboratory studies may be helpful in determining etiology.
- May be noninfectious causes of conjunctivitis.

## INFECTIOUS CONJUNCTIVITIS

### Bacterial Infections

Bacterial conjunctivitis is characterized by a rapid onset of unilateral conjunctival hyperemia, lid edema, and mucopurulent discharge. The second eye typically becomes involved 1–2 days later.

The pathogenesis of bacterial conjunctivitis usually involves a disruption of the host defense mechanisms, for example, abnormalities of the ocular surface secondary to eyelid abnormalities, tear film abnormalities, or systemic immunosuppression.<sup>1,2</sup> Bacterial conjunctivitis can be classified into three clinical types: acute, hyperacute, and chronic (see Table 4.6.1 for a list of common pathogens).<sup>1</sup>

Conjunctival membranes and pseudo-membranes may occur in bacterial conjunctivitis in association with *Neisseria gonorrhoeae*,  $\beta$ -hemolytic streptococci, and *Corynebacterium diphtheria*. Pseudo-membranes, which include inflammatory cells and an exudate containing mucus and proteins, are loosely adherent to the underlying conjunctival epithelium and can be peeled away with no bleeding or damage to the epithelium. True membranes occur with more intense inflammation. The conjunctival epithelium becomes necrotic, and firmer adhesions are formed between the necrotic cells and the overlying coagulum. When the membrane is peeled, the epithelium tears to leave a raw, bleeding surface.

### Acute Bacterial Conjunctivitis

Acute bacterial conjunctivitis usually begins unilaterally with hyperemia, irritation, tearing, mucopurulent discharge, and matting of the lids (Fig. 4.6.1). Punctate epithelial keratitis also may occur. The most common pathogens include *Staphylococcus aureus*, *Streptococcus pneumoniae*, and *Haemophilus influenzae*.<sup>1</sup> Other common ocular manifestations include blepharitis, keratitis, marginal ulcers, and phlyctenulosis.<sup>3</sup> The pathogens *H. influenzae*, *S. pneumoniae*, and *Moraxella catarrhalis* occur more commonly in young children and may occur in institutional epidemics.<sup>4</sup> *H. influenzae* is often associated with systemic infection, including upper respiratory infections, and acute otitis media.

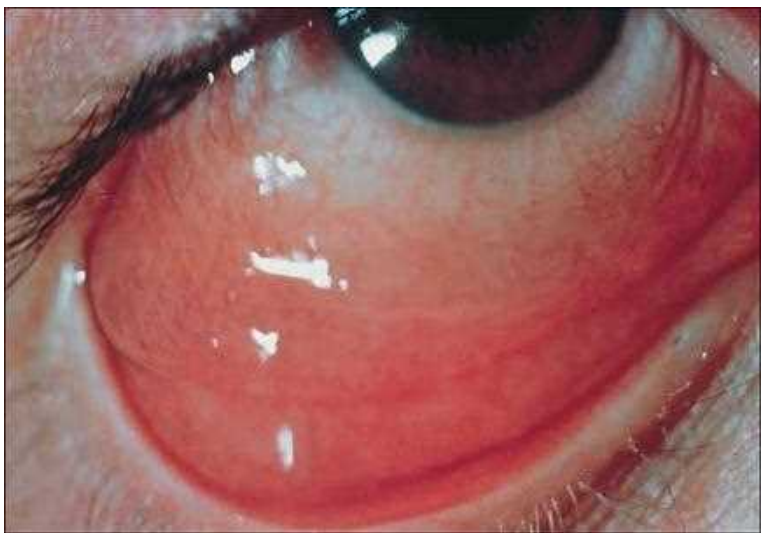
The treatment of acute bacterial conjunctivitis consists of topical antibiotic drops or ointments. Although these infections normally are

self-limiting, lasting 7–10 days, antibiotic therapy usually speeds the resolution and lessens the severity of the disease. A broad-spectrum antibiotic with good Gram-positive coverage, such as a third- or fourth-generation fluoroquinolone, 10% sodium sulfacetamide, or trimethoprim-polymyxin, may be used for 7–10 days.

### Hyperacute Bacterial Conjunctivitis

The most common cause of hyperacute bacterial conjunctivitis is *N. gonorrhoeae*.<sup>1</sup> This oculo-genital disease is seen primarily in neonates and sexually active young adults. Transmission is by contact with infected urine or genital secretions. Symptoms develop within 24 hours, and signs include profuse, thick, yellow-green purulent discharge, painful hyperemia, chemosis of the conjunctiva, and tender preauricular nodes. Untreated cases may lead to peripheral corneal ulceration and eventual perforation with possible endophthalmitis. A similar, but milder form of conjunctival and corneal disease is caused by primary or secondary infection with *Neisseria meningitidis*. Primary meningococcal conjunctivitis is extremely rare in adults and can be invasive (followed by systemic meningococcal disease) or noninvasive (isolated conjunctival infection).<sup>5</sup> If invasive disease is present, close contacts should receive prophylaxis with a single dose of ciprofloxacin 500 mg or rifampin 600 mg twice daily for 2 days.<sup>6</sup>

Treatment is directed at the specific pathogen. Conjunctival scraping for Gram staining and culture on blood and chocolate agar are strongly recommended. Gram-negative diplococci are suggestive of *Gonococcus*. An effective regimen for gonococcal conjunctivitis is a single dose of 1 g of intramuscular ceftriaxone. If a corneal ulcer is present, hospitalization with 1 g intravenous ceftriaxone for 3 days is recommended. Topical medications may include bacitracin, ciprofloxacin, or erythromycin ointment every 1–2 hours. Frequent irrigation, every 30–60 minutes, with normal saline or balanced salt solution, also is recommended. Adults are often treated empirically for concurrent chlamydial infection with azithromycin 1 g once or doxycycline 100 mg twice a day for 7 days.<sup>7</sup> In meningococcal conjunctivitis, systemic treatment includes intravenous penicillin, or for penicillin-resistant infections, intravenous cefotaxime or ceftriaxone.<sup>5</sup> Patients need to be seen daily to rule out corneal involvement.

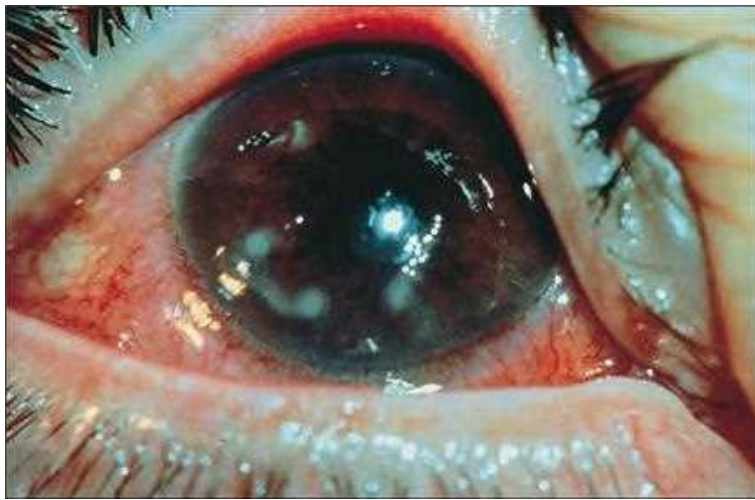


**Fig. 4.6.1 Acute Bacterial Conjunctivitis.** This patient was culture-positive for *Pneumococcus*.

**TABLE 4.6.1 Pathogens That Cause Bacterial Conjunctivitis**

Acute	Hyperacute	Chronic
<i>Staphylococcus aureus</i>	<i>Neisseria gonorrhoeae</i>	<i>Staphylococcus aureus</i>
<i>Streptococcus pneumoniae</i>	<i>Neisseria meningitidis</i>	<i>Moraxella lacunata</i>
<i>Haemophilus influenzae</i>		Enteric bacteria





**Fig. 4.6.2 Staphylococcal Marginal Keratitis.** Note the inferior marginal corneal ulcers and the blepharoconjunctivitis.

### Chronic Bacterial Conjunctivitis

Chronic bacterial conjunctivitis, lasting longer than 3 weeks, may result from a number of organisms and is often associated with blepharitis. The most common organisms are *S. aureus* and *Moraxella lacunata*; other causative organisms include the enteric bacteria *Proteus mirabilis*, *Escherichia coli*, *Klebsiella pneumoniae*, *Serratia marcescens*, and *Branhamella catarrhalis* from the upper respiratory tract.<sup>1</sup> The most common causative agent is *S. aureus*, which colonizes the eyelid margin and then causes direct infection of the conjunctiva or conjunctival inflammation through its elaboration of exotoxins.<sup>8</sup> Chronic angular blepharoconjunctivitis of the inner and outer canthal angles most commonly results from *M. lacunata*. A chronic follicular conjunctivitis may accompany both types.

The clinical signs of chronic staphylococcal conjunctivitis include diffuse conjunctival hyperemia with papillae or follicles, minimal mucopurulent discharge, and conjunctival thickening. Erythema of the eyelid, telangiectasis, lash loss, collarettes, recurrent hordeolae, and ulcerations at the base of the cilia can be seen. The cornea may demonstrate marginal corneal ulcers (Fig. 4.6.2).

Treatment combines proper antimicrobial therapy and good lid hygiene, which includes warm compresses and eyelid scrubs. Azithromycin drops and erythromycin or bacitracin ointments are effective adjunctive topical antibiotics. When severe inflammation exists, antibiotic and corticosteroid combination drops or ointments can be rubbed into the lid margins after the lid scrubs. Oral therapy with tetracycline 250 mg four times a day, doxycycline 100 mg one to two times a day, or minocycline 50 mg one to two times a day may be needed for more severe infections.

### Adenoviral Conjunctivitis

Viral conjunctivitis is extremely common. The diagnosis usually can be made clinically.<sup>8</sup> Many different viruses cause conjunctivitis, and each produces a slightly different disease.

Adenoviruses produce the most common viral conjunctivides with varying degrees of severity. The spectrum consists of follicular conjunctivitis, pharyngoconjunctival fever, and epidemic keratoconjunctivitis. These infections are spread via respiratory droplets or direct contact from fingers to the lids and conjunctival surface. The incubation period is usually 5–12 days and the clinical illness is present for 5–15 days.<sup>9</sup>

#### Follicular Conjunctivitis

Follicular conjunctivitis is the mildest form and is associated with adenovirus serotypes 1 through 11 and 19.<sup>10</sup> It has an acute onset and is initially unilateral with possible involvement of the second eye within 1 week. It is manifested by a watery discharge and conjunctival hyperemia and usually is accompanied by follicular and papillary conjunctival changes with preauricular lymphadenopathy on the affected side. Most cases resolve spontaneously, without sequelae, within days to weeks.

#### Pharyngoconjunctival Fever

Pharyngoconjunctival fever is the most common ocular adenoviral infection<sup>11</sup> and is produced by adenovirus serotypes 3, 4, and 7. It is characterized by a combination of pharyngitis, fever, and conjunctivitis (Fig.



**Fig. 4.6.3 Acute Bilateral Viral Conjunctivitis.** This 22-year-old man has pharyngoconjunctival fever, and the conjunctivitis was preceded by a viral upper respiratory tract infection.



**Fig. 4.6.4 Epidemic Keratoconjunctivitis.** Early pseudo-membrane formation may be seen in the inferior fornix.

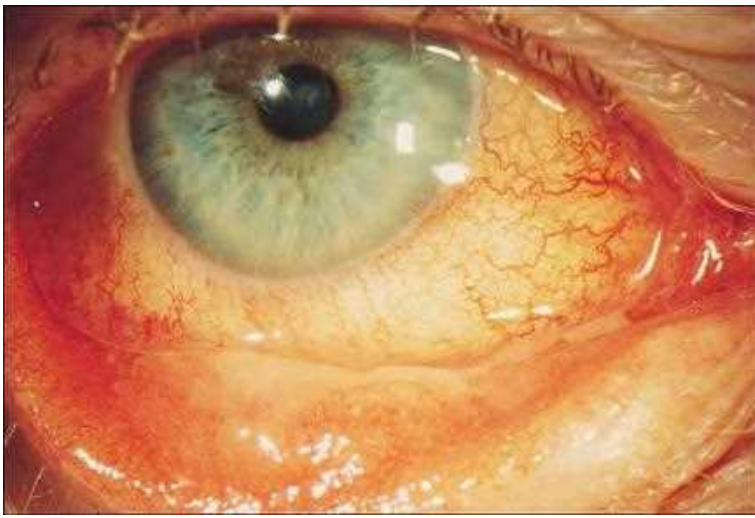
4.6.3). The conjunctivitis is predominantly follicular with a scant watery discharge, hyperemia, and mild chemosis. The cornea may be involved with a fine punctate epitheliopathy. Preauricular lymph nodes are enlarged in about 90% of cases. The disease resolves spontaneously within 2 weeks, so treatment is usually supportive with cold compresses, artificial tears, and judicious use of vasoconstrictor eyedrops.

#### Epidemic Keratoconjunctivitis

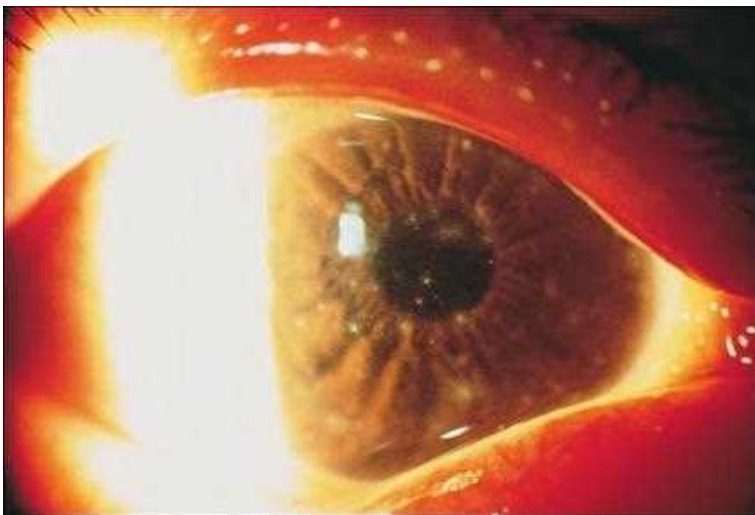
Epidemic keratoconjunctivitis (EKC) is produced by adenovirus serotypes 8, 19, and 37. It is a more severe type of conjunctivitis and typically lasts for 7–21 days. EKC produces a mixed papillary and follicular response of the conjunctival stroma with a watery discharge, hyperemia, chemosis, and ipsilateral preauricular lymphadenopathy (Fig. 4.6.4).<sup>8,11</sup> Subconjunctival hemorrhages, conjunctival membrane formation, and lid edema are common (see Fig. 4.6.4; Fig. 4.6.5).<sup>10</sup> Histologically, these conjunctival membranes consist of fibrin and leukocytes with occasional fibroblast infiltration. Both true membranes and pseudo-membranes may occur, and conjunctival scarring and symblepharon formation may follow their resolution.

Corneal involvement is variable. Most patients have a diffuse, fine, superficial keratitis within the first week of the disease. Focal, elevated, punctate epithelial lesions that stain with fluorescein develop by days 6–13 (Fig. 4.6.6), producing a foreign body sensation. By day 14, subepithelial opacities develop under the focal epithelial lesions in 20%–50% of cases (Fig. 4.6.7). These opacities often are visually disabling and may persist for months to years, but eventually they resolve with no scarring or vascularization.<sup>12</sup> The diagnosis of EKC is made clinically, but a rapid immunodetection assay (RPS Adeno Detector; Rapid Pathogen Screening; South

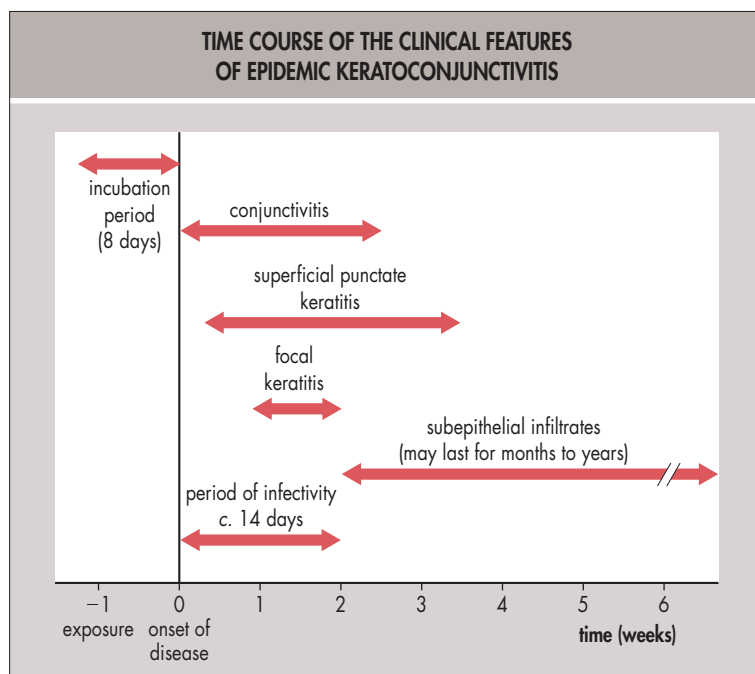




**Fig. 4.6.5 Pseudo-Membrane in Epidemic Keratoconjunctivitis.** An early pseudo-membrane is forming in the inferior fornix.



**Fig. 4.6.6 Epidemic Keratoconjunctivitis Subepithelial Infiltrates.** These infiltrates develop 2 weeks after the onset of the disease and persist for months to years.



**Fig. 4.6.7** Time course of the clinical features of epidemic keratoconjunctivitis.

Williamsport, PA) is now available and is capable of detecting all 53 adenoviral serotypes with a reported sensitivity of 89% and specificity of 94%.<sup>13</sup>

Treatment aims at alleviation of symptoms and minimization of transmission of this highly contagious disease. Patients may be infectious for up to 14 days after onset.<sup>10,14,15</sup> and outbreaks are especially common in ophthalmology offices and clinics. Transmission usually occurs from eye to fingers to eye; tonometers, contact lenses, and eyedrops are other routes of transmission. Preventive measures include frequent hand washing, relative isolation of infected individuals in an office setting, and disinfection of ophthalmic instruments.<sup>16,17</sup> During the stage of acute conjunctivitis, treatment usually is supportive and includes cold compresses and decongestant eyedrops. When patients have decreased visual acuity or disabling photophobia from subepithelial opacities, topical corticosteroid therapy may be beneficial. High-dose topical corticosteroids, such as 1% prednisolone acetate three to four times a day, or difluprednate twice a day, can help eliminate subepithelial infiltrates.<sup>18</sup> However, some believe that use of topical corticosteroids prolongs viral shedding and worsen symptoms if the infectious virus is herpes simplex. Cidofovir, an antiviral agent, has been investigated in the treatment of EKC.<sup>19,20</sup> Although the application of cidofovir drops may prevent the formation of corneal opacities, use has been limited by local toxicity and commercial unavailability. Others have advocated the use of topical gancyclovir. Currently, the utility of a povidone-iodine 0.4%/dexamethasone 0.1% combination ophthalmic suspension is being investigated.<sup>21</sup>

### Acute Hemorrhagic Conjunctivitis

Acute hemorrhagic conjunctivitis, also known as *Apollo disease*, was first described in Ghana in 1969.<sup>22</sup> Two picornaviruses, enterovirus 70 and coxsackievirus A24, are the usual causative agents.<sup>23,24</sup> Less commonly, it is caused by adenovirus type 11. A rapid onset of severe, painful follicular conjunctivitis occurs, with chemosis, tearing, lid edema, and tiny subconjunctival hemorrhages. The hemorrhages are petechial at first and then coalesce, appearing posttraumatic. The cornea may demonstrate a fine punctate keratopathy and, rarely, subepithelial opacities. The conjunctivitis resolves within 4–6 days, but the hemorrhages clear more slowly. The disease occurs in epidemics, especially in developing countries, with more than 50% of the local population affected in some cases. Very rarely, cases caused by enterovirus type 70 can result in a polio-like paralysis, which remains permanent in up to one third of affected individuals.

### Herpes Simplex Conjunctivitis

Primary herpes simplex conjunctivitis usually occurs in children under 5 years of age. Most cases are undocumented because of their nonspecific nature. Typical signs include ocular irritation, watery discharge, mixed papillary and follicular conjunctivitis, hemorrhagic conjunctivitis, and preauricular lymphadenopathy.<sup>25</sup> Most cases are unilateral but may become bilateral. Epidermal vesicular eruptions of the eyelids and lid margins may accompany the conjunctivitis (Fig. 4.6.8), and the cornea may be involved. Corneal involvement may include a coarse, punctate epithelial keratitis, marginal infiltrates, or a dendritic ulcer. Although herpetic blepharconjunctivitis is associated mainly with the primary disease, it may occur as a manifestation of recurrent disease with or without typical herpetic keratitis.<sup>25</sup> Most ocular herpetic infections result from herpes simplex virus type 1. Infections that result from the type 2 serotype may be seen in newborns or adults who have a history of oral–genital contact.<sup>26</sup>

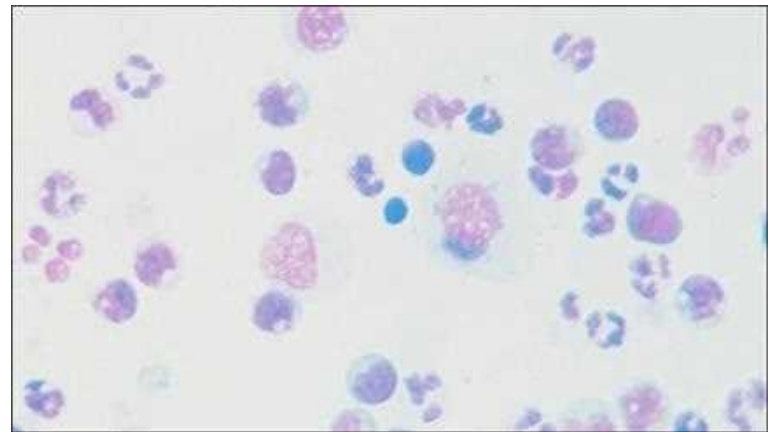
The conjunctivitis usually resolves spontaneously in 7–14 days without treatment,<sup>25</sup> although some physicians administer topical antiviral drops to patients with corneal involvement or to patients with lid vesicles, with the goal of preventing corneal involvement. Care should be taken to avoid the cavalier use of corticosteroids in the treatment of patients who have an acute follicular conjunctivitis because some of these patients may have herpetic disease and corticosteroids may enhance the severity of herpetic epithelial keratitis.

### Other Causes of Viral Conjunctivitis

Other causes of viral conjunctivitis include the rubella, rubeola, varicella-zoster, Epstein–Barr virus infection, Newcastle disease, and Zika virus infections.<sup>23</sup> Rubella virus produces a nondescript, catarrhal follicular conjunctivitis associated with the systemic disease. Rubeola produces a catarrhal, papillary conjunctivitis with tearing, pain, and photophobia. Pale, discrete, avascular spots, which resemble Koplik's spots seen in the mouth, may appear on the conjunctiva. Varicella-zoster virus produces pustules and phlyctenule-like lesions on the conjunctiva, and a follicular



**Fig. 4.6.8 Primary Herpes Simplex Blepharoconjunctivitis.** Note the bilateral vesicular eruptions in this child who has a primary herpes simplex infection.



**Fig. 4.6.9 Giemsa Staining of a Conjunctival Scraping.** The epithelial cells show basophilic cytoplasmic inclusions typical of a chlamydial infection.

#### BOX 4.6.1 Causes of Chronic Follicular Conjunctivitis

- Chlamydiasis
- Trachoma
- Adult inclusion conjunctivitis
- Molluscum contagiosum
- Drug-induced or toxic conjunctivitis
- Bacterial conjunctivitis
- Axenfeld's chronic follicular conjunctivitis
- Merrill–Thygeson-type follicular conjunctivitis
- Parinaud's oculoglandular syndrome
- Folliculosis of childhood

conjunctivitis may occur with recurrent skin disease. Follicular conjunctivitis associated with the Epstein–Barr virus occurs in association with infectious mononucleosis.<sup>27</sup> Newcastle disease viral conjunctivitis occurs in poultry workers and veterinarians in whom direct conjunctival inoculation of the virus has occurred while handling infected birds.<sup>28</sup> The disease is self-limiting, lasts 7–10 days, and leaves no ocular sequelae. Zika virus is a mosquito-borne infection that has led to many outbreaks in Africa and Asia, and most recently, in 2015, it has reached the Americas. The virus may present with fever, rash, arthralgia, and conjunctivitis in approximately 20% of cases. Symptoms are generally self-limiting, although fetal transmission may lead to brain defects.<sup>29</sup>

### Chronic Follicular Conjunctivitis

Chronic follicular conjunctivitis lasts more than 16 days (Box 4.6.1).<sup>8</sup> *Chlamydia trachomatis*, an obligate intracellular bacterium, is the most common cause; it causes three clinical syndromes—trachoma, adult inclusion conjunctivitis, and neonatal conjunctivitis.

#### Trachoma

Trachoma, which results from *C. trachomatis* serotypes A to C, is endemic in many parts of the world, including Africa, the Middle East, Latin America, Central Asia, and South-East Asia.<sup>30</sup> Current reports indicate that active trachoma affects approximately 150 million people worldwide, with about 10 million people developing secondary trichiasis and approximately 6 million blinded from sequelae of the disease. After an incubation period of 5–10 days, trachoma manifests as a mild, mucopurulent conjunctivitis that is typically self-limiting and heals without permanent sequelae.<sup>31</sup> Repeated infections, however, result in chronic inflammation, including follicular conjunctivitis and papillary hypertrophy of the upper palpebral conjunctiva, a superior superficial corneal pannus, and fine epithelial

keratitis. Eventually, multiple reinfections lead to scarring and cicatrization of the cornea, conjunctiva, and eyelids.

The trachoma complications that cause blindness occur as a result of corneal ulceration, severe conjunctival scarring, and eyelid deformities with their concomitant effects on the ocular surface.<sup>32</sup> Arlt's line (a horizontal line that results from conjunctival scarring at the junction of the anterior one third and posterior two thirds of the conjunctiva) is a characteristic finding on the superior pretarsal conjunctiva. Herbert's pits are a unique sequelae of trachoma<sup>33</sup>; these sharply delineated depressions occur after necrosis and cicatrization of limbal follicles, and the resultant clear space is filled with epithelium. A diffuse haze of the superior cornea may result after regression of the superior pannus. Eyelid deformities, such as trichiasis, distichiasis, entropion, and ectropion, all may occur. Corneal complications, including scarring, vascularization, ulceration, and perforation, lead to decreased visual acuity and possible blindness.

Treatment of trachoma usually consists of a 3- to 4-week course of oral tetracycline (tetracycline 1 g/day or doxycycline 100 mg/day) or oral erythromycin. The clinical response may be slow and take 9–18 weeks to be seen. More recently, a single 20 mg/kg dose of oral azithromycin has been shown in several randomized controlled trials to be as effective as 6 weeks of topical tetracycline.<sup>31,34,35</sup> Topical azithromycin 1.5% twice daily for 2–3 days has also been found to be as effective as the single oral dose with a low recurrence rate.<sup>36</sup> Widespread repeated use of systemic antibiotics in endemic areas has been tried in an attempt to eradicate the disease with slow resolution of active trachoma.<sup>37</sup>

#### Adult Inclusion Conjunctivitis

Adult inclusion conjunctivitis results from *C. trachomatis* serotypes D to K. It presents as a unilateral red eye with mucopurulent discharge, marked hyperemia, papillary hypertrophy, and a predominant follicular conjunctivitis. A tender, enlarged preauricular lymph node is common. Women often have a concomitant vaginal discharge secondary to a chronic cervicitis, and men may have symptomatic or asymptomatic urethritis. The conjunctivitis is often chronic, lasting many months. Keratitis may develop 1 week after onset. Corneal involvement includes a superficial punctate keratitis, small marginal or central infiltrates, EKC-like subepithelial infiltrates, limbal swelling, and a superior limbal pannus. The untreated disease has a chronic course, and keratitis or iritis can occur in the later stages of the disease.

Diagnosis is based on the clinical appearance plus laboratory test results. Basophilic intracytoplasmic epithelial inclusions are seen with Giemsa staining of conjunctival scrapings (Fig. 4.6.9). Immunofluorescent staining of the conjunctival scrapings is also useful. Serum immunoglobulin G titers to *Chlamydia* may be obtained.

The modes of transmission include orogenital activities and hand-to-eye spread of infective genital secretions. The incubation period is 4–12 days. One in 300 patients who have genital chlamydial disease develops adult inclusion conjunctivitis.<sup>38</sup> It is important to treat all sexual partners simultaneously to prevent reinfection and also to rule out other venereal diseases, such as gonorrhea and syphilis. Treatment consists of systemic antibiotics, as topical antibiotics are relatively ineffective in the treatment of the eye disease. A single 1-g dose of azithromycin or doxycycline 100 mg twice a day for 7 days is the recommended treatment. Tetracyclines should be avoided in children younger than 7 years of age and in pregnant or lactating women.



**TABLE 4.6.2 Causes of Neonatal Conjunctivitis**

Causes	Time of Onset (Postpartum)
Chemical (povidone-iodine)	1–36 hours
Chlamydia	5–14 days
<i>Neisseria gonorrhoeae</i>	24–48 hours
Bacteria ( <i>Staphylococcus</i> , <i>Streptococcus</i> , <i>Haemophilus</i> , <i>Moraxella</i> , <i>Escherichia coli</i> , <i>Pseudomonas</i> )	2–5 days
Virus (herpes simplex virus types 1 and 2)	3–15 days
The cause of the conjunctivitis is established by the clinical picture, time course, and laboratory confirmation.	

**TABLE 4.6.3 Guidelines for Treatment of Neonatal Conjunctivitis**

Infection	Treatment
Chlamydia	Oral erythromycin 50 mg/kg/day in four divided doses for 14 days
<b>Bacteria</b>	
Gram-positive	Erythromycin 0.5% ointment four times a day
Gram-negative, gonococcal	Intravenous or intramuscular ceftriaxone 25–50 mg/kg single dose
Gram-negative, others	Gentamicin or tobramycin ointments
Viral	Trifluorothymidine drops every 2 hours for 7 days

## Neonatal Conjunctivitis (Ophthalmia Neonatorum)

Conjunctivitis of the newborn is defined as any conjunctivitis that occurs within the first month of life (Table 4.6.2).<sup>39</sup> It may be a bacterial, viral, or chlamydial infection or a toxic response to topically applied chemicals. Because the infectious agent may produce a severe localized infection of the eye plus a potentially serious systemic infection, precise identification of the cause is essential.

Not all infants exposed to infectious agents in the birth canal develop conjunctivitis; the duration of the exposure is an important factor in the development of disease. Prevention with good prenatal care and treatment of chlamydial, gonococcal, or herpetic infections during pregnancy significantly lower the incidence of neonatal conjunctivitis. Proper eye cleaning using sterile cotton followed by the instillation of erythromycin or tetracycline antibiotic ointments immediately after birth helps prevent neonatal ocular infection. Previous studies suggested that instillation of 2.5% povidone-iodine as prophylaxis has superior bactericidal effects and also is active against viruses, most notably herpes simplex.<sup>40</sup> However, recent studies suggest topical tetracycline and erythromycin ointment may be more effective in prevention of ophthalmia neonatorum given that 5%–10% of patients treated with povidone-iodine developed a chemical conjunctivitis.<sup>41,42</sup>

### Chlamydial Infections

The most frequent cause of neonatal conjunctivitis in the United States is *C. trachomatis*. Infants whose mothers have untreated chlamydial infections have a 30%–40% chance of developing conjunctivitis and a 10%–20% chance of developing pneumonia.<sup>43</sup> Symptoms typically develop 5–14 days after delivery and may be unilateral or bilateral. Initially, infants have a watery discharge that may progressively turn mucopurulent. Signs include lid edema, a papillary conjunctival response, and pseudo-membrane formation (Fig. 4.6.10). Usually, the infection is mild and self-limiting; severe cases, however, may occur and result in conjunctival scarring and a peripheral corneal pannus with corneal scarring. If either erythromycin or tetracycline ointment is applied within 1 hour of delivery, the chance of developing chlamydial conjunctivitis is markedly decreased.<sup>44</sup>

Laboratory data are very helpful in the diagnosis. Enzyme-linked immunosorbent assay is nearly 90% sensitive and over 95% specific and provides results within several hours. A direct immunofluorescent monoclonal antibody stain of conjunctival smears is the most useful serological test because it has over 95% sensitivity and 77%–90% specificity for *Chlamydia*, depending on the prevalence of the disease. It may show infections missed by other assays and can be read immediately. Polymerase chain reaction (PCR) and ligase chain reaction also are available and are approximately 90% sensitive and 100% specific.<sup>45</sup>

Topical therapy alone is not sufficient to treat chlamydial conjunctivitis. The recommended treatment is oral erythromycin syrup 50 mg/kg/day in four divided doses for 14 days (Table 4.6.3). If complete response does not



**Fig. 4.6.10** A 10-day-old infant who has unilateral conjunctivitis. The mother had an untreated chlamydial infection of the birth canal.

occur, a second course of the same therapy may be given. The mother and her sexual partners should be treated with oral azithromycin 1 g in a single dose or oral amoxicillin 500 mg three times daily for 7 days.<sup>46</sup>

### Neisserial Infections

Neonatal conjunctivitis caused by *N. gonorrhoeae*, a Gram-negative diplococcus that can penetrate an intact epithelium, has decreased significantly since the advent of prophylactic agents. The clinical picture of gonococcal conjunctivitis consists of the development of a hyperacute conjunctivitis 24–48 hours after birth characterized by marked eyelid edema, profound chemosis, and excessive purulent discharge. The discharge often is so copious that it reaccumulates immediately after the eye has been wiped clean. Conjunctival membrane formation may occur. Because the organism may penetrate an intact epithelium, corneal ulceration with possible perforation can occur if the conjunctivitis is not treated adequately.<sup>47</sup>

Diagnosis is made by identification of Gram-negative intracellular diplococci on conjunctival smears. The organism is best cultured on chocolate agar or Thayer–Martin agar incubated at 37 °C in 10% carbon dioxide, and sensitivities should be obtained. Prompt diagnosis by examination of immediate Gram staining is essential to timely and effective therapy.

Local treatment consists of aqueous penicillin G drops 10 000–20 000 units. Drops are given every hour with a loading dose of one drop every 5 minutes for 30 minutes. Systemic therapy also should be instituted with intravenous or intramuscular ceftriaxone 25–50 mg/kg in a single dose (see Table 4.6.3). For disseminated disease, consultation with an infectious disease specialist is recommended. The mother and her sexual partners should be treated with intramuscular ceftriaxone 250 mg in a single dose.

### Other Bacterial Infections

Many different organisms can cause bacterial neonatal conjunctivitis. Bacteria are probably transmitted through the air to the infant shortly after birth and may be associated with nasolacrimal duct obstruction. These infections are usually caused by Gram-positive bacteria (*S. aureus*, *S. epidermidis*, *S. pneumoniae*, and *S. viridans*). Gram-negative organisms that have been implicated include *Haemophilus* species, *E. coli*, *Proteus* species, *K. pneumoniae*, *Enterobacter* species, and *Serratia marcescens*.<sup>48</sup> Rarely, *pseudomonas* sp. causes corneal ulceration and perforation.<sup>49</sup>

Typically, these infections arise 2–5 days after birth. Signs include lid edema, chemosis, and conjunctival injection with discharge. The work-up includes conjunctival scrapings for Gram staining and cultures, the results of which direct the choice of therapy. For Gram-positive organisms, erythromycin 0.5% ointment four times a day is administered. Gentamicin, tobramycin, or fluoroquinolone drops or ointment four times a day can be used for Gram-negative organisms (see Table 4.6.3).

### Viral Infections

Viral conjunctivitis of the newborn is rare but can be associated with significant morbidity and mortality. Both herpes simplex virus type 1 and herpes simplex type 2 can be associated with conjunctivitis, but type 2 infection is more common.<sup>50</sup> Type 1 may be transmitted by a kiss from an adult who has an active “cold sore,” and type 2 is more commonly transmitted through the birth canal. Onset is usually within the first 2 weeks of life



and may be associated with vesicular skin lesions of the lid or lid margin (see Fig. 4.6.8). The conjunctivitis may be followed by herpetic keratitis or keratouveitis. Vitritis, retinitis, retinal detachment, optic neuritis, and cataract all have been reported in association with neonatal ocular herpes. The diagnosis may be confirmed by the presence of eosinophilic intranuclear inclusions on smears, positive viral culture results, or positive results from monoclonal antibody immunoassays.

Treatment consists of trifluoridine 1% drops every 2 hours for 7 days, acyclovir ointment five times a day, or ganciclovir drops five times a day (see Table 4.6.3). Herpes simplex type 2 may be more resistant to treatment. In cases of systemic disease associated with pneumonitis, septicemia, and meningitis, systemic acyclovir or valacyclovir should be used. Good prenatal care and frequent culture and treatment of mothers who have known herpes genital infections decrease the incidence of herpetic neonatal conjunctivitis.

## Fungal and Parasitic Conjunctivitis

Focal eyelid or conjunctival granulomas can be caused by rare infections, including blastomycosis, sporotrichosis, rhinosporidiosis, cryptococcosis, leishmaniasis, and ophthalmomyiasis.

## Microsporidial Keratoconjunctivitis

Microsporidae are obligate, intracellular, spore-forming protozoan parasites that can cause disseminated disease or localized keratoconjunctivitis.<sup>51</sup> It is more commonly seen in immunocompromised patients but has been reported in immunocompetent patients with contact lens use, trauma, prior refractive surgery, or exposure to contaminated water or soil.<sup>52</sup> Clinical symptoms include pain, redness, and, occasionally, visual blurring. Superficial, multifocal, coarse, punctate epithelial keratitis, and a diffuse papillary conjunctivitis are typical.<sup>53</sup> Diagnosis is made with ocular surface scraping and the visualization of acid-fast spores in conjunctival epithelial cells upon staining with modified trichrome, potassium hydroxide plus calcofluor white, or Gram stain.<sup>52,53</sup> Confocal microscopy demonstrates spores that are hyperreflective dots. Electron microscopy is the gold standard for diagnosis. Treatment includes topical fumagillin and oral albendazole or itraconazole.<sup>52</sup> Topical fluoroquinolones are effective as monotherapy.<sup>54</sup>

## Loiasis

*Loa loa* is a filarial nematode that is transmitted from human to human by the bite of an infected female deer fly (genus *Chrysops*) that is indigenous to West and Central Africa. The adult worm can migrate subcutaneously from the bite area to the eye. Skin manifestations and conjunctivitis can be present. Extraction of the filarial worm is curative. Treatment consists of diethylcarbamazine 2 mg/kg three times daily for 3 weeks.<sup>55</sup> Ivermectin 150 mg/kg can be used, but significant side effects include subconjunctival and retinal hemorrhages and retinal “cottonwool” spots.<sup>56</sup> Concurrent corticosteroids and/or antihistamines can be used to decrease the side effects of treatment.

## Parinaud’s Oculoglandular Syndrome

Parinaud’s oculoglandular syndrome is an uncommon granulomatous conjunctivitis seen in approximately 5%–10% of patients with systemic infection caused by *Bartonella henselae* (cat scratch disease).<sup>57</sup> *B. henselae* are small, fastidious Gram-negative rods that affect approximately 22 000 patients in the United States per year.<sup>58</sup> Ocular symptoms include unilateral redness, epiphora, foreign body sensation, and mild lid swelling. Serous discharge may be present; if an abscess forms and ruptures, purulent discharge may be noted. Granulomatous nodules develop on the palpebral and bulbar conjunctiva approximately 3 days after inoculation (Fig. 4.6.11). Necrosis and ulceration of the overlying epithelium is common.<sup>59</sup> Firm and tender regional lymphadenopathy of the preauricular, submandibular, and, occasionally, cervical nodes are a hallmark of the disease (Fig. 4.6.12). Optic neuroretinitis and multifocal chorioretinitis may develop. Diagnosis can be made by indirect immunofluorescence antibody testing or by enzyme immunoassay. Serological testing includes cultures and PCR.

The course of the disease in immunocompetent patients is usually self-limiting, and the disease resolves without antibiotic therapy. Therapy is recommended for immunocompromised patients. Currently recommended therapies include oral erythromycin, doxycycline, or azithromycin. In adults, doxycycline 100 mg twice daily is thought to be more effective



**Fig. 4.6.11 Parinaud’s Oculoglandular Syndrome.** Granulomatous palpebral conjunctivitis.



**Fig. 4.6.12 Parinaud’s Oculoglandular Syndrome.** Prominent preauricular lymphadenopathy.



**Fig. 4.6.13 Molluscum Contagiosum Lesion on the Lower Eyelid.** This patient had an accompanying chronic follicular conjunctivitis secondary to the toxic effect of viral proteins from this lesion.

because of its superior intraocular and central nervous system penetration. In more severe infections, these medications can be given intravenously, and rifampin can be used as an adjuvant.<sup>59</sup>

## NONINFECTIOUS CONJUNCTIVITIS

### Toxic Follicular Conjunctivitis

Toxic follicular conjunctivitis follows chronic exposure of the conjunctiva to a variety of foreign substances, including molluscum contagiosum of the lid margin, infection of the lashes by *Phthirus pubis*, use of eye cosmetics, and prolonged use of eye medications. Molluscum contagiosum infections are caused by a poxvirus and are common in patients with HIV infection. The infection is characterized by elevated, round, pearly white, waxy, noninflammatory lesions with umbilicated centers (Fig. 4.6.13). When these lesions occur on or near the eyelid margin, the viral proteins

### BOX 4.6.2 Ocular Medications That Cause Toxic Follicular Conjunctivitis

- Neomycin
- Idoxuridine
- Gentamicin
- Trifluorothymidine
- Dipivefrin
- Pilocarpine
- Apraclonidine
- Eserine
- Atropine
- Epinephrine (adrenaline)
- Preservatives (thimerosal, benzalkonium chloride)

spill onto the conjunctiva to cause a chronic follicular conjunctivitis.<sup>60</sup> The virus itself does not grow in the conjunctiva; rather, the conjunctivitis is a toxic reaction to its proteins. Removal of the lesion or curettage until it bleeds internally eliminates this condition.

Most commonly, toxic follicular conjunctivitis occurs in association with eye medications, such as neomycin, gentamicin, idoxuridine, and other topical antivirals, as well as many glaucoma medications, including brimonidine, pilocarpine, and other miotics (Box 4.6.2). These drugs incite type IV delayed hypersensitivity reaction with periocular erythema and follicular conjunctivitis. In contact lens wearers, any proteolytic enzymes/chemicals used for contact lens cleaning or preservative-containing soaking solutions can cause toxic conjunctivitis. A marked follicular response also can accompany the use of eye cosmetics, such as mascara and eyeliner. A common finding is dark granules from the cosmetic incorporated in the follicles. If symptomatic, patients usually respond well to discontinuation of the cosmetic and substitution of smaller amounts of hypoallergenic preparations.

### Erythema Multiforme Major (Stevens–Johnson Syndrome) and Toxic Epidermal Necrolysis

Erythema multiforme, unlike cicatricial pemphigoid, is an acute, generally self-limiting, nonprogressive inflammatory disorder of the skin and mucous membranes; it is classified into minor and major forms. The minor form primarily involves the skin and lasts 2–3 weeks in its acute phase. Erythema multiforme major, also known as *Stevens–Johnson syndrome*, is the more serious variant, characterized by skin lesions and erosive involvement of mucous membranes that lasts up to 6 weeks.<sup>61</sup> Toxic epidermal necrolysis is a severe variant of erythema multiforme major that is characterized by massive denudation of the epidermis and is more commonly seen in children and in patients with AIDS.<sup>62</sup> Erythema multiforme major classically occurs in previously healthy young people, men more than women, in their first 3 decades of life.<sup>61</sup> A genetic predisposition may exist for the development of Stevens–Johnson syndrome with ocular involvement, in association with human leukocyte antigens HLA-Bw44 and HLA-B12.<sup>63</sup> The disease can be fatal in 2%–25% of patients, with death often secondary to sepsis. About 25% of those who have erythema multiforme suffer a recurrence over their lifetime.

The exact cause of erythema multiforme is unknown, although the disease seems to be precipitated by numerous antigens, including bacteria (e.g., *Mycoplasma pneumoniae*), viruses, fungi, and drugs. Herpes simplex virus and *Mycoplasma* have a particularly strong association. Coxsackievirus and *Histoplasma capsulatum* also have been implicated.<sup>64</sup> Drugs implicated in the development of erythema multiforme include the sulfonamides, penicillins, barbiturates, nonsteroidal anti-inflammatory medications, salicylates, mercurial agents, arsenic, allopurinol, phenylbutazone, phenytoin, and topical ophthalmic scopolamine (hyoscine), tropicamide, and proparacaine.<sup>65</sup> In addition, the onset of the disease has been related to neoplasms, radiation therapy, collagen vascular diseases, and vaccinations.<sup>62</sup>

Erythema multiforme often begins with a prodromal period for up to 2 weeks with symptoms of malaise, fever, headache, and an upper respiratory tract infection. Next, skin lesions develop symmetrically on the extremities with sparing of the trunk and can reoccur for 2–6 weeks before re-epithelization (Fig. 4.6.14). The primary cutaneous lesion is a round, erythematous macule that develops into a papule and then a vesicle or bulla. Eventually, large bullae can rupture, which results in epidermal necrosis.

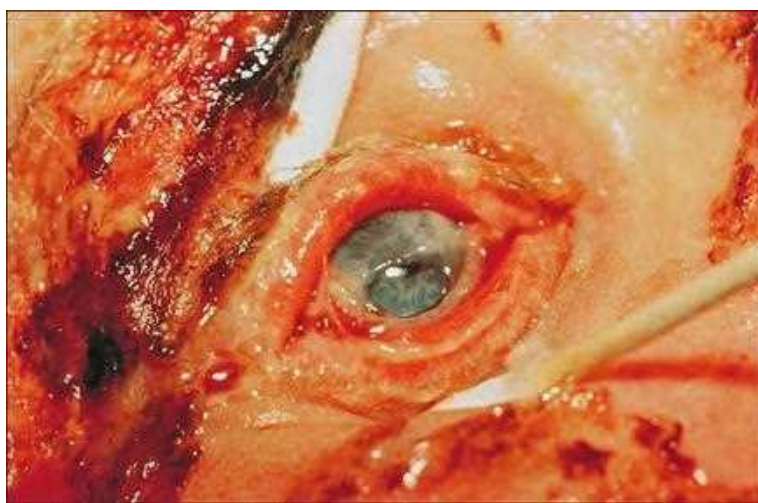


**Fig. 4.6.14 Acute Phase of Stevens–Johnson Syndrome.** This child has the typical target-shaped macular skin lesions. (A) The head, with an associated blepharoconjunctivitis. (B) The leg.

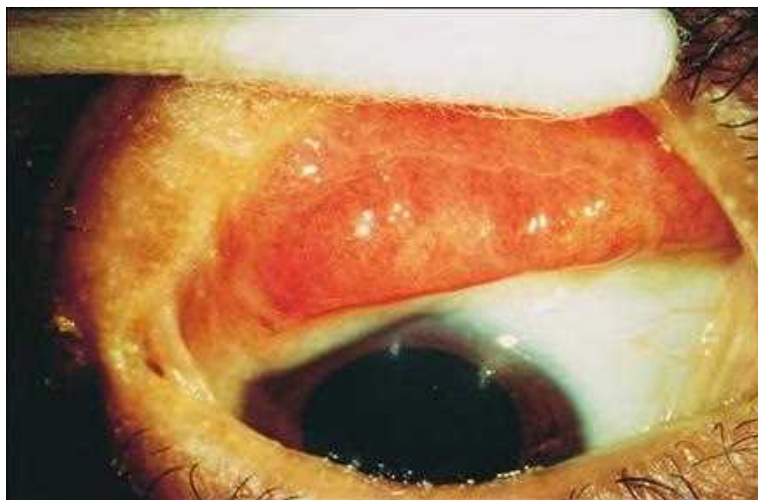
If extensive skin necrosis occurs, the condition is labeled *toxic epidermal necrolysis* (Fig. 4.6.15). The extent of mucous membrane involvement usually parallels the extent of skin involvement. Any mucous membrane may be involved, but the mouth and eyes are affected most frequently and most severely. In one study, 100% of patients had stomatitis and 63% had conjunctivitis.<sup>66</sup> The diagnosis is confirmed by skin or mucosal biopsy demonstrating multiple necrotic keratinocytes or full-thickness epidermal necrosis with subepidermal blistering.<sup>64</sup>

The acute phase of ocular involvement lasts 2–3 weeks.<sup>67</sup> The lids become swollen, ulcerated, and crusted. Patients develop an acute bilateral conjunctivitis, with chemosis, vesicles and bullae, pseudo-membranes or membranes, and eventual ulceration. A more purulent conjunctivitis may develop as a result of bacterial secondary infection.<sup>65</sup> The major ocular problems occur from the cicatricial stage, after the acute toxic episode subsides. Conjunctival scarring and symblepharon may occur despite all supportive measures (Fig. 4.6.16). Destruction of the conjunctival goblet cells, lacrimal gland, and accessory lacrimal gland tissue results in a severe dry





**Fig. 4.6.15 Severe Skin and Conjunctival Necrosis.** The patient has toxic epidermal necrolysis.



**Fig. 4.6.16 Stevens–Johnson Syndrome.** Residual conjunctival scarring is evident over the superior tarsal plate. Symblepharon formation and fibrous bands are present at the canthal angles.

eye, just as in cicatricial pemphigoid. Entropion, trichiasis, and lagophthalmos combined with the dry eye can produce severe corneal problems, such as ulceration, vascularization, opacification, limbal stem cell deficiency, and eventual perforation.<sup>67</sup> Although the acute phase of erythema multiforme may leave extensive conjunctival scarring in its wake, progressive scarring does not occur when the acute disease has subsided, unlike cicatricial pemphigoid. Fortunately, recurrences rarely involve the conjunctiva.

The histological changes in erythema multiforme suggest an underlying vasculitis or perivasculitis.<sup>61</sup> Mononuclear cells, eosinophils, and polymorphonuclear neutrophils accumulate around the vessels or within the vessel wall and induce fibrinoid necrosis of the wall. Subepithelial bullae are seen in the acute phase, and pseudo-membranes and true membranes are found. Conjunctival goblet cell densities are reduced. Immunoglobulins and complement are also deposited at the dermal–epidermal junction.

Treatment often varies with the severity of the condition. Patients who have a more severe initial presentation suffer the worst late ocular complications. In the acute phase, local treatment involves lubrication of the ocular surface. Frequent lysis of developing symblepharon may have no effect on the eventual structure. Unfortunately, local medical treatment of the acute condition often has little influence on the severity of the eventual cicatricial complications. However, systemic corticosteroids (prednisone 60–80 mg/day for 3–4 weeks) may help control the acute disease.<sup>68</sup> Plasmapheresis, systemic cyclosporine, and intravenous immunoglobulins have had variable results and remain controversial.<sup>64</sup> Secondary bacterial conjunctivitis should be suspected and treated, if present; an antibiotic that could, however, stimulate another toxic reaction should be avoided. The cicatricial stage is treated with frequent nonpreserved artificial tears and/or ointments, topical cyclosporine, autologous serum tears, punctal occlusion, and tarsorrhaphy to control dry eye symptoms and prevent sequelae. Surgery to correct lid keratinization, entropion, and trichiasis should be

considered. Unlike in cicatricial pemphigoid, eyelid or conjunctival surgery does not stimulate further scarring. Conjunctival or buccal mucous membrane grafts may be considered to restore the ocular surface. Transplantation of cryopreserved amniotic membrane grafts within the first 2 weeks of the onset of symptoms has been shown in numerous case reports to facilitate rapid epithelial healing and prevent many of the debilitating cicatricial complications.<sup>69</sup> Stem cell transplantation through the use of living-related or cadaveric conjunctival and limbal allografts is often done with subsequent penetrating keratoplasty or keratoprosthesis in patients with severe corneal complications.

## Epidermolysis Bullosa

Epidermolysis bullosa comprises a group of skin and mucous membrane diseases that are characterized by the tendency to form blisters after minor trauma.<sup>70</sup> Symptoms occur shortly after birth or in early childhood and have a tendency to recur throughout the patient's life. Men and women are affected equally, and both hereditary and acquired autoimmune forms exist.<sup>71</sup> The hereditary forms of epidermolysis bullosa may be classified as simple (autosomal dominant), junctional (autosomal recessive), and dystrophic (autosomal dominant or recessive).

Ocular problems have been described with all three types; they are, however, associated mostly with the dystrophic form, which is the most common form of the disease. Patients may have conjunctival blisters and marked conjunctival scarring, with symblepharon formation and eyelid ectropion or entropion.<sup>72</sup> A granular epithelial clouding of the cornea can occur, as can ulcers and opacification secondary to conjunctival scarring similar to that seen in cicatricial pemphigoid or erythema multiforme. Patients who have the junctional form, a rare type, have more primary corneal problems, such as recurrent erosions, and little conjunctival involvement. The acquired, autoimmune form may have both primary corneal subepithelial vesicles and secondary corneal involvement associated with conjunctival scarring and symblepharon.

Treatment is based on the severity of disease. A majority of patients can be treated conservatively with ocular lubricants. Various types of corneal surgery, including keratoplasty, may be indicated if significant scarring and visual loss occurs. Tarsorrhaphy and ectropion/entropion surgery may be considered for patients with more severe disease.<sup>73</sup>

## Graft-versus-Host Disease

Graft-versus-host disease (GVHD) is a common complication of allogeneic bone marrow transplantation and results from donor-grafted cells attacking host tissue antigens. Involved tissues include skin, gastrointestinal tract, lungs, liver, and eyes. Acute or chronic (developing after day 100 following transplantation) disease can occur, but ocular manifestations are more common with chronic GVHD. Ocular complications are secondary to two main mechanisms: conjunctival inflammation in acute disease secondary to T cell–mediated immunity and in chronic disease secondary to infiltration of the lacrimal gland by T lymphocytes causing destruction and fibrosis of the lacrimal gland and conjunctiva. Both pathways lead to keratoconjunctivitis sicca. Signs and symptoms include aqueous tear deficiency, conjunctival erosions, corneal epithelial erosions, and cicatricial lagophthalmos.<sup>73</sup> Histologically, the conjunctiva in GVHD is characterized by decreased conjunctival goblet cell density, increased squamous metaplasia, and infiltration of inflammatory cells.<sup>74</sup> Therapy consists mainly of aggressive lubrication, autologous serum tears, punctal plugs, and decreasing ocular inflammation with topical corticosteroids and/or topical cyclosporine or tacrolimus. Bandage contact lenses and fluid ventilated gas permeable sclera lenses also provide symptomatic relief. Mucolytic agents, such as 10% acetylcysteine, can be used to treat severe filamentary keratitis. Severe ocular disease accompanied by systemic complications warrants increased systemic immunosuppression. Malta et al. suggested that treatment with topical cyclosporine 1 month prior to bone marrow transplantation could help delay or prevent lacrimal gland damage and decrease the ocular symptoms of early GVHD.<sup>75</sup>

## Xeroderma Pigmentosa

Xeroderma pigmentosa is an autosomal recessive disease characterized by impaired ability to repair damage to DNA caused by ultraviolet radiation. Ocular manifestations include keratoconjunctivitis sicca, photophobia, tearing, blepharospasm, and burning. Conjunctival inflammation, telangiectasia, and hyperpigmentation are common findings. Patients often develop pingueculae or pterygia. The patient's impaired ability to



repair DNA leads to cutaneous neoplasms, including squamous cell carcinoma, basal cell carcinoma, and melanoma, in that order of frequency. Neoplasms of the ocular surface and eyelids occur in approximately 11% of patients and often are seen at the limbus. Progressive atrophy of the eyelids with madarosis, trichiasis, symblepharon, ectropion, and entropion can also occur.

## Kawasaki Disease

Kawasaki disease is a rare self-limiting vasculitis of childhood that presents with a host of symptoms, including fever, bilateral nonexudative conjunctivitis, diffuse rash involving the extremities, cervical lymphadenopathy, and erythema of the oral mucosa. Iridocyclitis is another common finding. There are no sequelae from the ocular symptoms, but prompt recognition and appropriate referral for treatment is important to decrease heart complications secondary to vasculitis.<sup>76</sup>

## Ligneous Conjunctivitis

Ligneous conjunctivitis is a very rare chronic disease characterized by development of pseudo-membranes predominantly on the palpebral conjunctiva. The thick pseudo-membranes evolve into “woody” lesions. Corneal involvement is noted occasionally, and it may lead to scarring and blindness. Some may develop pseudo-membranes over mucosal tissue elsewhere in the body. The disease predominantly is described in children but has been reported in both young and old. The etiology is unclear, but type I plasminogen deficiency is thought to be a predisposing factor for the disease. Management is difficult with frequent recurrences following excision. Topical plasminogen and fibrinolytic therapy has been tried with some success.<sup>77</sup>

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# Allergic Conjunctivitis

Jonathan B. Rubenstein, Tatyana Spektor

# 4.7

**Definition:** Allergic conjunctivitis is inflammation of the conjunctiva due to an immediate hypersensitivity reaction to environmental allergens.

## Key Features

- Itching and redness are common presenting symptoms.
- Treatment includes mast-cell stabilizers, antihistamines, combination medications, cool compresses, corticosteroids, and allergen avoidance.

## ACUTE ALLERGIC CONJUNCTIVITIS: SEASONAL/PERENNIAL

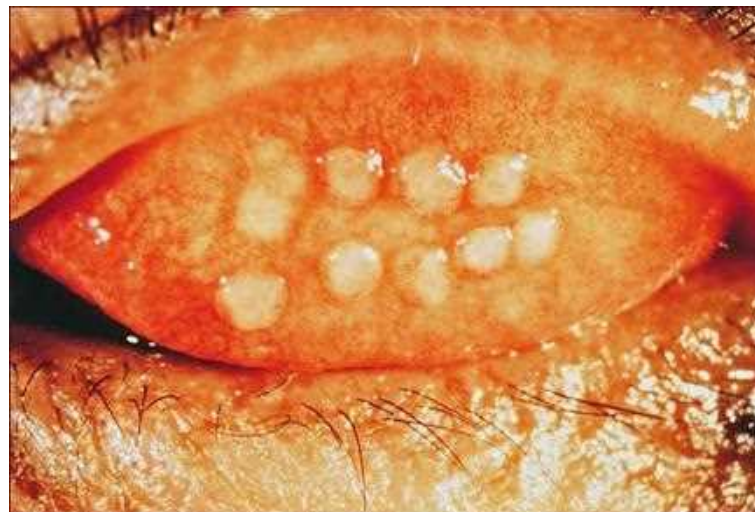
Acute allergic conjunctivitis is a type I immediate hypersensitivity reaction mediated by immunoglobulin E (IgE) and subsequent mast-cell activation,<sup>1</sup> stimulated by direct exposure to environmental allergens. The reaction may be limited to the eye, or it may be part of a generalized allergic reaction with nasal and respiratory symptoms. Often a family history of atopy is present. Cytological examination of conjunctival scrapings shows eosinophilic infiltration. Elevated levels of IgE and histamine are found in the tear film.<sup>2</sup> Acute allergic conjunctivitis is divided into seasonal allergic conjunctivitis (SAC) and perennial allergic conjunctivitis (PAC).<sup>3</sup> The onset of symptoms for SAC is seasonally related to circulating aeroantigens. PAC is considered a variant of SAC that persists throughout the year, although seasonal exacerbations often are seen.<sup>2</sup> Clinical symptoms and signs are typically bilateral and consist of itching, burning, and mild to moderate injection that can progress to various degrees of chemosis with superior tarsal conjunctiva papillary reaction. A watery or mucoid “stringy” discharge may be seen.<sup>4</sup>

## CHRONIC ATOPIC KERATOCONJUNCTIVITIS

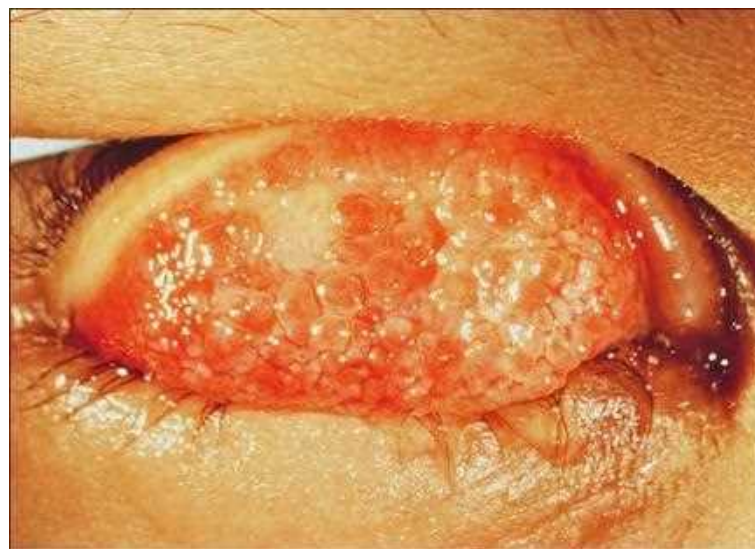
Chronic atopic keratoconjunctivitis (AKC) is an inflammatory disease that can lead to disabling symptoms involving both the conjunctiva and the cornea. It can present between the late teens through the fifth decade and has a slight male predilection. A large majority of patients have concomitant eczema or asthma.<sup>1</sup> Between 20% and 40% of patients with atopic dermatitis also have AKC.<sup>5</sup> Clinical symptoms include intense bilateral itching, tearing, burning, photophobia, blurred vision, and a stringy mucus discharge. Periorbital eczema, lid edema, conjunctival chemosis, and allergic shiners are common findings. Papillary hypertrophy of the upper tarsal conjunctiva is the most common sign (Fig. 4.71). Cobblestone papillae on the superior tarsal conjunctiva also may occur. Gelatinous limbal hyperplasia and nodules may be present with or without Horner–Trantas dots (areas of eosinophils and degenerating cellular debris). In severe cases, cicatrizing conjunctivitis with subepithelial fibrosis, symblepharon formation, and forniceal shortening may develop.<sup>2</sup> Histopathologically, a mixture of mast cells, eosinophils, and lymphocytes are found in the conjunctival epithelium.

## VERNAL CONJUNCTIVITIS

Vernal conjunctivitis is a bilateral, recurrent inflammation of the conjunctiva that tends to occur in children and young adults with a history of atopy. Its onset is most common in the spring and summer months, and the inflammation often goes into remission during the cooler months.<sup>6</sup> The highest incidence is in the warm, temperate Middle East–Mediterranean region and Mexico. Boys are affected twice as often as girls, with a peak



**Fig. 4.71 Chronic Atopic Conjunctivitis.** Mild conjunctival injection with numerous giant cobblestone papillae.

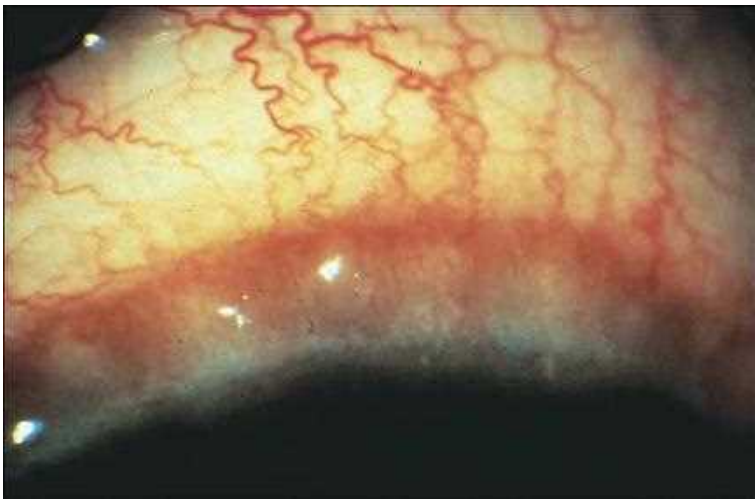


**Fig. 4.72 Vernal Conjunctivitis.** Cobblestone papillae cover the superior tarsal conjunctiva.

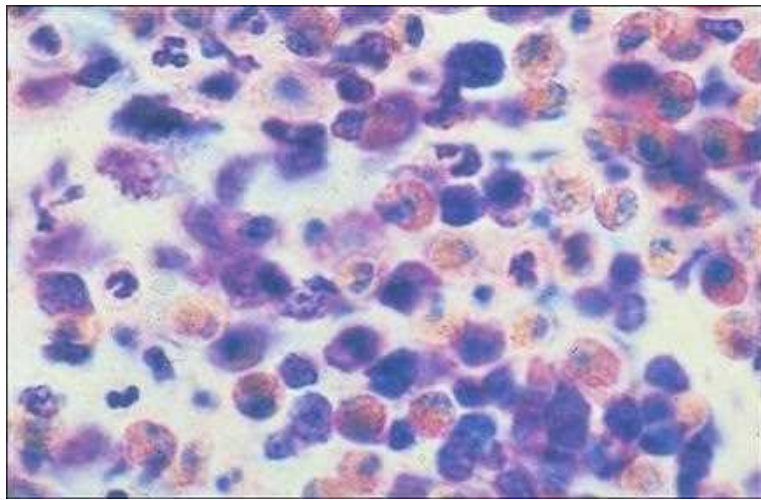
incidence between ages 11 and 13 years. Recent studies have found an association between low serum vitamin D levels in children with vernal conjunctivitis.<sup>7</sup> The prominent symptom is intense pruritus. Other complaints include photophobia, burning, tearing, mild ptosis, and a thick, ropy, yellow, mucoid discharge. It is classically thought to be an IgE-mediated type I hypersensitivity reaction; however, studies have also noted T helper 2 lymphocyte involvement in a type IV immune reaction.<sup>2</sup>

The three forms of the vernal conjunctivitis are palpebral, limbal, and mixed.<sup>8</sup> The palpebral form is marked by cobblestone papillae on the superior tarsal conjunctiva (Fig. 4.72) with minimal involvement of the lower lid. After initial papillary hypertrophy, the connective tissue of the substantia propria undergoes hyperplasia and proliferation to form giant papillae. The pressure of the cornea flattens the tops of the giant papillae to produce a cobblestone pattern. Tiny twigs of vessels are found in the centers of the papillae, which help differentiate these from the large follicles without the





**Fig. 4.7.3 Vernal Catarrh.** Clinical appearance of the less commonly seen limbal reaction. (Courtesy Dr. I. M. Raber.)



**Fig. 4.7.4 Vernal Catarrh.** Histological examination of a conjunctival smear shows the presence of many eosinophils. (Courtesy Dr. I. M. Raber.)

**TABLE 4.7.1 Medications Used in the Treatment of Allergic Conjunctivitis**

Category	Examples	Comments
Histamine 1 (H <sub>1</sub> ) receptor agonists	Levocabastine, emedastine difumarate	Use for isolated, acute allergic attacks. Use alone or in combination with mast-cell stabilizers and nonsteroidal anti-inflammatory drugs (NSAIDs).
Mast-cell stabilizers	Cromolyn sodium, lodoxamide, pemirolast, nedocromil sodium	Most useful for chronic allergies. May take 1–2 weeks to be effective. Pemirolast and nedocromil have antihistamine effects as well. Nedocromil also reduces eosinophil and neutrophil chemotaxis.
Antihistamines with mast cell–stabilizing activity	Olopatadine, alcaftadine, bepotastine, ketotifen fumarate, azelastine, epinastine, bepotastine	These medications combine the immediate effect of selective antihistamines with the long-term effects of mast-cell stabilization. They have convenient once- or twice-a-day dosing. Ketotifen and azelastine have anti-inflammatory properties as well.
Topical NSAIDs	Ketorolac, nepafenac, bromfenac	Can reduce itching, but stings when applied.
Vasoconstrictors	Naphazoline/pheniramine, naphazoline/antazoline	Available over the counter; instruction must be given to avoid chronic use because of the risk of rebound redness; relieves redness, but not other symptoms.
Topical corticosteroids	Loteprednol, fluorometholone, rimexolone	May be useful in serious cases or until control is achieved with other agents. Side-effects limit chronic use.
Oral antihistamines	Fexofenadine, loratadine, cetirizine, ebastine, mizolastine, desloratadine	Useful when systemic allergic symptoms are present but may cause dry eyes.
Immunomodulators	Tacrolimus, cyclosporine	Useful in refractory cases or situations where corticosteroid use is not appropriate.

central vessels seen in trachoma. The limbal form is marked by a broad, thickened, gelatinous opacification of the superior limbus that can override the cornea (Fig. 4.7.3). Tiny, twig-like vessels arise in the centers of these rounded lumps, as opposed to limbal follicles, where the vessels appear around the sides of the elevations. Histologically, the tissue is infiltrated with lymphocytes, plasma cells, macrophages, basophils, many eosinophils, and an increased number of conjunctival goblet cells (Fig. 4.7.4). Horner–Trantas dots, which are white, chalk-like gelatinous nodules composed of eosinophils and epithelial debris located at the limbus, are characteristic in limbal vernal keratoconjunctivitis (VKC). Patients with VKC also have elevated levels of histamine with other cytokines and immunological molecules in the tear film.

The cornea is involved in about half the cases. Corneal manifestations include a superficial pannus and a punctate epithelial keratitis. Small, gray patches of necrotizing epithelium may involve the upper one third to two thirds of the cornea—in severe cases, the cornea appears to be dusted with flour.<sup>8</sup> The affected area stains with fluorescein. A vernal “shield ulcer” develops as a horizontal oval, shallow, nonvascularized, indolent ulcer of the superior cornea (see Fig. 4.7.4) that leads to severe discomfort. The edges are composed of shaggy, gray, dead epithelial cells, and infiltration of the underlying superficial stroma is present. After the ulcer heals, a mild corneal opacity may persist at the level of Bowman’s layer.

## TREATMENT OF ALLERGIC/ATOPIC KERATOCONJUNCTIVITIS

Treatment of all of the above conditions is based on the severity and chronicity of the disease in each patient. For all cases, cold compresses,

preservative-free artificial tears (refrigerated), and avoidance of allergens can help alleviate symptoms. Unfortunately, avoidance of the offending antigens is often difficult, thus medications are used for further symptomatic control (Table 4.7.1).

Treatment regimens include topical decongestants, antihistamines, mast cell–stabilizing agents, and anti-inflammatory agents. Topical decongestants, which act as vasoconstrictors, can be used symptomatically with mild allergic reactions to alleviate erythema and tearing. However, chronic use can lead to rebound hyperemia that limits their efficacy. Histamine (H<sub>1</sub> receptor–specific) antagonists (see Table 4.7.1) can be used for intermittent, acute allergic reactions from a limited exposure to the antigen. Mast-cell stabilizers (see Table 4.7.1) are used as long-term maintenance therapy for chronic allergies.<sup>9</sup> They act by reducing intracellular, calcium-dependent secretory events and decreasing synthesis/secretion of leukotrienes, chemokines, and other proinflammatory mediators.<sup>10</sup> Combination medications that act as both mast-cell stabilizers and H<sub>1</sub>-specific antagonists (see Table 4.7.1) have become a mainstay of treatment.<sup>3,10</sup>

Preseasonal treatment with a combination medication has been shown to suppress clinical symptoms in patients with SAC.<sup>11</sup> Noncorticosteroidal anti-inflammatory agents and topical corticosteroids can be used to reduce the acute inflammatory response in severe cases until the mast-cell stabilizers and antihistamines take effect. Corticosteroids are then tapered off as the therapeutic effects of the maintenance medications take hold. Topical cyclosporine 0.5%–2% has also been effective in the treatment of VKC, atopy, and other forms of severe allergic disease.<sup>12</sup> Topical tacrolimus ointment, which is known to inhibit T-lymphocyte activation, has been used to treat corticosteroid-resistant or unresponsive AKC, VKC, and severe cases of GPC.<sup>5,13</sup> Evaluation by an allergist is recommended in severe cases.



**Fig. 4.7.5 Allergic Dermatoconjunctivitis.** Contact allergy of the eyelids after exposure to neomycin eyedrops. The skin shows a typical eczematous dermatitis.

## ALLERGIC DERMATOCONJUNCTIVITIS

Contact allergy of the eyelids and conjunctiva represents the most common form of allergic reaction seen by the ophthalmologist. It represents a delayed, cell-mediated (type IV) hypersensitivity reaction. In patients with previous sensitization, the immune reaction can take 48–72 hours to develop. Common stimuli include eyedrops (neomycin, gentamicin, idoxuridine, atropine, thimerosal, and penicillin<sup>13</sup>), cosmetics, clothing, jewelry, plastics, animal or vegetable products, and industrial chemicals.<sup>14</sup> The reaction usually begins with severe itching and a papillary conjunctivitis that is worse on the inferior palpebral conjunctiva. A mucoid or mucopurulent discharge is seen. The adjacent skin of the lower lids and lateral canthi becomes involved in a typical eczematous dermatitis (Fig. 4.7.5). Chronic exposure can lead to keratinization of the lid with punctal edema and stenosis. The cornea may show punctate epithelial keratitis and erosions. Conjunctival scrapings show monocytes, polymorphonuclear neutrophil leukocytes, mucus, and eosinophils. Treatment includes eliminating the antigenic stimulus and quieting the eye with antihistamines, mast-cell stabilizers, and topical corticosteroids.

## MICROBIAL ALLERGIC CONJUNCTIVITIS

Microbial allergic conjunctivitis is a type IV hypersensitivity response to the toxic protein breakdown products of bacterial disintegration, most commonly from chronic staphylococcal blepharoconjunctivitis. The formation of bacterial breakdown products causes an allergic response in the conjunctiva and cornea.<sup>15</sup> Typically, patients do not have a history of atopy. Marginal infiltrates of the cornea can be associated with this condition (Fig. 4.7.6).<sup>14</sup>

Phlyctenular keratoconjunctivitis is another manifestation of microbial allergic conjunctivitis. In the past, it was commonly associated with tuberculosis. Today, it is most frequently seen with chronic staphylococcal blepharoconjunctivitis. Other possible sources include *Candida albicans*, *Coccidioides immitis*, *Chlamydia*, parasites, and lymphogranuloma venereum. Phlyctenular disease presents as slightly raised, small, pinkish white or yellow nodules surrounded by dilated vessels located on conjunctiva near the limbus or into peripheral cornea. After a few days, the center of the lesion then ulcerates, sloughs, and clears without scarring. Classically, there is no clear zone between the limbus and the lesion. Involvement is usually bilateral and seasonal (occurring more in spring and summer), and the condition occurs most frequently in children and young adults.

Treatment includes identifying the inciting organism and eradicating it. Twice-daily lid scrubs (mechanical debridement of the lid margins with dilute baby shampoo or commercially prepared lid scrub pads) can usually achieve symptomatic improvement. Topical antibiotic or antibiotic-corticosteroid combination ointments or drops rubbed into the lid margins may reduce the number of bacterial colonies. Corticosteroids are reserved for chronic recalcitrant blepharoconjunctivitis and are beneficial early in the treatment of phlyctenular disease. Tuberculosis should be ruled out, when appropriate. Systemic antibiotics, such as oral tetracycline 250 mg four times a day or oral doxycycline 100 mg twice a day, can help in



**Fig. 4.7.6 Microbial Allergic Keratoconjunctivitis Associated With Staphylococci.** A staphylococcal marginal infiltrate is seen in the superior cornea.



**Fig. 4.7.7 Giant Papillary Conjunctivitis.** Giant papillae cover this patient's superior tarsal conjunctiva after chronic exposure to soft contact lenses.

cases of nontuberculous phlyctenular disease or persistent staphylococcal blepharoconjunctivitis.

## GIANT PAPILLARY CONJUNCTIVITIS

Giant papillary conjunctivitis (GPC) is a syndrome of inflammation of the upper palpebral conjunctiva associated with contact lens wear, ocular prostheses, and protruding ocular sutures.<sup>16,17</sup> It is primarily linked to contact lens wear and is seen 10 times more frequently in soft lens wearers than in rigid lens wearers.<sup>17</sup> The average time for the development of symptoms is 8 months for soft lens wearers and 8 years for hard lens wearers. Estimates of the prevalence vary from 1% to 5% of soft lens users to 1% of rigid lens users.

Patients complain of mild itching after removal of the contact lenses and increased mucus on the lenses and in the nasal canthus upon awaking. They also complain of increased lens awareness, blurring of vision after hours of lens wear, excessive lens movement, and eventual contact lens intolerance. Signs initially include a generalized thickening and hyperemia of the superior pretarsal conjunctiva. The normally small papillae become elevated. The conjunctiva becomes more translucent and eventually becomes opaque secondary to cellular infiltration. Macropapillae (0.3–1.0 mm) and giant papillae (1.0–2.0 mm) then form (Fig. 4.7.7). Trantas dots and gelatinous nodules may develop at the limbus.<sup>18</sup> Inspection of the contact lenses almost always reveals whitish protein deposits.

The histology of GPC shows irregular thickening of the conjunctival epithelium over the papillae, with epithelial downgrowth into the stroma. The epithelium and stroma show infiltration of lymphocytes, plasma cells, polymorphonuclear neutrophil leukocytes, eosinophils, basophils, and macrophages along with fibroblast proliferation. The number of eosinophils and basophils is considerably lower than that seen in vernal conjunctivitis.

The cause of GPC is multifactorial. Patients likely have environmental antigens that adhere to the mucus and proteins that normally coat the surface of all contact lenses.<sup>19</sup> These antigens, which persist as deposits on the contact lenses, are forced into repeated contact with the superior tarsal conjunctiva with blinking. Mechanical trauma also is an important factor in the pathogenesis of GPC and develops in patients who have ocular prostheses and exposed suture ends. The repeated mechanical trauma induces expression of interleukin-8 with recruitment of dendritic cells that increases the number of antigen-presenting cells.<sup>5</sup> Repeated exposure to antigens combined with the trauma from contact lens wear may stimulate a type IV basophil hypersensitivity of the conjunctiva. A type I IgE-mediated immediate hypersensitivity reaction occurs as well.

Treatment of the condition requires removal of the inciting factor. Loose sutures should be removed, and ocular prostheses may need to be refitted. In contact lens wearers, initial discontinuation of lens wear is necessary until the inflammation subsides, which can take months. Lens wear may resume once symptoms improve, but decreasing daily wear time and good lens hygiene are essential. Patients must be instructed to clean their contacts thoroughly each night, and an attempt should be made to remove preservatives from the lens care system. Disinfection with a hydrogen peroxide system and regular enzymatic treatment help decrease buildup on the lenses. Often switching to a different lens polymer allows more than 80% of patients to continue contact lens wear.<sup>20</sup> Daily disposable soft contact lenses should be encouraged and often are well tolerated. If soft lenses do not work, a rigid gas-permeable lens can be tried. In the early stages of GPC a combination drop of antihistamine and mast-cell stabilizer can be effective in the resolution of some symptoms. Maintenance therapy with combination drops is typically necessary to prevent recurrence. A short course of topical corticosteroids or corticosteroid-sparing medications, such as cyclosporine or tacrolimus, can lessen the symptoms in severe cases.

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# Tumors of the Conjunctiva

James J. Augsburger, Zélia M. Corrêa, Bitá Esmaeli

## 4.8

**Definition:** Spectrum of malignant and benign neoplasms, choristomas, and hamartomas arising from or occurring within the conjunctiva, and nonneoplastic epibulbar tumors frequently misdiagnosed clinically as a conjunctival malignant neoplasm.

### Key Features

- Solid mass or discrete lesion of conjunctiva.
- Wide spectrum of color, texture, and size of tumor and associated features.
- Substantial differences in age at onset and clinical behavior after detection.

## CONJUNCTIVAL MALIGNANT NEOPLASMS

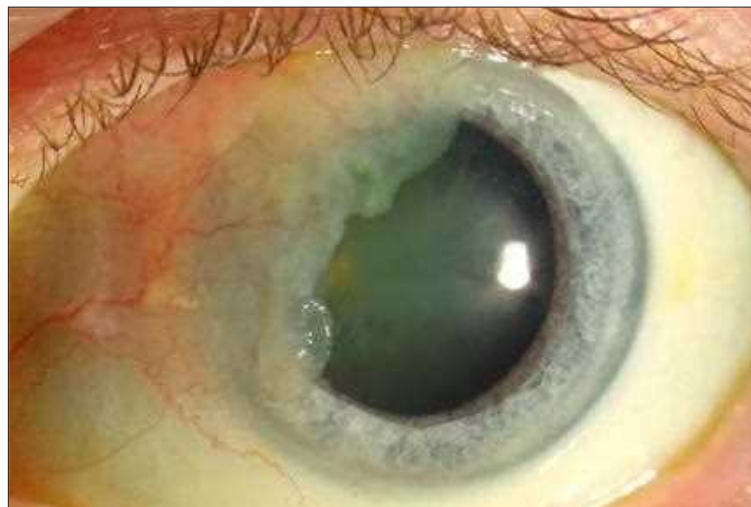
A conjunctival malignant neoplasm is a tumor (three-dimensional mass) composed of cancer cells involving the conjunctival epithelium, the stroma, or both. The lesions mentioned in this section are all malignant neoplasms (cancerous tumors) and neoplasias of the conjunctiva. There are three principal categories of malignant neoplasms and neoplasias of the conjunctiva: (1) ocular surface squamous neoplasms and neoplasias (squamous cell carcinoma and its variants), (2) conjunctival melanoma, and (3) conjunctival lymphoma. Several other uncommon but clinically important conjunctival neoplasms will also be mentioned.

### Ocular Surface Squamous Neoplasia

The term ocular surface squamous neoplasia (OSSN) encompasses a number of related nonmelanocytic cancers that arise within the epithelium of the conjunctiva, cornea, or both. These cancers range from conjunctival and *corneal intraepithelial neoplasia* (CIN) (essentially carcinoma in situ within the ocular surface epithelium) to nodular squamous cell carcinoma and variants thereof, including mucoepidermoid carcinoma.

Conjunctival/corneal intraepithelial neoplasia is a localized or diffuse replacement of normal conjunctival or corneal epithelium by malignant cells derived from the stratified squamous epithelium.<sup>1</sup> CIN becomes evident clinically when it involves the corneal epithelium and produces a translucent whitening or graying of the involved portions of that epithelium (Fig. 4.8.1). The lesion can cause substantial impairment of visual acuity if it involves the central cornea. When malignant epithelial cells involve only a portion of the thickness of the epithelium pathologically, the condition is called conjunctival or corneal *squamous epithelial dysplasia*. When neoplastic epithelial cells replace full-thickness conjunctival epithelium but do not invade the substantia propria, the condition is referred to as *squamous cell carcinoma in situ*. Most ocular tumor specialists advise excision of conjunctival lesions suspected of being ocular surface squamous neoplasms, and surgical scraping of abnormal appearing corneal epithelium suspected of being corneal intraepithelial neoplasia with submission of the excised specimens to pathology to confirm or rule out the clinical diagnosis before initiating therapies such as topical interferon therapy or topical chemotherapy (see “[Management of Conjunctival Tumors Suspected of Being Malignant Neoplasms or Neoplasias](#)” below).

*Squamous cell carcinoma* of the conjunctiva is a malignant neoplasm of the stratified squamous epithelium of the conjunctiva.<sup>2,3</sup> It appears as a hypervascularized epibulbar tumor that is located most frequently at the limbus medially or temporally. Such tumors occur in three principal clinical patterns. The *leukoplakic tumor* (Fig. 4.8.2) is characterized by hard,



**Fig. 4.8.1 Conjunctival and Corneal Intraepithelial Neoplasia (CIN).** The corneal epithelium is thickened and translucent in the medial and superomedial portions of the cornea.

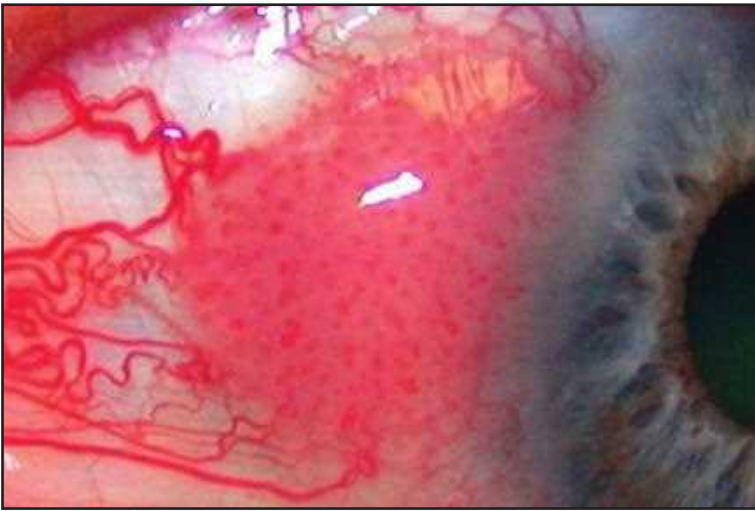


**Fig. 4.8.2 Leukoplakic Squamous Cell Carcinoma of Conjunctiva.** The discrete white hyperkeratotic limbal plaque is associated with prominent conjunctival blood vessels.

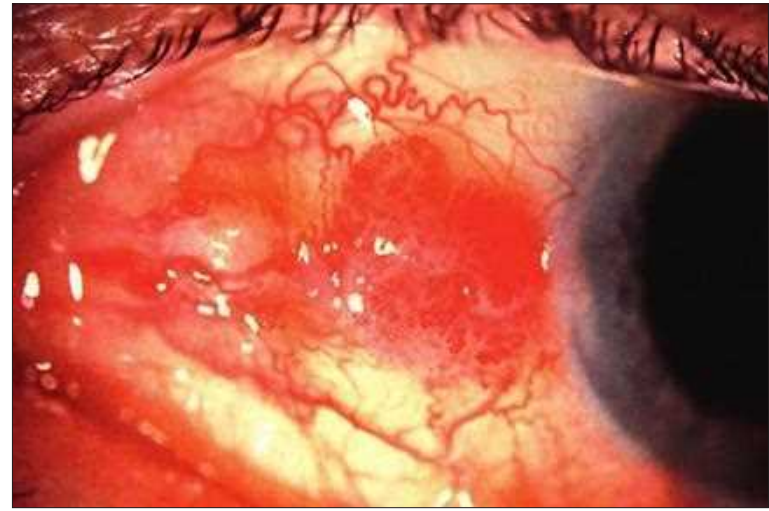
white accumulation of abnormally keratinized conjunctival epithelium overlying the tumor proper. The gelatinous tumor (Fig. 4.8.3) appears as a translucent nodule fed and drained by prominent dilated epibulbar blood vessels. The papillary tumor (Fig. 4.8.4) appears as a pink to reddish mass that exhibits prominent vascular loops internally on slit-lamp biomicroscopy. Many larger tumors exhibit more than one or these clinical patterns (Fig. 4.8.5). Some larger tumors also exhibit ulceration or even intracorneal or intraocular invasion that can be determined by slit-lamp biomicroscopy or ultrasound biomicroscopy (UBM). Aggressive and neglected tumors can invade the orbit and extend partially around the eye, a circumstance that may necessitate exenteration of the orbit.

*Mucoepidermoid carcinoma* (Fig. 4.8.6) is a particularly aggressive form of OSSN that has a strong tendency to recur following attempted excision, invade the eye wall, and invade the orbit.<sup>4</sup> It resembles conventional

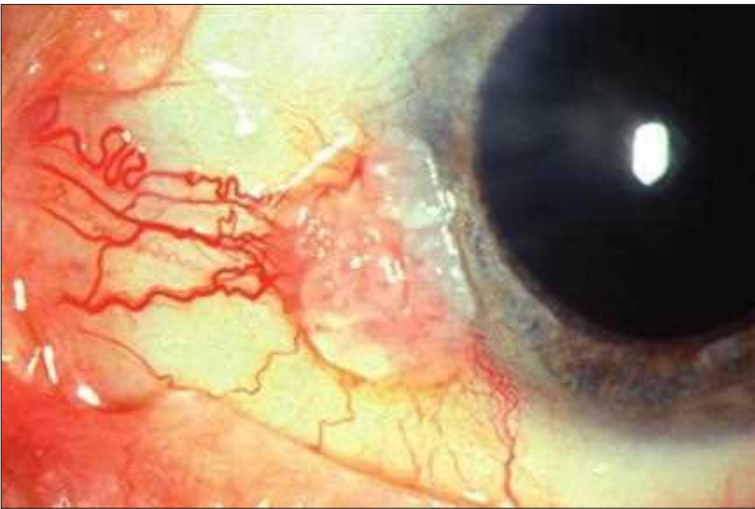




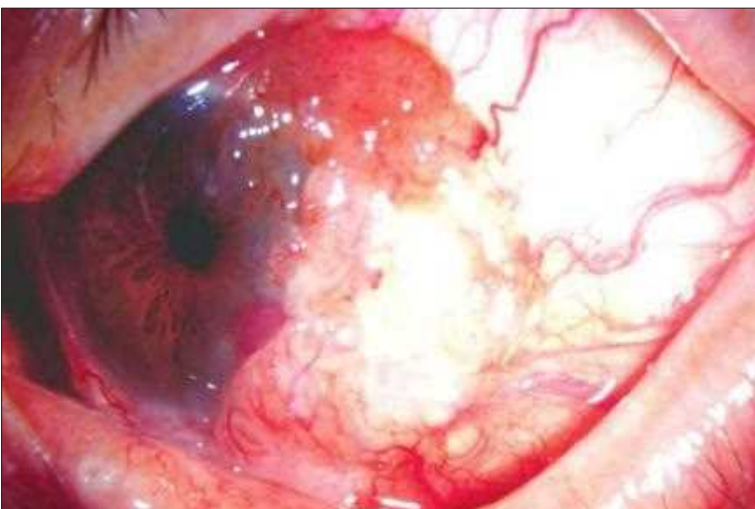
**Fig. 4.8.3 Papillomatous Squamous Cell Carcinoma of Conjunctiva.** The pink limbal tumor contains multiple fine intralesional corkscrew blood vessels and is associated with dilated afferent and efferent conjunctival blood vessels.



**Fig. 4.8.6 Mucoepidermoid Carcinoma of Conjunctiva.** This tumor resembles a papillary squamous cell carcinoma near the limbus but has a nodular subepithelial portion extending posteriorly.



**Fig. 4.8.4 Gelatinous Squamous Cell Carcinoma of Conjunctiva.** The translucent limbal mass is associated with dilated afferent and efferent conjunctival blood vessels.



**Fig. 4.8.5 Invasive Squamous Cell Carcinoma of Conjunctiva Exhibiting Leukoplakic, Papillary and Gelatinous Components Plus Central Ulceration.** Note blood within the corneal stroma at the pupillary margin of the tumor.

squamous cell carcinoma quite closely clinically and on routine hematoxylin and eosin-stained microslides but can be distinguished by the presence of prominent goblet cells containing mucin (revealed by stains, such as Alcian blue and mucicarmine) and positive immunoreactivity to immunostain CK7. Because of its aggressively invasive behavior, this ocular surface squamous neoplasm ultimately prompts exenteration in many cases.

Squamous cell carcinoma of the conjunctiva and its variants are the most common primary conjunctival malignant neoplasms encountered in clinical practice.<sup>5</sup> The average annual incidence of squamous cell carcinoma of the conjunctiva across all age groups has been estimated to be approximately 17–20 new cases per million persons per year. For a population with an average life expectancy of 70 years, this average annual incidence translates to a cumulative lifetime incidence of approximately 1 case per 700–850 persons. Most tumors of this category are encountered in persons over age 50 years. Risk factors for occurrence include a history of repeated, intense, sunlight exposure; male gender; outdoor occupations; advanced age; cigarette smoking; a history of squamous cell carcinoma of the skin of the head and neck; blond hair and light complexion; xeroderma pigmentosum; acquired immunodeficiency syndrome (AIDS); and conjunctival infection by human papilloma virus (HPV) types 16 and 18.

## Conjunctival Melanoma

*Malignant melanoma of the conjunctiva* is a cancerous neoplasm that arises from melanocytes that are present normally within the basal layers of the conjunctival epithelium.<sup>6,7</sup> This form of cancer ranges from a flat patch of acquired conjunctival and corneal intraepithelial melanocytic intraepithelial neoplasia (conjunctival–corneal melanoma in situ, malignant primary acquired melanosis) to nodular epibulbar tumors. Most conjunctival melanomas are dark brown but some appear partially if not entirely amelanotic. The only reliable way to distinguish an amelanotic conjunctival melanoma from squamous cell carcinoma or other amelanotic malignant neoplasm is by pathological analysis of the excised or biopsied tumor.

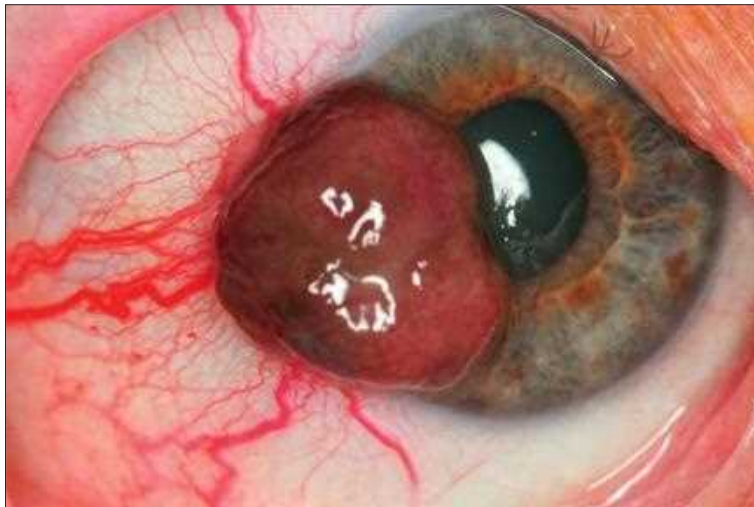
*Primary acquired melanosis (PAM)* of the conjunctiva refers to a patch of intraepithelial melanocytic hyperplasia to neoplasia that develops from a previously unaffected region of the conjunctiva in an adult individual (Fig. 4.8.7).<sup>6</sup> Such melanotic conjunctival patches may contain only benign or mildly atypical intraepithelial melanocytes (benign acquired melanosis) or markedly atypical malignant melanoma cells (malignant PAM or PAM with severe atypia). Although larger and more heterogeneously melanotic conjunctival lesions are more likely to contain malignant melanoma cells compared with smaller and more homogeneously melanotic lesions, no reliable clinical way exists to distinguish between benign and malignant PAM. Excision or biopsy of the lesion with pathological analysis of the intraepithelial melanocytes is necessary for its classification as benign PAM versus PAM with severe atypia (intraepithelial melanoma). Nodular conjunctival melanoma frequently develops from patches of malignant PAM. Underlying PAM should be suspected in cases with nodular conjunctival melanoma associated with patchy flat melanotic conjunctiva.

*Nodular conjunctival melanoma* appears as a solid epibulbar tumor fed and drained by prominent conjunctival blood vessels (Fig. 4.8.8). Such a

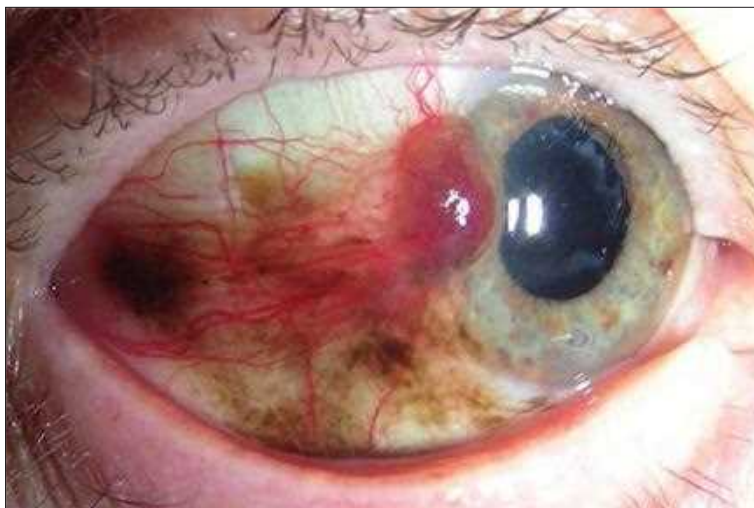




**Fig. 4.8.7 Primary Acquired Melanosis of Conjunctiva and Cornea.** The lesion is completely flat within the corneal, limbal, and bulbar conjunctival epithelium.



**Fig. 4.8.8 Nodular Melanotic Conjunctival Melanoma at Limbus.** Note dilated conjunctival blood vessels associated with lesion.



**Fig. 4.8.9 Conjunctival Melanoma Associated With Primary Acquired Melanosis of Conjunctiva.** The nodular conjunctival tumor adjacent limbus is almost completely amelanotic.

tumor can arise *de novo* (i.e., from conjunctiva that appeared normal prior to the tumor's development) or from a patch of PAM. As indicated above, most conjunctival melanomas are melanotic (brown); however, some are hypomelanotic or amelanotic (Fig. 4.8.9). The most common location for development of a conjunctival melanoma is at or adjacent to the limbus medially or temporally. Such tumors are less likely to metastasize compared with those that develop in the caruncle or semilunar fold or from the forniceal or palpebral conjunctiva. Conjunctival melanomas that



**Fig. 4.8.10 Malignant Lymphoma of Conjunctiva.** The tumor is a lumpy, pink, ridge-like mass involving inferior bulbar and forniceal conjunctiva.

metastasize tend to involve regional lymph nodes (preauricular, parotid, and submandibular) on the ipsilateral side of the head and neck initially.<sup>8</sup> Because of this, clinical evaluation should include palpation of the head and neck looking for enlarged lymph nodes. If lymph node metastasis is suspected clinically, lymph node mapping and excision should be considered in conjunction with initial treatment of the conjunctival tumor.

## Conjunctival Lymphoma

*Conjunctival lymphoma* is a form of extranodal non-Hodgkin's lymphoma that arises within the conjunctival substantia propria.<sup>9,10</sup> Tumors of this type appear as salmon-colored subepithelial masses (Fig. 4.8.10) that can be unilateral or bilateral and unifocal to multifocal in each affected eye. Pathological analysis of such tumors characteristically shows a monoclonal collection of atypical lymphoid cells that usually are of B-scan lineage. Different histopathological patterns are associated with varying likelihoods of systemic lymphoma ranging from very low (mucosa associated lymphoid tumor [MALT] lymphoma) to reasonably high (diffuse large B-cell lymphoma and mantle cell lymphoma). Because of this, histopathological analysis of a biopsy specimen from such a tumor always is appropriate to assess prognosis and develop a management plan. The most common current treatment for isolated low-grade conjunctival lymphoma is low-dose fractionated external beam radiation therapy with shielding of the cornea and lens.

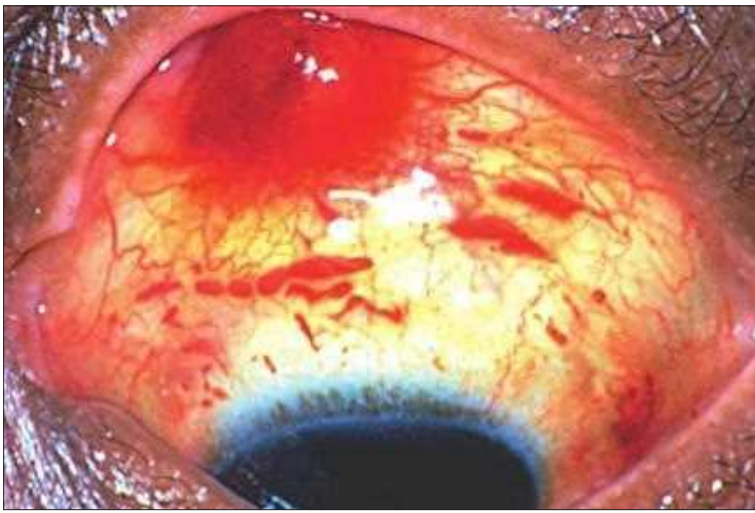
In addition to these three most common conjunctival malignant neoplasms, readers should be familiar with uncommon conjunctival malignant neoplasms described below.

*Conjunctival Kaposi's sarcoma* is a malignant neoplasm that arises from blood vessels and possibly other tissue elements within the conjunctival stroma.<sup>11,12</sup> It occurs predominantly in individuals with AIDS or other forms of systemic immunosuppression. The tumor characteristically appears as a dark red, frequently hemorrhagic, conjunctival mass (Fig. 4.8.11) that grows rapidly if untreated. Since introduction of therapeutic regimens that control many of the systemic features of human immunodeficiency virus (HIV) infection, such lesions are much less common than they were several decades ago.

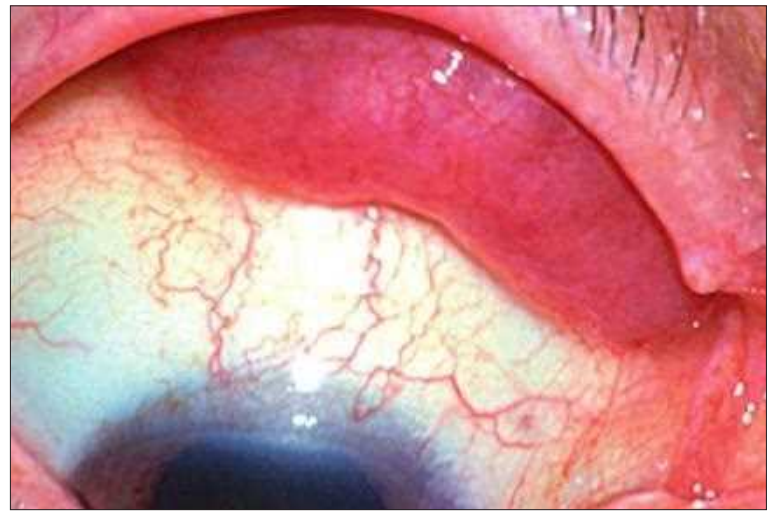
*Sebaceous cell carcinoma* (Fig. 4.8.12) is a malignant neoplasm that arises from the meibomian glands in the tarsal conjunctiva or the Zeis glands associated with the cilia at the lid margins.<sup>13,14</sup> It frequently is misdiagnosed as chronic blepharoconjunctivitis and treated as such for weeks to months before the correct diagnosis is suspected and confirmed pathologically. This form of ocular surface cancer has a strong tendency to involve the conjunctival epithelium diffusely (pagetoid spread), a feature that makes it extremely difficult to eradicate surgically. Histopathological analysis of a tumor specimen is the only reliable way to distinguish sebaceous carcinoma from squamous cell carcinoma and its variants.

*Rhabdomyosarcoma* is a malignant neoplasm that may arise from previously normal muscle cells. Primary orbital rhabdomyosarcoma is much more common than primary conjunctival rhabdomyosarcoma.<sup>15</sup> Primary conjunctival rhabdomyosarcoma usually appears as a rapidly enlarging pale pink to tan tumor within the conjunctival substantia propria (Fig. 4.8.13). The tumor usually develops during the first 2 decades of life. Biopsy of the tumor with pathological analysis of the specimen is essential for prompt





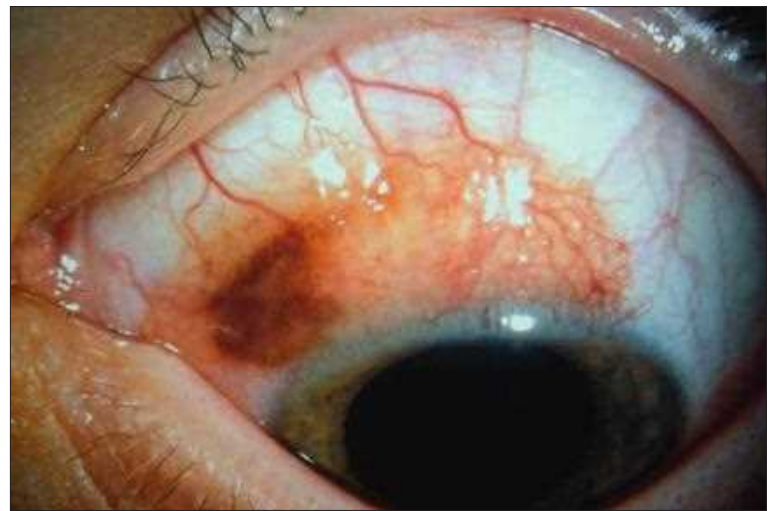
**Fig. 4.8.11 Kaposi's Sarcoma of Conjunctiva.** Note the intensely red color of the tumor and presence of associated subconjunctival blood. This patient had underlying acquired immunodeficiency syndrome (AIDS).



**Fig. 4.8.14 Leukemic Tumor of Conjunctiva.** The tumor is a well-defined, reddish-pink, ridge-like mass involving the superior fornix.



**Fig. 4.8.12 Sebaceous Carcinoma of Conjunctiva.** The tumor replaces semilunar fold and caruncle and involves much of the palpebral conjunctiva and lid margin of the lower eyelid.



**Fig. 4.8.15 Conjunctival Nevus.** The tumor is partly melanotic but predominantly tan and associated with moderately prominent conjunctival blood vessels.



**Fig. 4.8.13 Rhabdomyosarcoma of Conjunctiva and Orbit Presenting as Epibulbar Tumor.** The tumor appears as a pink mass arising from the superior fornix.

diagnosis and successful treatment. Treatment usually consists of debulking of the tumor followed by several cycles of systemic chemotherapy and orbital external beam radiation therapy.

*Leukemic conjunctival tumors* of the substantia propria develop in some patients with leukemia.<sup>16,17</sup> Tumors of this type (Fig. 4.8.14) appear similar to conjunctival lymphomas. They are extremely uncommon but can be the

presenting sign of leukemia in some individuals, and the initial manifestation of relapse of some previously treated leukemias.

## BENIGN CONJUNCTIVAL NEOPLASMS AND NEOPLASIAS

A *benign conjunctival neoplasm* is an acquired tumor composed of noncancerous cells and develops within previously normal-appearing conjunctival epithelium, substantia propria, or both. A *conjunctival choristoma* is a congenital tumor of the conjunctiva composed of noncancerous cells that are not normally present within that tissue. A *conjunctival hamartoma* is a congenital tumor of the conjunctiva composed of noncancerous cells that are present normally in that tissue but are present in excessive number and with atypical or disorganized tissue architecture. Although tumors of the latter two types are not precisely “neoplasms,” they are lumped together with benign neoplasms and neoplasias in this section.

### Conjunctival Nevus

The *conjunctival nevus* is a benign neoplasm consisting of mildly atypical but noncancerous melanocytes that arose from normal conjunctival melanocytes within the basal layers of the conjunctival epithelium.<sup>18</sup> This tumor is, by far, the most common primary ocular neoplasm encountered in clinical practice. The typical lesion is not present at birth in most patients but develops later in life (most frequently within the first 2 decades of life) from previously normal appearing conjunctiva, typically at the limbus medially or temporally. The lesion appears as a discrete brown to tan conjunctival tumor in most patients (Fig. 4.8.15) but is completely amelanotic and





**Fig. 4.8.16 Benign Acquired Melanosis of Conjunctiva.** The bulbar conjunctival melanosis is more prominent OS (left eye) than OD (right eye) but was evident along the limbus OU (both eyes) symmetrically in this dark-skinned individual.



**Fig. 4.8.17 Conjunctival and Intrascleral Hemangioma.** This congenital vascular tumor is composed of bright red superficial blood vessels and darker intrascleral blood vessels.

translucent in some persons. The lesion is typically not associated with any prominent dilated tortuous epibulbar feeder and drainer blood vessels. On slit-lamp biomicroscopy, numerous intraepithelial microcysts commonly are evident within such a lesion. Limited slow enlargement and darkening of such lesions is frequently reported by the parents of the affected child. Such lesions appear to have very limited malignant potential.

### Benign Acquired Melanosis of Conjunctiva

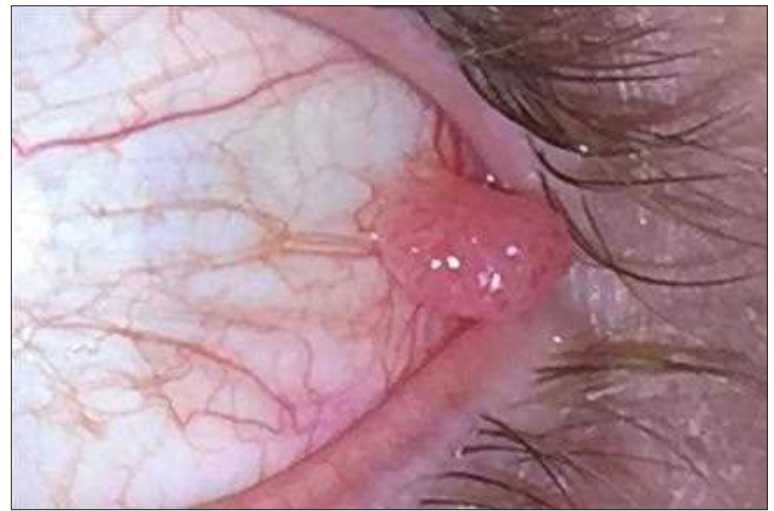
Many patients (particularly those of races with dark pigmentation) develop progressive acquired conjunctival melanosis, almost always bilaterally and most frequently in the limbal region (Fig. 4.8.16), as they age.<sup>19</sup> In some patients, the melanosis also involves the bulbar, forniceal, and even palpebral conjunctiva in patchy fashion. This form of acquired conjunctival melanosis is almost always benign histopathologically and rarely gives rise to conjunctival melanoma.

### Conjunctival Hemangioma

A *conjunctival hemangioma* is a benign blood vessel tumor of the conjunctival stroma.<sup>20</sup> In many patients, the lesion is present at birth. In such patients, the lesion should probably be regarded as a hamartoma. Small lesions of this type are usually asymptomatic and can be left alone. In contrast, complex epibulbar hemangiomas (Fig. 4.8.17) can be objectionable cosmetically. Repeated sessions of cryotherapy often are quite effective in reducing the size and decreasing the brightness of such lesions. In the authors' experience, attempts to excise such lesions or treat them with sclerosing solutions usually are unsuccessful and frequently make the situation worse. Fortunately, such tumors have limited if any malignant potential.

### Conjunctival Squamous Papilloma

A *benign squamous papilloma* of the conjunctiva is a neoplasm composed of nonmalignant vascularized fronds of subepithelial connective tissue covered by intact stratified squamous epithelium (Fig. 4.8.18).<sup>21</sup> It may be columnar or sessile in shape. Many lesions of this type that have been evaluated microbiologically have been found to harbor HPV type 6 or 11, and others have been linked to other HPV subtypes.



**Fig. 4.8.18 Squamous Papilloma of Conjunctiva.** The tumor is a pink columnar tumor arising from the peripheral bulbar conjunctiva.



**Fig. 4.8.19 Lymphangioma of Conjunctiva.** The limited bulbar conjunctival tumor consists of dilated lymphatic channels filled with yellow-tinted clear fluid.

### Conjunctival Lymphangioma

A *conjunctival lymphangioma* (Fig. 4.8.19) is an ill-defined tumor of the conjunctival substantia propria composed of mature lymphatic channels in excessive amounts.<sup>22</sup> In most cases, the conjunctival tumor is the anterior and, therefore, visible portion of a more extensive orbital lymphangioma. Such tumors are probably congenital in many cases (in which case they should be categorized as conjunctival hamartomas) but frequently do not show up until late in childhood to early adult years, typically in association with an upper respiratory or sinus infection. The lesion may enlarge abruptly and sometimes fills with blood. Piecemeal excision of the lesion, supplemented by cryotherapy, frequently is performed to treat prominent tumors of this type.

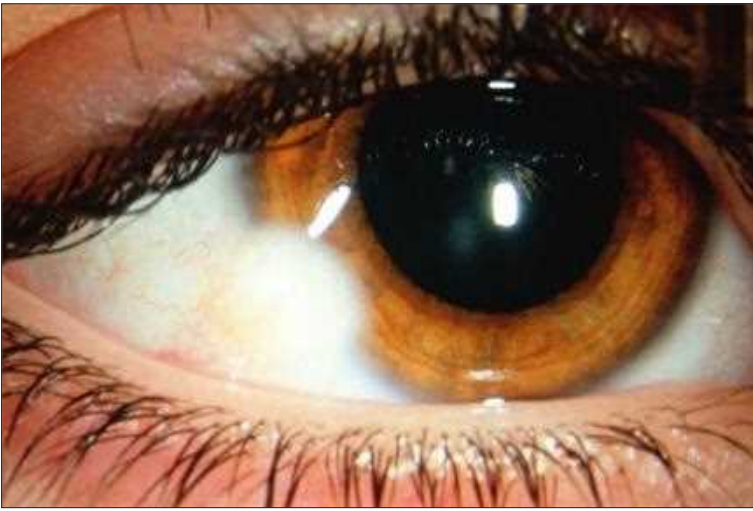
### Conjunctival Choristomas

*Conjunctival choristomas* are benign congenital tumors composed of non-malignant cells and tissues that do not occur normally in the conjunctiva. The cells and tissues that comprise the tumor are generally arranged haphazardly. The tumor frequently contains both mesodermal and ectodermal elements, in which case it is referred to as a *dermoid tumor*. Because many of the conjunctival tumors categorized as choristomas are not detected until late childhood to early adulthood, their congenital nature frequently cannot be verified. Several discrete subtypes of conjunctival choristomas exist, including those discussed below.

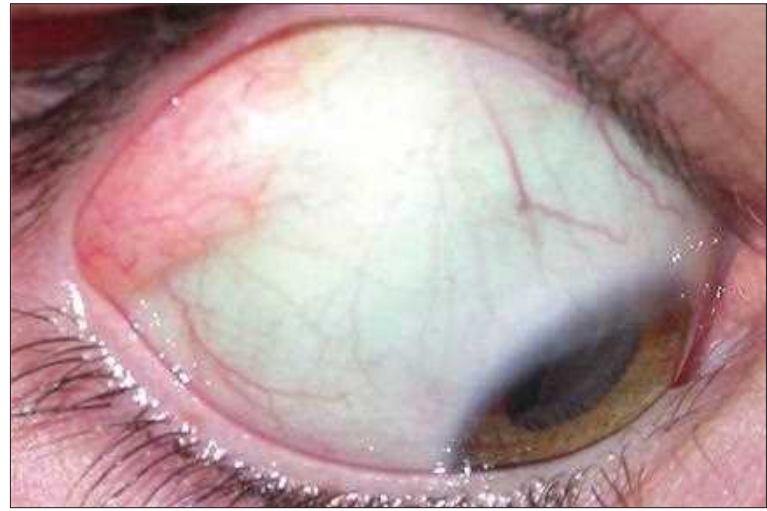
### Limbal Dermoid

The *limbal dermoid* is the most frequently encountered type of conjunctival choristoma. This lesion is present at birth and appears as an off-white to fleshy tumor overlying the corneoscleral limbus, most commonly inferotemporally (Fig. 4.8.20).<sup>23</sup> The typical tumor contains both mesodermal elements (most commonly fibroblasts, hair follicles, and fat) and ectodermal

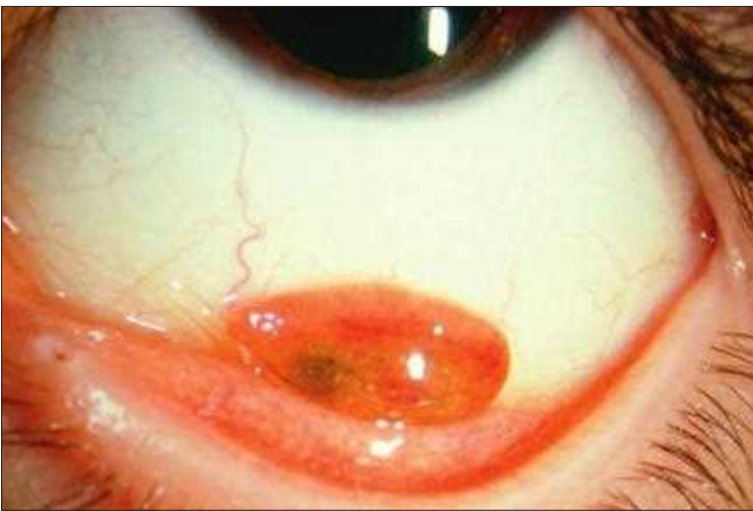




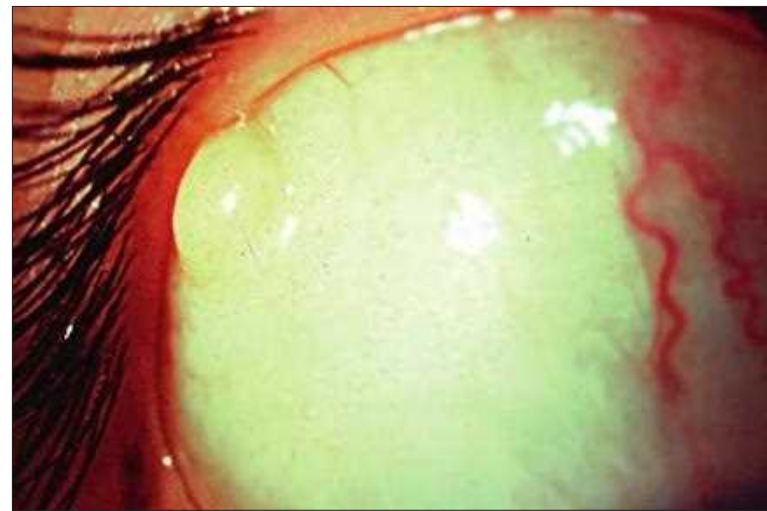
**Fig. 4.8.20 Limbal Dermoid Tumor.** The tumor is an off-white, discoid mass straddling the limbus inferotemporally.



**Fig. 4.8.22 Dermolipoma of Conjunctiva.** This tumor is pale pink with a yellowish tint and soft to palpation.



**Fig. 4.8.21 Solid Dermoid Tumor of Conjunctiva.** The tumor is heterogeneously pigmented and contains several protruding hair shafts.



**Fig. 4.8.23 Conjunctival Osteoma.** This epibulbar tumor is hard but nontender. It is off-white in color and therefore difficult to image well.

elements (epithelial cells). Such lesions are a typical feature of Goldenhar's syndrome and often are bilateral in individuals with this disorder. Excision of the lesion by lamellar or penetrating keratoplasty can be performed if the lesion is objectionable cosmetically, causing induced astigmatism with potential for amblyopia.

### **Conjunctival Solid Dermoid**

The conjunctival solid dermoid is a nodular nonlimbal conjunctival tumor composed of benign mesodermal and ectodermal cells.<sup>24</sup> A tumor of this type is generally heterogeneously pigmented and frequently exhibits prominent hair shafts protruding from its surface (Fig. 4.8.21). Such tumors are commonly not noted until late childhood or early adolescence, and the timing of development of these lesions is unknown. Treatment is simple excision.

### **Conjunctival Dermolipoma**

The *conjunctival dermolipoma* is a soft tissue tumor composed almost exclusively of fat within the substantia propria of the conjunctiva, almost always superotemporally.<sup>25</sup> The tumor appears similar to a prolapsed orbital fat pad that develops in some older adults (Fig. 4.8.22); true conjunctival dermolipomas, however, tend to become apparent much earlier in life.

### **Conjunctival Osteoma**

The *conjunctival osteoma* is a rare benign conjunctival choristoma composed predominantly of bone that develops within the substantia propria, most commonly in the superotemporal fornix region (Fig. 4.8.23).<sup>26</sup> The lesion enlarges slowly and asymptotically and usually is not noted until the teenage years. It generally is found when the affected individual rubs the eye and identifies a hard epibulbar lesion. The lesion is usually excised to reassure the patient and family of its benign character.

## **NONNEOPLASTIC LESIONS AND DISORDERS SIMULATING MALIGNANT CONJUNCTIVAL NEOPLASMS AND NEOPLASIAS**

A wide variety of completely benign nonneoplastic lesions and disorders can simulate malignant conjunctival neoplasms and neoplasia, including congenital anomalies, degenerative lesions, foreign bodies, various types of inflammatory lesion, secondary acquired pigmentations, and others. In the following section, we mention several of the lesions in this category most commonly mistaken for the three principal types of malignant conjunctival neoplasms and neoplasia.

### **Lesions Simulating Ocular Surface Squamous Neoplasms and Neoplasias**

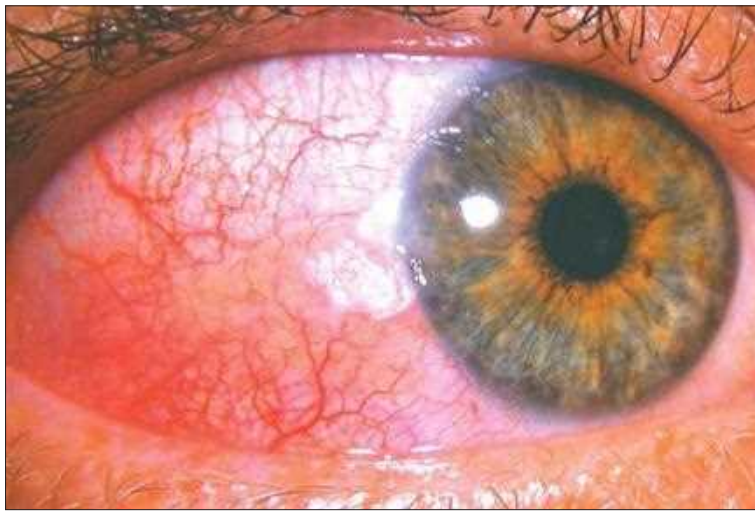
#### **Conjunctival Hyperplasia**

*Conjunctival hyperplasia* is a noncancerous thickening of the stratified squamous epithelium of the conjunctiva due to abnormal proliferation of epithelial cells.<sup>27</sup> In most cases, some of the transition from columnar basal cells to flattened external surface cells is retained. Histopathologically, the lesion is generally described as *pseudo-adenomatous hyperplasia* (when the thickened epithelium contains dilated "glandular" spaces) and as *squamous cell hyperplasia* (when it does not contain such spaces).

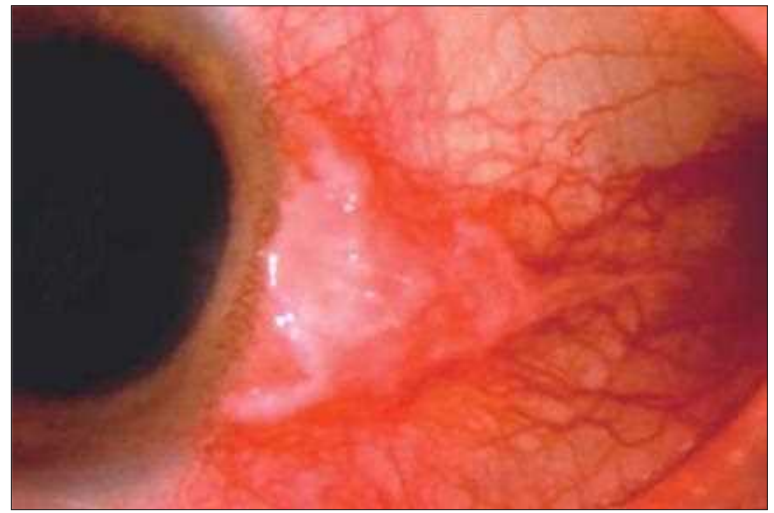
#### **Conjunctival Keratosis/Hyperkeratosis/Dyskeratosis**

*Conjunctival keratosis* is a localized degenerative lesion of the limbal conjunctiva, in which focally abnormal stratified squamous epithelium produces superficial keratin (which is not elaborated by normal conjunctiva).<sup>27,28</sup> A





**Fig. 4.8.24 Actinic Keratosis of Conjunctiva Simulating Ocular Surface Squamous Neoplasia.** This tumor exhibits limited overlying leukoplakia.



**Fig. 4.8.26 Atypical Pinguecula Simulating Ocular Surface Squamous Neoplasia.** This lesion is thickened, exhibits whitish keratinization on its surface and is associated with dilated surrounding conjunctival blood vessels.



**Fig. 4.8.25 Bilateral Hereditary Intraepithelial Dyskeratosis of Conjunctiva Simulating Ocular Surface Squamous Neoplasia.** This lesion resembles squamous cell carcinoma of the conjunctiva quite closely. A similar lesion was present on the fellow eye of this patient.



**Fig. 4.8.27 Pyogenic granuloma of palpebral conjunctiva simulating ocular surface squamous neoplasia.**

lesion of this type is indistinguishable clinically from leukoplakic squamous cell carcinoma (Fig. 4.8.24). When the amount of keratin produced by the conjunctiva at the affected site is prominent, it is referred to as *hyperkeratosis*. *Conjunctival dyskeratosis* refers to nonmalignant aberrant maturation of the conjunctival stratified squamous epithelium associated with thickening of the epithelium and elaboration of keratin. This lesion is most characteristically encountered bilaterally in an autosomal dominantly inherited condition known as *bilateral hereditary intraepithelial dyskeratosis* (Fig. 4.8.25).<sup>29</sup>

#### Inflamed Pinguecula/Hypertrophic Pterygium

*Pinguecula* and *pterygium* are common degenerative conjunctival lesions that usually are easy to distinguish from ocular surface squamous neoplasms and neoplasias. However, atypical pingueculae and pterygia that become inflamed, abnormally thick, and hypervascularized can be difficult to distinguish from squamous cell carcinoma and its variants (Fig. 4.8.26). In addition, conjunctival epithelial dysplasia and invasive neoplasia have been identified histopathologically in association with some prominent pingueculae and pterygia that have been excised. Because of this, all lesions suspected to be an atypical pinguecula or a pterygium that come to excision should be submitted for histopathological analysis.

#### Inflammatory Granuloma of Conjunctiva

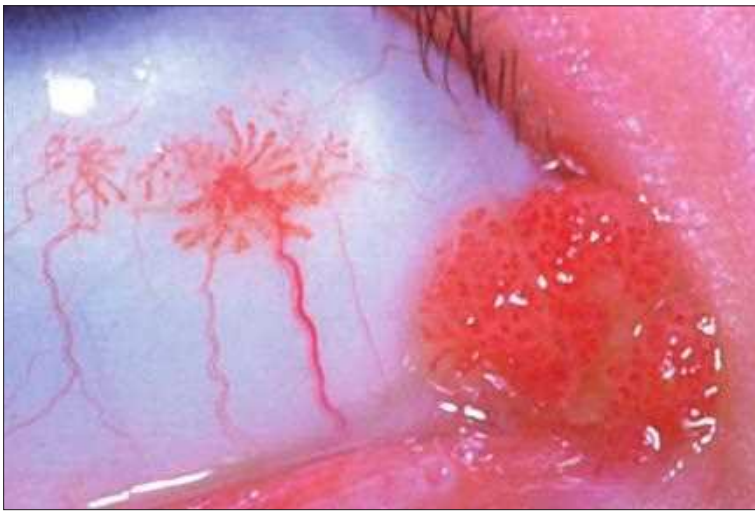
A variety of inflammatory tumors of the conjunctiva composed in large part of nonneoplastic chronic and acute inflammatory cells can simulate conjunctival squamous cell carcinoma quite closely. The most common of these is undoubtedly the *pyogenic granuloma* of the conjunctiva.<sup>30,31</sup>

This tumor is a nonneoplastic mass composed of aggregates of immature blood vessels and fibroblastic stroma, accompanied by lymphocytes, plasma cells, and scattered neutrophils. It is believed to be a focally aberrant form of conjunctival healing following an injury (which may be surgical incision). The lesion appears a vascularized pink to red conjunctival tumor that projects abruptly from the conjunctival surface (Fig. 4.8.27). Such lesions frequently recur after a simple excision, and intensive focal anti-inflammatory drug therapy and cryotherapy to the involved conjunctiva coupled with excision often are required to eradicate them. Other inflammatory lesions of the conjunctiva of interest to ophthalmologists include juvenile xanthogranuloma, foreign body granuloma, microbial granuloma (including tuberculoma), and various nonmicrobial inflammatory granulomas associated with systemic condition (e.g., sarcoidosis, lupus).<sup>32-35</sup>

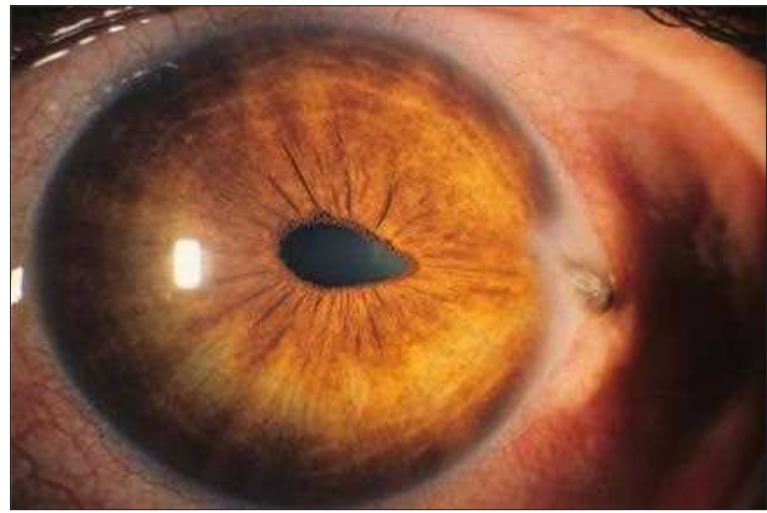
#### Viral Papilloma of Conjunctiva

The *viral papilloma of the conjunctiva* is a reactive inflammatory lesion induced by conjunctival infection by human papilloma virus.<sup>36</sup> The lesion frequently resembles conjunctival squamous papilloma quite closely but is more likely to be multifocal (Fig. 4.8.28) and much more likely to affect young children and adolescents. Attempts to excise such lesions frequently result in exuberant proliferation of new lesions. Cryotherapy to individual lesion is sometimes effective in destroying them. However, recurrent lesions following excision with cryotherapy frequently require supplemental treatment with topical interferon drops or chemotherapeutic drops (mitomycin C, 5-fluorouracil). Some success has also been reported when such lesions were treated by oral cimetidine.





**Fig. 4.8.28** Viral papillomas of conjunctiva simulating papillary conjunctival squamous cell carcinoma.



**Fig. 4.8.30** Uveal prolapse and incarceration in eye wall laceration simulating conjunctival melanoma.



**Fig. 4.8.29** Iridociliary melanoma with anterior transcleral extension simulating conjunctival melanoma.



**Fig. 4.8.31** Nodular Anterior Scleritis Simulating Conjunctival Neoplasm. The conjunctiva and sclera are thickened and hyperemic diffusely, and this lesion was tender to palpation.

## Lesions Simulating Conjunctival Melanoma and Malignant Primary Acquired Melanosis

### Posterior Uveal Melanoma With Anterior Transcleral Extension

Some *uveal melanomas* that involve the ciliary body extend transclerally to the episcleral surface via scleral neural or vascular foramina.<sup>37,38</sup> The epibulbar tumor in such cases usually is dark brown and frequently associated with prominently dilated epibulbar blood vessels (Fig. 4.8.29). The distinguishing feature that is obvious on slit-lamp biomicroscopy is the absence of conjunctival epithelial involvement. Ocular transillumination typically reveals a distinct shadow produced by the ciliary body portion of the tumor. Ocular ultrasonography (possibly UBM) will confirm the presence of the underlying ciliary body tumor.

### Occult Eyewall Laceration With Incarceration of Uveal Tissue

Some individuals who have suffered a conjunctival and *eye wall laceration* will not recognize the extent of their injury and not get evaluated by an eye specialist for weeks to years following that injury.<sup>39</sup> In some such cases, uveal tissue is incarcerated into the wound (Fig. 4.8.30). This uveal tissue can be mistaken for a conjunctival melanoma.<sup>40</sup>

### Nodular Anterior Scleritis

*Nodular anterior scleritis* is a severe inflammatory reaction to some inciting event that develops within the anterior sclera.<sup>41</sup> The eye is painful and the affected area of the sclera and overlying conjunctiva are extremely reddened and thickened (Fig. 4.8.31). The eye is frequently very tender to

palpation of the reddened area through the eyelid. UBM can demonstrate the localized scleral thickening in such cases. Treatment usually consists of corticosteroids and, if necessary, other anti-inflammatory drugs.

### Ciliary Body Staphyloma

The *ciliary body staphyloma* is a localized thinning of the sclera, usually in response to a prior injury or surgery or a prior episode of nodular or necrotizing scleritis, that then bulges as a result of intraocular pressure.<sup>42</sup> In most cases, the lesion appears as a smoothly elevated bluish-brown scleral mass without involvement of the overlying conjunctiva and without prominently dilated epibulbar blood vessels in that location (Fig. 4.8.32). Ocular transillumination shows prominent transmission of light through the eye wall corresponding to the visible dark lesion. UBM can confirm the thinning of the eye wall and absence of any underlying ciliary body tumor.

### Conjunctival Argyrosis

*Conjunctival argyrosis* is an acquired dark gray to black pigmentation of the conjunctiva that develops in response to chronic application of silver nitrate drops.<sup>43</sup> Affected individuals often were given some silver nitrate drops many years ago as treatment for a conjunctival infection and continued to take the drops for years after the original problem resolved. The conjunctival pigmentation can simulate primary acquired melanosis of the conjunctiva quite closely (Fig. 4.8.33).

## Lesions Simulating Conjunctival Lymphoma

### Benign Reactive Lymphoid Hyperplasia of the Conjunctiva

Benign reactive lymphoid hyperplasia (BRLH) of the conjunctiva is a nonmalignant infiltrative mass of the conjunctiva composed principally

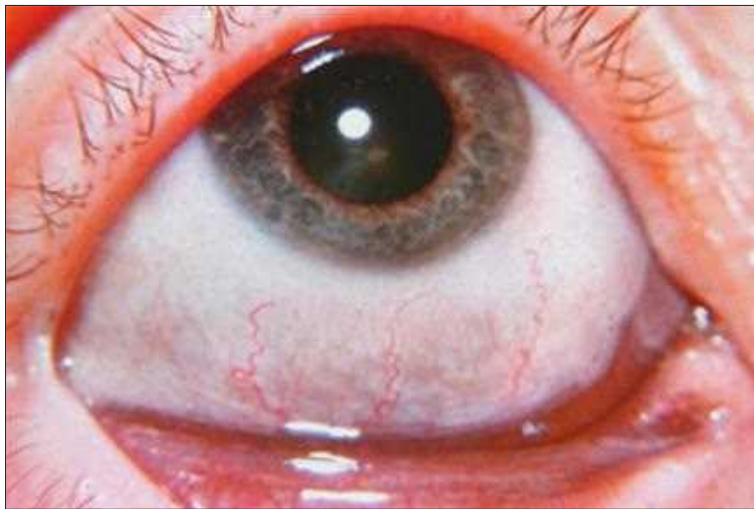




**Fig. 4.8.32** Ciliary Body Staphyloma Simulating Conjunctival Melanoma. Note the absence of prominently dilated conjunctival blood vessels associated with this lesion.



**Fig. 4.8.35** Sarcoid granulomas of inferior forniceal and palpebral conjunctiva simulating conjunctival lymphoma.



**Fig. 4.8.33** Argyrosis of conjunctiva simulating primary acquired melanosis of conjunctiva.



**Fig. 4.8.34** Benign lymphoid hyperplasia of conjunctival simulating conjunctival lymphoma.

of benign or mildly atypical lymphocytes.<sup>44</sup> The infiltrate is characterized pathologically by a polyclonal accumulation of benign appearing lymphoid cells, usually in a follicular pattern. The lesion can affect one or both eyes and usually involves the forniceal conjunctiva predominantly (Fig. 4.8.34). It resembles malignant lymphoma quite closely, and only histopathological and immunopathological analysis can distinguish between these entities.

Limited lesions may be left untreated, but extensive lesions of this type usually are treated by low-dose external beam radiation therapy.

### **Inflammatory Granulomas of Conjunctiva**

Certain *inflammatory granulomas of the conjunctiva*, including those caused by microbial organisms (e.g., tuberculoma), nonmicrobial inflammatory disorders (e.g., sarcoid granuloma), and foreign bodies, can resemble malignant lymphoma of the conjunctival quite closely (Fig. 4.8.35).<sup>33-35</sup> Biopsy or excision of the mass with histopathological and microbiological analysis of the specimen generally is required for diagnosis and to guide subsequent patient management.

## **MANAGEMENT OF CONJUNCTIVAL TUMORS SUSPECTED OF BEING MALIGNANT NEOPLASMS OR NEOPLASIAS**

Clinically suspected conjunctival malignant neoplasms and neoplasias usually are managed by surgical excision<sup>45,46</sup> (if possible) or biopsy (if the lesion involves an extensive portion of the conjunctiva) followed by supplemental therapy of the retained conjunctiva by methods such as cryotherapy<sup>47</sup> (liquid nitrogen spray or cryoprobe therapy), topical immunotherapy<sup>48,49</sup> (interferon eyedrops [off-label therapy]), topical chemotherapy<sup>50-52</sup> (mitomycin C or 5-fluorouracil eyedrops [off-label therapy]), or radiation therapy<sup>46,53</sup> (epibulbar strontium-90 applicator therapy, radioactive plaque brachytherapy, or external beam radiation therapy) if malignant neoplasia is confirmed pathologically. The goal of treatment is complete eradication of the cancer cells with preservation of the eye and retention or recovery of good vision. Surgical excision of suspected conjunctival neoplasms and neoplasias should include at least a 1-mm margin of clinically uninvolved conjunctiva around the visible lesion, whenever possible. The ophthalmic surgeon should give thoughtful consideration to closure of the surgical defect by mobilizing the retained conjunctiva around the defect and creating relaxing conjunctival incisions for advancement flaps as needed or arranging for implantation of a mucous membrane (e.g., amniotic membrane) graft when primary closure is impossible.<sup>54,55</sup> In general, lamellar sclerectomy and keratectomy should be avoided, whenever possible, and suspected scleral or corneal invasion by the neoplasia should be managed by supplemental cryotherapy, radiation therapy, or both as indicated subsequent to the excisional procedure.

Because conjunctival melanomas tend to metastasize via lymphatics to lymph nodes in the head and neck, all patients with a newly diagnosed conjunctival melanoma should be evaluated by palpation of the head and neck ipsilateral to the tumor to search for clinically detectable lymph nodes.<sup>56</sup> Those with suspicious lymph nodes by palpation should be evaluated by computed tomography or magnetic resonance imaging of the head and neck to confirm or rule out the physical examination findings. Patients having an extremely large conjunctival melanoma, especially if it involves the fornices or palpebral conjunctiva, and those whose tumor exhibits ulceration and numerous mitotic figures histopathologically<sup>57,58</sup> should be considered for sentinel lymph node mapping and biopsy.<sup>59-61</sup> If melanoma node metastasis is confirmed by biopsy, complete neck dissection with

wider lymph node excision may be considered,<sup>58</sup> and systemic immunotherapy for that metastatic melanoma is likely to be initiated.<sup>62</sup>

In contrast, squamous cell carcinomas and variants and other malignant conjunctival neoplasms rarely metastasize to regional lymph nodes. Consequently, lymph node mapping and sentinel lymph node biopsy generally are not indicated for such neoplasms. Some aggressive and locally advanced conjunctival melanomas, variants of squamous cell carcinoma (especially mucoepidermoid carcinoma), and sebaceous carcinomas of the conjunctiva will have invaded the orbit extensively prior to diagnosis, and such cases may be treated by orbital exenteration if complete excision is not possible.<sup>63,64</sup>

Suspected lymphomas of the conjunctiva warrant a special comment. Optimal current analysis of such lesion involves testing of both fixed tissue and fresh tumor specimens (for flow cytometry and gene rearrangement studies).<sup>9,10</sup> When such lesions are excised or a biopsy performed, the tissue obtained in the procedure should be divided in approximately equal parts in the operating room. One of these specimens should be submitted in formalin for conventional histopathological and immunohistochemical studies. The other half should be submitted as moistened fresh tumor to the pathology laboratory for flow cytometry and gene rearrangement testing. The most common treatment for localized low-grade conjunctival lymphoma is low-dose external beam radiation therapy.<sup>65</sup>

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# Pterygium and Conjunctival Degenerations

## 4.9

Roni M. Shtein, Alan Sugar

**Definition:** Secondary deterioration or deposition in the conjunctiva, distinct from dystrophies.

### Key Features

- Common.
- Bilateral usually.
- Typically does not affect vision.

### Associated Features

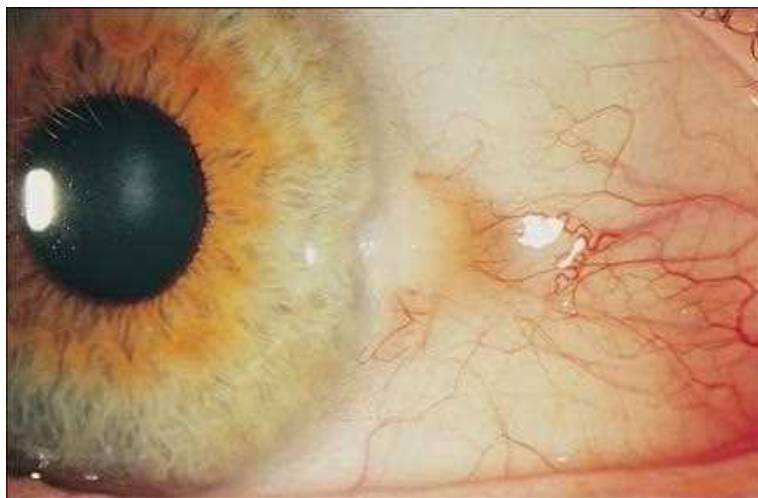
- Increased prevalence with age.
- Often associated with chronic light exposure.
- May occur after past inflammation.
- Not inherited.

## INTRODUCTION

Degenerations of the conjunctiva are common conditions that, in most cases, have relatively little effect on ocular function and vision. They increase in prevalence with age as a result of past inflammation, long-term toxic effects of environmental exposure, or aging itself. Conjunctival degenerations may be associated with chronic irritation, dryness, or previous history of trauma. Progression to involve the cornea may occur, as in pterygium.

## PINGUECULA

*Pingueculae* are elevated, horizontally oriented areas of bulbar conjunctival thickening that are white to yellow in color and adjoin the limbus in the palpebral fissure area (Fig. 4.9.1). They are less transparent than normal conjunctiva, often have a fatty appearance, are usually bilateral, and are



**Fig. 4.9.1 Nasal Pinguecula.** Elevated conjunctival lesion encroaches on nasal limbus.

located nasally much more often than temporally. When a pinguecula crosses the limbus onto the cornea, it is called a *pterygium*. Current information, however, suggests that pinguecula do not progress to pterygium and that the two are distinctly different disorders. Pingueculae are associated with a two- to threefold increased incidence of age-related macular degeneration, possibly through a common light exposure effect.<sup>1</sup>

The causes of pingueculae are not known with certainty. There is, however, good evidence of an association with increasing age and ultraviolet light exposure. Pingueculae are seen in most eyes by age 70 years and in almost all by age 80 years.<sup>2</sup> Chronic sunlight exposure has been found to be a factor by association with outdoor work and equatorial residence. In some studies, the strength of this association is less than that for pterygium.<sup>3</sup> It is thought that the predominantly nasal location is related to reflection of light from the nose onto the nasal conjunctiva. The effect of ultraviolet light may be mediated by mutations in the *p53* gene.<sup>4</sup>

Pingueculae rarely are associated with symptoms other than a minimal cosmetic defect. They may become red with surface keratinization. When inflamed, the diagnosis of pingueculitis is made.

Distinguishing pingueculae from other lesions usually is not a problem because of the typical appearance. Conjunctival intraepithelial neoplasia may be difficult to differentiate from keratinized pinguecula. Gaucher's disease type I may be associated with tan pingueculae, but this is not a specific finding.<sup>5</sup>

Histopathologically, pingueculae are characterized by elastotic degeneration of the collagen with hyalinization of the conjunctival stroma, collection of basophilic elastotic fibers, granular deposits, and noninvolvement of the cornea.<sup>6</sup>

Pingueculitis responds to a brief course of topical corticosteroids or nonsteroidal anti-inflammatory agents.<sup>7</sup> Chronically inflamed or cosmetically unsatisfactory pingueculae rarely warrant simple excision.

## PTERYGIUM

*Pterygium* is a growth of fibrovascular tissue on the cornea and conjunctiva. It occurs in the palpebral fissure, much more often nasally than temporally, although either or both ("double" pterygium) occur (Fig. 4.9.2). Elevated whitish opacities ("islets of Vogt") and an iron deposition line ("Stocker") may delineate the head of the pterygium on the cornea. Like pinguecula, it is a degenerative lesion, although it may appear similar to pseudo-terygium, which is a conjunctival adhesion to the cornea secondary to previous trauma or inflammation, such as peripheral corneal ulceration. A pseudo-terygium often has an atypical position and is not adherent at all points, so a probe can be passed beneath it peripherally.

Like pinguecula, pterygium is associated with ultraviolet light exposure.<sup>3</sup> It occurs at highest prevalence and most severely in tropical areas near the equator and to a lesser and milder degree in cooler climates.<sup>8</sup> Outdoor work and both blue and ultraviolet light have been implicated in its causation. The use of hats and sunglasses is protective.<sup>8</sup> Theories of pathogenesis of pterygia include the possibility of damage to limbal stem cells by ultraviolet light and by activation of matrix metalloproteinases.<sup>9</sup> The histopathology of pterygium is similar to that of pinguecula except that Bowman's membrane is destroyed within the corneal component and vascularization is seen.<sup>9</sup> Evaluation using spectral domain optical coherence tomography reveals pterygium as an elevated, wedge-shaped mass of tissue separating the corneal epithelium from Bowman's membrane, which appears abnormally wavy and interrupted and often destroyed, with satellite masses of subepithelial pterygium tissue beyond the clinically seen margins.<sup>10</sup>



**Fig. 4.9.2 Double Pterygium.** (A) Note both nasal and temporal pterygia in a 57-year-old farmer. (B) It is the invasion of the cornea that distinguishes a pterygium from a pinguecula.

Pterygia warrant treatment when they cause discomfort (not responsive to conservative therapy), encroach upon the visual axis, induce significant astigmatism, or become cosmetically bothersome. Aggressive or recurrent pterygia may cause restrictive strabismus and distortion of the eyelids. A variety of surgical techniques have been developed. The goal of treatment is prevention of recurrence. The recurrence rates after simple excision are very high: Of recurrences, 50% reoccur within 4 months of excision and nearly all within 1 year.<sup>11</sup> Beta-radiation applied postoperatively to the pterygium base was popular for many years but is associated with late scleral necrosis.<sup>12</sup> Currently, the most widely used techniques are conjunctival autografting and amniotic membrane transplantation.<sup>12</sup> Adjuvant use of mitomycin-C application—either pre-, intra-, or postoperatively—has been associated with scleral melt in some situations.<sup>13</sup> Fibrin-based glues have been used to minimize operating time and discomfort associated with sutures, and to reduce the amount of suturing required.<sup>14</sup>

## SENILE SCLERAL PLAQUES

Senile scleral plaques occur in the sclera of elderly patients and often are misinterpreted as a melting process similar to that of corneal degenerations or as conjunctival depositions. These lesions appear as yellow, gray, or black vertical bands just anterior to the insertion of the medial and lateral rectus muscles (Fig. 4.9.3). They become more common after age 60 years and, like pinguecula and pterygium, may be related to ultraviolet light exposure.<sup>15</sup> Histologically, calcium deposits along with decreased cellularity and hyalinization are seen. These lesions do not need therapy.

## CONJUNCTIVAL AMYLOID

Deposition of amyloid in the conjunctiva has been reported in both primary and secondary localized forms (Fig. 4.9.4) and secondary to systemic processes.<sup>16</sup> Chronic conjunctival inflammation may cause secondary localized amyloidosis, a true degenerative change. In the primary localized forms, light-chain immunoglobulins deposited by monoclonal B cells and plasma cells have been demonstrated by immunohistochemistry.



**Fig. 4.9.3 Senile Scleral Plaque.** Calcium deposition appears as a gray scleral plaque under the medial rectus muscle insertion.



**Fig. 4.9.4 Primary Localized Conjunctival Amyloid.** There is irregularity of the conjunctiva superonasally with fixed folds. Resolving subconjunctival hemorrhages noted superiorly are associated with amyloid deposition in blood vessel walls.

In lesions secondary to systemic disease, other forms of amyloid protein may be seen.<sup>17</sup> All patients should be evaluated for lymphoproliferative and systemic diseases. Amyloid involving the skin of the eyelids has been suggested to be a sign of systemic involvement.<sup>18</sup>

Conjunctival amyloid may appear as a yellowish, well-demarcated, irregularly elevated mass. It generally involves the fornices, with the superior fornix and tarsal conjunctiva most commonly affected. In vivo confocal microscopy of conjunctival amyloid shows hyporeflective material in a lobular pattern in the substantia propria and around the blood vessels in the conjunctiva without associated inflammation.<sup>19</sup> Recurrent subconjunctival hemorrhages may be associated with amyloid deposition in blood vessel walls. Biopsy is required for definitive diagnosis.<sup>17</sup>

Lesions generally are treated symptomatically, although debulking excision can be performed for chronic irritation. Although it may not cause full regression of deposited amyloid, radiotherapy may be used to prevent progression.<sup>20</sup>

## CONJUNCTIVAL MELANOSIS

Conjunctival melanosis is a common finding with advancing age. The appearance is that of a flat, pigmented area on the conjunctiva. Primary acquired melanosis is a risk factor for development of conjunctival melanoma and is discussed in detail in Chapter 4.8.

Secondary melanosis of the conjunctiva is generally benign and tends to be more frequently bilateral. Secondary melanosis occurs following trauma, chronic inflammation of the conjunctiva, and in individuals with darker skin pigmentation.<sup>21</sup> Secondary melanosis generally is not associated with atypia and can be observed. If the lesions are noted to be elevated or where uncertainty exists, biopsy should be performed.

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# Ocular Cicatricial Pemphigoid/Mucous Membrane Pemphigoid

Ahmed Al-Ghoul, Steven Kane, Deepinder K. Dhaliwal

4.10

**Definition:** A heterogeneous group of chronic, systemic, inflammatory, subepithelial, blistering diseases.

### Key Features

- Subepithelial bulla formation, rupture, and scarring of mucous membranes and skin.
- Female-to-male ratio of 2:1.
- Type II immune linear deposition of immunoglobulin A (IgA), IgG, IgM, and/or complement (C3) on the conjunctival epithelial basement membrane.
- Systemic immunosuppressive treatment is critical in suppressing conjunctival inflammation and disease progression.

### Associated Features

- Be aware of the significant extraocular morbidities that can occur, such as esophageal stricture formation.
- Surgical management of ocular cicatricial pemphigoid traditionally carries a poor prognosis.

## INTRODUCTION

Ocular cicatricial pemphigoid (OCP) is an autoimmune disease characterized by chronic progressive conjunctival inflammation and scarring. This condition belongs to a heterogeneous group of chronic, systemic, inflammatory, subepithelial, blistering diseases termed mucous membrane pemphigoid.<sup>1</sup> They share the similar manifestations of subepithelial bulla formation, rupture, and scarring of mucous membranes and skin.<sup>2</sup>

The incidence of mucous membrane pemphigoid varies between 1 in 20000 to 1 in 46000 in the ophthalmic literature, with a female-to-male ratio of approximately 2:1.<sup>2</sup> The average age of diagnosis is in the seventh decade of life (age range 30–90 years), and an average diagnostic lag of 2.8 years has been reported because of the nonspecific nature of early disease.<sup>3,4</sup> No racial or geographical predilection has been reported. Oral involvement in mucous membrane pemphigoid occurs in up to 84% of cases. The risk of ocular disease in patients seen with only extraocular manifestations is estimated to be 5% per annum for the first 5 years of follow-up with eventual involvement in up to 80% of cases.<sup>5,6</sup> Approximately 50% of patients presenting with OCP will have extraocular lesions.<sup>7</sup> The clinical presentation and frequency of extraocular tissue involvement is listed in Table 4.10.1.

## PATHOGENESIS

Although the cause of mucous membrane pemphigoid remains unknown, research continues to unravel more clues as to the pathogenesis of this complex condition. The hallmark of this autoimmune disease is the type II immune linear deposition of immunoglobulin A (IgA), IgG, IgM, and/or complement (C3) on the conjunctival epithelial basement membrane. Autoantibodies form against different components of the basement membrane, with certain autoantigens being more specific for particular mucosal regions in the body. This likely explains the clinical heterogeneity seen in mucous membrane pemphigoid.<sup>8</sup> Multiple target autoantigens,

TABLE 4.10.1 Clinical Features and Frequency in Mucous Membrane Pemphigoid

Site	Clinical Features	Frequency (%)
Oral mucosa and pharynx	Oral mucosal vesicles/bullae Desquamative gingivitis Pharyngitis and scarring	30–84
Conjunctiva	Conjunctivitis and progressive scarring	60–80
Nose/sinus	Epistaxis Nasal mucosa/turbinate ulcers	18–50
Skin	Localized, erythematous plaques with recurrent vesicles and bullae on the scalp and face that heal with atrophic scars Recurrent vesiculobullous eruptions of the inguina and/or extremities	17–23
Esophagus	Dysphagia Esophageal strictures	7–27
Larynx	Intermittent hoarseness or dysphonia Supraglottic inflammation and scarring	5–30
Anus/vagina	Blisters, erosions, and scarring with or without fusion of tissues	5–11

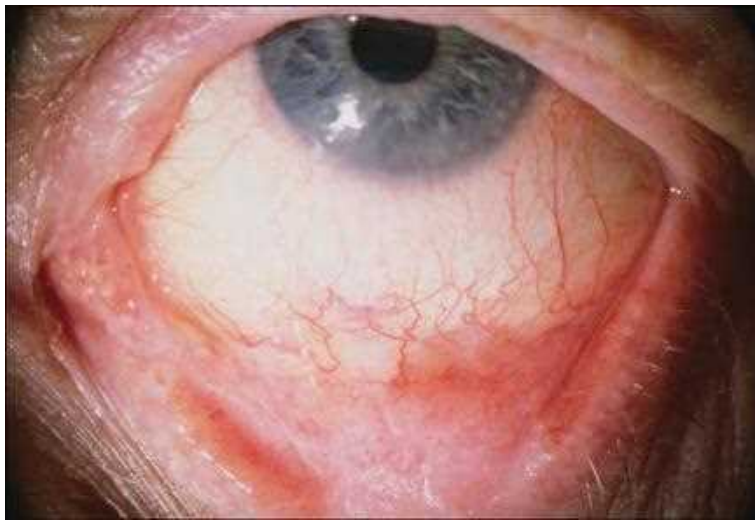
Adapted from Chang JH, McCluskey PJ. Ocular cicatricial pemphigoid: manifestations and management. *Curr Allergy Asthma Rep* 2005;5:333–8; Foster CS. Cicatricial pemphigoid. *Trans Am Ophthalmol Soc* 1986;84:527–663; Foster CS, Sainz de la Maza M. Ocular cicatricial pemphigoid review. *Curr Opin Allergy Clin Immunol* 2004;4:435–9; Mondino BJ, Brown SI. Ocular cicatricial pemphigoid. *Ophthalmology* 1981;88:95–100; Thorne JE, Anhalt GJ, Jabs DA. Mucous membrane pemphigoid and pseudopemphigoid. *Ophthalmology* 2004;111:45–52; Hardy KM, Perry HO, Pingree GC, et al. Benign mucous membrane pemphigoid. *Arch Dermatol* 1971;104:467–75; and Elder MJ, Lightman S. The immunological features and pathophysiology of ocular cicatricial pemphigoid. *Eye* 1994;8:196–9.

including BP180, BP230,  $\alpha_6 \beta_4$  integrin, laminin 5, and type VII collagen, have been identified in patients with mucous membrane pemphigoid. In particular,  $\alpha_6 \beta_4$  integrin has been strongly linked with OCP. This antigen is an important component of hemi-desmosomes required for epithelial cell attachment to the basement membrane, and its targeting may explain the formation of subepithelial bullae seen in OCP.<sup>9</sup> Recent studies have shown abnormal serum levels of interleukin-4 (IL-4), IL-5, IL-6, tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), and transforming growth factor-beta (TGF- $\beta$ ) during the active phase of the disease, suggesting an abnormal immune system regulation. Further support for the autoimmune nature of mucous membrane pemphigoid comes from the observed association with other autoimmune diseases, such as rheumatoid arthritis, systemic lupus erythematosus, and polyarteritis nodosa.<sup>3,10</sup> A genetic predisposition for developing mucous membrane pemphigoid also has been postulated by linkage studies. Specific human leukocyte antigen (HLA) class II alleles, such as the DQB1\*0301, are significantly associated with severe disease phenotype and anti-basement membrane zone IgG antibody response in mucous membrane pemphigoid.<sup>1</sup>

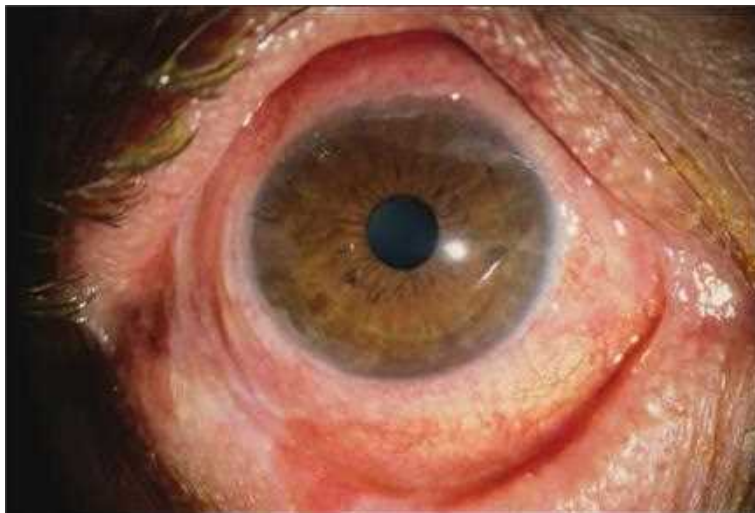
The histopathology of OCP demonstrates local infiltration by macrophages, neutrophils, T cells, mast cells, and eosinophils into the conjunctiva.<sup>2,11</sup> The presence of these cells in conjunction with antibody/complement deposition results in the inflammatory response with subsequent bullae formation, rupture, and eventual scarring.

## CLINICAL FINDINGS

Ocular cicatricial pemphigoid presents with nonspecific symptoms of irritation, burning, and tearing and can manifest as recurrent papillary



**Fig. 4.10.1** Stage I ocular cicatricial pemphigoid (OCP) characterized by conjunctival subepithelial scarring.



**Fig. 4.10.2** Stage II ocular cicatricial pemphigoid (OCP) characterized by forniceal foreshortening.



**Fig. 4.10.3** Stage III ocular cicatricial pemphigoid (OCP) characterized by symblepharon formation.

conjunctivitis. In some cases, patients do not experience ocular symptoms even with advanced signs of conjunctival scarring. The ocular involvement initially can be unilateral but progresses, usually within 2 years, to bilateral involvement with asymmetry in the severity and rate of evolution.<sup>4,12</sup>

The disease progression of OCP has classically been documented into one of four stages (Figs. 4.10.1–4.10.4).<sup>4</sup> Stage I denotes chronic conjunctivitis with subepithelial fibrosis and an unstable tear film. This leads to dryness and exacerbation of the cicatrization process.<sup>2,12,13</sup> Stage II refers



**Fig. 4.10.4** Stage IV ocular cicatricial pemphigoid (OCP) showing end-stage findings of keratinization of the ocular surface and ankyloblepharon.

to inferior fornix foreshortening. Stage III describes symblepharon formation typically starting with the inferior fornix. As a result of the cicatrizing process, lid abnormalities become a major confounder in the overall prognosis. Trichiasis, entropion, and lagophthalmos contribute to the exposure and abrasion of the corneal surface.<sup>12</sup> Damage to mucin-producing goblet cells, meibomian glands, and lacrimal glands leads to keratinization, which along with ankyloblepharon formation and corneal scarring define the end-stage, which is stage IV. As such, in addition to staging disease progression, the extent of conjunctival inflammation should be graded from inactive (0) to severe (4+).<sup>4</sup> By assessing the stage of the disease process and degree of conjunctival inflammation, appropriate therapy for these patients can be determined more accurately.

## DIAGNOSIS

Early diagnosis is the key to preventing the blinding consequences of OCP. The diagnosis ideally rests on both clinical suspicion and immunopathology of biopsied conjunctiva and/or other involved tissues.<sup>14</sup> Biopsy using immunopathological techniques provides the only definitive evidence of ocular cicatricial pemphigoid, and should encompass an area with both inflamed and noninflamed tissues. Active oral lesions may be biopsied to aid in diagnosis.<sup>15</sup> Tissue samples should be fresh or fixed in Zeus' or Michel's fixative for no more than 5 days.<sup>1</sup> Linear deposition of IgG, IgA, IgM, and/or complement (C3) at the epithelial basement membrane zone of inflamed conjunctiva is seen using direct immunofluorescence (DIF) techniques, with a sensitivity between 20% and 84%.<sup>2,16</sup> If the DIF study findings are negative and the clinical suspicion is high, a more sensitive test, such as the immunoperoxidase assay, should be employed.<sup>1</sup> To date, indirect immunofluorescent testing to detect circulating autoantibodies in patients' sera has a limited role. Newer serological tests that show promise in the diagnosis of mucous membrane pemphigoid are being developed.<sup>3</sup> Serum and saliva IgG and IgA antibodies may be helpful diagnostic markers and have shown high positive predictive value.<sup>17</sup>

In making the diagnosis of OCP, other causes must be considered. Adenovirus and herpes simplex virus infections, chlamydia, diphtheria, gonorrhea, and beta-hemolytic *Streptococcus* infection can all cause a membranous conjunctivitis that results in conjunctival scarring. Radiation, thermal, and chemical burns, as well as mechanical or surgical trauma, can cause conjunctival shrinkage and symblephara. Systemic practolol and D-penicillamine and topical epinephrine, echothiophate iodide, and pilocarpine all have been associated with inducing ocular pemphigoid-like features. Allergic and inflammatory conditions, such as atopic and rosacea keratoconjunctivitis, respectively, as well as systemic conditions such as Sjögren's syndrome, sarcoidosis, and progressive systemic sclerosis also can present as cicatrizing conjunctivitis. Other autoimmune diseases, such as pemphigus vulgaris, erythema multiforme, Stevens–Johnson syndrome, toxic epidermal necrolysis, epidermolysis bullosa acquisita, lichen planus, dermatitis herpetiformis, and linear IgA disease, among others, are associated with cicatrizing conjunctivitis to varying degrees. Biopsy results in addition to clinical history, presentation, and course can help distinguish all of these differential diagnoses from the systemic, chronic, progressive, and bilateral ocular cicatricial pemphigoid.<sup>1–3,5</sup>



## TREATMENT

The goal of therapy in OCP is to suppress inflammation, promote healing, and prevent cicatrization. Local measures include the use of lubricating drops, punctal occlusion, autologous serum, and contact lenses for the dry eye component, and lid hygiene and oral tetracyclines for the blepharitis, and epilation for trichiasis management.

Systemic immunosuppressive treatment for OCP is critical to prevent the otherwise invariable progression to conjunctival and corneal scarring and eventual blindness. The use of such agents is particularly challenging because patients usually are older, the disease is chronic, other extraocular tissues can be involved, and the systemic immunosuppressive agents required to control the disease have many side effects. In addition, the majority of patients are diagnosed late in the course of the disease, thus requiring aggressive and long-term therapy.<sup>18</sup> Therefore, the use of systemic agents should be co-managed with the patient's primary care physician, rheumatologist, or oncologist.

Clinical studies regarding systemic therapy in OCP remain limited. When choosing an immunosuppressive agent, the stage of ocular disease and the degree of inflammation should be considered. Although dapsone and sulfasalazine were historically the first-line treatment for mild to moderate inflammation, other immunosuppressive agents have shown better efficacy and fewer side effects. Mycophenolate mofetil may be a better first-line agent of choice for OCP presenting without sight-threatening complications.<sup>19–21</sup> Methotrexate also may be a good first-line option, although it may have more side effects (including hepatic and pulmonary fibrosis) compared with mycophenolate mofetil.<sup>22</sup> For vision threatening, progressive OCP cyclophosphamide, either alone or in conjunction with prednisone, may be the treatment of choice.<sup>7,23,24</sup> Use of low-dose intravenous pulses of cyclophosphamide, according to the findings of the Euro-Lupus trials, may improve the side-effect profile.<sup>25</sup> Given their dangerous long-term side-effect profile, systemic corticosteroids should only be used as a temporizing measure until other immunomodulatory medications take effect.<sup>5</sup> Options to achieve remission for patients with contraindications or adverse reactions to conventional treatment or who failed conventional therapy include intravenous immunoglobulin and rituximab.<sup>26–29</sup> Biological agents may be considered in patients whose conditions are resistant to cyclophosphamide. Anti-TNF- $\alpha$  medications including etanercept, infliximab, and pentoxifylline have shown benefit.<sup>15,21</sup>

Surgical management of OCP traditionally has carried a poor prognosis.<sup>12</sup> It is important to completely suppress the inflammatory component of the disease prior to surgical intervention. Repairing trichiasis and entropion helps reduce ocular surface irritation and decompensation. Corneal transplantation for scarred and opaque cornea, ocular surface reconstruction with limbal stem cell transplantation and amniotic membrane

transplantation, and type I Boston keratoprosthesis implantation for visual rehabilitation are potential surgical options but are often unsuccessful as a result of the autoimmune inflammatory nature of the disease.<sup>5</sup> A type II Boston keratoprosthesis or osteo-odonto-keratoprosthesis, each with its own set of complications, can be a limited, but viable, last resort.<sup>30</sup>

## CONCLUSIONS

The prognosis of OCP depends on how soon diagnosis and treatment is initiated. Up to 60% of patients diagnosed with OCP are at an advanced stage (stage III or more) at the time of diagnosis. Nevertheless, control of the ocular inflammation in OCP can be achieved in up to 90% of patients when appropriately treated.<sup>31</sup> Because of the generalized mucosal involvement of this disease, one should be aware of the significant extraocular morbidities that can occur. In particular, esophageal stricture formation can be fatal secondary to reflux into the trachea.<sup>2</sup>

In summary, ocular cicatricial pemphigoid remains a very difficult condition to treat as a result of its progressive autoimmune nature and the lack of sensitive techniques to detect the disease at earlier stages. As newer diagnostic techniques and therapeutic options evolve, the overall outcome for patients will continue to improve.

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# Episcleritis and Scleritis

Sarju S. Patel, Debra A. Goldstein

# 4.11

**Definition of Episcleritis:** Inflammation of the connective tissue between the sclera and the conjunctiva.

## Key Features

- Self-limiting.
- Less painful than scleritis.
- Blanches with topical neosynephrine.
- Does not cause damage to the globe.

## Associated Feature

- Systemic association in less than one third of patients.

**Definition of Scleritis:** A disorder of inflammation and necrosis centered on the sclera.

## Key Features

- Focal or diffuse redness or violaceous discoloration.
- Scleral thickening, acutely.
- May develop scleral thinning.
- Nodules.
- Necrosis.
- Pain.

## Associated Features

- Rheumatoid arthritis, granulomatosis with polyangiitis (Wegener's granulomatosis), other vasculitic/connective tissue diseases.
- Keratitis and iritis.
- Glaucoma.
- Exudative retinal detachment.

## INTRODUCTION

The sclera is a dense, poorly vascularized connective tissue structure composed of collagen, elastin, proteoglycans, and glycoproteins. It is embryologically derived from the neural crest and the mesoderm.

The sclera may be affected by a number of inflammatory and noninflammatory processes. This chapter will describe episcleritis, focusing on scleritis, a more serious and often vision-threatening condition.

## INFLAMMATORY DISEASES

### Episcleritis

#### Epidemiology and Pathogenesis

*Episcleritis* refers to inflammation of the loose connective tissue between the sclera and the conjunctiva. Patients often complain of discomfort or irritation rather than true pain. Slit-lamp microscopic examination usually localizes any edema to the area that overlies the sclera. The sclera itself is not thickened. Accompanying uveitis is very rare.

Episcleritis is a self-limiting condition, generally running its course in a few days, although nodular disease may last for weeks. Recurrence is common, but structural damage to the eye does not occur.

#### Diagnosis and Ocular Manifestations

Episcleritis can be described as *simple*, in which all or part of the episclera is diffusely inflamed, or *nodular*, in which inflammation is confined to a localized area with the presence of well-defined, red nodules. Nodular episcleritis often is associated with a more discomfort and a more prolonged course compared with simple episcleritis. Bilateral inflammation is seen in 40% of patients.<sup>1</sup> Topical phenylephrine blanches overlying conjunctival vessels and inflamed episcleral vessels.

#### Differential Diagnosis

The differential diagnosis includes conjunctivitis, which is more superficial; phlytenulosis, which is typically mobile; and scleritis, which is deeper and more painful.

#### Systemic Associations

An underlying cause for episcleritis is found in approximately one third of cases.<sup>1,2</sup> In two series of 94 and 85 patients with episcleritis, 68%–73% were found to have no associated disease; 13%–15% had a connective tissue or vasculitic disease; 7% had rosacea; 1%–7% had atopy; and 1%–6% had an associated infection (herpes zoster, herpes simplex, cat scratch disease, Lyme disease).<sup>1,2</sup>

#### Treatment

Some patients may benefit from treatment for cosmesis or alleviation of discomfort. Many physicians elect to treat with topical corticosteroids, demonstrated in a randomized double-masked trial to be superior to placebo for the treatment of episcleritis.<sup>3</sup> However, the use of topical corticosteroids may be detrimental because of the risk of rebound inflammation when the drugs are tapered.<sup>2</sup> Some patients respond well to topical nonsteroidal anti-inflammatory drugs (NSAIDs). Systemic NSAIDs also may be used for the treatment of severe or recurrent episcleritis, although significant side effects may be associated with their use (see section on [scleritis](#)). Treatment of underlying blepharitis is important.

### Scleritis

#### Epidemiology and Pathogenesis

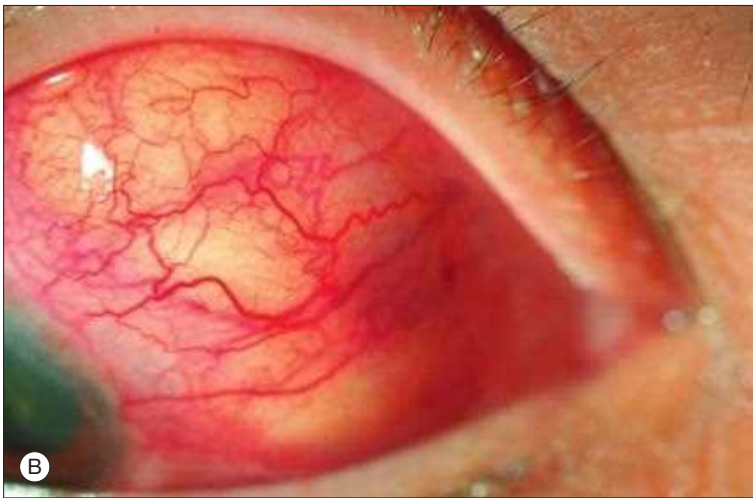
Scleritis is more associated with different systemic diseases compared with uveitis, so the evaluation and treatment for both conditions differ. In most cases, scleral inflammation is noninfectious. However, scleral infection caused by bacterial, protozoan, or fungal organisms, such as *Pseudomonas*, *Mycobacterium*, *Acanthamoeba*, or *Aspergillus*, may cause severe scleritis that is difficult to treat (Fig. 4.11.1). Scleritis typically occurs in the sixth decade of life, but may occur in adolescents and in very old adults. Females are more commonly affected, and bilateral inflammation occurs in nearly 40% of cases.<sup>1</sup>

#### Ocular Manifestations

Scleritis may be unilateral, bilateral, or alternate from eye to eye. The duration of inflammation is variable and may last only a few months or persist for years. The involved area may appear violaceous because the inflammation occurs in deeper tissues (Fig. 4.11.2). The whole eye may be involved, or inflammation may localize to one or more quadrants. The involved area usually is tender to palpation, although pain may occur in seemingly uninvolved areas. The pain typically is deep and boring in nature and often wakes the patient from sleep.

On slit-lamp microscopy, the overlying conjunctival vessels usually are found to be engorged. The episclera may be edematous and inflamed. At times, the secondary inflammation in the conjunctiva and episclera makes it difficult to appreciate the underlying scleral inflammation. Topical

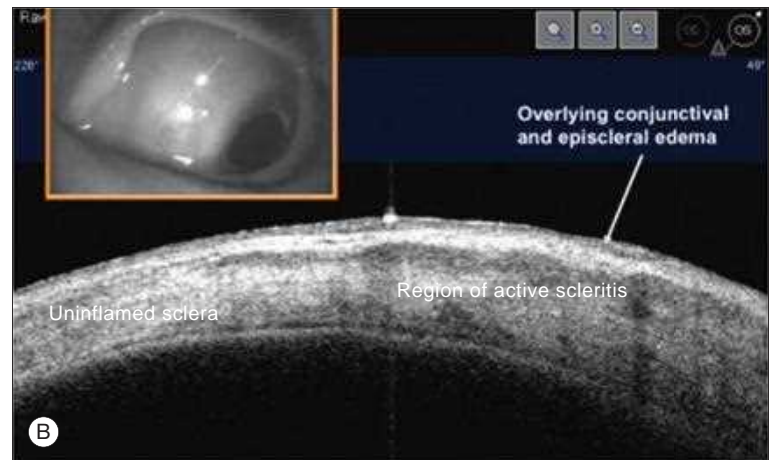




**Fig. 4.11.1** (A,B) Tuberculous scleritis. Note yellow necrotizing nodules in two patients with mycobacterial scleritis. Both patient spontaneously perforated and required enucleation, despite four-drug therapy for tuberculosis and concomitant immunomodulatory therapy. (C) Necrotizing *Acanthamoeba* sclerokeratitis in a 72-year-old female. Note the diffuse deep injection, the area of profound scleral thinning superiorly and active necrotizing, nodular scleritis nasally.



**Fig. 4.11.2** Scleritis With a Violaceous Hue Caused by Deep Inflammation. Vessels do not blanch with topical phenylephrine.

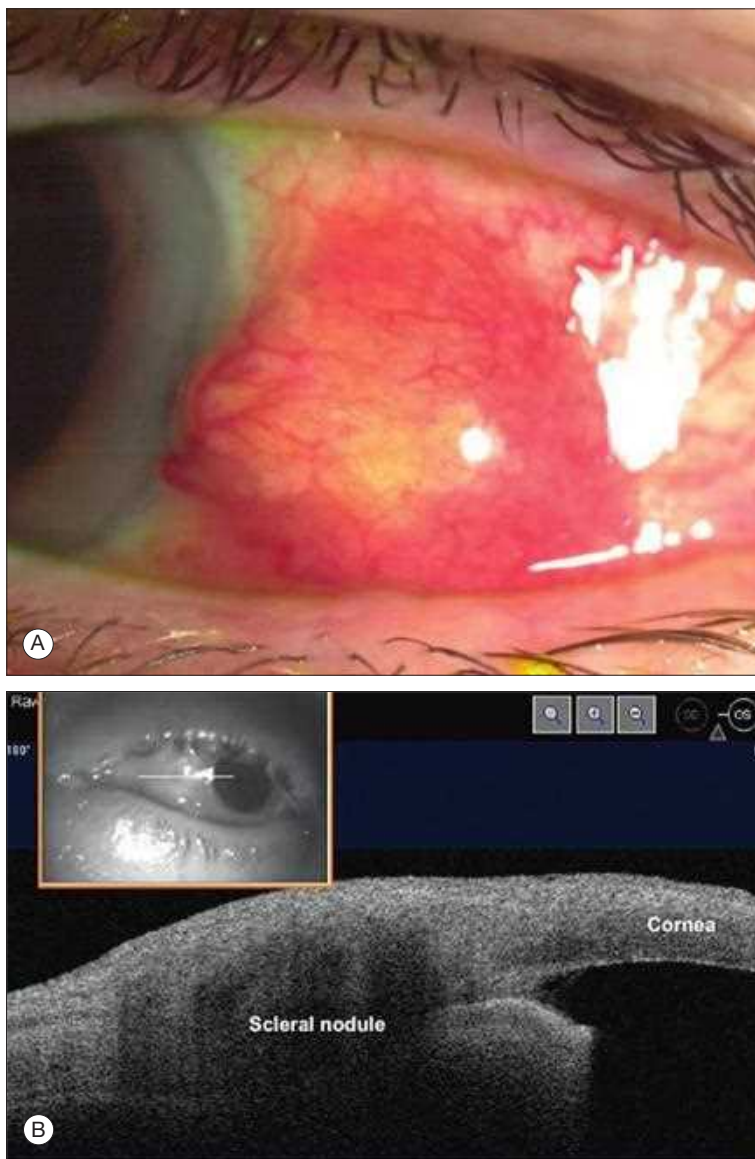


**Fig. 4.11.3** Diffuse scleritis in a patient with rheumatoid arthritis (A). Note that on anterior segment optical coherence tomography, there is diffuse scleral thickening with normal globe contours in the affected area compared with the adjacent unaffected sclera (B).

phenylephrine blanches the overlying conjunctiva and, to a much lesser extent, the episclera and may permit better delineation of the depth of inflammation. The red-free (green) light on the slit lamp may be used to determine the level of inflammation.

Anterior scleritis is classified as diffuse (Fig. 4.11.3A) or nodular (Fig. 4.11.4). It also may be necrotizing or nonnecrotizing. Necrotizing scleritis usually is extremely painful and presents with areas of avascularity in the sclera. Avascular areas may result in scleral thinning, which can progress to staphyloma formation and exposure of bare uvea (Fig. 4.11.5). A simple grading system for scleritis, which has been described in the literature, has helped standardize the assessment of scleritis (Fig. 4.11.6).<sup>4</sup>





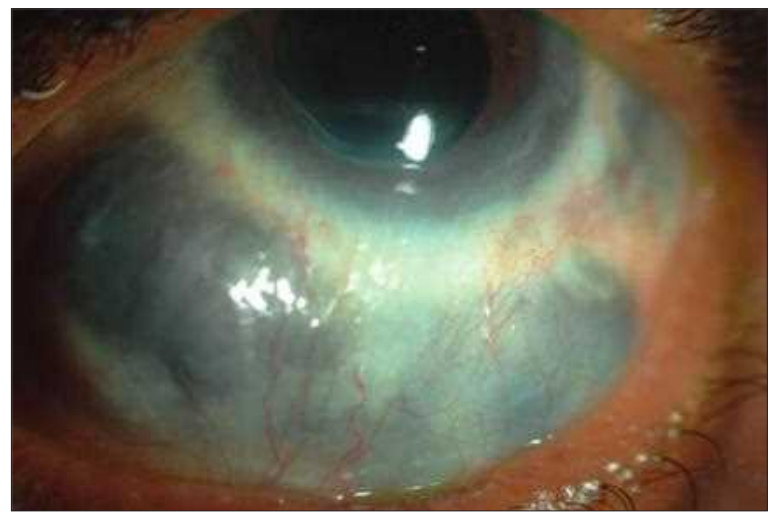
**Fig. 4.11.4 Large Scleral Nodule of Undetermined Etiology.** Note the yellow area, which probably represents scleral necrosis (A). A representative anterior segment optical coherence tomography image also illustrates a very thickened and disorganized sclera with a central zone of activity and possible necrotic activity (B).

*Scleromalacia perforans* is a very rare type of painless necrotizing scleritis, which typically occurs in women with a long-standing history of rheumatoid arthritis.

*Posterior scleritis* refers to inflammation behind the equator of the globe and may be difficult to diagnose if anterior scleritis is not also present. Symptoms of posterior scleritis may include pain, blurred vision, and photophobia, although the patient may be fairly asymptomatic. Some patients with posterior scleritis develop proptosis, shallowing of the anterior chamber, exudative retinal detachments, choroidal detachments, disc swelling, and chorioretinal changes (Figs. 4.11.7A and 4.11.8A). Chorioretinal changes may consist of subretinal exudates and hemorrhages, as well as a stippled appearance to the retinal pigment epithelium in long-standing disease.

Scleral inflammation may cause structural damage to the eye, resulting in scleral translucency and thinning (see Fig. 4.11.5). Ocular complications were encountered in nearly 45% of cases in one study, including anterior uveitis (26%), decreased vision (16%), peripheral keratitis (13%), and ocular hypertension (14%).<sup>1</sup> Decreased vision is associated most with necrotizing and posterior scleritis, although vision may be decreased as a result of cystoid macular edema in any type of scleritis. Significant amounts of induced astigmatism necessitate performance of retinoscopy in all patients with anterior scleritis and reduced vision.

Scleritis adjacent to the cornea may be associated with a focal or diffuse keratitis. Focal keratitis may manifest as a ring infiltrate at the limbus, without the peripheral clear zone that is seen with staphylococcal marginal infiltrates (Fig. 4.11.9). Sclerokeratitis also may present with crystalline



**Fig. 4.11.5 Inactive Necrotizing Scleritis in a Patient With Long-Standing Rheumatoid Arthritis.** The patient has had episodes of marked inflammation, but the disease has been quiescent on long-term immunosuppressive therapy.

deposits that have the appearance of spun sugar or cotton candy in the deep cornea (Fig. 4.11.10). This variant is known as *sclerosing keratitis*.<sup>5</sup>

A number of mechanisms may result in elevation of intraocular pressure (IOP). Inflammatory cells may block scleral emissary vessels, which results in elevated episcleral venous pressure and hence elevated IOP. Ciliary body effusion may cause angle closure as the lens-iris diaphragm rotates anteriorly. Accompanying uveitis may be responsible for glaucoma if the trabecular meshwork is clogged with inflammatory cells and debris. Corticosteroid use may result in secondary elevation of IOP.

### Differential Diagnosis

Conjunctivitis usually can be differentiated from scleritis by the presence of discharge, superficial inflammation, and the lack of severe aching or pain. Episcleritis may sometimes be confused with scleritis, although the two conditions can usually be differentiated based on history and clinical examination.

Ciliary flush (injection) that accompanies acute iritis may be confused with scleritis. However, the ciliary flush usually is restricted to the area adjacent to the limbus, and iritis appears to be the predominant finding.

Solid-appearing subretinal masses that mimic melanomas can occur in patients with scleritis (Fig. 4.11.11).<sup>6,7</sup> Computed tomography (CT) may be helpful in making the diagnosis of scleritis in these cases, demonstrating a contrast-enhancing mass that is uniformly isodense with sclera. A-scan ultrasonography usually demonstrates high internal reflectivity in scleritis (as opposed to low internal reflectivity in melanoma), and a B-scan may demonstrate thickened sclera.

### Diagnosis and Ancillary Testing

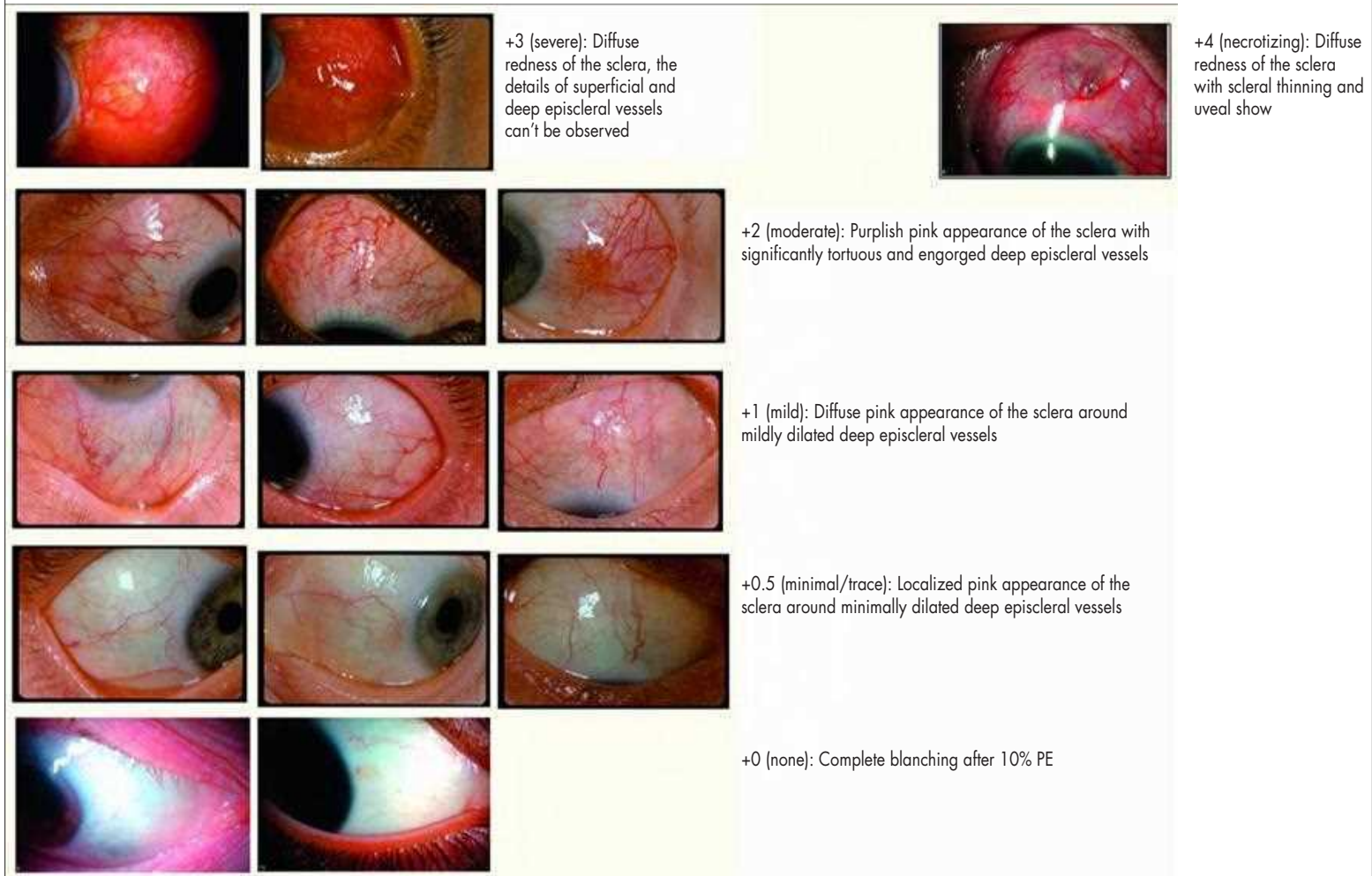
The diagnosis of anterior scleritis is clinically based. It is important to examine the patient with the room lights on. The lid should be lifted and the eyes examined from a distance, as scleritis may be missed if the patient is examined only at the slit lamp in a dark room.

The diagnosis of posterior scleritis can be difficult. Fluorescein angiography may be helpful because it may demonstrate characteristic subretinal leakage spots that coalesce as the study progresses (see Fig. 4.11.8B). Only Vogt-Koyanagi-Harada syndrome has a similar picture on fluorescein angiogram.<sup>8</sup>

B-scan ultrasonography is extremely useful in the diagnosis of posterior scleritis. The T-sign, representing fluid in Tenon's capsule, is highly characteristic of posterior scleritis, although it is not always present (see Fig. 4.11.7C). Thickening of the posterior sclera usually can be demonstrated on B-scan.<sup>9</sup> CT of the orbits with contrast material may show the so-called ring sign of enhancement of the sclera, suggestive of posterior scleritis. Magnetic resonance imaging has not proved to be any more useful than CT and may even be less helpful,<sup>10</sup> although it avoids the radiation risks associated with CT. Ultrasound biomicroscopy and anterior segment optical coherence tomography may help characterize severity and extent of disease (see Figs. 4.11.3B and 4.11.4B).<sup>11</sup>

The workup of a patient with scleritis includes an evaluation for systemic vasculitis, connective tissue disease, and infection. Much of this information can be gained from a detailed history. Laboratory tests might

### Scleritis Grading (Following 10% Phenylephrine application)



**Fig. 4.11.6** Standardized grading system for scleritis. (Reproduced from Sen HN, Sangave AA, Goldstein DA, et al. A standardized grading system for scleritis. *Ophthalmology* 2011;118:768–71.)

include erythrocyte sedimentation rate, rheumatoid factor, anticitrullinated protein antibody, antineutrophil cytoplasmic antibodies (C- and P-ANCA), antiproteinase 3, antimyeloperoxidase antibodies (anti-PR3, anti-MPO), and antinuclear antibody. Review of systems and a relevant family history may prompt the clinician to order human leukocyte antigen B27 or inflammatory bowel serology. Specific serological test for syphilis (including fluorescent treponemal antibody absorption test, microhemagglutination test for *Treponema pallidum*, syphilis immunoglobulin G enzyme immunoassay) should be obtained for all patients with ocular inflammation. A complete blood count and urinalysis may be considered. Chest radiography may be performed to look for evidence of tuberculosis, sarcoid, or granulomatosis with polyangiitis (GPA). ANCA, anti-PR3, and anti-MPO testing often is positive in cases of GPA, microscopic polyarteritis, and other related vasculitides.<sup>12</sup> Two different patterns of immunofluorescence staining have been identified. Classic ANCA (C-ANCA) and anti-PR3 are more specific for GPA and other closely related vasculitides. The positivity of this test may depend, in part, on disease activity; in some patients, the test becomes negative with treatment or a decrease in disease activity.<sup>13</sup>

#### Systemic Associations

Underlying systemic disease is present in approximately 35%–50% of patients with scleritis.<sup>1,14</sup> Rheumatoid arthritis is the most frequently associated condition,<sup>15</sup> and scleritis may be the first manifestation, preceding joint disease.<sup>16</sup> Other connective tissue diseases that can present with scleritis include GPA, polyarteritis nodosa, systemic lupus erythematosus, and relapsing polychondritis (Fig. 4.11.12).

Psoriatic arthritis and ankylosing spondylitis, although usually associated with acute iritis, can at times be associated with scleritis.<sup>15</sup> Inflammatory bowel disease, especially Crohn's disease, can be associated with

scleritis. Scleritis has been observed in 18% of patients with inflammatory bowel disease and may correspond to gastrointestinal (GI) disease activity, as does accompanying large joint peripheral arthritis.<sup>17</sup> Pyoderma gangrenosum and Cogan's syndrome can be associated with scleritis.<sup>18</sup> Sarcoidosis can cause granulomatous scleritis.

Infectious conditions, such as tuberculosis, acanthamoebiasis, syphilis, and leprosy, may result in granulomatous, nodular scleritis (see Fig. 4.11.1A). Herpes zoster and herpes simplex may cause scleritis (Fig. 4.11.13). When herpesviruses cause scleritis, it usually is in the late recovery phase of the disease rather than during acute infection.<sup>14</sup>

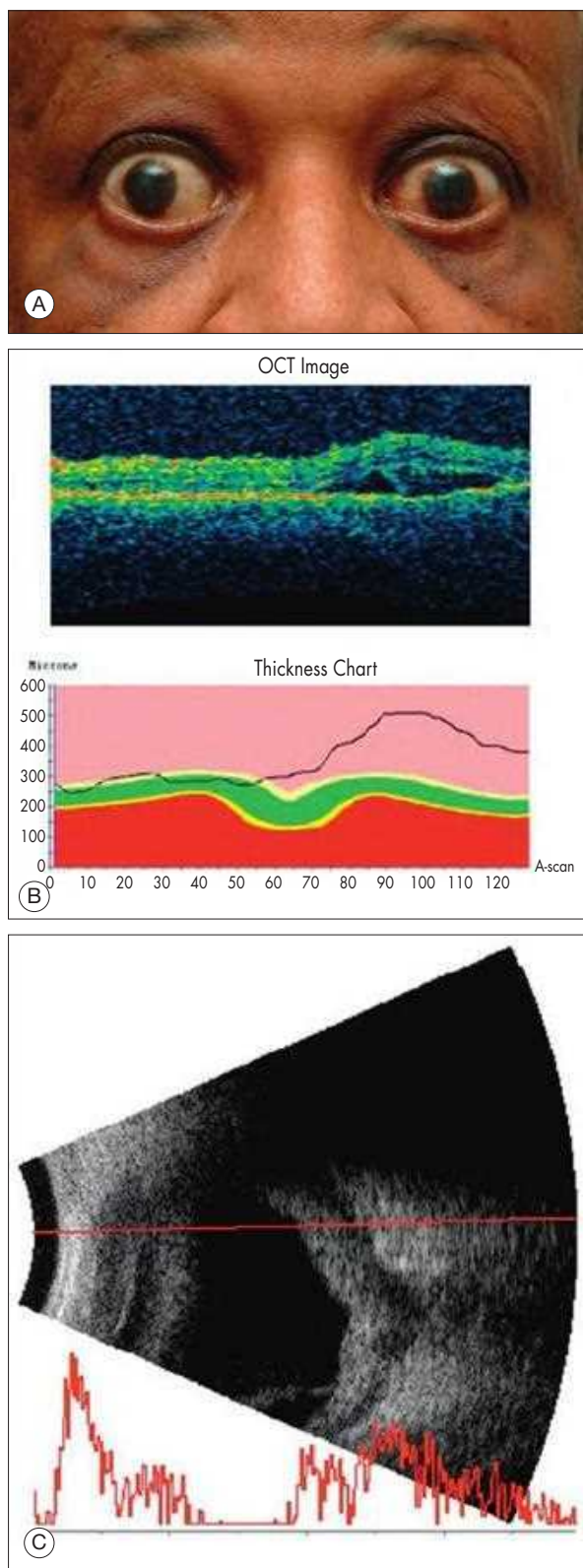
Necrotizing scleritis can be triggered by ocular surgery (Fig. 4.11.14); it has been reported weeks to months after cataract surgery, penetrating keratoplasty, muscle surgery, glaucoma surgery, and even pterygium surgery.<sup>19–21</sup> Evidence exists of underlying connective tissue disease in some of these patients, but in others, no causative factor can be found. Infectious causes must be sought in all patients with postoperative scleritis.

#### Pathology

Scleral biopsy should be done only in exceptional circumstances. The surgeon should be prepared either to place a scleral reinforcement graft or use some other tissue, such as periosteum, to replace the sclera that has been sampled for biopsy, as severe thinning of the sclera can result in an unexpected encounter with intraocular contents.

Histopathological examination may reveal one of four patterns of inflammation, which can correlate with disease etiology<sup>22,23</sup>: zonal, necrotizing granulomatous; diffuse, nonnecrotizing; necrotizing with microabscesses; and nonzonal, nondiffuse granulomatous. Antigen–antibody complexes mediate zonal, necrotizing granulomatous inflammation, which is most often associated with systemic disease.<sup>22,23</sup> Lymphocytes





**Fig. 4.11.7** (A) A 72-year-old male with bilateral posterior scleritis. Note the bilateral proptosis. (B) Optical coherence tomography demonstrating subretinal fluid. (C) B-scan demonstrating T-sign, and marked choroidal thickening. The T-sign is believed to be due to fluid in Tenon's capsule and is very characteristic of posterior scleritis, although it is not always present.

and plasma cells appear in diffuse nonnecrotizing inflammation, which is often idiopathic.<sup>22,23</sup> Necrotizing inflammation with microabscesses is observed in infectious scleritis.

## Treatment

### Medical Treatment

Most patients who have active scleritis require therapy. Some physicians recommend that treatment be continued until all redness is gone from the eye. However, if no pain and no evidence of any damage to the eye exist, the side effects of the therapy may outweigh the benefits. Some patients

who have only mild redness, no active secondary uveitis or keratitis, and no visual problems may not require therapy, but must be closely monitored.

Topical nonsteroidal agents may be of some benefit in patients who have mild episcleritis, but they are of no benefit in true scleritis. Most topical corticosteroids do not have any marked beneficial anti-inflammatory effect in cases of true scleritis, although they may be helpful in controlling secondary uveitis. Difluprednate, a newer topical corticosteroid, has been shown to have scleral penetration in rabbit models and may be a useful therapeutic agent in scleritis, but clinical data on its use in human scleritis are lacking.<sup>24</sup>

Oral NSAIDs should be considered the first line of treatment in patients with mild and moderately severe scleritis. They have been reported to be effective in diffuse scleritis and mild nodular scleritis.<sup>25</sup> Indomethacin 50 mg three times a day or, in the sustained-release form, 75 mg twice a day, can be very effective. Other nonsteroidal agents that appear to work well are piroxicam and naprosyn. Ibuprofen, diclofenac, tolmetin, sulindac, and others also may be of benefit.

All systemic nonsteroidal agents carry the risk of significant side effects. Long-term therapy may result in allergic reactions, GI problems, and kidney damage. An increased risk of cardiac events has been reported with both cyclooxygenase-2 (COX-2)-specific and COX-2-nonspecific NSAIDs. These medications should be avoided in those patients with significant cardiac risk factors, especially in patients with prior myocardial infarction, prior stroke, or recent cardiac arrhythmias.<sup>26</sup> Patients who take NSAIDs may require other medications to prevent or treat GI side effects. Options include histamine 2 (H<sub>2</sub>) receptor antagonists (e.g., ranitidine, famotidine, cimetidine), coating agents (e.g., sucralfate), gastric acid secretion inhibitors (e.g., the synthetic prostaglandin E<sub>1</sub> analogue misoprostol), and proton pump inhibitors (e.g., omeprazole). The NSAIDs that are selective COX-2 inhibitors may have fewer GI side effects but appear to be less potent anti-inflammatory agents.

Systemic corticosteroids often are used as initial therapy for patients with moderate to severe scleritis. The usual starting dose is 1 mg/kg/day of prednisone, but in severe cases, doses up to 1.5 mg/kg/day or even intravenous pulse corticosteroids may be required. The prednisone is then slowly tapered to a best-tolerated dose. Many patients require therapy for 6 months to a year or longer. Patients who require more than 3 months of treatment or 5 mg of chronic daily prednisone should be considered for corticosteroid-sparing agents. Occasionally, patients who take their full dose of oral prednisone in the morning experience pain at night. If the dose is divided and taken twice a day, this night pain may be relieved without increasing the total dose.

Pulse intravenous methylprednisolone at 0.5–1 g may be required in some patients with severe scleritis. This high dose may be used once a day for 3 days or once every other day for three doses and then reduced to once a week. Oral prednisone is often required to supplement the pulses.<sup>27</sup>

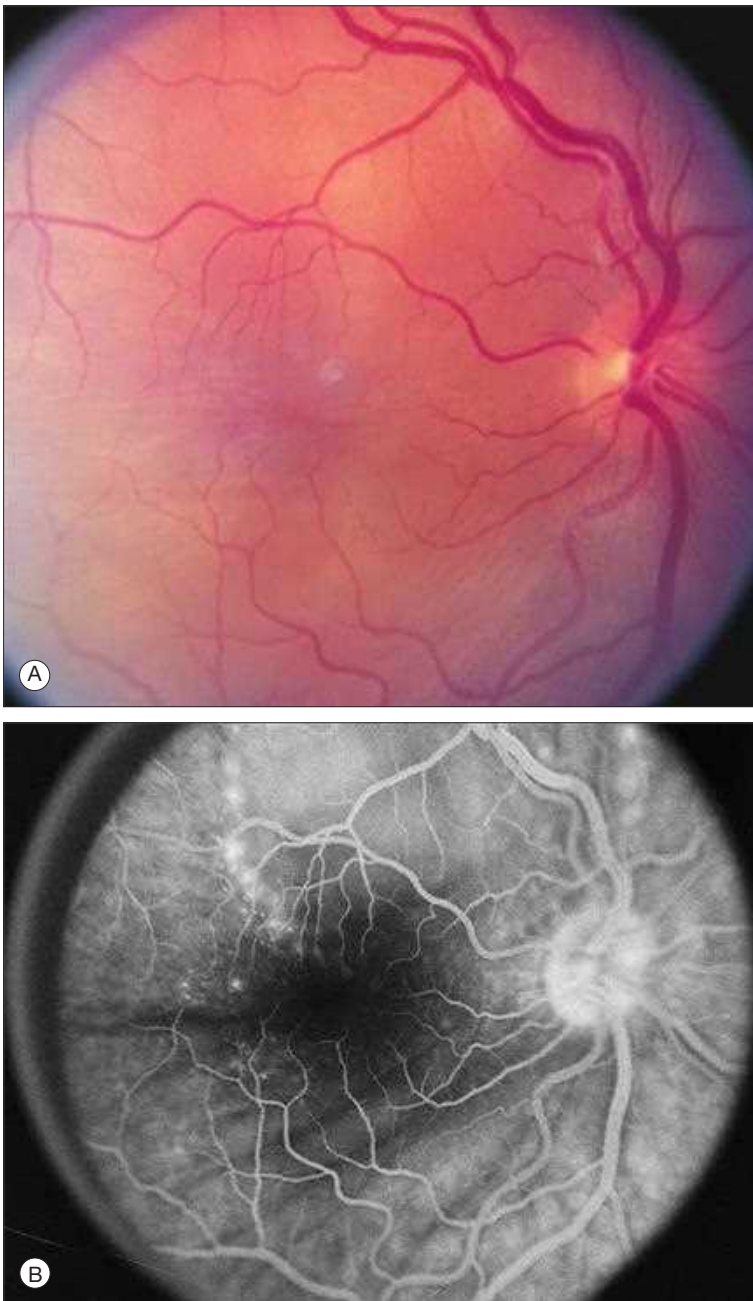
All systemic corticosteroids may result in adrenal suppression, weight gain, mood changes, blood pressure elevation, blood sugar elevation, osteoporosis, and aseptic necrosis of the femoral head. Any patient who is on oral prednisone for longer than 1 year, even on an every-other-day schedule, should have a bone density evaluation.

Subconjunctival injection has been proposed as a method of corticosteroid delivery in cases of nonnecrotizing anterior scleritis.<sup>28</sup> Its use typically is limited to adjunctive therapy in cases of nonnecrotizing localized disease, cognizant of the at least theoretical risk of scleral thinning and perforation.

Immunosuppressive or immunomodulatory therapy may be required in patients with scleritis who are unresponsive to or intolerant of prednisone, or who require long-term therapy (see Fig. 4.11.5). In patients with severe rheumatoid arthritis and GPA, morbidity and mortality are reduced with the use of immunosuppressive agents.<sup>29</sup> Many patients with necrotizing scleritis require immunosuppressive therapy to preserve vision. Evidence exists that well-managed immunosuppressives have less long-term toxicity compared with high- or moderate-dose prednisone.<sup>30</sup> All immunomodulatory therapy for scleritis is used off label.

Oral or subcutaneous methotrexate (7.5–25 mg weekly) has been reported to be of benefit in reducing or eliminating the need for systemic corticosteroid therapy.<sup>31</sup> Azathioprine at a dose of 1.5–2 mg/kg/day also may reduce or eliminate the need for corticosteroids.<sup>25,30</sup> However, both these agents can result in hepatic and hematological toxicity. Mycophenolate mofetil, another antimetabolite drug, may have lower toxicity and higher efficacy.<sup>32</sup>

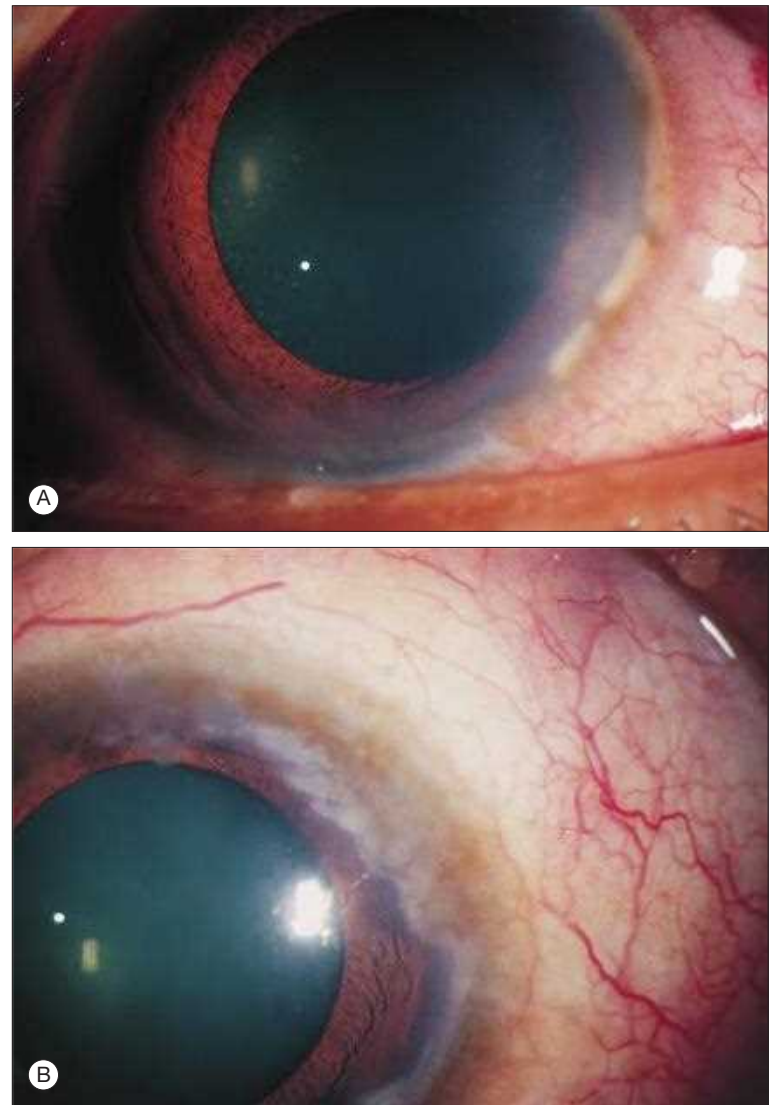
Cyclosporine, which acts in part by interfering with interleukin-2, has been used with some success in the treatment of scleritis.<sup>30</sup> At doses of 10 mg/kg/day, it is nephrotoxic, so it is almost always used at lower doses,



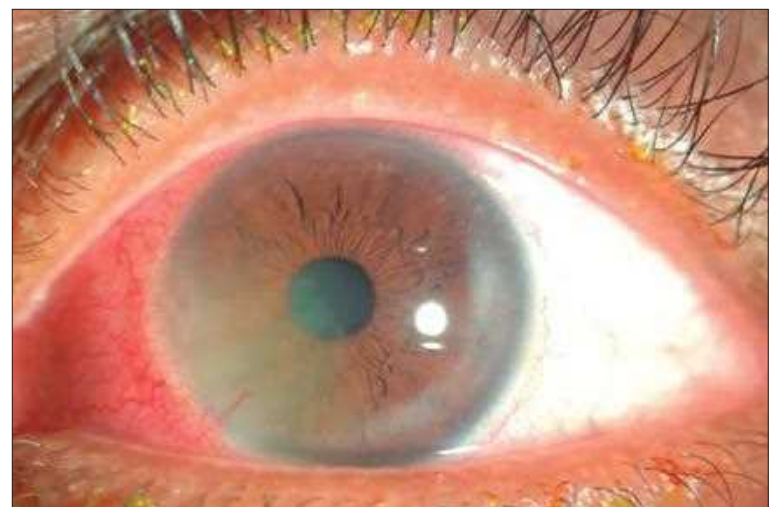
**Fig. 4.11.8 Fluorescein Angiography.** (A) Fundus photograph demonstrating exudative retinal detachment and choroidal folds in posterior scleritis. (B) The same eye shows choroidal folds and areas of subretinal leakage, which increase in intensity in the late phases of the angiogram. Only Vogt-Koyanagi-Harada syndrome and posterior scleritis exhibit this subretinal leakage pattern. Many patients with posterior scleritis do not have this leakage pattern, however.

such as 5 mg/kg/day as an initial dose and 3–5 mg/kg/day as a maintenance dose. However, at these doses, it may be impossible to discontinue the use of corticosteroids. As such, cyclosporine is used as an adjunctive therapy, permitting lower doses of systemic corticosteroids, or in combination with other agents such as antimetabolites.<sup>33,34</sup> Systemic hypertension, renal failure, hirsutism, and gingival hyperplasia all may occur with cyclosporine. Tacrolimus (FK-506) has a different structure from that of cyclosporine but has similar intracellular actions and is supplied in a topical ointment that has been shown to be effective in a small number of scleritis cases.<sup>35</sup>

Biological medications have been shown to be particularly effective in treating scleritis. Tumor necrosis factor inhibitors, which include infliximab, adalimumab, etanercept, certolizumab, and golimumab, typically act rapidly in controlling inflammation. The majority of data in uveitis and scleritis are for infliximab and adalimumab. Although adalimumab recently received U.S. Food and Drug Administration approval for the treatment of noninfectious intermediate, posterior, and panuveitis in adults, its use in scleritis is still off label. In addition, rituximab has been shown to have excellent efficacy in refractory cases of scleritis.<sup>36</sup>



**Fig. 4.11.9 Ring Corneal Ulcer in a Patient With Rheumatoid Arthritis and Scleritis.** (A) Note the white, creamy infiltrates in the cornea, indicating active inflammation, and the lack of a lucid interval between the limbus to the ulcer. (B) Other eye of the same patient. Note the scarring and vascularization from a previously active ring ulcer.



**Fig. 4.11.10 Diffuse Scleritis Active Nasally.** Note the active sclerosing keratitis nasally and chronic changes from prior sclerosing keratitis temporally. The temporal scleritis has completely resolved.

These agents are usually prescribed and monitored in conjunction with a rheumatologist.

Alkylating agents, such as chlorambucil and cyclophosphamide, may be of benefit and usually enable oral prednisone to be tapered or discontinued.<sup>37,38</sup> In some cases, a 3- to 6-month course of chlorambucil, with





**Fig. 4.11.11 Subretinal Mass Mimicking an Amelanotic Melanoma in a Patient With Scleritis.** In this patient, the mass disappeared with cyclophosphamide therapy.

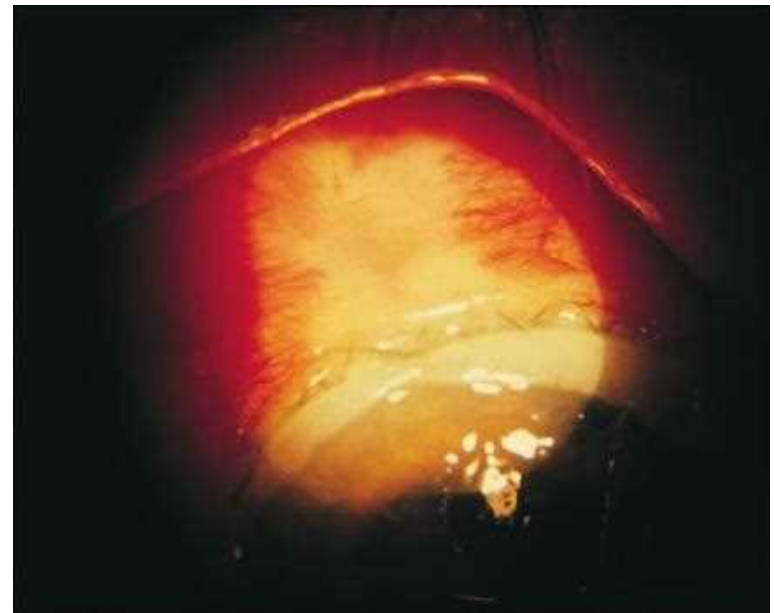


**Fig. 4.11.12 Patient With Relapsing Polychondritis.** Note inflammation of the superior half of the pinna.

reduction of the white blood cell count to 2400–3500, results in prolonged remission of ocular inflammatory disease.<sup>37,38</sup> Alkylating agents may have hematological toxicity, and blood counts must be monitored frequently. Cyclophosphamide has the added risk of hemorrhagic cystitis, so adequate hydration is imperative. Cyclophosphamide works more rapidly (frequently within a few days to a week) compared with chlorambucil. Pulse intravenous cyclophosphamide also has been used in severe sight- or life-threatening disease. Because alkylating agent use may increase the risk of late malignancy and sterility, detailed informed consent should be obtained before starting therapy. These agents may result in premature gonadal failure in males and females and are also teratogenic, so patients must be counseled carefully.

### Surgical Treatment

Surgery for scleritis may be performed when scleral perforation or extensive thinning exists with significant risk for scleral rupture. However, most patients who have thin sclera and even staphyloma formation do not require structural reinforcement. If the decision is made to reinforce the sclera, available agents include fresh or preserved donor sclera, periotum, or fascia lata. Donor sclera is relatively easy to use, but after several months, it may start to dissolve, as did the originally diseased tissue. Autologous periosteum can be harvested from the tibial crest and may be a better agent to use, as it may be less likely to necrose compared with donor sclera.<sup>39</sup>



**Fig. 4.11.13 Necrotizing Anterior Scleritis Secondary to Herpes Zoster.** The patient underwent extracapsular cataract extraction 2 weeks earlier, which precipitated ophthalmic zoster.



**Fig. 4.11.14 Necrotizing Scleritis Induced by Trabeculectomy Surgery.** Note the large conjunctival vessels seen in this 75-year-old woman; these are frequently seen after severe scleritis.

Many patients who have scleritis develop cataracts. Surgery for cataracts in such patients should be undertaken only when the disease has been in remission for at least 3 months. The physician should be alert to recognize recrudescence of scleral inflammation after surgery.

### Course and Outcome

Most patients with mild or moderate scleritis maintain excellent vision. The length of time during which scleritis is active varies from patient to patient. In a minority of patients, the disease is active for months and then goes into long-term remission. In other patients, the disease is active for several years. In some patients, the disease seems to move from eye to eye or to move from one area of sclera to another.

Necrotizing scleritis portends a worse prognosis compared with non-necrotizing disease. Patients with necrotizing scleritis have a high incidence of visual loss and a 21% 8-year mortality.<sup>14,40</sup> Immunosuppressive therapy appears to lessen these risks.

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## Bacterial Keratitis

Jeremy D. Keenan, Stephen D. McLeod

4.12

**Definition:** Corneal disease caused by bacterial organisms.**Key Feature**

- Cellular infiltration of the corneal epithelium or stroma, corneal inflammation, and necrosis.

**Associated Features**

- Lid edema.
- Conjunctival inflammation.
- Discharge.
- Anterior chamber reaction.
- Hypopyon.

**INTRODUCTION**

Infectious keratitis is one of the leading causes of blindness in the world. Because, in most cases, these infections represent preventable or treatable ophthalmic diseases, a thorough understanding of the epidemiology, diagnosis, and treatment of the various forms of infectious keratitis is essential for eye-care practitioners and public health officials.

**EPIDEMIOLOGY AND PATHOGENESIS**

The estimated incidence of ulcerative keratitis in the United States is 28 per 100 000 person years, with a higher incidence among contact lens wearers (130 per 100 000 person years).<sup>1</sup> The incidence of infectious keratitis in the developing world is even higher, with estimated incidence rates ranging from 100 to 800 per 100 000 person years.<sup>2</sup> Given the potential blinding complications of severe bacterial keratitis, these infections are a significant public health issue.<sup>3</sup> A host of bacterial organisms can cause infectious keratitis. The incidence of infection by specific organisms varies by region. Practitioners should be aware of the local epidemiological patterns of corneal infection. Whereas staphylococcal species are most commonly seen in Canada and the eastern and northeastern United States, *Pseudomonas* infection is more common in the southern United States. *Streptococcus pneumoniae* was once the most common pathogen isolated from bacterial corneal ulcers, but as contact lens wear and related infectious keratitis have increased, the relative incidence of pseudomonal and staphylococcal infection has increased. These two organisms account for the majority of infections associated with contact lens wear, followed by *Serratia marcescens*. Corneal infections that occur in patients with systemic debilitating conditions, such as alcohol abuse, malnutrition, or diabetes often are associated with *Moraxella*. In the developing world, streptococcal corneal infection remains the most common, followed by staphylococcal and pseudomonal keratitis.

The corneal surface is normally well protected by a variety of mechanisms.<sup>4</sup> The eyelids and eyelashes form a physical outer barrier to foreign material, and the blink reflex sweeps away debris trapped in tears. A second line of defense is the tear film, which contains a variety of antimicrobial and anti-inflammatory factors, such as lactoferrin, lysozyme, beta-lysin, tear-specific albumin, and immunoglobulin A (IgA). Finally, the corneal and conjunctival epithelial cells provide a barrier via their tight junctions, express molecules important for innate immunity (e.g., toll-like receptors), and produce a variety of antimicrobial peptides.

The conjunctiva provides additional protection from infection. The conjunctiva contains mast cells, which, when activated, induce vascular

dilatation and increased vascular permeability, which results in the production of an antimicrobial transudate. The conjunctiva also contains conjunctiva-associated lymphoid tissue (CALT), which consists of nodules of small and medium-sized lymphocytes responsible for local antigen processing. Plasma cells, macrophages, and a variety of T cells also are present, as well as IgG, IgA, and IgM, which are brought in by the conjunctival vasculature.

The natural microbial environment of the ocular surface consists of both sessile and free-floating bacteria. This population is kept in check by the antimicrobial features of the tear film, and by the products of resident microbes; these products, called *bacteriocins*, are high-molecular-weight proteins that inhibit the growth of pathogens, such as pneumococci and Gram-negative bacilli.

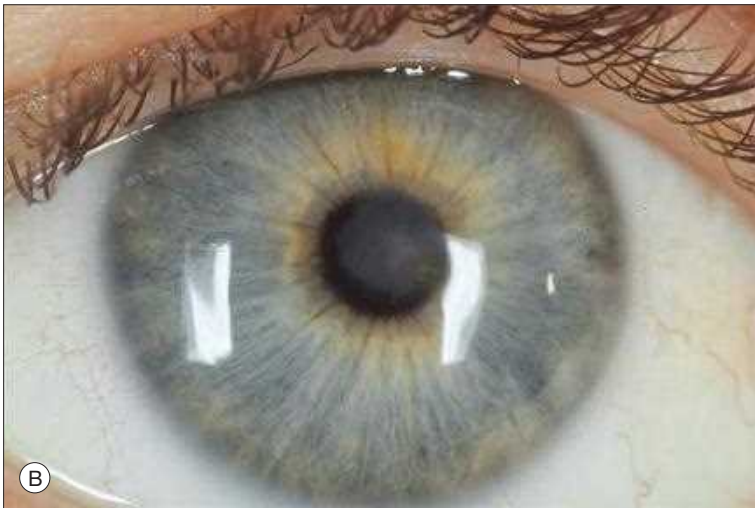
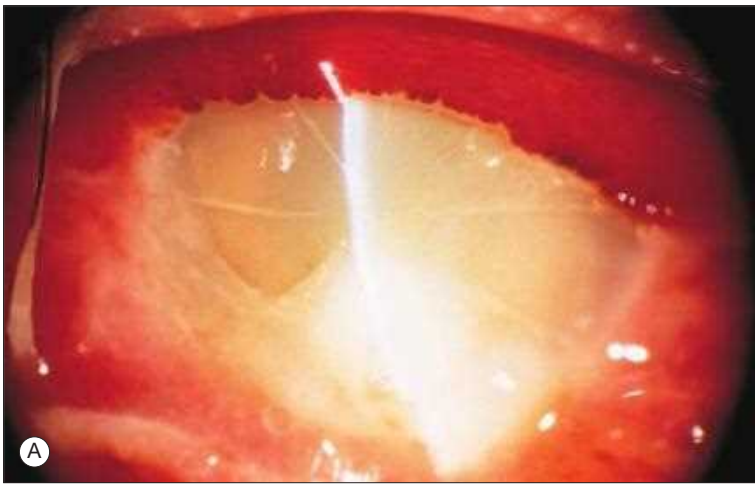
In the majority of cases where bacterial keratitis develops, at least one risk factor that represents a compromise of one or more of these defense mechanisms can be identified. In developed countries, soft contact lens wear is the most important risk factor. Contact lenses likely cause physiological and traumatic changes to the ocular surface, additionally providing a scaffold for bacterial biofilm formation.<sup>5,6</sup> Extended or overnight contact lens wear and poor lens hygiene substantially increase the risk; unfortunately, daily disposable lenses may not reduce this risk. Corneal trauma, as well as keratorefractive procedures, such as laser in situ keratomileusis (LASIK), can disrupt the epithelial barrier and allow invasion of infectious organisms into the stroma (Fig. 4.12.1).<sup>7</sup> Lid abnormalities, such as entropion or ectropion, exposure of the corneal surface, or trichiasis, can cause breakdown of the protective corneal epithelium. Poor tear production can lead to a reduction of antimicrobial tear components and epithelial desiccation and damage. Epithelial problems, such as bullous keratopathy, medication toxicity, and prior herpetic infection, can allow microbial adherence and invasion. Drugs that may be smoked, such as cocaine and methamphetamine, have been associated with microbial keratitis, probably because of a direct toxic effect, exposure keratopathy, neurotrophic changes, or mechanical trauma (Fig. 4.12.2). Local or systemic immune compromise can lead to impairment of local immune defenses. This is most commonly caused by the use of topical corticosteroids, but immunosuppression, malignancy, malnutrition, or extensive burns also can cause it. Occasionally, keratitis can be established via the corneoscleral limbus by hematogenous spread.

**CLINICAL FEATURES**

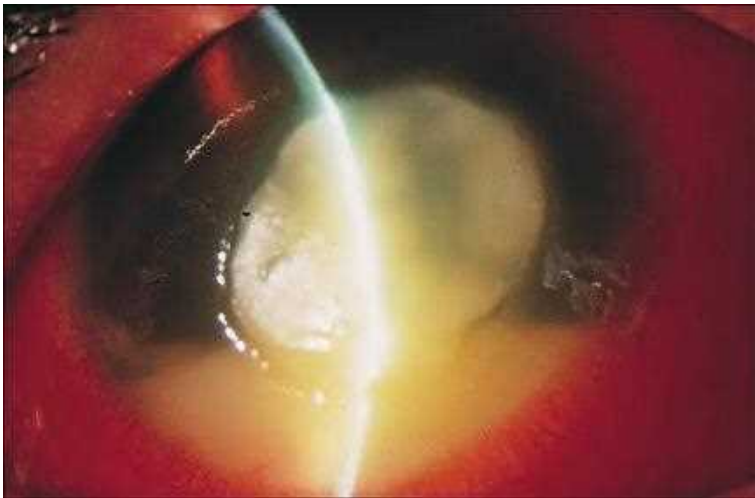
The clinical signs and symptoms of bacterial keratitis depend greatly on the virulence of the organism and the duration of infection. Other influential factors include the previous status of the cornea and the use of corticosteroids. Patients may describe decreased vision, pain, and photophobia. The cardinal corneal sign is a localized or diffuse infiltration of the epithelium or stroma (Fig. 4.12.3). Commonly, epithelial absence over a gray-white necrotic stromal infiltrate occurs. Less commonly, a stromal abscess can appear beneath an intact epithelium. Infiltration and edema of the cornea can appear distant to the primary site of infection. Occasionally, bacterial keratitis can present with predominantly multifocal epithelial infiltration, especially in the setting of soft contact lens wear.

Other ocular structures usually demonstrate associated inflammation. Some degree of lid erythema and edema, conjunctival injection and chemosis, tearing, and discharge often occur. A nonspecific conjunctival papillary response might be seen. Anterior chamber inflammation often is present, ranging from cells and flare in milder cases to hypopyon in more severe cases. The aqueous might become dense and fibrinoid, and fibrinous endothelial plaques may develop. The hypopyon usually is sterile unless accompanied by a full-thickness corneal perforation.





**Fig. 4.12.1 Keratitis.** (A) Severe keratitis caused by *Pseudomonas* following radial keratotomy. (B) Scarring at the interface of a LASIK flap and bed following *Aspergillus* keratitis.



**Fig. 4.12.2 Epithelial Defect, Stromal Infiltrate, and Hypopyon Associated With Crack Cocaine Use.** *Candida*, *Streptococcus*, and *Haemophilus* species were recovered from scrapings of the infiltrate.

## Gram-Positive Cocci

### Staphylococcus

Staphylococci are Gram-positive cocci, which, on stained smears, tend to appear singly or in pairs, although clusters of organisms can be seen. The two most common species that cause keratitis are *Staphylococcus aureus* and *Staphylococcus epidermidis*, both of which are commonly found on skin, eyelids, and the conjunctiva. Although non-*aureus* strains are usually less virulent, antibiotic resistance tends to be more common, and aggressive keratitis occasionally occurs.



**Fig. 4.12.3** Bacterial corneal infection with dense central necrotic ulcer and infiltrate.



**Fig. 4.12.4** Streptococcal bacterial keratitis with infiltration of the central cornea.

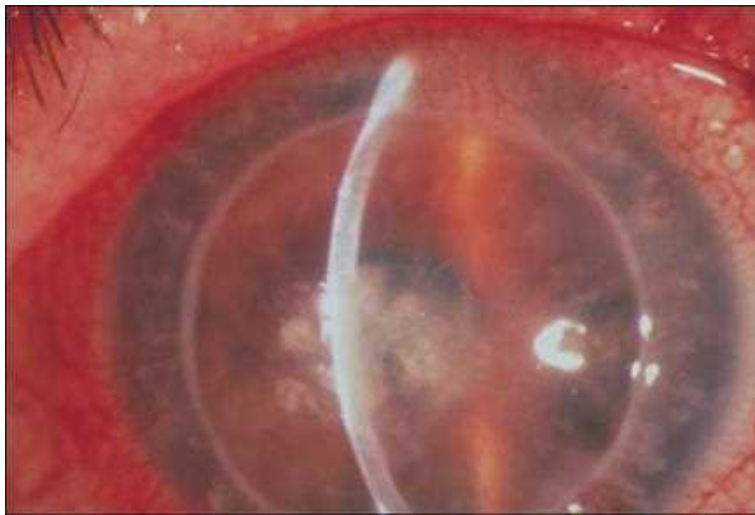
Infection tends to occur in compromised corneas, such as those with bullous keratopathy, herpetic disease, and persistent epithelial defect. Usually a well-defined, cream-colored or gray-white stromal infiltrate with an overlying epithelial defect is seen. Sometimes multiple foci of abscesses can develop that resemble fungal satellite lesions. *S. aureus* tends to cause more severe infiltration and necrosis than *S. epidermidis*. Over time, the former can extend deep into the stroma, and necrosis of this abscess can lead to perforation. A hypopyon and endothelial plaque can be seen.

### Streptococcus

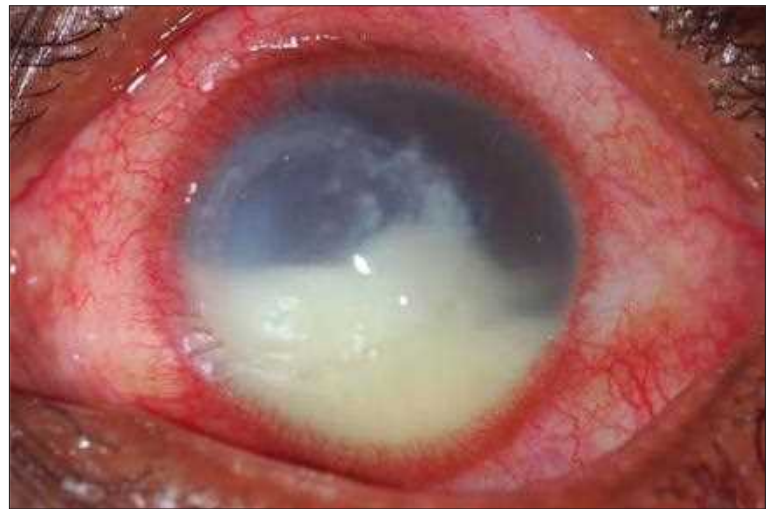
Streptococci are Gram-positive cocci. On stained smears, most species tend to appear in chains, but they also can be arranged singly, in pairs, or in loose clusters. The most common species causing keratitis is *Streptococcus pneumoniae* (*Pneumococcus*), which appears as lancet-shaped diplococci arranged with the flattened ends together. Streptococcal species are distinguished by their ability to hemolyze red blood cells. *Streptococcus viridans* and *S. pneumoniae* do so partially (alpha-hemolysis), *S. pyogenes* completely (beta hemolysis), and gamma-hemolytic species do not hemolyze red blood cells at all.

Pneumococcal infections can readily spread, producing a deep stromal abscess, fibrin deposition, plaque formation, severe anterior chamber reaction, hypopyon, and iris synechiae (Fig. 4.12.4). The advancing necrosis often produces an undermined leading edge with overhanging tissue. Infection by *Streptococcus pyogenes* occurs less frequently but has a similar, severe presentation and course. Group viridans *Streptococcus* spp. tend to cause less aggressive disease and are associated with a more indolent course, as is seen in infectious crystalline keratopathy.

Infectious crystalline keratopathy describes a particular pattern of corneal infiltration characterized by needle-like opacities that can be found at all levels of the corneal stroma (Fig. 4.12.5). The crystalline opacities range from fine, feathery, and white to thick, brown, arborizing aggregations, without apparent cellular infiltrate or ocular inflammation. The entity most frequently occurs in corneal grafts but has also been associated with



**Fig. 4.12.5** Infectious crystalline keratopathy caused by *Streptococcus viridans*.



**Fig. 4.12.6** Serrated border and satellite lesions in keratitis caused by *Nocardia*.

other conditions, such as incisional keratotomy, epikeratophakia, contact lens wear, chemical burns, and topical anesthetic abuse. Long-term corticosteroid therapy is thought to play a role in the pathogenesis. Although the viridans group of streptococci accounts for most cases, other organisms associated with infectious crystalline keratopathy include *S. pneumoniae*, *Haemophilus aphrophilus*, *Peptostreptococcus*, *Pseudomonas aeruginosa*, and a number of other bacteria, as well as *Candida* and *Alternaria* fungal species.

## Gram-Positive Bacilli

### Bacillus

*Bacillus cereus* is an aerobic, spore-forming, typically Gram-positive rod, although considerable variability in staining characteristics has been noted. They are ubiquitous and are found in water, in soil, and on vegetation. Corneal infection, therefore, can be seen after penetrating injury, especially when soil contamination occurs. *Bacillus* infection also has been reported in contact lens-related keratitis. Posttraumatic infection characteristically develops within 24 hours of injury and is associated with chemosis, profound lid edema, and proptosis. A diffuse or a peripheral ring of microcystic edema often occurs, followed by a circumferential corneal abscess. This is an extremely virulent organism, and perforation of the cornea can develop within hours.

### Corynebacterium

The corynebacteria, which include *C. diphtheriae*, are Gram-positive, club-shaped or pleomorphic rods arranged in the so-called Chinese-letter formation, Y's, or palisades. An infrequent cause of keratitis, the clinical picture characteristically begins with diffuse epithelial haze, followed by stromal necrosis and melting.

### Listeria

*Listeria monocytogenes* is a Gram-positive, short, rod-shaped facultative anaerobe. Infection usually occurs in animal handlers. It can colonize persistent epithelial defects and lead to a necrotizing keratitis. Typically, a ring ulcer and an exuberant anterior chamber reaction with fibrinous exudate and a hypopyon occur.

### Clostridium

Clostridia are anaerobic, spore-forming, Gram-positive bacilli. Infrequently, clostridial conjunctivitis can be associated with the development of a marginal keratitis. Direct corneal infection is associated with marked edema and a frothy, bullous keratitis caused by trapped intraepithelial, subepithelial, and intrastromal gas produced by the organism. Gas might also be seen in the anterior chamber.<sup>8</sup>

### Propionibacterium acnes

*Propionibacterium acnes* is an anaerobic, nonspore-forming, Gram-positive rod. It forms part of the normal flora of the eyelid and conjunctiva. Keratitis can be established in the setting of corneal disease, trauma, surgery, contact lens wear, or chronic topical corticosteroid use.<sup>9</sup> Although keratitis caused by *P. acnes* can assume the appearance of typical infectious

keratitis, the infection can be indolent, with a stromal abscess covered by an intact epithelium.

## Filamentous Bacteria

### Actinomyces and Nocardia

*Actinomyces* and *Nocardia* are Gram-positive, filamentous bacteria. *Actinomyces* is obligatorily anaerobic and nonacid-fast, whereas *Nocardia* is obligatorily aerobic and variably acid-fast. On Gram staining, the filaments of these organisms are seen as branching and intertwined; some might display terminal clubs, and the filaments often fragment into bacillary and coccoid forms.

Actinomycotic keratitis is usually part of a mixed infection with other organisms that might have different antibiotic sensitivities. Infection is rare and usually follows trauma. Typically, the ulcer bed appears dry and necrotic and is surrounded by a yellow demarcating gutter.<sup>10</sup> Alternatively, ring abscesses have been described. Inflammation can be severe, with iritis and a hypopyon.

Infections by *Nocardia* also tend to follow trauma, especially if soil contamination occurs. The ulcer is characteristically superficial, with a wreath-shaped gray-white infiltrate and an undermined necrotic edge (Fig. 4.12.6). The base might assume a cracked windshield appearance. *Nocardia* keratitis often resembles fungal infection, with a filamentous-appearing border and satellite lesions.

## Gram-Negative Rods

### Pseudomonas

*Pseudomonas aeruginosa* is the most common Gram-negative organism isolated from corneal ulcers and is a frequent cause of contact lens-associated keratitis. These aerobic bacilli are found in moist environments and frequently contaminate inadequately chlorinated swimming pools and hot tubs, ventilators, nebulizer and vaporizer solutions, and ophthalmic solution bottles. The organism readily adheres to damaged epithelium. Stromal invasion is rapid.

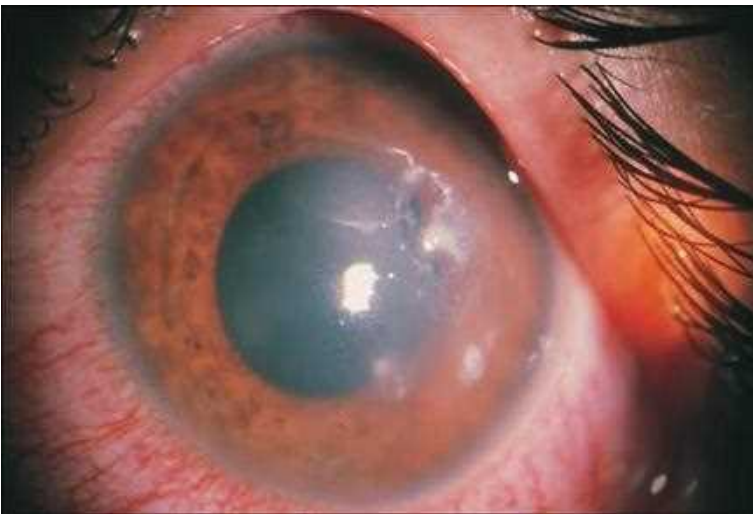
*Pseudomonas* keratitis tends to progress rapidly if inadequately treated. Most commonly, the organism produces destructive enzymes, such as protease, lipase, elastase, and exotoxin, which result in necrotic, soupy ulceration. The organism's surface glycocalyx protects it against phagocytosis and complement attack. The ulcer often extends peripherally and deeply within hours and rapidly can involve the entire cornea (Fig. 4.12.7). Ring ulcers can develop. The corneal epithelium peripheral to the primary ulcer typically develops a diffuse gray, ground-glass appearance. The corneal stroma appears to dissolve into a greenish-yellow mucous discharge that fluoresces under ultraviolet (but not under cobalt blue) light. The suppurative ulcer frequently thins to a descemetocoele that perforates. The ulcer often is associated with a marked anterior chamber reaction and hypopyon formation. Extensive keratitis can extend to the limbus and produce an infectious scleritis.

Less virulent strains follow a more indolent course. Multifocal epithelial infection also can be seen, with multiple intraepithelial gray-white nodules accompanied by a granular-appearing stromal infiltrate and anterior





**Fig. 4.12.7** Infection of the Cornea Caused by *Pseudomonas*. There is liquefying necrosis, advanced central thinning, and hypopyon formation.



**Fig. 4.12.8** Intraepithelial infiltration of the cornea by *Pseudomonas* in a hydrophilic contact lens wearer.

chamber inflammation (Fig. 4.12.8). Diffuse epithelial disease is most commonly seen in association with hydrophilic contact lens wear.

### Serratia

These Gram-negative rods are found in soil, water, food, and the gastrointestinal tract. Keratitis often occurs in association with hydrophilic contact lens wear. The infection may begin as a superficial central or paracentral ulcer that invades the deeper layers of the cornea, producing a deep, ring-shaped keratitis. Exotoxins and protease can produce aggressive ulceration and perforation. Contact lens-associated disease also can present with multiple gray intraepithelial nodules that assume a branching linear pattern, accompanied by a granular-appearing stromal infiltrate and anterior chamber inflammation.

### Escherichia, Klebsiella, and Proteus

Infection by this group of Gram-negative rods is associated with contact lens wear and diseased eyes. The features of corneal infection can be similar to those seen in a virulent pseudomonal infection, with aggressive necrosis, ring ulcer formation, and perforation. Alternatively, the keratitis might be less aggressive with indolent ulceration and a moderate anterior chamber reaction. Suppurative keratitis caused by *Escherichia coli* is typically more indolent but is usually accompanied by severe iridocyclitis and hypopyon formation.

### Moraxella

*Moraxella* species are large, Gram-negative (or Gram-variable) bacilli that are described as having a square “boxcar” shape. They are found in pairs and chains. Moraxella keratitis occurs most frequently in patients with alcoholism and debilitated patients. Marginal ulcers occur in association

with angular blepharoconjunctivitis characterized by a gray, ulcerated infiltrate separated from the limbus by a clear crescent. Central indolent ulcers also occur. These most often develop in the lower half of the cornea as a gray infiltrate that eventually forms an oval-shaped ulcer. The infection tends to extend deeply rather than peripherally and does so slowly. The anterior chamber reaction can be vigorous. Uncommonly, perforation can occur.

### Haemophilus

*Haemophilus influenzae* is a Gram-negative bacillus or coccobacillus that can cause conjunctivitis that leads to keratitis. Infrequently, keratitis has been associated with contact lens wear and chronic corneal disease. The infection usually is superficial but extensive; it can be suppurative and might be associated with a hypopyon.

### Gram-Negative Cocci

#### Neisseria

*Neisseria gonorrhoeae* and *N. meningitidis* are Gram-negative, intracellular diplococci. In corneal and conjunctival scrapings they are found within epithelial cells. In a newborn with ophthalmia neonatorum, gonorrheal conjunctivitis is a significant concern because the organism can invade through an intact epithelium. Corneal infection often is peripheral and can progress to perforation and endophthalmitis. In adults, ocular gonorrhea is accompanied by a copious weeping, hyperpurulent discharge. Keratitis most commonly occurs after prolonged conjunctivitis. The transient, usually peripheral subepithelial infiltrates that might be seen likely represent a type III hypersensitivity reaction. Keratitis is characterized by diffuse edema or a ring ulcer with hypopyon. A significant risk of corneal necrosis and perforation exists.

Meningococcal conjunctivitis also can be complicated by keratitis, although this is less common than with gonococcal conjunctivitis. Typically, the keratitis is multifocal, and a peripheral infiltrate progresses to ulceration.

#### Moraxella (Branhamella) catarrhalis

*Moraxella catarrhalis* is a Gram-negative diplococcus that resembles *N. gonorrhoeae*. However, on smears of the conjunctiva, it is not found within epithelial cells. It can be a constituent of the normal flora of the conjunctiva and is an opportunistic pathogen. Although it can be associated with both neonatal and adult conjunctivitis, it is an infrequent cause of keratitis.

### Mycobacteria

#### Nontuberculous Mycobacteria

Of this group of organisms, the *Mycobacterium abscessus/chelonae* complex and *M. fortuitum* are most commonly associated with ocular disease, although *M. avium-intracellulare* and *M. gordonae* also have been reported to cause infectious keratitis.<sup>11,12</sup> These long rods are acid-fast; that is, they retain red basic fuchsin dye with Ziehl–Neelsen staining. Nontuberculous mycobacteria can grow in disinfectant and are found free in the environment, including soil. Keratitis most commonly follows trauma or surgery and has been associated with penetrating keratoplasty and refractive surgery. These corneal ulcers tend to be indolent and have been confused with mycotic keratitis. The infiltrated base of this typically nonsuppurative ulcer characteristically assumes a “cracked windshield” appearance, with multiple radiating lines. Satellite lesions, immune ring, and endothelial plaque formation might develop as the infection progresses.

### DIAGNOSIS

The presumptive diagnosis of infectious keratitis is based primarily on clinical history and physical examination, but confirmation of infectious infiltration and definitive identification of the offending organism can be achieved only by examining stained smears of corneal scrapings and laboratory cultures of these scrapings. In practice, specific identification of the offending organism and antibiotic sensitivity data are necessary only if they can guide modification of antibiotic treatment if the initial antibiotic regimen fails. Approximately 95% of suspected bacterial ulcers respond favorably to a well-chosen initial antibiotic regimen, so treatment modification rarely is necessary.<sup>13,14</sup> Many practitioners, therefore, defer diagnostic stains and cultures for selected cases of suspected bacterial keratitis. Some evidence exists that small infiltrates that are not associated with advanced suppuration or severe intraocular inflammation respond favorably to this approach.<sup>14</sup> Scrapings are mandatory if the infection is advanced or central



TABLE 4.12.1 Common Culture Media		
Medium	Organism	Comment
Blood agar	Aerobic bacteria Saprophytic fungi	37 °C for bacteria Room temperature for fungi
Chocolate agar	<i>Haemophilus</i> , <i>Neisseria</i> , <i>Moraxella</i>	5%–10% carbon dioxide
Brain–heart infusion (BHI)	Bacteria Fungi	
Sabouraud’s dextrose agar	Fungi	Room temperature
Enriched thioglycollate broth	Aerobic and anaerobic bacteria	Good for small inocula but prone to contamination
Löwenstein–Jensen agar	Nontuberculous mycobacteria	
<i>Escherichia coli</i> plated nonnutrient agar	<i>Acanthamoeba</i>	Transport sample to plate in Page’s saline

TABLE 4.12.2 Stains for Smears and Corneal Scrapings		
Stain	Organism	Comment
Gram	Bacteria, fungi, <i>Acanthamoeba</i> , microsporidia	Stains walls of fungi
Giemsa	Bacteria, fungi, chlamydial inclusions, <i>Acanthamoeba</i> , microsporidia	All stain blue; does not demonstrate intranuclear inclusions; stains fungal cytoplasm
Gomori’s methenamine silver (GMS)	Fungi	Difficult technique
Ink–potassium hydroxide	Fungi	Displays fungal walls
Periodic acid–Schiff (PAS)	Fungi	
Acridine orange	Bacteria, fungi, <i>Acanthamoeba</i>	Requires fluorescent microscope
Calcofluor white	Fungi, <i>Acanthamoeba</i>	Requires fluorescent microscope
Weber	Microsporidia	
Ziehl–Neelsen	Mycobacteria, <i>Nocardia</i> , <i>Actinomyces</i>	

or if history or examination is at all suggestive of filamentous bacterial, nontuberculous mycobacterial, gonococcal, mycotic, or protozoal infection.

When scrapings of corneal ulcers are obtained, material should be taken from the most active regions. The eye is anesthetized with topical anesthetic, and a heat-sterilized platinum spatula or blade is used to firmly scrape the leading edges of the ulcer. Multiple areas of a large ulcer should be sampled. If significant corneal thinning is evident, care must be exercised not to precipitate perforation. Some investigators have reported acceptable organism recovery rates with scrapings performed with a calcium alginate swab moistened with soy broth.<sup>15</sup> Scrapings should be placed on a slide for staining and directly applied to culture media to maximize the chance of recovery.

Commonly used culture media are described in Table 4.12.1. Multiple C-streaks should be used on agar plates because it is often difficult to identify an organism recovered in culture as the offending pathogen, and growth outside of the C-streak might indicate contamination. The most commonly applied stains are Gram and Giemsa stains (Table 4.12.2). Gram stain is useful to identify bacteria and yeasts. Giemsa stain is useful for cytology and to identify bacteria (all stain blue), fungi, and chlamydial inclusions. If filamentous bacterial or nontuberculous mycobacterial infection is suspected, Ziehl–Neelsen staining should be performed. Molecular diagnosis of bacterial keratitis is possible with polymerase chain reaction assays targeting 16S ribosomal RNA; however, this approach is limited by false positives, presumably from normal ocular surface flora.<sup>16</sup>

Corneal biopsy is indicated when an apparent infection fails to resolve in spite of antimicrobial treatment, when the identity of the organism is in doubt or when conventional scrapings have failed to demonstrate a reasonably culpable organism.<sup>17</sup> Corneal stromal biopsy is sometimes necessary to identify protozoan, mycobacterial, or mycotic organisms. As with corneal scrapings, the corneal biopsy specimen should incorporate the active edge and base of the ulcer. If the infiltrate is sequestered within the stroma, a lamellar technique is required. Tissue obtained through biopsy should be sectioned, with a portion submitted to the pathologist for microscopic examination, and a portion used for direct inoculation of plates and broth for culture and sensitivity studies.

BOX 4.12.1 Differential Diagnosis of Corneal Infiltration and Ulceration

- Infectious**
  - Bacteria
  - Fungi
  - Parasites
    - *Acanthamoeba*
    - *Microsporidiosis*
    - *Onchocerciasis*
  - Viruses
    - Herpes simplex virus
    - Varicella-zoster virus
    - Epstein–Barr virus
    - Measles
    - Mumps
  - Spirochetes
    - Syphilis
    - Lyme disease

**Noninfectious**
  - Chronic epithelial defect
  - Autoimmune disease
  - Rheumatoid arthritis
  - Mooren’s ulcer
  - Terrien’s marginal degeneration
  - Staphylococcal marginal disease
  - Phlyctenulosis
  - Contact lens–related infiltration
  - Vernal keratoconjunctivitis (shield ulcer)
  - Smokable drug–induced
  - Anesthetic abuse
  - Xerophthalmia, keratomalacia

DIFFERENTIAL DIAGNOSIS

See Box 4.12.1.

SYSTEMIC ASSOCIATIONS

Mechanisms that protect the cornea from infection involve both mechanical and immunological strategies. Systemic conditions that affect the mechanical protective function of the lids as a result of lagophthalmos or reduced blinking include chronic alcoholism, dementia, parkinsonism, general anesthesia, and coma. Bullous conditions that affect both skin and eye, such as erythema multiforme and ocular cicatricial pemphigoid, are associated with an increased risk of infectious keratitis not only because of lagophthalmos but also because of inflammatory cicatricial conjunctival changes. Patients with human immunodeficiency virus infection are more likely to develop infectious keratitis and have a more fulminant presentation, presumably as a result of impaired local immune defenses.<sup>1,18</sup> Malnutrition and conditions caused by vitamin deficiency, such as xerophthalmia and scurvy, appear to increase the risk of posttraumatic infection.

PATHOLOGY

Histopathologically, bacterial keratitis is characterized by inflammation, necrosis, and angiogenesis. Bacteria and host each contribute to the inflammatory response. Although virulence factors are specific to each organism, bacteria generally produce a variety of toxins and proteases that result in degradation of connective tissue and host defense factors, and necrosis.<sup>19</sup> Corneal infection results in recruitment of inflammatory cells, with a predominance of polymorphonuclear leukocytes (PMNs) that arrive initially via the tear film and later via proliferating limbal blood vessels. PMNs not only phagocytize bacteria and necrotic stroma but also release lysosomal enzymes that contribute to stromal necrosis and corneal thinning. If the bacterial population overwhelms the cornea’s protective mechanisms or if the necrosis progresses unchecked, corneal perforation and possibly endophthalmitis will result. However, if the infection is brought under control, the infiltrate will decrease in size and the epithelium will heal over the ulcer. Scar tissue is produced by activated keratocytes and transformed histiocytes. Angiogenesis might be stimulated by the inflammation, but these vessels usually regress with time.

TREATMENT

Infectious keratitis should be considered an ocular emergency. Antibiotic therapy must be initiated promptly.<sup>20</sup> Topical administration is the route of choice because it provides rapid, high levels of drug in the cornea and anterior chamber (Table 4.12.3). Subconjunctival injection may be helpful in cases with scleral spread or in patients unable to instill frequent eyedrops. Systemic administration results in relatively low antibiotic levels in the cornea and is generally advised only when keratitis is complicated by scleritis or a risk of perforation or endophthalmitis exists.<sup>21</sup> Antibiotic-soaked collagen shields enhance topical delivery in animal models, but the clinical usefulness of this method has not been established.<sup>22</sup> Severe or central ulcers are typically treated with a loading dose (e.g., every 5–15 minutes for the first hour) followed by application every 30–60 minutes. If a combination of two antibiotics is prescribed, the drops

TABLE 4.12.3 Commonly Used Antibiotics for the Treatment of Bacterial Keratitis

Antibiotic	Concentration	Route	Activity
<b>Aminoglycosides</b>			Gram-negatives, staphylococci, some streptococci (not pneumococcus)
Amikacin	20–50 mg/mL 50 mg/mL	Topical Subconjunctival	Also active against nontuberculous mycobacteria
Gentamicin	14 mg/mL 40 mg/mL	Topical Subconjunctival	
Tobramycin	14 mg/mL 40 mg/mL	Topical Subconjunctival	
<b>Cephalosporins</b>			Active against Gram-positive organisms and some Gram-negative bacilli
Cefazolin	50–100 mg/mL 200 mg/mL	Topical Subconjunctival	
<b>Fluoroquinolones</b>			Active against Gram-negatives, fair to good against Gram-positives
Besifloxacin	6 mg/mL	Topical	
Ciprofloxacin	3 mg/mL	Topical	
Gatifloxacin	3 mg/mL	Topical	
Levofloxacin	5–15 mg/mL	Topical	
Moxifloxacin	5 mg/mL	Topical	
Ofloxacin	3 mg/mL	Topical	
<b>Penicillins</b>			
Penicillin G	100 000 U/mL 1 000 000 U/mL	Topical Subconjunctival	Active against nonpenicillinase-producing Gram-positive organisms
Methicillin	50 mg/mL 200 mg/mL	Topical Subconjunctival	Active against penicillinase-producing Gram-positive organisms
Piperacillin	7 mg/mL 200 mg/mL	Topical Subconjunctival	Active against Gram-positives and some Gram-negatives, including <i>Pseudomonas</i>
<b>Vancomycin</b>	33 mg/mL 100 mg/mL	Topical Subconjunctival	Active against Gram-positive organisms, including methicillin-resistant staphylococci

are given in an alternating fashion. Subsequent reductions are dictated by the response of the infection.

Initially, empirical topical therapy should be instituted with a broad-spectrum antibiotic regimen.<sup>23</sup> The most commonly used regimens include fluoroquinolone monotherapy or combination therapy with a cephalosporin and aminoglycoside; these two regimens are thought to have similar efficacy in most cases, with approximately 90% of cases responding to therapy (see Table 4.12.3).<sup>13,24</sup>

Fluoroquinolone antibiotics demonstrate excellent activity against Gram-negative organisms and good to excellent activity against Gram-positive organisms. Of the commercially available ophthalmic fluoroquinolones, the newer agents (levofloxacin, moxifloxacin, gatifloxacin, and besifloxacin) offer enhanced Gram-positive coverage compared with the older agents (ofloxacin and ciprofloxacin).<sup>25</sup> Ciprofloxacin remains the fluoroquinolone of choice for *P. aeruginosa*. Although fluoroquinolone monotherapy is thought to be effective in most cases, emerging resistance has been noted for several organisms responsible for infectious keratitis, including *P. aeruginosa* and *S. aureus*.<sup>26,27</sup> Therefore, fluoroquinolone monotherapy should be applied with great caution and with careful observation for a clinical response.

The aminoglycosides most commonly used for the treatment of infectious keratitis are gentamicin and tobramycin. Both are prepared at a “fortified” concentration of 9–20 mg/mL. These antibiotics provide excellent Gram-negative coverage and also are active against staphylococci and some streptococci but not against pneumococci. Tobramycin may be more active than gentamicin against *P. aeruginosa*.<sup>28</sup> Amikacin is a semisynthetic aminoglycoside that is useful in the treatment of Gram-negative organisms resistant to gentamicin and tobramycin, as well as nontuberculous mycobacterial organisms. Because infectious keratitis following refractive surgery often is caused by mycobacteria, amikacin may be given empirically in this situation.<sup>29</sup> Aminoglycosides tend to inhibit epithelial wound healing and can cause a punctate epitheliopathy.

The cephalosporins are a class of beta-lactam antibiotics with efficacy against Gram-positive organisms and some Gram-negative bacilli, such as *E. coli*, *Klebsiella*, and *P. mirabilis*. Cefazolin, a first-generation cephalosporin, is relatively nontoxic to the corneal epithelium, and the agent most commonly used for treatment of infectious keratitis. A third-generation agent, ceftazidime, has efficacy against *P. aeruginosa* and is an option for resistant cases.

The penicillins are effective against many Gram-positive organisms, such as streptococcal and staphylococcal species, as well as gonococcal and some anaerobic species. However, many staphylococcal strains produce beta-lactamase, which inactivates penicillin. Moreover, approximately 10% of patients have an allergic reaction to penicillins. The penicillin and penicillin-derived antibiotics can be administered both topically and subconjunctivally.

Vancomycin is a useful agent against staphylococcal organisms when cephalosporins are ineffective or poorly tolerated. Vancomycin is a glycopeptide antibiotic with activity against methicillin-resistant staphylococci and other Gram-positive organisms. However, to minimize the development of resistance, empirical therapy should be used judiciously.<sup>30</sup>

Empiric therapy may need to be altered depending on the results of microbiological tests. Keratitis caused by *Neisseria gonorrhoeae* should be treated systemically with a single dose of intramuscular ceftriaxone, and the patient should be given systemic azithromycin or doxycycline for possible chlamydial co-infection.<sup>31</sup> In addition, patients with gonococcal keratitis should have the conjunctival sac irrigated frequently with normal saline, followed by topical administration of a fluoroquinolone antibiotic solution. Keratitis caused by *N. meningitidis* should prompt empiric therapy with a third-generation cephalosporin, which can be changed to penicillin depending on the results of susceptibility testing. Actinomyces infections generally have poor in vitro susceptibility to aminoglycosides and fluoroquinolones, and usually are treated with topical sulfacetamide or penicillin, as well as with subconjunctival penicillin. Nocardia keratitis is typically treated topically with amikacin or a sulfonamide, and oral trimethoprim and sulfamethoxazole for cases that progress on topical therapy.<sup>32</sup> Nontuberculous mycobacterial keratitis has been successfully treated with fluoroquinolone antibiotics, although in general the susceptibilities of amikacin and clarithromycin are superior to those of the fluoroquinolones.<sup>12</sup> Prolonged therapy of these recalcitrant mycobacterial infections often is needed, and in certain cases, lamellar or penetrating keratoplasty might be necessary.

If antibiotic susceptibility testing is available, these data can be used as a relative guide in choosing antibiotics that might have a higher probability of eradicating the offending microbe. Antibiotic sensitivities are most commonly measured by disc diffusion or serial dilution methods. These tests typically report the susceptibility of the bacterial isolate to each tested drug based on the minimum inhibitory concentration (MIC), which is the lowest concentration of antibiotic that inhibits bacterial growth. However, it is important to recognize that most laboratories base the definition of resistance on MIC thresholds that have been established for the expected serum concentration of the antibiotic. With frequent ophthalmic application of a topical antibiotic preparation, relatively high corneal concentrations of many antibiotics can be established; therefore, organisms cultured from a corneal infiltrate may be reported as “resistant” to a particular antibiotic but respond to treatment because of the effect of high local concentration.<sup>33</sup> Nonetheless, higher MICs are associated with larger corneal scars and worse visual acuity, which suggests that tailoring therapy based on MIC may be of benefit.<sup>34</sup>

If a single antibiotic is chosen initially and is effective in treating the infection, there is seldom a reason to change therapy. If a combination of antibiotics is initially effective, administration of the less effective (by susceptibility studies) of the two often can be halted after a few days. Fortified preparations can be replaced by commercial preparations, and the frequency of application can be gradually tapered. Treatment should be continued at least until the epithelium has completely healed. *Pseudomonas aeruginosa* can reappear after apparent resolution if treatment is halted early; antibiotic administration should be maintained for at least a week after epithelial healing.

The initial sign of effective treatment is failure of the infiltrate to worsen; however, it is not uncommon for ulcers to initially worsen before stabilizing, even with an effective initial antibiotic regimen. The early signs of a resolving infection include stabilization of the area and depth of the infiltrate and reduced activity at the infiltrate’s margins. Signs of continuing improvement include progressive healing of the epithelial defect, clearing of the infiltrate, reduced corneal edema adjacent to the infiltrate, and decreasing inflammation and anterior chamber reaction. It is important to

note that corneal stromal necrosis might progress in spite of effective antimicrobial treatment because of the lytic activity of immigrant leukocytes. In addition, immunological ring infiltrates can appear many days after the initiation of effective antimicrobial treatment and might be erroneously interpreted to indicate worsening of the infection.

If the corneal ulcer fails to improve, corneal scraping should be performed (or repeated) for smear and culture. In the case of indolent infections, antibiotic treatment might be interrupted for 24–48 hours to decrease the inhibitory effect of antibiotic treatment and, thus, increase the probability of recovering the organism. If no organism is recovered in bacterial culture and the disease worsens, noninfectious and nonbacterial causes of ulcerative keratitis must be considered (see Box 4.12.1). Appropriate cultures for nontuberculous mycobacteria, fungi, and protozoal organisms should be obtained. If repeat cultures are negative and the ulcer does not improve, corneal biopsy might be necessary. When obtaining corneal biopsy, the specimen should be sent for both microbiological and histopathological evaluation.<sup>17</sup>

Besides antimicrobial therapy, adjunctive treatments have been employed in an effort to minimize the adverse sequelae of corneal infection, such as perforation, vascularization, and scarring. Corticosteroids can be used to suppress the inflammatory response that leads to these adverse sequelae. Corticosteroids reduce the host inflammatory response, thereby improving patient comfort and theoretically resulting in less stromal scarring. However, corticosteroids also have been shown to delay re-epithelization of corneal ulcers, and if antibiotic therapy is inadequate, to promote bacterial replication.<sup>35</sup> The Steroids for Corneal Ulcers Trial (SCUT) was a randomized placebo-controlled trial that found that topical corticosteroid therapy started after at least 48 hours of antibiotics did not significantly improve visual acuity at 3 months, although corticosteroids were associated with improved vision in the most severe ulcers.<sup>36</sup> The rate of corneal perforation was similar in the two treatment groups. Subgroup analyses produced similar findings for pseudomonal ulcers, but not for *Nocardia* ulcers, which had significantly worse outcomes with corticosteroid treatment.<sup>37,38</sup> A secondary analysis of SCUT found that corticosteroids significantly improved 3-month visual acuity if started within 3 days of initiating antibiotic therapy, but had no effect if the delay was 4 days or later.<sup>39</sup> This suggests that corticosteroids may be safely used for non-*Nocardia* bacterial keratitis to reduce pain and inflammation and that severe ulcers given prompt corticosteroid therapy may even have a benefit in visual outcomes. However, corticosteroids should not be used if there is any suspicion of fungal or amoebic keratitis, or if doubt exists about the efficacy of the antimicrobial regimen. Nonsteroidal anti-inflammatory agents might help reduce the adverse sequelae of infectious inflammation, but, again, they should be used only in the presence of effective antimicrobial treatment.<sup>40</sup> Cycloplegic agents are useful in reducing discomfort caused by ciliary body spasm and can be used periodically to decrease synechiae formation. Finally, *in vitro* studies have suggested that stromal necrosis may be prevented by several potential collagenase inhibitors, including acetylcysteine, citrate, and doxycycline.<sup>41</sup> The clinical utility of these collagenase inhibitors, however, remains unclear.

Surgical intervention is warranted when necrosis progresses to perforation or impending perforation and may be considered for corneal ulcers that are unresponsive to medical therapy. For small perforations without extensive surrounding necrosis, cyanoacrylate glue can be applied (Fig. 4.12.9). Small perforations also have been successfully managed with fibrin glue and multilayered amniotic membrane grafts.<sup>42</sup> If the perforation is large or necrosis is extensive, corneal transplantation might be necessary. The choice between a small-diameter patch graft and a large-diameter graft and between a penetrating procedure and a lamellar procedure depends on the size, depth, and location of the ulcer. Deep anterior lamellar keratoplasty is an option for corneas that have not yet perforated; this technique may reduce the risk of graft failure and appears to have similar rates of disease recurrence compared with penetrating keratoplasty.<sup>43</sup> Therapeutic keratoplasty can result in favorable surgical outcomes, although the procedure can be complicated by the difficulties involved in operating on a perforated globe, concurrent infection, and inflammation that threatens graft success. Conjunctival flaps can be used to treat infections that fail to improve with medical therapy; this strategy might be especially useful in peripheral infectious ulceration. The vascularized conjunctival tissue helps admit blood vessels that aid in healing and scarring. Conjunctival flaps should not be placed over a corneal perforation.



**Fig. 4.12.9** Bacterial infection leading to central necrosis, thinning, and perforation, sealed with cyanoacrylate tissue adhesive.

## OUTCOME

The visual outcomes of bacterial keratitis vary greatly. In general, the most important predictor of final visual outcome is the visual acuity at diagnosis; patients with worse vision at diagnosis will have worse vision after the ulcer has healed.<sup>44</sup> Relatively small infiltrates that do not involve the central cornea might leave stromal scarring that is only faintly discerned on slit-lamp microscopy and has no visual consequence; more extensive ulceration and infiltration can result in significant scarring and irregular astigmatism. Residual scarring is thought to cause vision loss by blocking light, causing light scatter, and/or inducing irregular astigmatism. Persistent anterior stromal scars can sometimes be removed by excimer laser phototherapeutic keratectomy, but deeper scars require lamellar or penetrating keratoplasty. In the absence of significant opacification, irregular astigmatism is best treated with a rigid contact lens. Corneal inflammation can lead to neovascularization; these vessels may regress with time, and regression might be aided by corticosteroid therapy. Ocular inflammation also can lead to synechiae formation, elevated intraocular pressure, and cataract.

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# Fungal Keratitis

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4.13

**Definition:** Corneal disease caused by fungal organisms.

## Key Feature

- Cellular infiltration of the corneal epithelium or stroma, corneal inflammation, and necrosis.

## Associated Features

- Long-term corticosteroid use.
- Trauma involving vegetative matter.
- Corneal infiltrate with feathery borders or satellite lesions.

## INTRODUCTION

Fungal infections of the cornea are relatively infrequent in the developed world but cause a large proportion of keratitis in many parts of the developing world. Although these infections can cause devastating damage if allowed to progress unchecked, advances in antimicrobial therapy and surgical technique have improved their prognosis. Recognition and prompt, aggressive therapy of fungal infections are extremely important.

## EPIDEMIOLOGY AND PATHOGENESIS

Fungi are ubiquitous organisms that are recognized more frequently as ocular pathogens in agrarian, tropical countries than in the developed world. For clinical purposes, fungi can be classified on a morphological basis into filamentous, yeast, and diphasic forms. Filamentous organisms are multicellular with branched hyphae. Septate filamentous organisms, such as *Fusarium* and *Aspergillus*, have hyphae that are divided by cell walls. Other filamentous fungi, including *Mucor* and *Rhizopus*, are nonseptate. Septate filamentous fungi can be further divided into nonpigmented hyaline species (e.g., *Fusarium*, *Aspergillus*) and pigmented dematiaceous species (e.g., *Alternaria*, *Curvularia*). Yeasts, such as *Candida* and *Cryptococcus*, are unicellular fungi that reproduce by budding, but in tissue, they might develop elongated buds (pseudo-hyphae) or real hyphae. Dimorphic fungi, such as *Histoplasma*, *Coccidioides*, and *Blastomyces*, demonstrate both a yeast phase that occurs in tissues and a mycelial phase that appears on culture media and saprophytic surfaces.

The incidence of fungal keratitis in the United States has historically been quite low, but rates of *Fusarium* keratitis increased dramatically in the mid-2000s because of an epidemic related to a contact lens solution.<sup>1</sup> Although the rate of *Fusarium* keratitis decreased after the solution was withdrawn from the market, microbiology laboratories have continued to detect elevated numbers of filamentous fungi. Fungal keratitis is more common in tropical climates. In these areas, septate filamentous fungi, most notably *Fusarium* and *Aspergillus*, are the most common causative organisms. In contrast, *Candida* is the predominant cause in more temperate climates.

The risk factors associated with fungal keratitis depend on the setting.<sup>2</sup> In the tropics, corneal trauma, which might be trivial, frequently precedes infection. Concurrent contamination with plant material presents an increased risk for fungal keratitis. However, in colder climates, where *Candida* infections predominate, fungal infections are more commonly seen in patients with corneal pathology or with an ocular surface that is locally immunosuppressed by chronic corticosteroid use or systemic disease.

## CLINICAL FEATURES

Fungal infection tends to arise in traumatized, diseased, and immunocompromised corneas. The keratitis tends to be slowly progressive and insidious, but rapid infiltrate development does not rule out fungal infection. In some cases, the epithelium might heal over an intrastromal infiltrate that produces little inflammation and minimal discomfort. Conversely, inflammation might be so severe as to result in satellite lesions and hypopyon formation. The ulcer and infiltrate itself can assume protean appearances and might be indistinguishable from a bacterial ulcer. However, certain features suggest a filamentous fungal infection, including feathery edges or a dry, gray, elevated infiltrate and satellite lesions (Fig. 4.13.1).<sup>3</sup> Compared with other fungal pathogens, *Aspergillus* may be more likely to have a ring infiltrate, and dematiaceous fungi may be more likely to have a pigmented or raised infiltrate.<sup>4,5</sup> Although a ring infiltrate and endothelial plaque are suggested as indicators of fungal keratitis, many cases do not demonstrate these features, which merely reflect corneal and anterior chamber inflammation.

## DIAGNOSIS

A high level of suspicion for nonbacterial keratitis must be maintained at all times, especially in those areas where the incidence of fungal keratitis is relatively high (Fig. 4.13.2). Important historical elements include pre-existing corneal disease, chronic corticosteroid use, trauma, contact lens wear, and recent surgery, including laser-assisted in situ keratomileusis (LASIK).<sup>6</sup>

Definite diagnosis requires laboratory confirmation. Scrapings for stains and culture should be obtained as described for bacterial keratitis. If fungal infection is suspected after LASIK, the flap must be elevated to obtain samples. Smear diagnosis is primarily made with Giemsa or ink-potassium hydroxide stains, though fungal elements are also visible on Gram stain (Fig. 4.13.3). Gomori's methenamine silver stain is generally considered the stain that best demonstrates fungal organisms.

Culture media used to demonstrate fungal growth include Sabouraud's agar, potato dextrose agar, and brain-heart infusion broth, although many fungi will grow on blood agar kept at room temperature. Most ocular

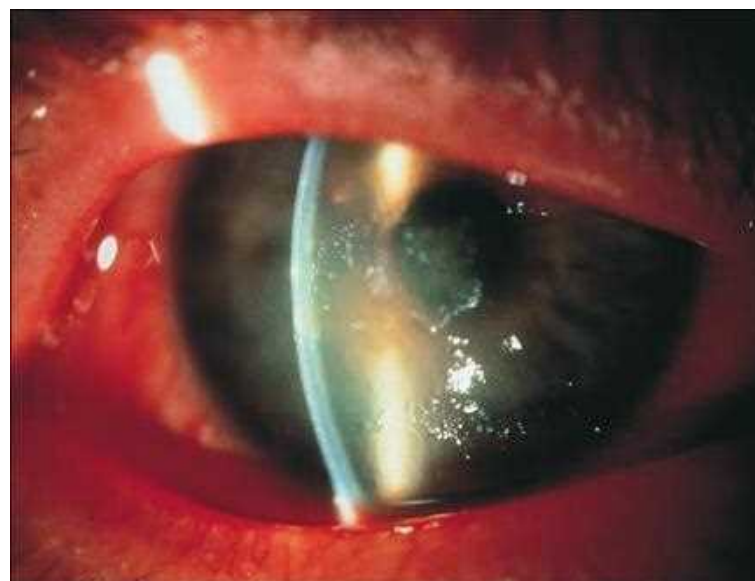
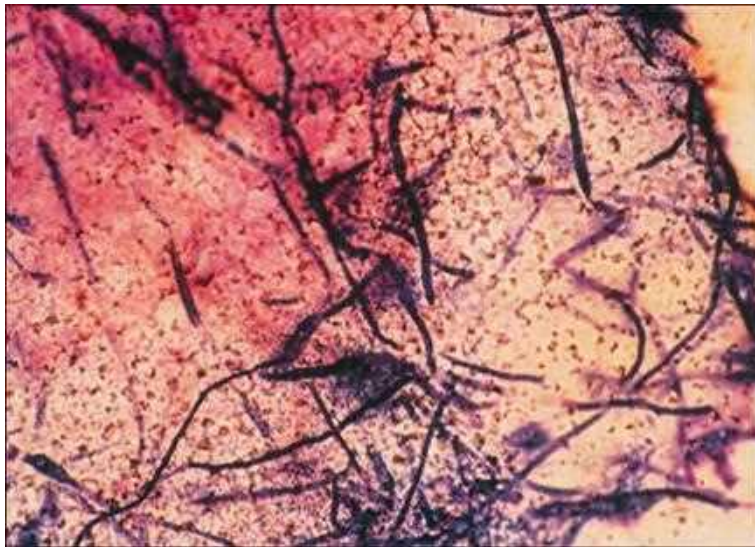


Fig. 4.13.1 Feathery stromal infiltrates typical of fungal keratitis.



**Fig. 4.13.2** *Fusarium* fungal keratitis.



**Fig. 4.13.3** Gram stain of scraping from corneal ulcer caused by *Fusarium* demonstrating branching fungal hyphae.

fungal isolates demonstrate growth within 2–3 days, although it is prudent to wait 2 weeks before confirmation of no growth. Fungal susceptibility criteria are poorly standardized and not performed at most laboratories.

Corneal scrapings can be investigated with polymerase chain reaction techniques that target a common fungal ribosomal RNA (rRNA), although the high sensitivity of these methods carries the risk of false positives because of contamination, either at the site of corneal scraping or in the laboratory.

In vivo confocal microscopy can be used to detect fungal hyphae and is particularly useful for diagnosis of deep infections that cannot easily be scraped.<sup>7</sup> Fungal filaments appear as highly reflective double-walled structures measuring between 3 and 8  $\mu\text{m}$ .<sup>8</sup>

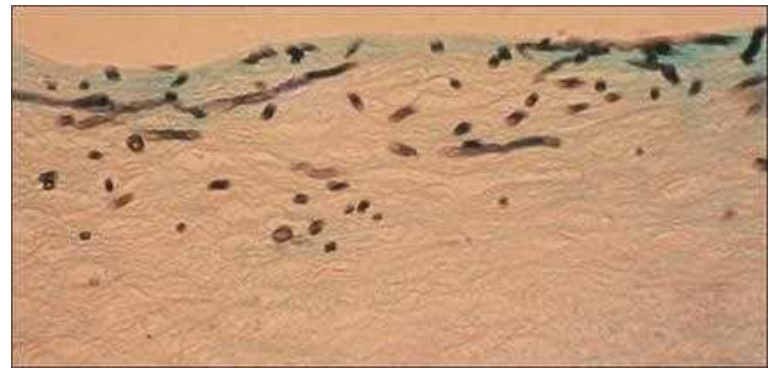
Since some cases of keratitis may develop deep in the stroma with intact overlying corneal tissue, a deep corneal biopsy might be necessary to obtain tissue for laboratory studies (Fig. 4.13.4).

## DIFFERENTIAL DIAGNOSIS

For the differential diagnosis of fungal keratitis, see Box 4.12.1. As a result of indolent progression and failure to respond to antibacterial medication, fungal keratitis often is misdiagnosed as herpetic or amebic disease. Fungal infection following LASIK must be differentiated from the sterile interface infiltration of post-LASIK diffuse lamellar keratitis and from infection caused by bacterial species.

## SYSTEMIC ASSOCIATIONS

Fungal keratitis caused by less virulent organisms, such as *Candida*, often is associated with conditions that lead to immunocompromise, such as



**Fig. 4.13.4** Keratoplasty specimen demonstrating fungal infiltration of the anterior stroma and inflammatory cells.

**TABLE 4.13.1** Antifungals

Agent	Route	Dosage/Concentration
<b>Polyenes</b>		
Amphotericin B	Topical Subconjunctival Intracameral	0.15% 0.5–1 mg 7.5–10 $\mu\text{g}$ in 0.1 mL
Natamycin	Topical suspension	5%
<b>Imidazoles</b>		
Clotrimazole	Topical	1%
Econazole	Topical	2%
Ketoconazole	Topical Oral	5% 300 mg/day
Miconazole	Topical suspension Topical cream Subconjunctival	1% 2% 5–10 mg
<b>Triazoles</b>		
Fluconazole	Topical Oral	0.2% 200 mg/day
Itraconazole	Topical Oral	1% 100–200 mg twice daily
Voriconazole	Topical Oral Intracameral Intrastromal	1% 200 mg twice daily 100 $\mu\text{g}$ in 0.1 mL 50 $\mu\text{g}$ in 0.1 mL
Posaconazole	Oral	200 mg four times daily
<b>Pyrimidines</b>		
Flucytosine	Topical Oral	2% 50–150 mg/kg/day divided twice daily
<b>Echinocandins</b>		
Caspofungin	Topical	0.5%
Micafungin	Topical	0.1%

alcoholism, diabetes, and vitamin A deficiency. Fungal keratitis is not associated with systemic fungemia.

## PATHOLOGY

Destructive fungal infection is advanced by organism adherence, invasion, growth, and subsequent damage caused by direct toxicity and host response. The mycelia of filamentous organisms tend to extend along the corneal lamellae, whereas more virulent organisms can cross lamellae and even penetrate Descemet's membrane, leading to intracameral infection.<sup>9,10</sup> The inflammatory host response is similar to that described in bacterial infection, with both mycotic and host factors leading to an inflammatory cell infiltrate, necrosis, and neovascularization.

## TREATMENT

The efficacy of currently available antifungal agents is limited, and a relatively high medical treatment failure rate exists. The agents most commonly used for fungal keratitis include the polyenes and azoles (Table 4.13.1).

Polyene medications, such as amphotericin B, natamycin, and nystatin, bind to fungal cell wall ergosterol, thus disrupting the cell. The polyenes are effective against both filamentous and yeast forms. Amphotericin B is



particularly effective against yeasts and is the agent of choice for keratitis caused by *Candida* species, but it is less effective against filamentous organisms. Natamycin is effective against yeasts and has a broad spectrum of activity against filamentous organisms. The polyenes do not penetrate well through in an intact corneal epithelium.<sup>11</sup> Periodic debridement of the cornea may enhance penetration of topical medications, although it is unclear that debridement results in better outcomes.<sup>12</sup>

Azole medications, which include the imidazoles (e.g., miconazole, clotrimazole, and ketoconazole) and the triazoles (e.g., fluconazole, itraconazole, posaconazole, and voriconazole) inhibit synthesis of ergosterol in the cell wall. Azoles generally have good activity against yeasts but have more variable activity against filamentous organisms. Voriconazole has good corneal penetration when given topically, and good intraocular concentrations when given orally. Voriconazole can be administered as an intracameral or intrastromal injection.<sup>13</sup> Potential adverse effects of oral voriconazole include visual phenomena and hepatotoxicity; liver function therefore should be monitored.

Other antifungal agents have a role for treatment of fungal keratitis. The pyrimidine flucytosine blocks fungal thymidine synthesis. Flucytosine is well absorbed when administered orally, and it also can be applied as a topical solution. Echinocandins, such as caspofungin and micafungin, inhibit beta-glucan in cell walls and have shown promise as a topical therapy for fungal keratitis.

Once the diagnosis has been made, fungal keratitis should be treated with frequently applied topical antifungal medication. An oral triazole should be considered for deep stromal infection. Ulcers are typically treated with a loading dose (e.g., every 5–15 minutes for the first hour) followed by application every 30–60 minutes. The frequency of applications is reduced on the basis of clinical response. Intracameral injections of amphotericin B or voriconazole can be administered for infections that have penetrated Descemet's membrane.

The Mycotic Ulcer Treatment Trial (MUTT) was a randomized controlled trial that found that fungal ulcers randomized to natamycin had better vision at 3 months compared with those randomized to voriconazole—a result driven largely from the efficacy of natamycin among *Fusarium* ulcers.<sup>14</sup> A companion trial found no benefit to oral antifungal therapy: in MUTT II, fungal ulcers were treated with topical therapy and randomized to oral voriconazole or placebo. After 3 months, the rate of perforation or therapeutic keratoplasty was not significantly different between the voriconazole and placebo groups.<sup>15</sup>

Because these infections can be tenacious, and host suppression of infection is very important, corticosteroid use is generally not recommended in the management of fungal keratitis. However, patients who are already using corticosteroids at the time of diagnosis should have their medication gradually tapered off because abrupt cessation of corticosteroid therapy can result in an intense host inflammatory response leading to perforation.<sup>16</sup> The propensity for corticosteroids to enhance microbial viability can present a particular dilemma for the treatment of fungal infection in a corneal graft. In vitro studies have suggested that topical cyclosporine A might possess antifungal properties, and this agent has been used as an alternative for reducing inflammation and the subsequent risk of graft failure in the setting of fungal graft infection.<sup>17</sup>

The course of treatment is typically protracted. Antifungal treatment is usually maintained over 12 weeks, with strict vigilance as medicines are tapered. If fungal keratitis fails to respond to medical therapy, surgical intervention should be considered. Because of the propensity for fungal elements to invade deeply and, in some cases, penetrate Descemet's membrane, advanced cases require penetrating keratoplasty to ensure complete removal of the invading fungus. In general, penetrating keratoplasty should be performed sooner rather than later to maximize the probability of a graft margin free of infection and to minimize the risk of endophthalmitis or infectious scleritis. As generous a clear margin as possible should be included in the excised cornea.<sup>18</sup> Less advanced cases might be amenable to lamellar keratoplasty, but the surgeon must be confident that the entire infection has been encompassed by the lamellar dissection. If there is any question about the depth of infection, the procedure should be converted to a full-thickness penetrating excision.<sup>19</sup>

## OUTCOME

Patients with deep stromal infection and those treated with corticosteroids appear to respond particularly poorly to medical therapy. Medical failure occurs in approximately 15%–20% of cases.<sup>12</sup> Although penetrating keratoplasty can successfully eliminate the organism and restore the integrity of the eye, a delay in surgery or advanced disease might allow catastrophic extension of infection to the anterior chamber and sclera, especially in the case of preoperative topical corticosteroid use, perforation, or limbal involvement.<sup>20</sup>

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# Parasitic Keratitis

Jeremy D. Keenan, Stephen D. McLeod

# 4.14

**Definition:** Corneal disease caused by protozoal organisms.

## Key Feature

- Cellular infiltration of the corneal epithelium or stroma, corneal inflammation, and necrosis.

## Associated Features

- Delay in diagnosis is common.
- Pain may be greater than physical findings.
- Early cases may demonstrate pseudo-dendrites.
- Later cases may show ring infiltrate in the cornea.

## INTRODUCTION

Parasitic infections of the cornea are a significant cause of ocular morbidity. *Acanthamoeba* keratitis is increasingly recognized in the developed world as a potentially disastrous complication of contact lens wear and requires early, aggressive treatment. *Onchocerca* infection is still encountered in some parts of the developing world.

## ACANTHAMOEBA KERATITIS

### Epidemiology and Pathogenesis

*Acanthamoebae*, found ubiquitously in water, soil, and air, are free-living protozoans that exist in an active trophozoite form and a dormant cyst form. The trophozoite feeds on microorganisms and reproduces by binary fission, but if deprived of a food source, it will encyst. Cysts are resistant to desiccation, temperature extremes, and various chemicals and can remain dormant for years. *Acanthamoebae* are typically speciated according to morphological characteristics, although they can also be classified into one of 15 genotypes. The vast majority of keratitis is caused by the T4 genotype.<sup>1</sup>

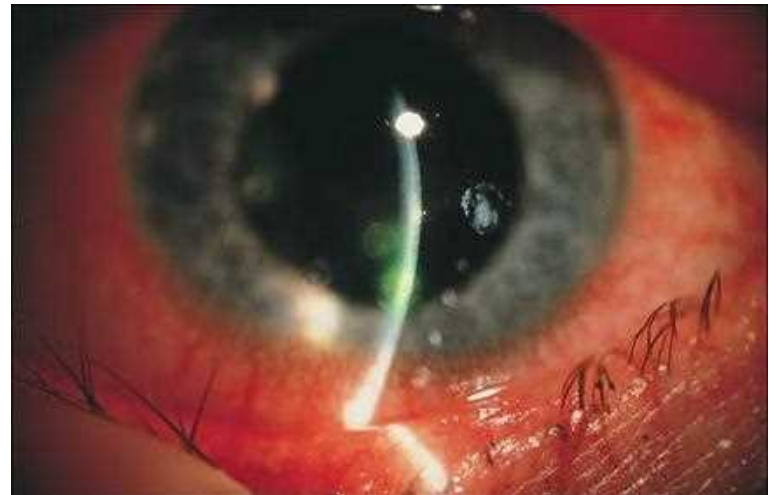
Keratitis caused by *Acanthamoeba* is less common than that caused by bacteria or fungi, although the incidence of *Acanthamoeba* keratitis increased in the United States for several years in the mid-2000s because of an epidemic related to a contact lens solution.<sup>2</sup> The biggest risk factor for *Acanthamoeba* keratitis in the developed world is contact lens wear, with approximately 90% of cases occurring in contact lens wearers.<sup>3</sup> Most cases are seen in soft contact lens wearers, although orthokeratology may convey increased risk. Trauma is the other major risk factor and accounts for the vast majority of *Acanthamoeba* keratitis seen in developing countries.<sup>4</sup> Other risk factors include exposure to water, especially fresh water sources, swimming pools or hot tubs, and homemade contact lens solutions.

### Clinical Features

Since a delay in treatment has been shown to adversely affect visual outcome, clinicians must be acutely aware of the sometimes subtle early signs of *Acanthamoeba* infection. Early infection is confined to the epithelium, which demonstrates irregularity and multifocal infiltration, pseudo-dendrites, or elevated epithelial ridges (Fig. 4.14.1). Stromal radial perineuritis is thought to be very specific for *Acanthamoeba* keratitis, although it does not appear in many cases (Fig. 4.14.2). Limbitis is common, and may account for significant pain. Later stages of infection are characterized by nonspecific stromal infiltration (Fig. 4.14.3) or a



**Fig. 4.14.1** Epithelial ridges seen in *Acanthamoeba* keratitis. (Courtesy Joel Sugar, MD.)

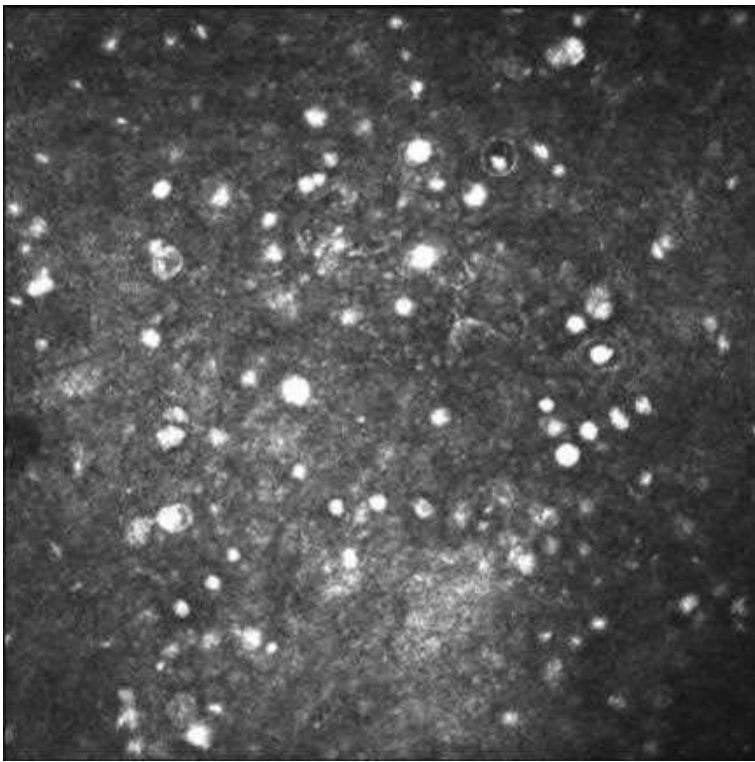


**Fig. 4.14.2** Perineuritis seen in *Acanthamoeba* keratitis. (Courtesy Joel Sugar, MD.)



**Fig. 4.14.3** Ring infiltrate in corneal *Acanthamoeba* infection.





**Fig. 4.14.4** Double-walled and bright spot cystic structures on confocal microscopy.

characteristic ring infiltrate (Fig. 4.14.4), and uveitis.<sup>5</sup> When present, fluctuating, nongranulomatous anterior chamber inflammation may contribute to the formation of cataract or elevated intraocular pressure. In the most severe cases, hypopyon, anterior scleritis, or perforation (sometimes associated with optic neuritis) can occur.<sup>6</sup>

It has been reported frequently that patients experience severe pain far out of proportion to clinical findings, but this is an unreliable diagnostic sign, and some patients have reduced or absent corneal sensation.

## Diagnosis

Diagnosis is based on characteristic clinical findings and supported by microbiological investigations. Cysts are visible with routine stains, such as Giemsa, Gram, and ink-potassium hydroxide, and with stains that require fluorescent microscopy, such as Calcofluor white and acridine orange.<sup>7</sup> Scrapings should be plated on nonnutrient agar and overlaid with *Escherichia coli* to assess for growth of trophozoites; plates should be observed for longer than 7 days. If plates are not available, scrapings can be transported to the laboratory in Page's saline. Culture and smear of samples from contact lens cases and cleaning solutions also can reveal *Acanthamoeba*.

Polymerase chain reaction (PCR) assays targeting *Acanthamoeba* 18S ribosomal RNA (rRNA) have been shown to be more sensitive than culture or smear but are not currently available at most laboratories.<sup>8</sup>

In vivo confocal microscopy can be used to visualize *Acanthamoeba* cysts in the corneal epithelium and stroma. Cysts appear as round, hyper-reflective structures measuring 10–25  $\mu\text{m}$ , often with a “bright spot” or double-walled morphology (see Fig. 4.14.4).<sup>9</sup> The technique has been shown to have good sensitivity and specificity.<sup>10</sup>

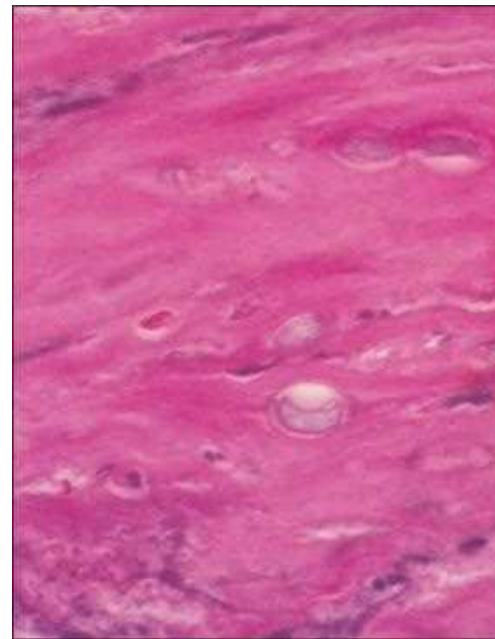
Corneal biopsy should be considered for cases with only deep stromal involvement or when microbiological tests are negative (Fig. 4.14.5). Biopsies should be stained with hematoxylin and eosin, periodic acid–Schiff, and methenamine silver stains.

## Differential Diagnosis

See Box 4.12.1. The pseudo-dendrites of early disease and the ring infiltrate of more advanced disease are often mistakenly identified as representing herpetic keratitis. In those cases that are refractory to treatment, herpetic keratitis and bacterial superinfection should be considered.

## Pathology

Trophozoites bind to the corneal epithelium and establish infection. This is followed by thinning and necrosis of the epithelium, which allow the



**Fig. 4.14.5** Light microscopic view of a corneal section demonstrating *Acanthamoeba* cysts. (Courtesy Joel Sugar, MD.)

organism to enter the stroma, where it may enter progressively deeper layers of the stroma. The organism can become encysted in the corneal stroma and can cause inflammatory sequelae for months after successful antimicrobial treatment.<sup>11</sup>

## Treatment

Treatment of *Acanthamoeba* keratitis is based on eradication of cysts from the cornea.<sup>12</sup> Although trophozoites are susceptible to many antimicrobial agents, the cysts are largely resistant. The most effective medications are the biguanide antiseptic agents chlorhexidine and polyhexamethylene biguanide (PHMB), which act by inhibiting membrane function and are consistently cysticidal (Table 4.14.1).<sup>13</sup> Second-line agents include the diamidines (hexamidine, pentamidine, and propamidine), which inhibit DNA synthesis. Diamidines also generally are cysticidal, though their activity is more variable. Azole medications have activity against trophozoites but are generally not cysticidal. There are reports of effective treatment with oral and topical voriconazole, although the in vitro susceptibility patterns for this agent have not been well characterized. Aminoglycosides such as neomycin and paromomycin were used in the past, but these agents are not cysticidal and cause significant corneal toxicity, so there is little rationale to support their use.

There is little consensus on the best way to treat *Acanthamoeba* keratitis. A clinical trial compared chlorhexidine monotherapy and PHMB monotherapy and found no significant differences, with high success rates in both groups (78% and 86%, respectively).<sup>14</sup> Because cysts can be difficult to eradicate, many clinicians treat with multiple agents, usually with one of the biguanide agents and one of the diamidines. As with other types of infectious keratitis, topical therapy initially should be applied frequently (every 30–60 minutes), and then the frequency can be reduced based on the clinical response. Topical medications generally are continued for many months. Pain should be addressed with cycloplegics and oral nonsteroidal anti-inflammatory drugs.

The role of corticosteroids in the treatment of *Acanthamoeba* infection has not been established. Corticosteroids promote excystment and proliferation of trophozoites and lead to worse visual outcomes when used before starting anti-amebic treatment.<sup>15,16</sup> However, corticosteroids also reduce pain and inflammation and may reduce the likelihood of corneal vascularization. A large retrospective study found that initiation of corticosteroids after a median of 2 weeks of antiamebic therapy was not associated with worse outcomes in eyes with *Acanthamoeba* keratitis and persistent inflammation, providing some reassurance for patients requiring anti-inflammatory therapy.<sup>17</sup> Antiamebic agents should be started before and continued during corticosteroid therapy.

The role of therapeutic keratoplasty for active *Acanthamoeba* keratitis is controversial. Recurrence of *Acanthamoeba* infection has been reported to occur in more than half the grafts, leading to poor postoperative visual outcomes.<sup>18</sup> Others have found much lower rates of recurrence, and good

TABLE 4.14.1 Antiamoebic Medications

Agent	Trade Name	Manufacturer	Dosage Form	Concentration for Ocular Use	Availability	Comment
Cationic Antiseptics						
Chlorhexidine			Solution	0.02%	As 20% concentrate	Used as disinfectant
Polyhexamethylene biguanide (PHMB)	Baquacil	Zeneca	Solution	0.02%	As 20% pool disinfectant	Used also as a preservative, contact lens solutions
Aromatic Diamidines						
Propamidine isethionate	Brolene	Mays & Baker	Solution	0.1% w/v 10 mL	Over-the-counter in UK	
Hexamidine	Désomédine	Chauvin	Solution	0.1%	Available in Europe	
Azoles						
Clotrimazole	Lotrimin	Schering	Suspension	1%	As powder from manufacturer	Poor suspension; difficult to make
Fluconazole	Diflucan	Roerig	Solution	0.2%	As 2 mg/mL solution	Withdraw from vial with filter needle
Ketoconazole	Nizoral	Janssen	Oil solution	5%	As 200 mg tablet	In mortar, dissolve 2.5200 mg tablets in 10 mL of peanut oil
Miconazole	Monistat	Janssen	Solution	1%	As 10 mg/mL solution	Simple 1:1 solution or directly from vial via filter
Voriconazole	Vfend	Pfizer	Oral	200 mg twice daily 1%	As 200 mg tablet As 200 mg vial	Monitor liver function

(Adapted from Richard G. Fiscella, RPh, MPH.)

visual outcomes.<sup>19</sup> Antiacanthamebic medications should be continued after keratoplasty.

Outcome

With timely diagnosis, Acanthamoeba organisms can be eradicated from the cornea by medical therapy. A minority of patients develop rapidly progressive cataract and glaucoma, presumably from prolonged exposure to topical medications or to the host inflammatory response.<sup>20</sup> Severe corneal inflammation and necrosis can result in substantial scarring, necessitating penetrating keratoplasty for visual rehabilitation. Optical keratoplasty performed well after eradication of Acanthamoeba infection carries a good prognosis, but results of therapeutic keratoplasty performed during active infection are much more variable.<sup>18,21</sup>

MICROSPORIDIOSIS

Epidemiology and Pathogenesis

Microsporidia are ubiquitous obligate intracellular parasites closely related to fungi.<sup>22</sup> Although it is a rare disease, diagnosis of microsporidial keratitis is increasing. This is especially true in Asia, where the disease may correspond with the monsoon season.<sup>23</sup> Several risk factors occur for microsporidial keratitis. Immune compromise is the most notable risk factor, especially in persons with human immunodeficiency virus (HIV) infection. Other states of immunosuppression, including local immunosuppression with topical corticosteroids, make infection more likely. Other major risk factors include trauma, which is often associated with exposure to water or mud, and contact lens wear.<sup>24</sup> Although previously considered to occur primarily in the setting of HIV, infection is increasingly being observed in immunocompetent persons.

Clinical Features

Two distinct clinical presentations are possible with ocular microsporidial infection: superficial keratoconjunctivitis, which is caused by encephalitozoon species, and deep stromal keratitis, which is caused by nosema, vittaforma, and trachiplestophora species. The keratoconjunctivitis form usually was seen in immunocompromised persons in the past, although this entity is now recognized in immunocompetent persons as well.<sup>25</sup> Microsporidial keratoconjunctivitis is characterized by minimal conjunctivitis, diffuse punctate epitheliopathy, and coarse epithelial opacities, some of which stain with fluorescein. Symptoms include pain, photophobia, blurred vision, and foreign body sensation. Microsporidial stromal keratitis usually is seen in immunocompetent individuals, where it is often misdiagnosed as herpetic keratitis. Stromal infection is characterized by deep stromal infiltrates with or without corneal neovascularization and uveitis.

Diagnosis

Diagnosis of microsporidial keratitis usually is made by inspection of smears obtained from corneal or conjunctival scrapings. Several stains

can be used, with potassium hydroxide plus Calcofluor white, Gram, and modified Ziehl–Neelsen most consistently detecting microsporidia.<sup>26</sup> Giemsa staining characteristics are more variable. Microsporidia are difficult to recover in culture. PCR assays that target the 16S rRNA subunit have been developed but are not performed by most laboratories.<sup>27</sup> The confocal microscope can reveal intraepithelial microsporidia, but these organisms, which measure 1–5 μm, approach the resolution limits of this instrument.<sup>28</sup> Electron microscopy performed on body fluids is considered the gold standard for diagnosis of microsporidial infection.

Differential Diagnosis

See Box 4.12.1.

Systemic Associations

Microsporidial infection can involve nearly every organ system in severely immunocompromised patients with HIV infection (usually CD4 cell counts <100/μL). The gastrointestinal system is most commonly involved, representing a major cause of malabsorption and diarrhea in patients with acquired immunodeficiency syndrome (AIDS). Ocular infections are second in frequency and may result from nasopharyngeal infection or from urine-to-finger-to-eye contamination. When ocular microsporidial infections are diagnosed, the patient must be fully examined for other areas of involvement. Other common infections include sinusitis, hepatitis, peritonitis, cholangitis, myositis, bronchiolitis, pneumonia, encephalitis, cystitis, and nephritis. Rare manifestations include urethritis, prostatic abscess, tongue ulcer, and skeletal and cutaneous involvement.

Treatment

The optimal treatment regimen for ocular microsporidiosis is not well defined. Several medications are currently used, including oral agents, such as albendazole and itraconazole, and topical agents, such as fumagillin, propamidine, chlorhexidine, PHMB, voriconazole, and the fluoroquinolones. Fumagillin is one of the more frequently used medications; a 10 mg/mL suspension can be applied hourly for 24 hours and then tapered based on clinical response. Albendazole has been used when ocular microsporidiosis was refractory to topical therapy.<sup>29</sup> A placebo-controlled randomized clinical trial performed with immunocompetent patients found no benefit of PHMB.<sup>30</sup> This trial found that the disease may be self-limiting in immunocompetent patients; the placebo group experienced clinical cure an average of 9 days after diagnosis.

Outcome

Treatment of microsporidial keratoconjunctivitis is usually successful, especially in immunocompetent patients. Immunocompromised persons can develop chronic infections when antimicrosporidial treatment is withdrawn. In such an event, a low maintenance dose of one drop a day might be sufficient to control the keratoconjunctivitis. Visual acuity improvement is usually seen after the superficial keratitis resolves.<sup>30</sup> Disease involving

the corneal stroma is difficult to treat, and recrudescence is common. Some authors advocate full-thickness keratoplasty in these cases because microsporidia can invade the anterior chamber, and lamellar keratoplasty does not preclude recurrence.<sup>31</sup>

## ONCHOCERCIASIS

### Epidemiology and Pathogenesis

Onchocerciasis, also known as “river blindness,” is a major cause of blindness worldwide. Onchocerciasis affects approximately 18 million people, of whom 270 000 are rendered blind.<sup>32</sup> The vast majority of cases occur in the 34 countries in Africa where the disease is still endemic. The causative organism, *Onchocerca volvulus*, is a filarial nematode that is transmitted by the Simulium black fly, which breeds in the fast-flowing rivers and streams of Africa, Brazil, Mexico, the Middle East, and parts of Central America. The fly introduces larvae of *O. volvulus* into the skin during a blood meal, forming a skin nodule of adult worms. After developing into adult worms, females shed hundreds of thousands of microfilariae that migrate through skin and have particular affinity for eyes. Dying microfilariae incite an inflammatory reaction that results in the cutaneous and ocular clinical manifestations. An endosymbiont bacteria, *Wolbachia*, plays an important role in development of larvae, and also possibly in the long-term survival of adult worms.<sup>33</sup>

Eye disease is related to the inflammatory response generated by the nematodes, which can be found in the conjunctival epithelium, corneal stroma, iris, ciliary body, sclera, extraocular muscles, and optic nerve sheath. The severity of ocular findings depends on the strain of microfilariae; strains from the savanna regions of West Africa induce a more severe inflammatory response and sclerosing keratitis, which is typically absent in infections caused by the rain forest strain.<sup>34,35</sup>

### Clinical Features

Early infection with the *Onchocerca* worm is marked by a diffuse papular dermatitis, accompanied by intense pruritus.<sup>32</sup> Other cutaneous findings can range from lichenification to asymptomatic depigmentation to subdermal nodules. Onchocerciasis can involve virtually all ocular tissues. Lid nodules and edema, chronic conjunctivitis with injection, chemosis, and phlyctenule-like conjunctival masses can develop. Corneal involvement is marked by a fine interpalpebral epithelial punctate keratitis that overlies white subepithelial flake-like opacities and discrete nummular scars, and stromal edema caused by an intrastromal worm. These worms can be visualized at the slit lamp on retroillumination at all corneal levels as S- or C-shaped fine, motile filaments. Sclerosing keratitis represents more severe, blinding corneal disease. It tends to appear as an anterior stromal haze centered at the 3 and 9 o'clock positions separated from the limbus by a clear zone. Both infiltration and neovascularization are progressive and can encroach on the visual axis as the entire cornea becomes involved. Calcific band keratopathy and uveitis can develop, as well as scleritis.

Microfilariae might be observed in the anterior chamber, especially in the inferior angle on gonioscopy, or on the anterior lens capsule. In some cases, the accompanying uveitis can be severe, leading to corectopia, synechiae, occluded pupil, and secondary glaucoma. Chorioretinal lesions appear as asymmetrical lesions peripheral to the macula or around the optic nerve. Peripapillary chorioretinitis with optic nerve edema can result in optic atrophy, another significant cause of visual impairment.

### Diagnosis

Diagnosis is based on observation and identification of the worm. It can be recovered from skin from an excised nodule or from a bloodless skin snip from the scapula, iliac crest, or lower calf. The worm count in skin snips is correlated with the intensity of infection. Serological tests are available, although some have difficulty discriminating *O. volvulus* from other filarial infections.<sup>36</sup>

### Differential Diagnosis

Similar skin lesions can be seen in association with microfilarial infection caused by *Mansonella perstans*. Skin nodules and uveitis also can be seen with sarcoidosis.

### Systemic Associations

Besides being present in skin lesions, the microfilariae can be identified in blood vessels, visceral organs, the central nervous system, urine, and sputum. Superficial lymph nodes draining areas with cutaneous concentrations of the worms can become painlessly enlarged.

### Pathology

The destructive inflammation caused by *Onchocerca* infection is stimulated by antigens released by dead and dying organisms. The host immune response results in migration of eosinophils and neutrophils into the corneal stroma. Degranulation of these inflammatory cells releases cytotoxic proteins that disrupt the normal functioning of the corneal cells, resulting in corneal opacity.<sup>37</sup>

### Treatment

The skin nodule containing the adult worms should be surgically removed. Oral ivermectin kills microfilariae but not adult worms. A 6-week course of doxycycline 100–200 mg/day is used to clear *Wolbachia* endosymbionts and results in long-term sterilization of adult worms.<sup>38</sup> Ivermectin has been shown to reverse even advanced sclerosing keratitis and iridocyclitis, but treatment is not effective for chorioretinal lesions, which progress despite treatment.<sup>39</sup> Iridocyclitis should be treated with corticosteroids and cycloplegia. From a public health perspective, the mainstay of treatment is oral ivermectin given as a single dose (150 µg/kg) repeated annually or biannually. Mass drug administrations are delivered to entire communities in endemic areas.

### Outcome

Although anterior segment inflammation and lesions respond well to treatment, severe visual impairment can result from chorioretinitis, which, in advanced cases, often continues to progress in spite of treatment. Health programs are aimed at blindness prevention through mass treatment, prevention, and vector control. Evidence exists that prolonged repeated mass ivermectin distributions can disrupt transmission of *O. volvulus*, suggesting that elimination of disease may eventually be possible.<sup>40</sup>

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# Herpes Simplex Keratitis

Sonal S. Tuli, Matthew J. Gray

4.15

**Definition:** Herpes simplex viral infection of the cornea.

**Key Features**

- Dendritic ulcer: classic feature of epithelial disease.
- Focal endotheliitis (disciform keratitis): classic feature of stromal disease.

**Associated Features**

- Decreased corneal sensation.
- Underlying granulomatous keratic precipitates.

**EPIDEMIOLOGY**

Human herpesviruses (Table 4.15.1) have in common a state called “latency,” where the virus remains dormant in cells and periodically reactivates. Herpes simplex viruses 1 and 2 (HSV-1 and HSV-2) have an affinity for the sensory ganglion cells and, therefore, are called *neurotrophic viruses*. These viruses are ubiquitous, and in most parts of the world, exposure to HSV-1 is almost universal by late adulthood.<sup>1,2</sup> HSV keratitis (HSVK) is the most common cause of corneal blindness in developed nations.<sup>3</sup> In the United States, the incidence of new cases of HSVK is estimated at 24000 per year, and the total number of episodes at 58000 per year with a prevalence over 400000.<sup>4,5</sup> HSV-1 infections more commonly occur in the orolabial area and HSV-2 in the genital area.<sup>6</sup>

**HERPES SIMPLEX VIRUS**

HSV, a large double-stranded DNA virus, has an icosahedral capsid surrounded by a poorly defined tegument enclosed in a host cell membrane-derived envelope with viral-derived glycoprotein projections (Fig. 4.15.1).

Newly formed virions, which replicate in the cell nucleus, egress by budding from the cell membrane, destroying the cell in the process. Recurrent infections progressively destroy sensory ganglion cells, diminishing corneal sensation, one of the hallmarks of HSVK.

Serum antibody production to HSV infections is inconsistent and only partially protective. The major immune response to HSV is T lymphocyte mediated.<sup>7,8</sup>

**Life Cycle of HSV**

Initial HSV infection is usually asymptomatic and occurs by direct contact of mucous membranes with infected secretions rather than by fomites

or aerosolization. The virus enters epithelial cells on contact, replicates, enters the sensory nerve endings, and travels in a retrograde fashion to the trigeminal ganglion, where it remains *latent* (Fig. 4.15.2). The cornea also may be a site of HSV latency and replication.<sup>9–13</sup> After an initial round of replication in the trigeminal ganglion, the virus travels back down the nerve in an antegrade fashion, causing *primary* infection in about 6% of patients. It then remains latent until certain triggers cause it to reactivate, replicate, and travel back down the nerve to cause *recurrent* infection. It is not clear if the initial infection occurs by direct contact of ocular tissues with infected secretions, or if the initial infection occurs in the orolabial area with the virus then spreading to the neurons supplying the eye in the trigeminal ganglion (back-door spread).<sup>12</sup>

**PRIMARY HSV INFECTION**

Primary HSV ocular infection most commonly manifests as blepharoconjunctivitis (often with conjunctival ulceration) that heals without scarring (Fig. 4.15.3). The associated follicular conjunctivitis is often mistaken for adenoviral conjunctivitis (Fig. 4.15.4); up to a third of unilateral follicular conjunctivitis may be culture-positive for HSV.<sup>14–16</sup> Other features include lid vesicles and conjunctival dendrites. Keratitis is rare, occurring in only 3%–5% of cases, although severe bilateral disease can occur in atopic or immunocompromised patients.<sup>5,17–19</sup>

**RECURRENT HSV INFECTIONS**

Multiple factors are thought to trigger recurrence, including fever, menses, sunlight, irradiation, and emotional stress. Anecdotal reports have also implicated prostaglandin analogues, immunosuppression, and refractive surgery. Recurrent disease, estimated to occur in 27% of patients at 1 year and over 60% at 20 years, commonly causes keratitis (HSVK), although it can affect all parts of the eye.<sup>5</sup> The risk of a subsequent recurrent infection increases with the number of recurrences to 83% at 20 years after one or more recurrences.<sup>5</sup>

HSVK is broadly classified into epithelial and stromal/endothelial keratitis. This classification not only is anatomical but also is important for understanding the pathophysiology of HSVK and for planning treatment.

TABLE 4.15.1 Human Herpesviruses of Medical Importance		
Abbreviation	Nomenclature	Disease Caused
HSV-1	Herpes simplex type-1	Oral, ocular, genital herpes, whitlow
HSV-2	Herpes simplex type-2	Genital, oral, ocular herpes, whitlow
VZV	Varicella zoster virus	Chickenpox, herpes zoster (shingles)
CMV	Cytomegalovirus	Retinitis, range of systemic diseases
EBV	Epstein–Barr virus	Infectious mononucleosis
HHV-6	Human herpesvirus-6	Exanthem subitum (roseola)
HHV-7	Human herpesvirus-7	Exanthem subitum (roseola)
KSRV	Kaposi’s sarcoma–related virus	Kaposi’s sarcoma

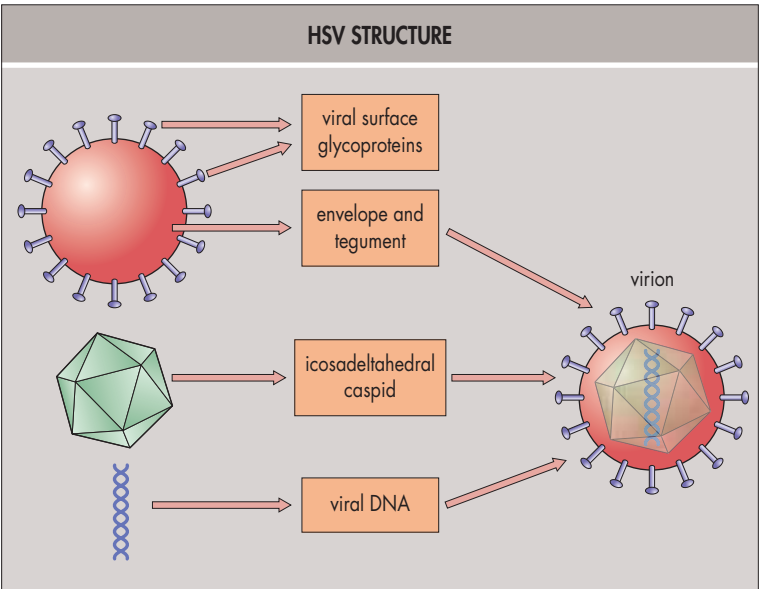


Fig. 4.15.1 Herpes simplex virus (HSV) structure.

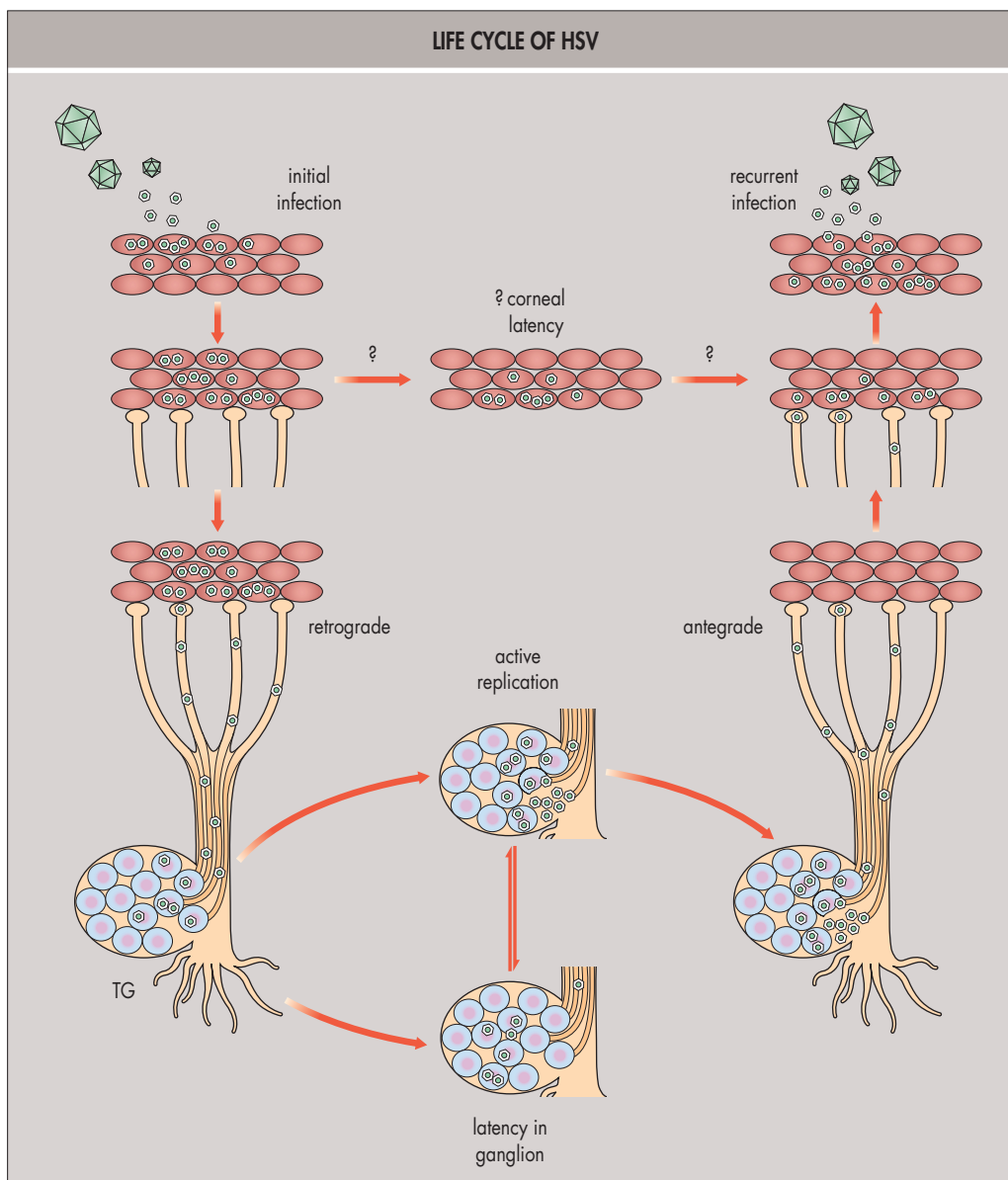


Fig. 4.15.2 Life cycle of herpes simplex virus (HSV).

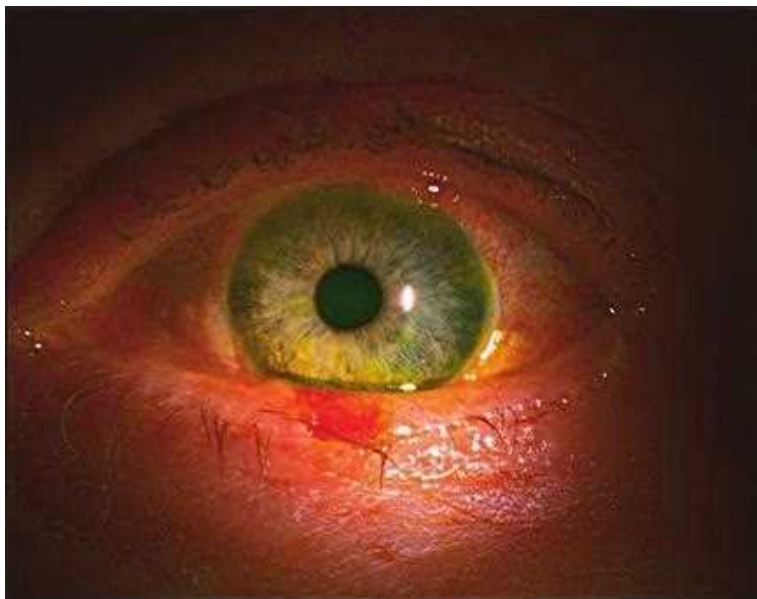


Fig. 4.15.3 Blepharoconjunctivitis.

### Epithelial Keratitis

Caused by actively replicating virus on the corneal surface, this usually starts as epithelial vesicles, punctate keratitis, or opaque plaques that coalesce and break down centrally. Initial episodes present with foreign body sensation, but subsequent episodes usually are painless because of



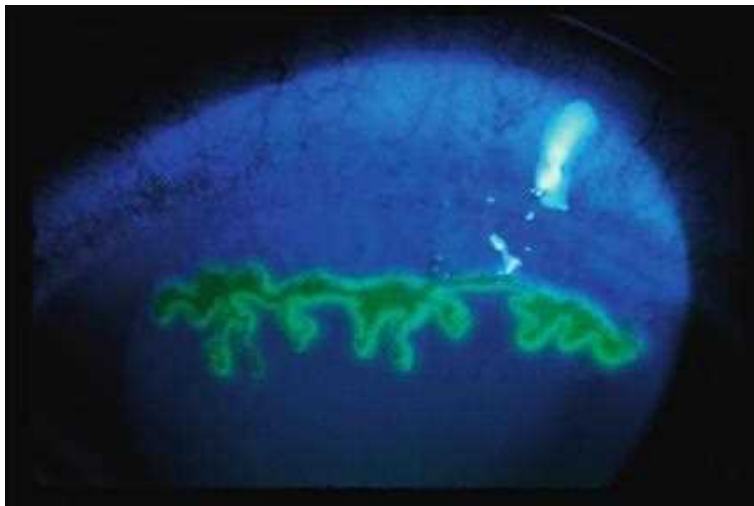
Fig. 4.15.4 Follicular conjunctivitis.

corneal hypoesthesia.<sup>20</sup> However, the associated inflammation may cause significant photophobia. It includes the conditions discussed below.

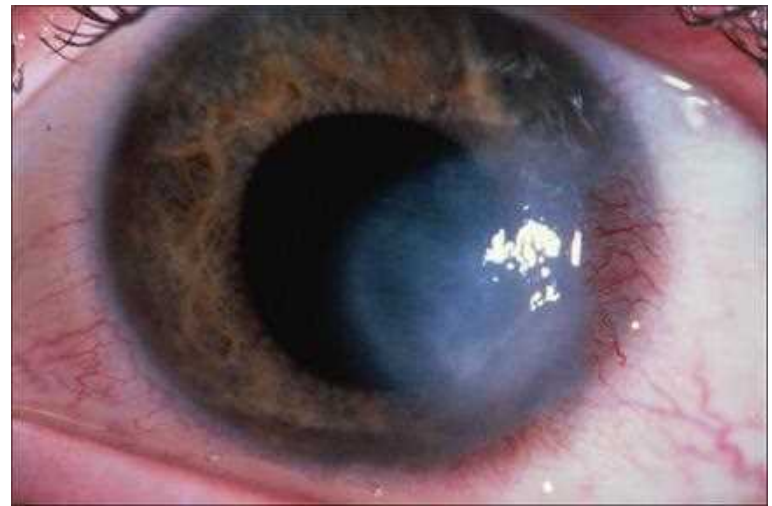
### Dendritic Ulcer

This classic herpetic lesion consists of a linear, dichotomously branching lesion with terminal bulbs (Fig. 4.15.5). The borders consist of acantholytic, infected cells and are slightly raised, grayish, and stain with Rose Bengal

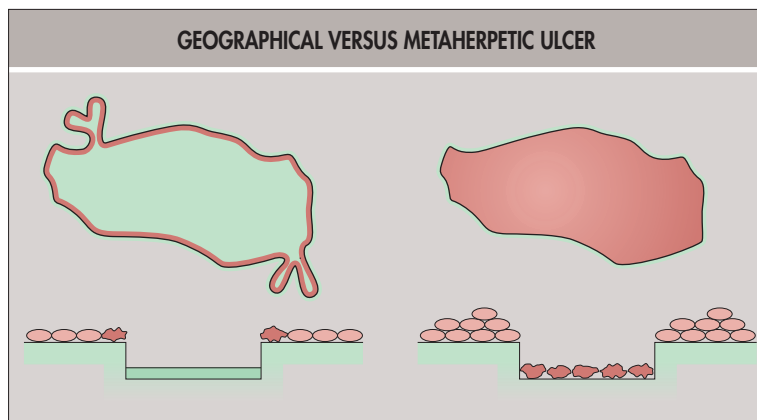




**Fig. 4.15.5** Dendrite.



**Fig. 4.15.7** Disciform keratitis.



**Fig. 4.15.6 Geographical Versus Metaherpetic Ulcer.** Geographical ulcer (*left*): large fluorescein-staining epithelial defect with peripheral dichotomous branching and terminal bulbs that stain with Rose Bengal metaherpetic ulcer (*right*): Rose Bengal staining of unhealthy epithelial cells across ulcer base and fluorescein leakage into stroma and periphery (reverse staining). Note heaped up epithelial cells at ulcer edge.

stain. The central epithelial defect stains with fluorescein. The underlying stroma may have minimal inflammation. On resolution, a dendrite-shaped scar, called *ghost dendrite*, may remain in the superficial stroma.

### Geographical Ulcer

Patients who are immunocompromised, on topical corticosteroids, or have long-standing, untreated ulcers can develop very large epithelial defects.<sup>21</sup> However, dichotomous branching and terminal bulbs are often seen at the periphery and the staining is similar to dendritic keratitis.

### Marginal Keratitis

These lesions located near the limbus can resemble staphylococcal catarrhal ulcers. An epithelial defect and lack of corneal sensation can aid in diagnosis. Significant stromal inflammation can occur because of the proximity to limbal blood vessels. More resistant to treatment, they frequently become trophic ulcers.<sup>22</sup>

### Metaherpetic (Trophic) Ulcer

This is not associated with live virus and results from inability of the epithelium to heal (Fig. 4.15.6). It is called a *trophic ulcer* if it arises de novo or a *metaherpetic ulcer* if it follows a dendrite or geographical ulcer, although the terms are used interchangeably. The causes are multifactorial and include toxicity from antiviral medications, unrecognized trauma, lack of neural-derived growth factors, poor tear surfacing, and underlying, low-grade stromal inflammation. Neurotrophic ulcers start as roughened epithelium that breaks down to produce an epithelial defect with smooth margins. The borders are grayish, elevated, and consist of multiple layers of epithelium. In contrast to geographical ulcers, Rose Bengal stains the unhealthy epithelial cells attempting to migrate across the base of the ulcer

while fluorescein leaks between these poorly adherent cells into the stroma and stains the periphery—so-called “reverse staining” (see Fig. 4.15.6).

## Stromal/Endothelial Keratitis

Usually an immune-mediated response to nonreplicating viral particles, stromal keratitis can affect all layers of the cornea and may even involve the trabecular meshwork and iris. It is classified based on the predominant site and type of involvement.

### Endotheliitis

This is the most common form, and it manifests as overlying stromal edema from endothelial dysfunction. Long-standing stromal edema leads to permanent scarring and decreased vision.

### Localized Endotheliitis

This appears as a disc-shaped area of corneal edema called *disciform keratitis* (Fig. 4.15.7). Minimal stromal inflammation occurs without epithelial involvement, although microcystic edema and bullae may develop later in some cases. Focal keratic precipitates underlying the edema are highly suggestive but may be difficult to visualize. Sharp demarcation between involved and uninvolved stroma distinguishes this from other causes of stromal edema.

### Diffuse and Linear Endotheliitis

These are rare and usually accompanied by trabeculitis and elevated intraocular pressure. Pseudo-guttae and Descemet's folds may cause confusion with Fuchs' dystrophy. Linear keratic precipitates can resemble allograft rejection.

### Necrotizing Keratitis

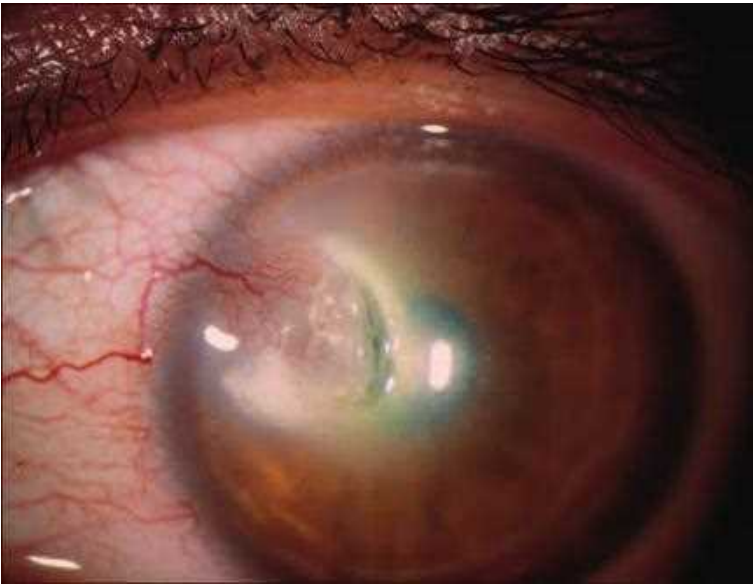
The significantly greater inflammation is thought to be a reaction to live viral particles in the corneal stroma (Fig. 4.15.8). It is most commonly seen in patients with multiple recurrences, especially with HSV-2. Difficult to distinguish from other causes of microbial keratitis without a high index of suspicion, it may cause corneal melting and perforation. Frequently, it is associated with uveitis and trabeculitis that may lead to recalcitrant glaucoma.

### Immune Stromal Keratitis

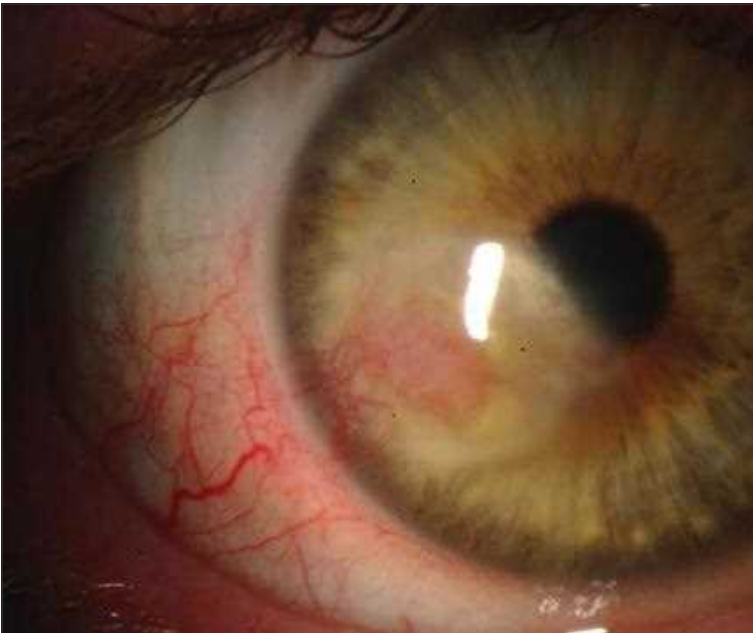
This manifests as focal, multifocal, or diffuse stromal opacities or an immune ring (Fig. 4.15.9). It often is accompanied by stromal edema and a mild anterior chamber reaction. The epithelium and endothelium are relatively spared. It also is called interstitial keratitis (IK) and can lead to deep stromal vascularization. HSV is now the most common cause of IK, especially unilateral, in the United States.<sup>13</sup> Unlike syphilitic IK, HSV neovascularization is usually unilateral, sectoral, at multiple levels within the stroma, and leads up to a stromal scar.

### Lipid Keratopathy

Newly formed or inflamed vessels are permeable to lipid because of the action of vascular endothelial growth factor. Once exuded, the lipid collects



**Fig. 4.15.8** Necrotizing keratitis.



**Fig. 4.15.9** Interstitial keratitis with lipid keratopathy.

within keratocytes and intercellular matrix and is the major cause of vision loss requiring corneal transplantation in patients with HSV.

### Keratouveitis

Uveitis is usually granulomatous with large “mutton fat” keratic precipitates on the endothelium (Fig. 4.15.10). Although often immune mediated, sectoral iritis with a plasmoid aqueous is caused by release of live virus from the sympathetic nerves.<sup>23</sup> It can lead to significant morbidity from synechiae, iris atrophy, cataracts, and glaucoma. Unilateral uveitis with high intraocular pressure often is caused by HSV.

### Miscellaneous Syndromes

Herpes has been implicated in various chronic, unilateral diseases of the iris and trabecular meshwork. HSV DNA has been isolated by polymerase chain reaction (PCR) from the endothelium of corneas with iridocorneal endothelial (ICE) syndrome and from the aqueous humor of patients with Posner–Schlossman syndrome and Fuchs’ heterochromic iridocyclitis.<sup>24–26</sup>

## DIAGNOSIS

Diagnostic testing is seldom needed in epithelial HSVK because of its classic clinical features and is not useful in stromal keratitis as live virus rarely is present.



**Fig. 4.15.10** Keratouveitis.

## Culture

Corneal swabs placed in viral or chlamydia transport media are transported at 4°C. Cultures following Rose Bengal corneal staining may be falsely negative as Rose Bengal is virucidal with exposure to light.<sup>27</sup> Unfortunately, intracellular HSV is unaffected, and Rose Bengal cannot be used in vivo.<sup>28</sup>

## DNA Testing

PCR is very rapid and extremely sensitive and specific. Strains also can be identified for epidemiological purposes. This is rapidly becoming the testing of choice for viral diseases.

## Fluorescent Antibody Testing

A nitrocellulose membrane or corneal swab smeared on a slide may be used. This gives rapid results, but sensitivity and specificity are lower than those of culture. Fluorescein staining interferes with this test.<sup>29</sup>

## Tzanck’s Smear

Papanicolaou or Giemsa stains of corneal smears show multinucleated giant cells and intranuclear eosinophilic inclusion bodies (Cowdry type A). Although low in sensitivity and specificity, this rapid and cheap test can be done in most laboratories.

## Serum Antibody Testing

Immunoglobulin M (IgM) or rising titers of IgG may be present in children but most adults have IgG to HSV, limiting its use in diagnosis.<sup>1</sup>

## HERPETIC EYE DISEASE STUDY

Prior to the Herpetic Eye Disease Study (HEDS), the standard therapy for all forms of HSVK was with topical antivirals. The HEDS was undertaken to assess the effect of adding corticosteroids and acyclovir to conventional therapy with trifluridine (TFT). It was a prospective, randomized, double-masked, placebo-controlled, multicenter study divided into six trials: three therapeutic, two preventive, and one cohort.

1. **Herpes Stromal Keratitis, Not on Corticosteroid Trial:** Compared with the placebo group, patients receiving prednisolone phosphate drops had faster resolution and fewer treatment failures. However, delaying corticosteroid treatment did not affect the eventual visual outcome.<sup>30</sup>
2. **Herpes Stromal Keratitis, on Corticosteroid Treatment:** There was no apparent benefit in adding oral acyclovir to topical corticosteroids and TFT. However, visual acuity improved over 6 months in more patients on acyclovir.<sup>31</sup>
3. **Herpes Simplex Virus Iridocyclitis, Receiving Topical Corticosteroids:** More treatment failures occurred in the placebo group than in the acyclovir group, indicating a potential benefit to adding oral acyclovir to topical corticosteroids and antivirals.<sup>32</sup>

A meta-analysis of these three trials evaluated the risk of subsequent epithelial keratitis in patients with stromal keratouveitis. Although the risk was higher in the corticosteroid-alone group, it was not statistically

TABLE 4.15.2 Current Antivirals

Drug (Trade Name)	Route	Dose	Frequency	Adverse Effects
Trifluridine (Viroptic)	Topical drops	1.00%	Every 2 hours	Follicular conjunctivitis, epitheliopathy
Vidarabine (Ara-A)(compounded)	Topical ointment	3.00%	Five times a day	As above
Ganciclovir (Zirgan)	Topical gel	0.15%	Five times a day	Stinging, burning, blurring of vision
Acyclovir (Zovirax)	Topical ointment Oral – treatment Oral –prophylaxis	3.00% 400 mg 400 mg	Five times a day Five times a day Twice a day	Headache, nausea, nephrotoxicity, neurotoxicity
Valacyclovir (Valtrex)	Oral –treatment Oral –prophylaxis	500 mg 500 mg	Three times a day Once a day	As above, thrombotic thrombocytopenic purpura and hemolytic uremic syndrome in immunosuppressed
Famciclovir (Famvir)	Oral –treatment Oral –prophylaxis	250 mg 250 mg	Three times a day Once a day	As acyclovir

significant. The risk was also higher in patients with a previous history of epithelial keratitis and in nonwhite patients.<sup>33</sup>

4. **Herpes Simplex Virus Epithelial Keratitis Trial:** In the treatment of acute HSV epithelial keratitis with TFT, the addition of oral acyclovir offered no additional benefit in preventing subsequent stromal keratitis or iritis.<sup>34</sup>
5. **Acyclovir Prevention Trial:** Oral acyclovir reduced the risk of any form of recurrent ocular herpes by 41% and stromal keratitis by 50%. The risk of multiple recurrences decreased from 9% to 4%. However, the protection did not persist once acyclovir was discontinued.<sup>35</sup>
6. **Ocular HSV Recurrence Factor Study:** No association was found between psychological or other forms of stress and HSV recurrences.<sup>36</sup> Previous episodes of epithelial keratitis were not a predictor for future occurrences, whereas previous, especially multiple, episodes of stromal keratitis markedly increased the probability of subsequent stromal keratitis.<sup>37</sup>

This study had some limitations:

1. Many of the trials had inadequate recruitment or high dropout rate.
2. Oral acyclovir in the prevention trials was only used for 3 weeks.
3. The corticosteroid regimen was standardized and not tailored to inflammation.
4. TFT was used in both the study and placebo groups in all the therapeutic trials.

## TREATMENT

Treatment of HSV is diametrically different for epithelial and stromal keratitis, reflecting the fact that epithelial disease is caused by live replicating virus, whereas stromal disease is essentially an immune response to viral antigen. Prompt and appropriate treatment may minimize the risk of scarring, the major cause of morbidity from HSVK.

### Infectious Epithelial Keratitis

Although epithelial keratitis spontaneously resolves in approximately 50% of cases, treatment is advised for ulcers larger than 4 mm, marginal ulcers, and ulcers with underlying stromal inflammation. Topical antivirals, the mainstay of treatment, are very effective and have a low incidence of resistance. Both topical trifluridine and ganciclovir have proven to be successful in the treatment of epithelial keratitis and are commercially available in the United States.<sup>38,39</sup> Gentle wiping debridement is a very good adjunct therapy as infected cells are poorly adherent. This results in much faster resolution, less inflammation, and consequently less scarring.<sup>40</sup> Off-label use of oral antivirals also appears to be a safe and effective alternative to topical therapy.

### Stromal Keratouveitis

The mainstay of treatment is topical corticosteroids because they decrease inflammation and, thus, scarring. Simultaneous antiviral prophylaxis is recommended because evidence suggests that HSV reactivation while on corticosteroids results in severe epithelial disease or necrotizing keratitis. Oral antivirals are preferred because they decrease the risk of HSV reactivation at the ganglion level and do not have the corneal toxicity associated with topical antivirals. Aggressive topical and systemic antivirals along with corticosteroids are necessary in necrotizing keratitis and focal serous iritis.

### Metaherpetic Keratitis

The basic principle is surface support including elimination of toxic medications, punctal occlusion, artificial tear supplements, bandage contact lenses, autologous serum tears, and amniotic membrane grafts.<sup>41</sup> The cautious use of topical corticosteroids may be necessary if there is significant underlying inflammation.

## Medications

### Antivirals

All current antivirals are nucleoside analogs that competitively inhibit viral DNA polymerase (Table 4.15.2). They also may interfere with host DNA synthesis and cause significant toxicity. Acyclovir and ganciclovir are the most specific for viral polymerase and thymidine kinase and, therefore, are the least toxic. Acyclovir resistant HSV-1 has been reported and requires monitoring for cases of HSVK refractory to this treatment.<sup>42–44</sup>

### Corticosteroids

Typically, either 1% prednisolone acetate or 0.1% dexamethasone are used. The frequency should be based on the severity of inflammation and tapering must be very gradual to prevent rebound inflammation.

## Surgery

Surgery is usually performed when corneal scarring limits vision. However, surgery also may be necessary as a therapeutic measure in patients with nonhealing ulcers or impending perforations from necrotizing keratitis.

### Penetrating Keratoplasty

When penetrating keratoplasty is considered, it is preferable to wait at least 6 months after an episode of HSVK before attempting corneal transplantation because the success rate increases in a quiescent eye.<sup>45</sup> Unfortunately, the results of corneal transplantation for HSVK are uniformly poor. Reactivation and rejection occur in 44% and 46%, respectively, by 2 years.<sup>45</sup> Prophylactic acyclovir started prior to surgery and continued for at least 6 months to 2 years decreases the risk of HSVK recurrence and graft failure.<sup>46,47</sup> Lifelong oral prophylactic antivirals may be considered because the HEDS found that the risk of recurrence increases to baseline on stopping antiviral prophylaxis. Lamellar grafts are not recommended because recurrence occurs at the interface.

### Conjunctival Flap

This may be useful in patients with medical contraindications for surgery or chronically inflamed keratitis. Ambulatory vision may be possible through the flap.

### Amniotic Membrane Transplantation

Amniotic membrane transplantation aids the healing of neurotrophic ulcers in HSVK, presumably by decreasing inflammatory cell and matrix metalloproteinase levels in the cornea.<sup>48</sup>

## FUTURE DIRECTIONS

Heat shock and glycoprotein subunit vaccines have shown some promise in clinical trials in decreasing the number and severity of recurrences.<sup>49</sup> Immunomodulatory factors, such as cytokines may serve as adjuncts to corticosteroid therapy by skewing the immune response toward milder disease.<sup>50</sup> Newer antivirals such as cidofovir may be more effective and



cause less toxicity compared with current therapy.<sup>51,52</sup> Interferon, although ineffective as monotherapy, increases the efficacy of antivirals, and other agents, such as nerve growth factor and apolipoprotein E mimetic peptide, have shown a benefit in animal models of HSVK.<sup>40,51–54</sup> Gene therapy may prove to be useful in the future—ribozymes and small interfering RNAs have shown promise in cell culture experiments, but their instability in vivo has been a barrier to clinical use.<sup>55</sup>

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## Peripheral Ulcerative Keratitis

Sarkis H. Soukiasian

4.16

**Definition:** Destructive inflammation of the peripheral cornea associated with corneal epithelial sloughing and keratolysis.

**Key Features**

- Peripheral corneal ulceration.
- Unilateral or bilateral.
- Progresses circumferentially and posteriorly and may perforate.
- May be associated with systemic collagen vascular diseases.
- Can be a presenting feature of a previously undiagnosed systemic collagen vascular disorder.
- Frequently requires systemic immunosuppressive immunomodulatory therapy.
- Imperative to exclude a primary or secondary infectious etiology.

**Associated Features**

- Episcleritis.
- Scleritis.
- Iridocyclitis.

**INTRODUCTION**

Peripheral ulcerative keratitis (PUK) is used to describe a group of destructive inflammatory diseases involving the peripheral cornea whose final common pathway is characterized by sloughing of corneal epithelium and keratolysis (corneal “melting”). The vast majority of cases are mediated by local and systemic immunological processes, although some cases may be infectious in origin and must be properly evaluated. PUK may be associated with systemic vasculitides, particularly the collagen vascular diseases, in about half of the noninfectious cases.<sup>1</sup> Necrotizing scleritis often is associated in such cases<sup>1</sup> and is suggestive of possible active vasculitis, with PUK being the presenting feature of a systemic inflammatory condition, such as granulomatosis with polyangiitis (GPA) (formerly known as Wegener’s granulomatosis) or polyarteritis nodosa. If not properly treated, PUK can progress to perforation resulting in significant ocular morbidity, and when associated with a systemic autoimmune condition, may be potentially life-threatening.<sup>2</sup>

**ANATOMY AND PATHOGENESIS**

The unique characteristics and anatomy of the peripheral cornea contributes to the predilection of this region to be involved in both local and systemic immunological reactions.<sup>3,4</sup> There are no clear-cut borders that delineate the peripheral cornea, with an arbitrary central limit beginning around 3.5–4.5 mm from the visual axis and extending out to the junction of the ill-defined transition between limbus and the sclera and conjunctiva. Distinct anatomical differences of the peripheral cornea include the greater thickness (up to 0.7 mm) with tight collagen bundle packing; a vascular arcade that originates from the anterior ciliary arteries and extends approximately 0.5 mm into the clear cornea (providing the nutritional supply but also access to the efferent arm of the immune response); and accompanying lymphatics, which drain to the regional lymph nodes.<sup>5</sup> There also are unique immunological characteristics of the peripheral cornea compared with the central cornea, including the presence of more Langerhans’ cells,<sup>6,7</sup> and higher concentrations of immunoglobulin M<sup>8</sup> and the first component of complement (C1) (important in the activation of the classic complement pathway), likely caused by limited central diffusion from the

limbal vessels resulting from the large size of the latter two molecules. Additionally, the adjacent conjunctival blood vessels and lymphatics not only provide peripheral corneal access to the afferent and efferent arcs of the immune system but may be sources of inflammatory effector cells and cytokines involved in the production of collagenase and proteoglycanase, which may contribute to corneal degradation.<sup>9,10</sup>

Although the exact pathophysiological mechanisms of PUK are unclear, circulating immune complex deposition, autoimmune reactions to corneal antigens, and hypersensitivity reactions to exogenous antigens have been proposed, with evidence suggesting that both humoral and cell-mediated mechanisms (T cell and B cell) are involved.<sup>11–13</sup> Locally produced or circulating immune complexes lodged in limbal or peripheral corneal blood vessels may activate the classic complement pathway in the presence of C1 (the recognition unit of the classic complement pathway). Immune vasculitis resulting in damage to the vessel wall with leakage and the chemotaxis of various inflammatory cells, proteins, and proinflammatory cytokines and the production of metalloproteinases by local resident cells may accelerate and propagate the peripheral corneal destructive process.

**OCULAR MANIFESTATIONS**

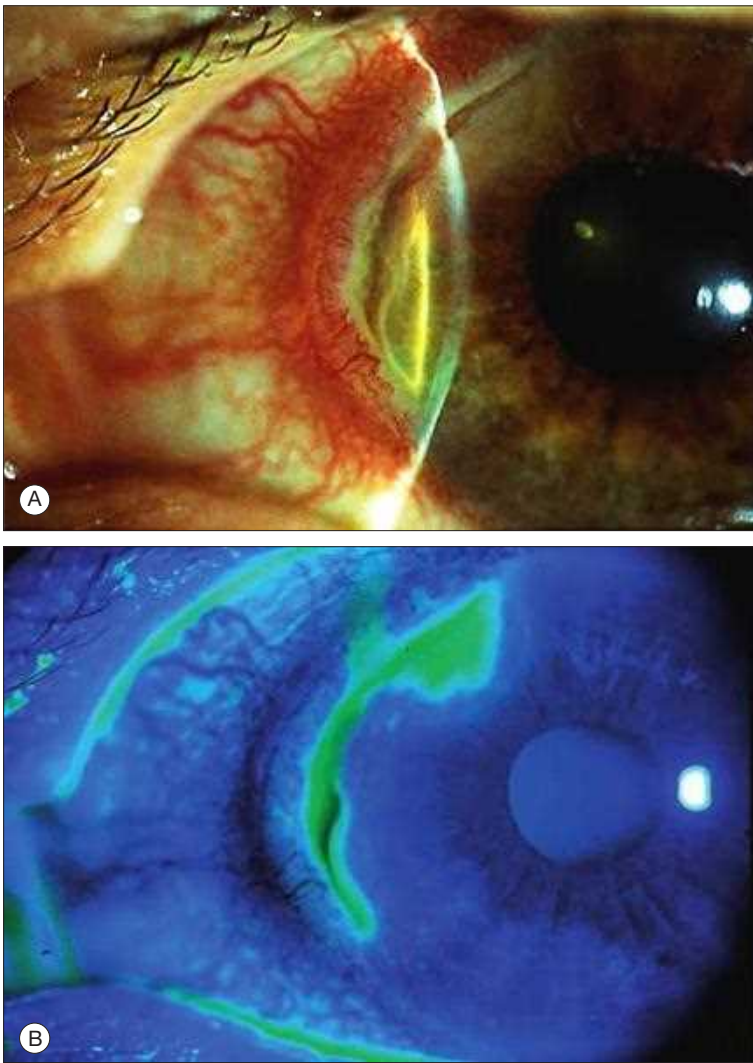
The presenting symptoms of PUK are not specific. Foreign body sensation, pain, and photophobia are seen when there is epithelial erosion and ulceration. Vision may be affected if the peripheral inflammatory process proceeds centrally or from induced astigmatism. Occasionally, an associated anterior uveitis may contribute to the photophobia with reduction of visual acuity. Pain may be severe if associated scleritis occurs.

The hallmark clinical features include epithelial loss, demonstrated with fluorescein staining, and various amounts of stromal inflammatory infiltration, and/or thinning caused by keratolysis (corneal melting), which may occur at any clock hour of the peripheral cornea, with or without an intervening clear zone from the limbus (Fig. 4.16.1). The process may progress circumferentially, centrally, and posteriorly, potentially resulting in perforation (Fig. 4.16.2). The specific clinical findings at presentation will depend on the severity and rate of progression of the disease, as well as the timing between the onset and clinical evaluation. Corneal melting, once initiated, may progress very rapidly. The amount of stromal loss may be underappreciated because of debris and necrotic material deposited at the



**Fig. 4.16.1 Patient With Early Nasal Peripheral Ulceration Measuring About 1 O’ Clock Hour.** There is inflammatory stromal infiltrate more central to the ulceration with associated episcleral inflammation.





**Fig. 4.16.2 Progressive Circumferential Peripheral Corneal Ulceration.** (A) A 60-year-old female with idiopathic peripheral ulcerative keratitis. Slit-lamp microscopy demonstrates depth of stromal necrosis. There is inflammatory infiltrate at both the peripheral and central edges. (B) Fluorescein staining demonstrates area of ulceration.

base of the ulcer but may become more apparent after corneal scrapings are performed to evaluate for infectious causes. Limbal, conjunctival, and episcleral injections occur frequently. Concurrent scleritis denotes a higher likelihood of active vasculitis.<sup>1</sup> The finding of PUK with scleritis portends a worse ocular and systemic outcome than when scleritis occurs alone.<sup>14</sup> Cataract and glaucoma may occur as a result of the inflammatory process or the use of corticosteroids.

## SYSTEMIC ASSOCIATIONS

Nearly 50% of patients with PUK have an associated systemic disease, with the large majority of these being the collagen vascular diseases (CVDs) (Box 4.16.1). Rheumatoid arthritis (RA) is the most common CVD associated with PUK, likely due to its high prevalence in the population (affecting 2.5%–3% of adults). Granulomatosis with polyangiitis (GPA) (formerly known as Wegener's granulomatosis) and other antineutrophil cytoplasmic antibody (ANCA)-associated vasculitides, although relatively rare, are an important cause of PUK. An associated scleritis may occur in a significant portion of patients, the presence of which, especially when necrotizing, suggests an active vasculitic process.<sup>1</sup> In general, patients with rheumatoid arthritis (RA)-associated PUK usually have an established systemic diagnosis with evidence of advanced disease (subcutaneous nodules, vasculitis, cardiac involvement<sup>15</sup>) or clinical findings supportive of the diagnosis of RA. However, in up to 25% of patients, the PUK may be the initial presenting feature of potentially lethal undiagnosed systemic vasculitis,<sup>1</sup> highlighting the importance of a thorough systemic evaluation. Additionally, in patients with scleritis, the additional presence of PUK portends poor ocular and systemic prognosis.<sup>14</sup>

### BOX 4.16.1 Etiologies of PUK

#### Ocular Noninfectious

- Idiopathic
- Acne rosacea (ocular)
- Mooren's ulcer
- Traumatic, postoperative (may be a presenting feature of a systemic autoimmune disorder)
- Exposure/neuroparalytic keratopathy

#### Ocular Infectious

- Bacterial (*Staphylococcus*, *Streptococcus*, *Gonococcus* [rare])
- Viral (herpes simplex and herpes zoster)
- Amebic (*Acanthamoeba*)
- Fungal

#### Systemic Noninfectious

##### Collagen Vascular Diseases/Vasculitis

- Rheumatoid arthritis (common)
- Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitides
- Granulomatosis with polyangiitis (previously Wegener's granulomatosis) (relatively common)
- Polyarteritis nodosa (less common)
- Microscopic polyangiitis (MPA) (less common)
- Churg–Strauss syndrome (less common)
- Relapsing polychondritis (uncommon)
- Systemic lupus erythematosus (less common)
- Progressive systemic sclerosis/scleroderma (rare)
- Giant cell arteritis (very rare)

##### Other Systemic Autoimmune

- Cicatricial pemphigoid (especially with trichiasis) (rare)
- Inflammatory bowel disease (very rare)
- Sarcoidosis (very rare)
- Sjögren's syndrome
- Leukemia/malignancy (very rare)
- Inflammatory bowel disease (usually associated with a nonulcerative peripheral keratitis)
- Giant cell arteritis (rare)

#### Systemic Infectious

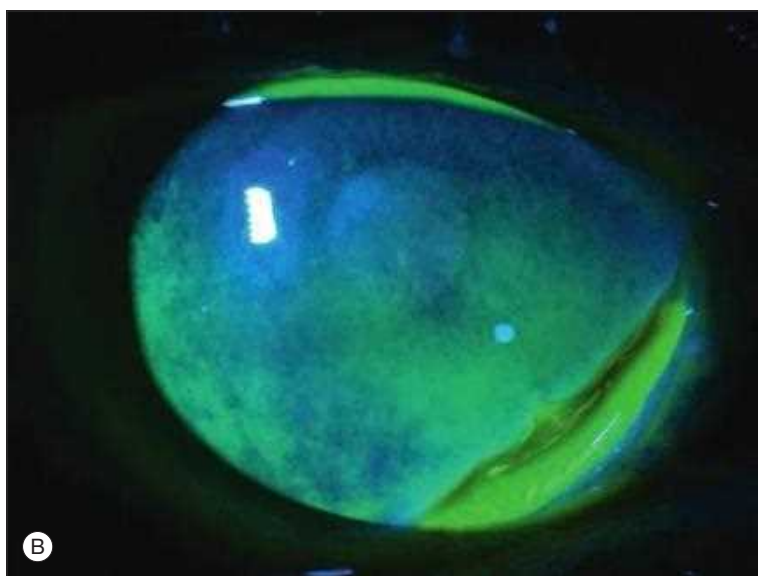
- Gonorrhea
- Bacillary dysentery
- Tuberculosis
- Borreliosis (Lyme disease—very rare)
- Varicella zoster
- Helminthiasis

## DIFFERENTIAL DIAGNOSIS

PUK is a clinical diagnosis and identifying the cause is paramount for the proper management. Infections may cause peripheral corneal inflammation and ulceration and must be rapidly recognized (see Box 4.16.1) because therapy is markedly different from that for PUK caused by autoimmune disease-mediated conditions (Fig. 4.16.3). However, patients with autoimmune disease-associated PUK may become secondarily infected, and thus infectious causes must always be excluded in the initial workup. Local inflammatory causes include *Staphylococcus* marginal ulcers, which begin with an infiltrate adjacent to the limbus separated by a characteristic clear zone with progression to ulceration and rosacea-associated blepharoconjunctivitis and which may result in a peripheral keratitis with or without a clear zone.

Mooren's ulcer is a specific form of unilateral or bilateral PUK that is characterized by a chronic, usually severely painful, single or multicentric corneal ulcer that begins in the periphery adjacent to the sclera with a characteristic steep, undermined, or overhanging central margin and occasionally infiltrated leading central border without associated scleritis<sup>16</sup> (see also Chapter 4.17).

Noninflammatory cause of thinning of the peripheral cornea, as seen with Terrien's marginal degeneration, pellucid marginal degeneration, and marginal furrow can be distinguished from PUK because of lack of inflammation and typically an intact epithelium.



**Fig. 4.16.3** Herpes Simplex Virus Peripheral Keratitis (Polymerase Chain Reaction Positive) (A). Image of the Same Patient With Fluorescein (B).

## DIAGNOSTIC AND ANCILLARY TESTING

A thorough history must be obtained about any previous history of ocular infections, including ocular and nonocular herpetic disease, contact lens wear, and current and previous medication, trauma, or surgery. Because PUK may be an initial or presenting feature of an underlying systemic collagen vascular disease (see [Box 4.16.1](#)), a comprehensive review of systems should be obtained, with particular questions related to various systems involved in the systemic diseases associated with PUK. A complete ophthalmic examination to exclude local pathologies is critical. A comprehensive physical examination should be performed by the appropriate specialist when an underlying systemic process is suspected.

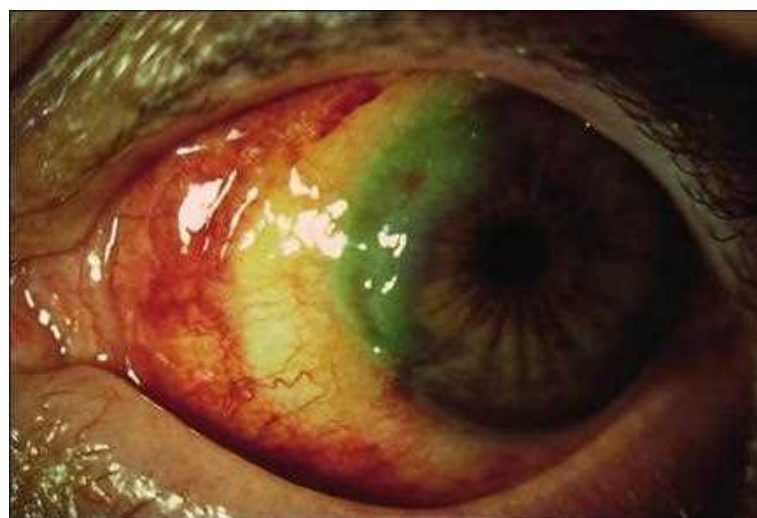
Laboratory tests are listed in [Box 4.16.2](#). Appropriate testing should exclude infectious etiologies.

## TREATMENT

### Medical Treatment

Prior to therapy, infectious causes need to be excluded by the appropriate culture techniques, with antimicrobial therapy administered if infections are suspected. Prophylactic topical antibiotics often are used to prevent secondary infections.

In milder, unilateral cases of peripheral ulcerative keratitis (and typically when not associated with a systemic CVD), topical corticosteroids may be considered as initial therapy (at times combined with conjunctival resection with the latter being not only therapeutic but of potential diagnostic value) ([Fig. 4.16.4](#)). Although topical corticosteroids may be a



**Fig. 4.16.4** Peripheral Ulcerative Keratitis (PUK) Following Conjunctival Resection for Diagnostic and Therapeutic Purposes. Same Patient as in [Fig. 4.16.2](#).

### BOX 4.16.2 Workup of Peripheral Ulcerative Keratitis (Noninfectious)

- CBC
- RF
- Anti-CCP
- c-ANCA and p-ANCA
- ESR and CRP, CIC
- Urine analysis
- Radiographs
  - Chest
  - Sinus

ANCA, antineutrophil cytoplasmic antibody; anti-CCP, anti-cyclic citrullinated protein antibodies; c-ANCA, antineutrophil cytoplasmic antibodies/cytoplasmic staining pattern; CBC, complete count; CIC, circulating immune complexes; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; MPA, microscopic polyangiitis; GPA, granulomatosis with polyangiitis; p-ANCA, antineutrophil cytoplasmic antibodies/perinuclear staining pattern; RF, rheumatoid factor.

useful adjunct in milder cases of RA-associated PUK, it is not effective in GPA, microscopic polyangiitis, Churg–Strauss syndrome, and polyarteritis nodosa. In these cases, topical corticosteroids may promote progression and even enhance perforation and thus must be used judiciously.<sup>17</sup> Topical cyclosporin A may have some benefit as an adjunct when combined with the appropriate systemic therapy.

Systemic corticosteroids, in the form of oral prednisone 1 mg/kg/day, are very commonly used for the acute management of more severe cases of PUK. If progression occurs, pulsed methylprednisolone (0.5–1.0 g) for three consecutive days may be effective.<sup>18</sup> However, corticosteroids alone may be inadequate to control the progressive ocular disease process or impact the systemic morbidity and mortality in patients who have active systemic autoimmune disease. The prolonged use of corticosteroids also will result in significant systemic side effects often necessitating alternative corticosteroid-sparing immunosuppressive agents.

In severe cases of PUK, where there is progression and threat of perforation, therapy with systemic corticosteroids at doses up to 100 mg/day combined with immunosuppressive agents must be used. The presence of vasculitis is a key factor in deciding if systemic immunosuppressive therapy will be required (with concurrent associated scleritis highly suggestive of an active vasculitis process). Other indications for systemic immunosuppressive therapy are noted in [Box 4.16.3](#).

Various systemic immunosuppressive agents, such as methotrexate, azathioprine, mycophenolate mofetil, cyclosporin A, and cyclophosphamide, have demonstrated some clinical efficacy for inflammatory eye disease, including PUK<sup>19,20</sup> ([Table 4.16.1](#)). Although the drugs chosen are somewhat nonspecific and the choices are limited by the lack of prospective clinical trials, accumulated data suggest that cyclosporin A with dosages in the range of 2.5 mg/kg/day may be a reasonable initial choice for idiopathic PUK, especially if nephrotoxicity is not a concern. It may be switched to or combined with an alternative immunosuppressive agent if



**TABLE 4.16.1 Immunomodulatory/Immunosuppressive Therapy in PUK**

Drug	Disease Indication	Dosage
Azathioprine	RA, GPA, and RP (second choice)	2 mg/kg/day
Cyclophosphamide	GPA and PAN (first choice), RA (severe), RP (second choice)	2 mg/kg/day
Methotrexate	RA (first choice), maintenance for GPA	10–25 mg/wk PO or SC
Cyclosporine A	Idiopathic (first choice), RA, RP (second choice)	2–2.5 mg/kg twice daily
Mycophenolate mofetil	Alternative to azathioprine	1 g twice daily, with maximum of 1.5 g twice daily
<b>Biological Agents</b>		
<b>Anti-TNF</b>		
Infliximab	RA, Crohn's disease	For RA 3 mg/kg IV infusion at 0, 2, 6 weeks then every 8 weeks For Crohn's disease, 5 mg/kg 0, 2, and 6 weeks; then every 8 weeks Dosage may be increased interval of treatment reduced
Adalimumab	RA, Crohn's disease	40 mg SC every 4 weeks
Anti-CD22 (B cell) Rituximab	RA, GPA, MPA	For GPA 375 mg/m <sup>2</sup> once weekly for 4 weeks For RA two 1000 mg IV infusion separated by 2 weeks, preceded by 30 minutes with 100 mg of IV prednisolone Dosage may be increased interval of treatment reduced

RA, rheumatoid arthritis; WG, Wegener's granulomatosis; GPA, granulomatosis with polyangiitis; RP, relapsing polychondritis; PAN, polyarteritis nodosa; PO, per os (oral); PUK, peripheral ulcerative keratitis; SC, subcutaneous; IV, intravenous.

### BOX 4.16.3 Indications for Systemic Immunomodulatory Therapy in Peripheral Ulcerative Keratitis (PUK)

1. PUK associated with a potentially lethal systemic disease, such as rheumatoid arthritis, Wegener's granulomatosis, relapsing polychondritis, polyarteritis nodosa
2. PUK with associated scleritis
3. Bilateral Mooren's ulcer
4. Disease progression despite local conjunctival resection and tectonic procedures (e.g., tissue adhesive)

inadequate response or progression occurs. However, if the PUK is found to be associated with a specific systemic CVD, then immunosuppressives proven to be effective for the treatment of the systemic disease should be considered. In cases of GPA-associated PUK (or with more severe or rapidly progressive PUK associated with other CVDs), especially when accompanying necrotizing scleritis exists, cytotoxic immunosuppressives, such as cyclophosphamide (2 mg/kg orally), together with corticosteroids (oral or pulse intravenous) are the first-line therapy, with oral or subcutaneously injected methotrexate useful for maintenance.

The role of biological agents, such as the anti-tissue necrosis factor (TNF) and anti-B cell monoclonal antibodies, in the treatment of PUK has become more accepted because of more cumulative experience in the form of case reports, small series, personal experiences of those who treat severe inflammatory eye disease<sup>21–24</sup> and because of their well-established efficacy in the treatment of systemic inflammatory diseases, such as RA, GPA, spondyloarthropathies, inflammatory bowel disease, and other systemic vasculitides. A recent study found systemic rituximab more effective in controlling GPA-associated progressive PUK (11 of 11) than cyclophosphamide (5 of 10).<sup>25</sup> However, the high cost of these drugs and the uncertain long-term side effects may be limiting more widespread use. Systemic therapy should be continued for a period of at least 6 months to 1 year after initial control of inflammation has been achieved with proper monitoring for drug-related side effects. Lymphoma and other malignancies, some fatal, have been reported in children and adolescent patients treated with

TNF blockers. Long-term close monitoring is required as disease recurrence and relapse may occur (especially when associated with systemic vasculitis), requiring immediate re-initiation of systemic therapy.<sup>25,26</sup>

A physician with expertise in the appropriate use and proper monitoring of potential complications should administer the immunosuppressive regimen.

## Surgical Treatment

Surgical treatments may be required in the management of PUK and to maintain the integrity of the globe but are typically adjunctive because when used alone, they will not influence the underlying immunological process and the potential lethal systemic consequences. Conjunctival resection<sup>27,28</sup> may temporarily remove the local cellular mediators and collagenases important in progression of the disease process and may be of great diagnostic help; for example, identification of significant microangiitis would support the use of immunosuppressive therapy (see Fig. 4.16.4). However, as a therapeutic adjunct, it is limited to localized unilateral disease without any associated systemic inflammatory disorder.

Cyanoacrylate adhesive<sup>29</sup> in conjunction with immunosuppressive therapy may be used in patients with impending perforation and may delay the need for tectonic corneal surgery. Conjunctival flaps, amniotic membrane grafts,<sup>30</sup> and tectonic lamellar and penetrating corneal grafts<sup>31</sup> may be required to preserve the integrity of the globe, with a guarded prognosis,<sup>32</sup> and should be used in conjunction with systemic immunosuppressive therapy.

## COURSE AND OUTCOME

The course, duration, and outcome are variable and dependent on the underlying cause of PUK and on prompt and appropriate management. Many patients with mild or moderate PUK may maintain good vision if the inflammatory process is rapidly controlled. The prognosis is more guarded when PUK is associated with a systemic CVD. Significant visual loss and ocular morbidity may develop with corneal perforation. Both ocular prognosis and systemic prognosis are more guarded when concomitant scleritis exists, especially necrotizing scleritis. Even in cases where no systemic condition can be identified initially, continued surveillance should be maintained. In up to 25% of cases, a systemic disorder is recognized after the presentation of the eye disease. Failure to identify and concurrently treat an associated systemic inflammatory disease may lead to significant ocular and systemic morbidity and even mortality. Systemic immunomodulatory therapy is required when progression occurs with local therapy, an association with collagen vascular diseases, or bilateral Mooren's disease.

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Noninfectious Keratitis

Roshni A. Vasaiwala, Charles S. Bouchard

4.17



**Definition:** Corneal inflammation with no known infectious etiology.

Key Feature

- Diverse group of diseases with corneal inflammation as the common feature.

Associated Feature

- Systemic inflammatory disease.

INTRODUCTION

In this chapter, well-characterized clinical entities that, to date, have no known infectious cause are presented. A list of noninfectious corneal inflammatory diseases is given in Table 4.17.1.<sup>1</sup>

The term *noninfectious keratitis* describes a wide range of entities with some common clinical features and of no known infectious etiology. These include focal or diffuse inflammation, abnormal epithelial healing, and neovascularization.<sup>1</sup> These findings result, in part, from the proximity of the peripheral cornea and its access to the afferent and efferent pathways of the limbal vasculature. Clinical symptoms associated with noninfectious keratitis include photophobia, pain, redness, and decreased visual acuity. Visual loss may result from an irregular surface, corneal opacity, or altered topography from corneal thinning. Approaches to management include (1) determination of the specific cause; (2) promotion of epithelial healing; (3) limitation of ulceration and stromal loss; and (4) support of repair.<sup>1</sup> Both local and systemic routes of therapy may be necessary for optimal outcomes.

THYGESON’S SUPERFICIAL PUNCTATE KERATITIS

Epidemiology and Pathogenesis

Thygeson’s superficial punctate keratitis (TSPK) is a bilateral, epithelial keratitis of unknown cause and was first described by Phillips Thygeson in 1950.<sup>2</sup> It is characterized by an insidious onset of focal corneal epithelial inflammation with a pattern of exacerbations and remissions. The disease can last from 1 month to 24 years, with an average duration of 3.5 years. TSPK usually begins in the second and third decades (mean age, 29 years), with a range of 2.5–70 years. No clear gender predilection exists, although a female preponderance has been suggested.

No established cause for this disease is known, and no clear trigger mechanisms or associated systemic illnesses have been identified. The clinical manifestations of TSPK resemble those of viral keratitis. There are conflicting reports about a viral cause.<sup>3,4</sup>

The characteristic exacerbations and remissions of the disease may be caused by an altered immune response to an unknown exogenous or endogenous antigen. A genetic predisposition may be present because some patients demonstrate an increase in human leukocyte antigen

TABLE 4.17.1 Noninfectious Keratitis

Dermatological	Mucous membrane pemphigoid
	Erythema multiforme (Stevens–Johnson syndrome, toxic epidermal necrolysis)
	Rosacea
Mechanical	Ectropion/entropion
	Contact lens–related keratitis
	Lid defects
	Trichiasis
	Lagophthalmos
	Exophthalmos
	Dellen
Immunological/Allergic	Collagen vascular disease (rheumatoid melting)
	Mooren’s ulcer
	Staphylococcal marginal infiltrate
	Phlyctenular keratoconjunctivitis
	Vernal keratoconjunctivitis
	Graft-versus-host disease
	Atopic keratoconjunctivitis
	Allograft rejection (penetrating keratoplasty [PKP], Descemet’s stripping endothelial keratoplasty [DSEK], Descemet’s membrane endothelial keratoplasty [DMEK])
Lacrimal	Keratoconjunctivitis sicca (primary, secondary)
Neurological	Neurotrophic keratitis (fifth cranial nerve, diabetes)
	Neuroparalytic keratitis (seventh cranial nerve)
Nutritional	Keratomalacia
Postinfectious	Viral (herpes simplex, herpes zoster)
	Bacterial
	Fungal
Postsurgical	Delayed epithelial healing (diabetes mellitus)
	Diffuse lamellar keratitis (DLK)
Traumatic	Chemical injury (alkali, acid)
	Thermal injury
	Radiation
Other	Thygeson’s superficial punctate keratitis
	Acute leukemia
	Pyoderma gangrenosum
	Cutaneous porphyria
	Terrien’s marginal degeneration

(Adapted from Kenyon KR. Decision-making in the therapy of external eye disease. Noninfected corneal ulcers. Ophthalmology 1982;89:44–51.)

(HLA)-Dw3 and HLA-DR3 expression, both of which are HLA loci associated with immune response genes.<sup>5</sup>

Ocular Manifestations

The lesions of TSPK typically appear in the central cornea as small, round or oval, discrete, granular, white-gray, fine, dot-like intraepithelial opacities. The number of lesions ranges from 3–40, and occasionally the lesions appear stellate (Fig. 4.17.1). Stromal edema and associated cellular



**Fig. 4.17.1** Corneal punctate lesions characteristic of Thygeson's superficial punctate keratopathy. These typically occur in a noninflamed eye. (Courtesy Joel Sugar, MD.)



**Fig. 4.17.2** A Patient Who Has Thygeson's Superficial Punctate Keratopathy. Slit-lamp appearance of the fine subepithelial haze and relative lack of corneal inflammation between lesions are shown.

infiltration generally are absent (Fig. 4.17.2). Subepithelial opacities occur in 44% of patients. TSPK is bilateral in 96% of patients. Conjunctival inflammation is absent.

Active lesions are resistant to mechanical removal and appear elevated following fluorescein staining with negative staining. During remissions, the epithelium is flat and without stain over the previous areas of keratitis. Although most lesions are central, peripheral lesions do occur and may be associated with delicate, peripheral vascularization in chronic cases.

Symptoms include tearing, foreign body sensation, photophobia, and burning. Visual acuity may be decreased by the subepithelial opacities but generally returns to normal following resolution of the keratitis.

## Diagnosis

Thygeson<sup>2</sup> outlined five characteristic features of TSPK: (1) chronic, bilateral punctate inflammation; (2) long duration, with remissions and exacerbations; (3) healing without significant scarring; (4) absent clinical response to topical antibiotics; and (5) striking symptomatic and clinical response to topical corticosteroids.

The diagnosis of TSPK generally can be made from the clinical history, results of slit-lamp examination, and the unusually rapid response to topical corticosteroids. No specific systemic associations have been reported for this disease.

## Differential Diagnosis

One of the most characteristic features of TSPK is its lack of associated conjunctival inflammation. All the other disease entities in Box 4.17.1 have either obvious associated features or signs of local or diffuse conjunctival inflammation.

### BOX 4.17.1 Differential Diagnosis of Thygeson's Superficial Punctate Keratitis

- Herpes simplex keratitis
- Other viral keratitis (adenovirus)
- Molluscum contagiosum keratitis
- Exposure keratitis
- Blepharokeratitis
- Neurotrophic keratopathy
- Staphylococcal keratitis
- Traumatic keratopathy
- Dry eye disease
- Acanthamebic keratitis (early)

## Pathology

Corneal scrapings of the lesions demonstrate atypical and degenerated epithelial cells and a mild mononuclear and polymorphonuclear cell infiltrate. Confocal microscopy has demonstrated the accumulation and aggregation of Langerhans' cells in the basal cell layer of the corneal epithelium in association with decreased density of the subepithelial nerve plexus of affected eyes, suggesting an immune response.<sup>6</sup>

## Treatment

Topical low-dose corticosteroids decrease the signs and symptoms of TSPK and probably are most effective during acute exacerbations. The course of the disease may be prolonged with the chronic use of corticosteroids. Topical 2% cyclosporine or tacrolimus<sup>7</sup> have been effective in the management of TSPK, with few side effects.<sup>8</sup> Therapeutic bandage contact lenses may be used to improve visual acuity and improve comfort in more symptomatic patients. The use of antiviral agents has been evaluated, but no convincing evidence exists that they are effective.<sup>9</sup> Photorefractive keratectomy may reduce the recurrences in the central ablated cornea, suggesting that some unknown inflammatory signal may reside in the superficial corneal stroma.<sup>10,11</sup>

## Course and Outcome

Most patients with TSPK recover completely with no loss of visual acuity, although up to 44% may be left with faint subepithelial opacities.

## SUPERIOR LIMBIC KERATOCONJUNCTIVITIS OF THEODORE

### Epidemiology and Pathogenesis

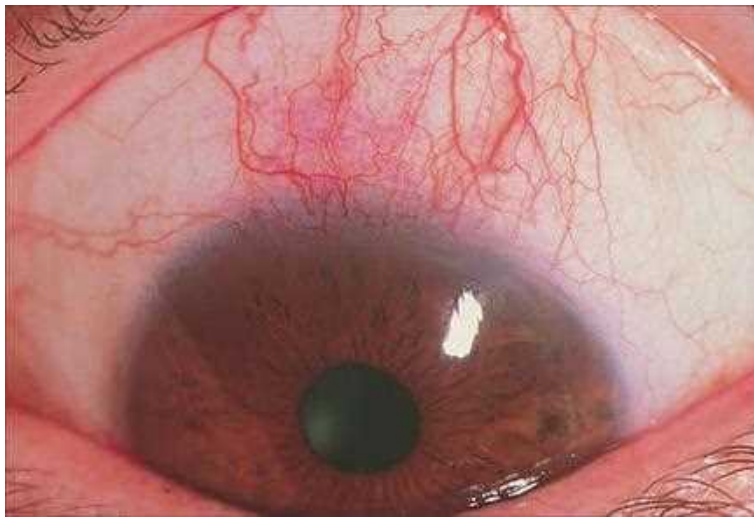
Superior limbic keratoconjunctivitis (SLK) is a chronic, focal, ocular surface disease characterized by episodes of recurrent inflammation of the superior cornea and limbus, as well as of the superior tarsal and bulbar conjunctiva.<sup>12</sup> It occurs primarily in adults age 30–55 years and is more common in women (3:1). It typically is bilateral, but unilateral disease may occur.

Although the pathophysiology is unclear, mechanical trauma from tight upper lids or loose redundant conjunctiva could lead to the known disruption of normal epithelial development.<sup>13</sup> This mechanical hypothesis is supported by the increased lid apposition in patients with exophthalmic thyroid disease, who are known to have an increased incidence of SLK,<sup>14</sup> as well as increased lubrication being an effective treatment modality.<sup>15</sup>

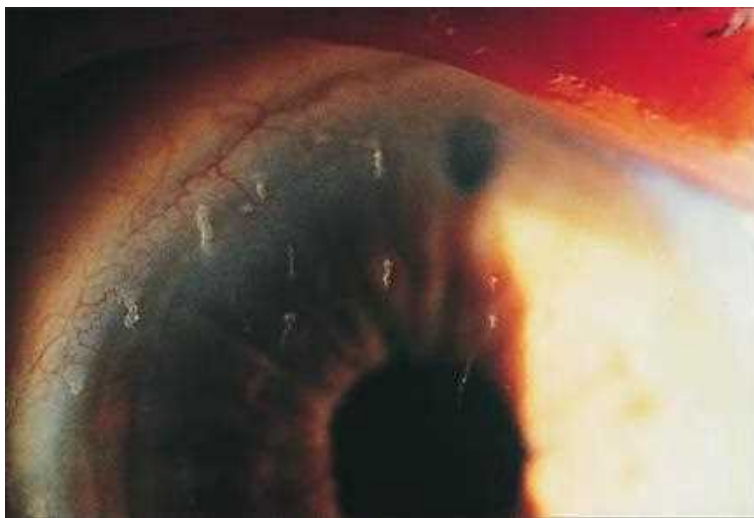
### Ocular Manifestations

The classic sign of SLK is bilateral local hyperemia of the superior bulbar conjunctiva (Fig. 4.17.3), which also appears keratinized, thickened, and redundant. The opposing superior palpebral conjunctiva demonstrates a delicate papillary reaction with associated hyperemia. Fine fluorescein or Rose Bengal punctate staining usually is present. Keratoconjunctivitis sicca occurs in 25%–50% of patients and must be evaluated in all patients with SLK.<sup>14</sup> A fine filamentary keratitis of the superior cornea and limbus may be present (Fig. 4.17.4). A delicate superior corneal pannus suggests more long-standing disease.





**Fig. 4.17.3 Superior Limbic Keratoconjunctivitis.** Slit-lamp appearance of focal superior bulbar conjunctival injection is shown with Rose Bengal staining.



**Fig. 4.17.4 Superior Limbic Keratoconjunctivitis.** Slit-lamp appearance of superior filamentary keratitis is shown.

Characteristic symptoms include a gradual onset of burning, tearing, foreign body sensation, mild photophobia, and sometimes mucus discharge. Patients may notice pain and decrease in vision if the filamentary component is severe or occurs within the visual axis.

## Diagnosis

The diagnosis of SLK is made from the history of irritation, photophobia, and the specific pattern of superior corneal and conjunctival inflammation and staining. Superior filamentary keratitis supports the diagnosis.

## Differential Diagnosis

The differential diagnosis of SLK is shown in [Box 4.17.2](#). Filamentary keratitis may occur in up to 40% of patients with SLK. The distribution of filaments on the upper cornea and limbus may help differentiate SLK from dry eye disease (DED), in which filaments occur more typically on the lower half of the cornea.

An inflammatory condition associated with soft contact lens wear may resemble SLK. Although many signs and symptoms of this contact lens-related SLK are similar to those of SLK of Theodore, filaments are usually absent, vision may be decreased (unusual in SLK), and no female predilection or associated thyroid dysfunction exists. More importantly, symptoms generally improve with discontinuation of contact lens wear. Contact lens-induced keratoconjunctivitis may be a more appropriate term for this entity, with SLK reserved for the specific condition described by Theodore.<sup>12</sup>

SLK-like inflammation can occur in patients with chronic ocular graft-versus-host disease (GVHD).<sup>16</sup> These patients present with the typical signs of SLK, including conjunctival injection and staining of the superior conjunctiva and cornea. They also tend to show good response to the

### BOX 4.17.2 Differential Diagnosis of Superior Limbic Keratoconjunctivitis of Theodore

#### Keratoconjunctivitis With Filaments

- Ptosis/lid occlusion
- Keratoconjunctivitis sicca
- Neurotrophic keratitis
- Herpes simplex epithelial keratitis
- Recurrent corneal erosion
- Trauma
- Bullous keratopathy
- Medicamentosa

#### Keratoconjunctivitis Without Filaments

- Keratoconjunctivitis induced by contact lens
- Limbal vernal keratoconjunctivitis
- Phlyctenulosis
- Thygeson's superficial punctate keratitis

common treatments for SLK. If this type of inflammation goes undiagnosed in patients with chronic GVHD, they can develop limbal stem cell deficiency, scarring, and loss of vision.<sup>16</sup>

## Systemic Associations

Systemic associations include thyroid disease and collagen vascular disease. In one study in a referral university setting, 65% of patients who had SLK were found to also have thyroid dysfunction.<sup>14</sup> Of those patients who had SLK and thyroid disease, 90% had ophthalmopathy, and 49% had severe thyroid disease necessitating orbital decompression. SLK is a strong negative prognostic factor for patients who have thyroid disease.<sup>14</sup>

## Pathology

The superior bulbar conjunctiva demonstrates keratinization of the epithelium with intracellular accumulation of glycogen and abnormal chromatin. A predominantly polymorphonuclear infiltrate occurs. Acanthosis, squamous metaplasia, dyskeratosis, balloon degeneration of nuclei, and decreased goblet cell density, and conjunctival stromal edema occur. Upregulation of transforming growth factor- $\beta_2$  and tenascin support an increase in mechanical stress.<sup>15</sup> Altered expression of cytokeratins also suggests an abnormality of epithelial differentiation.<sup>17</sup> One study found elevated levels of matrix metalloproteinases (MMP-1 and MMP-3) in surgical specimens from patients with SLK compared with controls, suggesting a possible role of MMP imbalance in the pathogenesis.<sup>18</sup>

Changes in the superior palpebral conjunctiva are somewhat different, with an increase in polymorphonuclear neutrophil leukocytes, lymphocytes, and plasma cells. The overlying epithelium contains hypertrophic goblet cells.

## Treatment

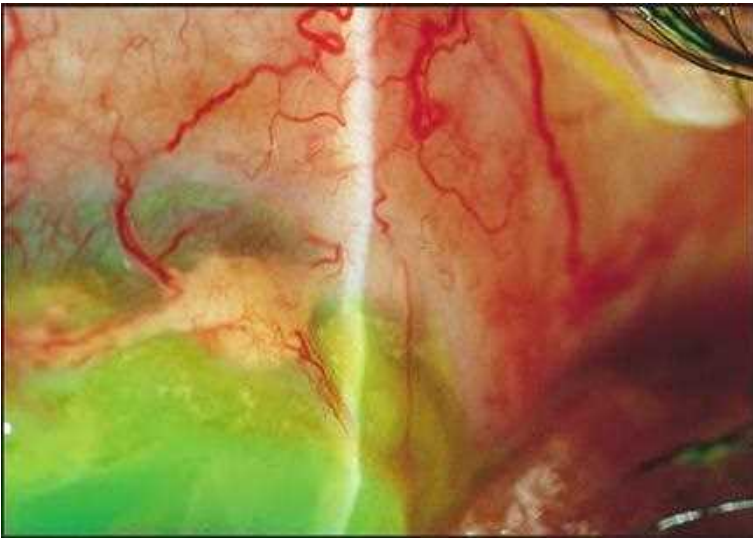
Because a large proportion (25%–50%) of patients who have SLK also have DED, care must be taken to treat any concurrent aqueous tear deficiency with unpreserved tears and, if indicated, punctal occlusion.<sup>19</sup> Associated blepharitis also must be managed. Any lid surgery, especially ptosis repair, should be evaluated carefully because possible exacerbation of SLK may be caused by lid tightening and possible secondary exposure.

Surgical approaches to treatment involve the destruction or resection of the presumed abnormal conjunctival epithelium. Simple resection or recession of the conjunctiva with Tenon's capsule can be very effective. Use of cryotherapy and thermocautery has been reported, with symptom improvement in 75% of patients treated with the latter.<sup>20</sup>

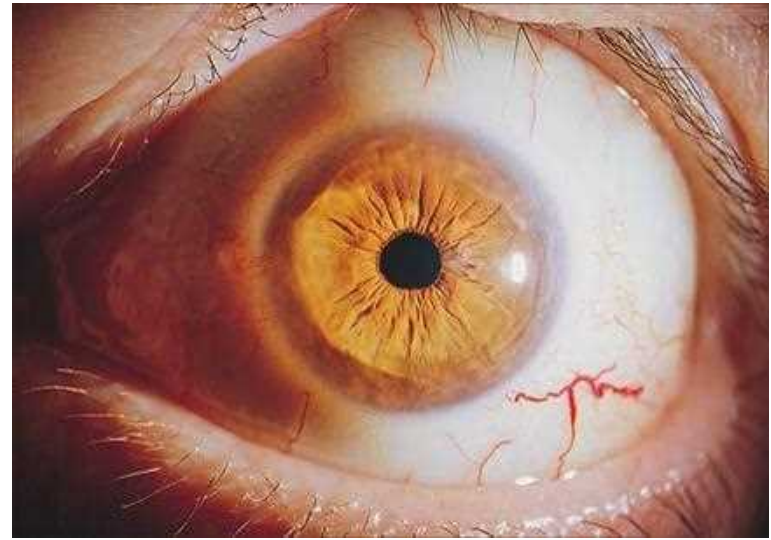
Bandage contact lenses and pressure patching have been used to manage severe symptoms of photophobia, ocular discomfort, and associated filamentary keratitis. SLK often recurs, however, after lens wear has been discontinued.

Topical hypertonic saline solutions may help reduce the excessive mucus production and associated filaments. *N*-acetylcysteine (Mucomyst), in 10%–20% solution, may offer relief in severe cases. Topical cromolyn or lodoxamide may offer symptomatic relief of itching.

The chronic use of topical corticosteroids should be discouraged. Topical cyclosporine A and autologous serum have been reported to be effective in



**Fig. 4.17.5 Acute Mooren's Ulcer.** Peripheral thinning and an overlying epithelial defect are present in an inflamed eye. (Courtesy Joel Sugar, MD.)



**Fig. 4.17.6 Mooren's Ulcer.** Peripheral thinning is present in a relatively quiet eye in this patient who had a history of Mooren's ulcer, now in remission.

some cases.<sup>21,22</sup> Topical vitamin A eyedrops may be variably effective during inflammatory periods.<sup>23</sup> Topical tacrolimus 0.03% ointment has been successful in the treatment of cases refractory to the above treatment modalities.<sup>24</sup> Topical rebamipide, a medication initially used to increase gastric mucosa mucin, has been shown to improve SLK in patients with thyroid disease.<sup>25</sup>

## Course and Outcome

Many of the proposed therapies have been effective, and the overall prognosis is excellent because the visual axis usually is not affected.

## MOOREN'S ULCER

### Epidemiology and Pathogenesis

Mooren's ulcer, a rare, chronic, painful, peripheral ulcerative keratitis (PUK), was first described in detail as a clinical entity by Mooren in 1867.<sup>26</sup> Two clinical types of primary Mooren's ulcer have been described.<sup>27</sup> The limited type is typically unilateral, occurs in the fourth decade or later, and is more responsive to local surgical and medical therapy. The second type, which is more resistant to systemic immunosuppression, involves a bilateral, painful, relentless, progressive destruction of the cornea, usually in younger individuals (third decade), many of whom are of African descent.

The pathogenesis of Mooren's ulcer is unknown but appears to involve an autoimmune reaction against a specific target molecule in the corneal stroma, which may occur in genetically susceptible individuals.<sup>28</sup> Both cellular and humoral mechanisms have been postulated.<sup>29</sup> The conjunctival epithelium demonstrates increased levels of several inflammatory mediators.<sup>30</sup>

Interestingly, there have been several reported cases of Mooren's ulcer in patients with concurrent hepatitis C whose corneal inflammation responded to systemic interferon- $\alpha$  (IFN- $\alpha$ ).<sup>31</sup> These cases suggest a common antigenic source.<sup>32</sup>

### Ocular Manifestations

Mooren's ulcer is characterized by a progressive, crescentic, peripheral corneal ulceration that is slightly central to the corneoscleral limbus. It is associated with a characteristic extensive, undermined, "overhanging" edge (Fig. 4.17.5). It progresses with an anterior, stromal, yellow-white infiltrate at the advancing margin. An overlying epithelial defect then develops. Progressive stromal melting follows, which affects first the deeper and subsequently the anterior stroma. The ulcer progresses circumferentially and centrally. A re-epithelialized, conjunctivalized, thinned cornea remains. Patients in whom Descemet's membrane has a minimal overlying stroma may be predisposed to perforation either spontaneously or following minor trauma.

In the more aggressive form of Mooren's ulcer, the inflammation may affect the entire cornea and perilimbal tissue. Perforation is not uncommon

in this form, occurring in about one third of patients. Associated cataract, secondary glaucoma, and uveitis may be seen.

Chronic Mooren's ulcer ultimately results in a central island of hazy stromal tissue with severe peripheral thinning (Fig. 4.17.6). No scleral involvement occurs, although associated conjunctival and episcleral inflammation may be seen. No clear zone exists between the ulcer and the limbus, which distinguishes Mooren's ulcer from other forms of PUK. Visual loss as a result of severe, irregular corneal astigmatism and scarring is common.

### Diagnosis

Mooren's ulcer is, by definition, not associated with any systemic abnormality, except for the occasional association with hepatitis C. Collagen vascular disease must be excluded. Patients should also be tested for hepatitis C virus.<sup>32</sup> Patients who have other systemic diseases, including leukemia, pyoderma gangrenosum, and syphilis, also may develop PUK.<sup>33</sup>

Patients complain of severe ocular pain, photophobia, and tearing. The overlying epithelium in other degenerative corneal lesions remains intact.

### Differential Diagnosis

Although there are many other causes of PUK (Box 4.17.3), Mooren's ulcer is an unusual and severe inflammatory disease without known associated systemic disease (except perhaps hepatitis C).

### Pathology

Three zones of corneal involvement have been described. The superficial stroma contains lymphocytes, plasma cells, polymorphonuclear leukocytes, disrupted collagen lamellae, and neovascular elements. The mid-stroma demonstrates an increase in the number of fibroblasts, and the deep stroma is infiltrated primarily by macrophages. The epithelial basement membrane is disrupted at the leading edge, and the characteristic infiltrate contains primarily neutrophils.

Conjunctival resections from patients with Mooren's ulcer demonstrate increased levels of inflammatory mediators, including vascular cell adhesion molecule-1 (VCAM-1), very late activation-4, intercellular adhesion molecule-1 (ICAM-1), and lymphocyte function-associated antigen-1.<sup>27</sup>

### Treatment

A stepladder approach to manage this aggressive disease has been proposed. This includes local, systemic, and surgical therapies.<sup>34</sup> Initial treatment should begin with topical corticosteroids, followed by conjunctival resection if the inflammation is not controlled. Topical cyclosporine drops and tacrolimus ointment have been effective in some cases.<sup>35</sup> In addition, bandage contact lenses, as well as amniotic membrane transplantation,<sup>36</sup> may reduce discomfort and promote epithelial healing in refractory cases. Topical administration of IFN- $\alpha$  may be helpful.<sup>37</sup>



**BOX 4.17.3 Differential Diagnosis of Mooren's Ulcer****Collagen Vascular Disease**

- Rheumatoid arthritis
- Juvenile rheumatoid arthritis
- Systemic lupus erythematosus
- Wegener's granulomatosis
- Progressive systemic sclerosis
- Relapsing polychondritis
- Polyarteritis nodosa
- Cogan's syndrome

**Oculodermatological Conditions**

- Stevens–Johnson syndrome
- Rosacea
- Psoriasis
- Benign mucous membrane pemphigoid
- Ichthyosis
- Pyoderma gangrenosum

**Corneal Degenerations**

- Terrien's marginal degeneration
- Pellucid marginal degeneration
- Involutional marginal degeneration

**Other**

- Staphylococcal marginal infiltrate

Systemic immunosuppression with cyclophosphamide followed by azathioprine may be initiated if treatment with conjunctival resection fails. Systemic immunosuppressive treatment of the more aggressive bilateral disease has included corticosteroids, cyclosporine, methotrexate, and infliximab.<sup>34,38,39</sup> Systemic IFN- $\alpha_{2b}$  has been effective in the treatment of patients who are positive for hepatitis C virus and have Mooren's ulcer.<sup>31</sup>

Systemic workup for vasculitis or collagen vascular disease is mandatory for patients who are suspected of having Mooren's ulcer. The primary goal of therapy is to slow the severe progression of the corneal loss, although 50% of cases may be unresponsive to all medical therapy.<sup>34</sup>

Small perforations can be managed with cyanoacrylate adhesive but large perforations require lamellar or full-thickness keratoplasty.

Surgical management for visual rehabilitation is a challenge as penetrating keratoplasty is usually associated with disease recurrence, graft rejection, and melting.

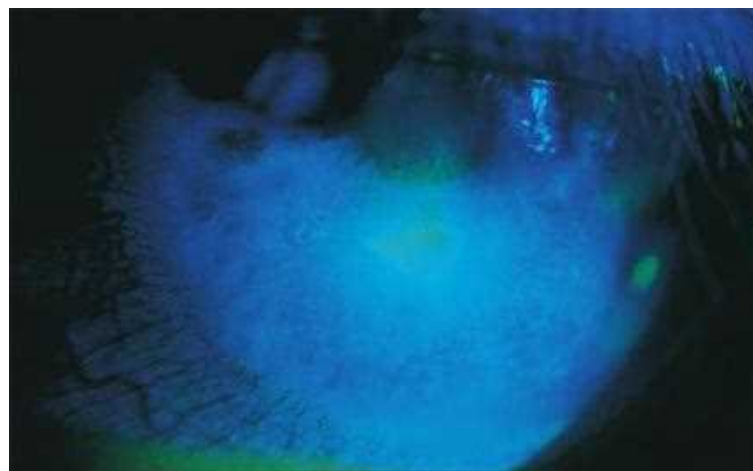
**Course and Outcome**

Most patients who have unilateral disease respond fairly well to topical corticosteroids and conjunctival resection. For more severe bilateral cases, the prognosis is poor.

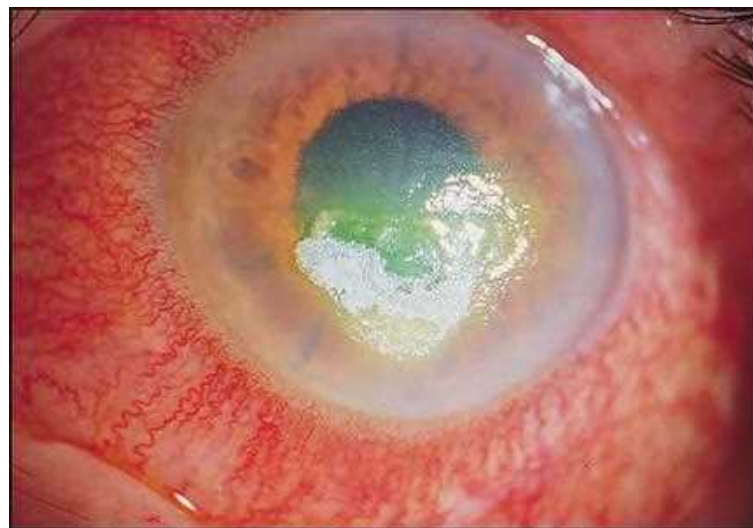
**NEUROTROPHIC KERATITIS****Epidemiology and Pathogenesis**

Lesions of the fifth cranial nerve from the trigeminal nucleus to the cornea may lead to abnormalities of the normal corneal sensation and trophic stimulation. The trophic ulceration that results leads to abnormal repair of corneal epithelium secondary to increased apoptosis and reduced proliferation of epithelial cells and reduced reflex tearing.<sup>40</sup> Normally, a bidirectional interaction occurs between epithelial cells and nerve endings. Adrenergic stimulation leads to increased cyclic adenosine monophosphate, which inhibits mitosis.<sup>41</sup> Cholinergic stimulation leads to increased cyclic guanosine monophosphate, which increases cell turnover.<sup>41</sup> Substance P may play a role in normal and abnormal epithelial cell turnover.<sup>41–43</sup> Disruption of the sensory and sympathetic pathways is thought to lead to decreased cell division.<sup>41</sup> Cells, therefore, fail to resist the effects of trauma (microtrauma) and desiccation, which normally lead to reflex tearing.<sup>44,45</sup> Increased inflammatory cytokines, such as interleukin-6 (IL-6), may play a role in nerve degeneration in herpes simplex infection.<sup>46</sup>

Varicella zoster keratitis (8% of patients) and herpes simplex keratitis are the most common causes of neurotrophic keratitis. In addition to traumatic damage to the ophthalmic branch of the fifth cranial nerve following various surgical procedures, stroke, irradiation to eye or adnexa, aneurysm, multiple sclerosis, toxic chemical reactions, and brainstem hemorrhages may lead to trigeminal dysfunction and corneal ulceration.



**Fig. 4.17.7 Neurotrophic Keratitis.** Slit-lamp appearance in a patient who developed a paracentral epithelial defect with minimal subepithelial inflammation.



**Fig. 4.17.8 Neurotrophic Keratitis.** Slit-lamp appearance in a patient who has a partial seventh nerve palsy. He was treated with ciprofloxacin and developed deposits of the antibiotic on the cornea.

**Ocular Manifestations**

Mackie<sup>47</sup> characterized three stages of neurotrophic keratitis. Stage I includes an often subtle irregular corneal surface, which later develops into an easily recognized punctate keratitis. Stage II is characterized by a frank epithelial defect, which typically is associated with mild anterior stromal edema and inflammation (Fig. 4.17.7). Folds in Descemet's membrane often develop. The epithelium at the edges of the defect tends to be characteristically "heaped up" or "rolled" with grayish, swollen epithelium. The ulcer usually is found in the lower, exposed, paracentral cornea and is generally oval in shape (Fig. 4.17.8). Stage III involves stromal melting and occasionally perforation. Characteristic symptoms include red eye, mild foreign body sensation, blurred vision, and lid edema.

**Diagnosis**

A history of surgery, irradiation, stroke, or decreased hearing should be established, in addition to a previous history of red eye. Decreased corneal sensation is evident with or without a decrease in conjunctival sensation. Decreased aqueous tear production may be associated with neurotrophic keratopathy.<sup>48</sup>

**Differential Diagnosis**

The differential diagnosis of decreased corneal sensation is given in Box 4.17.4. Herpes simplex and herpes zoster are the most common causes, and each has a characteristic initial clinical presentation. Topical drug toxicity, contact lens wear, dry eye, chronic exposure, and limbal stem cell deficiency may contribute to decreased corneal sensation. Finally, diabetes is a well-described cause of neurotrophic keratitis and may result in epithelial healing problems.



### BOX 4.17.4 Differential Diagnosis of Decreased Corneal Sensation

- Lesions to the ophthalmic division of the trigeminal nerve
  - Surgery
  - Acoustic neuroma
  - Trauma
- Infectious disease
  - Herpes simplex
  - Herpes zoster
- Contact lens wear
- Diabetes
- Topical agents
  - Anesthetics
  - Beta-blockers
  - Nonsteroidal anti-inflammatory agents

## Systemic Associations

Diabetic peripheral neuropathy may result in decreased corneal sensation.

## Pathology

Histological changes include acanthotic, hyperplastic epithelium with rete peg formation, stromal scarring, destruction or disruption of Bowman's membrane, and corneal neovascularization. Intracellular edema, irregularity and loss of the epithelial microvilli, and loss of the superficial epithelial cell layer of the cornea may be seen.<sup>40</sup> Epithelial cell attachments are abnormal.

## Treatment

The goals of treatment are to prevent progression of epithelial damage, promote healing, facilitate repair, and prevent recurrence. For mild punctate keratitis, frequent lubrication with unpreserved artificial tear drops and ointment may be effective. Aqueous tear deficiency should be documented. For more severe disease, punctal occlusion may be indicated.

For small epithelial defects, topical ointment with patching may aid in healing. Mild topical corticosteroids may reduce the associated anterior stromal scarring but should be used cautiously.

For persistent epithelial defects and stromal lysis, patching or soft contact lens wear may be tried, but patients usually respond best to lateral or medial tarsorrhaphy (temporary with suture or botulinum-A toxin injection,<sup>48</sup> or permanent). Improved corneal sensation and promotion of epithelial healing may occur following treatment with topical nerve growth factor.<sup>49,50</sup> Collagenase inhibitors play an important role in normal corneal health and repair.<sup>51</sup> Collagenase inhibitors may play a supportive role in the management of neurotrophic keratopathy.<sup>52</sup> Autologous serum may be effective.<sup>53,54</sup> Scleral contact lenses may offer superior long-term efficacy compared with soft bandage lenses.<sup>55,56</sup> Conjunctival flaps may be necessary in severe cases. Corneal perforation can be managed with cyanoacrylate glue and lamellar or penetrating keratoplasty. Amniotic membrane in its sutureless form or secured with or without fibrin glue has been used as an effective patch graft in the management of persistent epithelial defects and deep corneal neurotrophic ulcers refractory to conventional treatment.<sup>57–60</sup> Management of any eyelid abnormality must be aggressive.

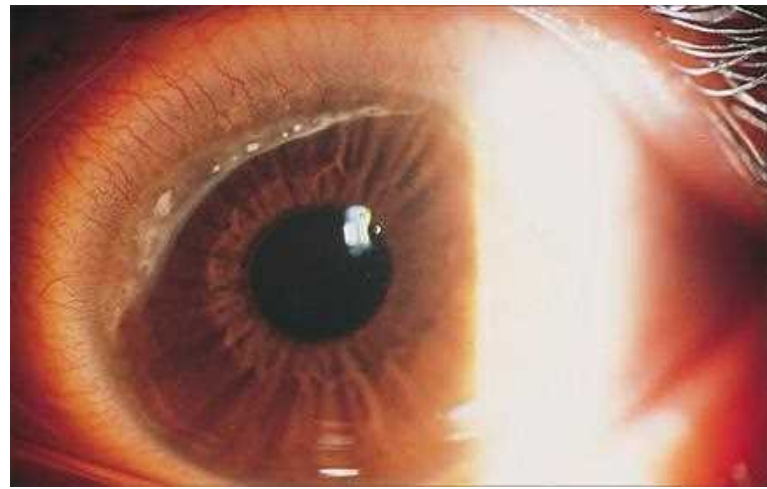
## Course and Outcome

Patients with superficial punctate staining should be maintained on daily and evening lubrication. Persistent epithelial defects respond best to tarsorrhaphy. Patients should be advised that neurotrophic ulcerations tend to recur and can be difficult to heal. More severe sterile or infectious ulcers may progress to descemetocoele or perforation.

## TERRIEN'S MARGINAL DEGENERATION

### Epidemiology and Pathogenesis

Terrien's marginal degeneration is a slowly progressive, bilateral, peripheral corneal thinning disorder associated with corneal neovascularization, opacification, lipid deposition, and thinning.<sup>61</sup> High degrees of astigmatism, particularly against-the-rule, may be seen. Up to one third of patients



**Fig. 4.17.9 Terrien's Marginal Degeneration.** Advancing lipid deposits and superficial vascular pannus are present. (Courtesy Joel Sugar, MD.)

may have episcleral or scleral inflammation. Patients typically are 20–40 years of age, although it may present in childhood. It is found more commonly in men than in women (3:1).<sup>62</sup>

The cause is unknown. Two types have been documented. One type occurs primarily in the older population. It usually is asymptomatic and slowly progressive. The other, more inflammatory type characteristically occurs in younger patients and may be associated with episcleritis or scleritis.<sup>63</sup>

## Ocular Manifestations

Terrien's degeneration usually starts superiorly with mild, punctate, sub-epithelial and/or anterior stromal opacities. A clear area exists between the opacities and the limbus. This opacification is followed by the development of a peripheral, superficial, fine vascular pannus, which progresses over years to include a linear subepithelial opacity at the advancing edge. The thinning slowly begins between the limbus and the line of lipid deposition. Typically, a steeper sloping of the cornea occurs at the advancing edge (Fig. 4.17.9), without the overlying edge characteristic of Mooren's ulcer. The thinning progresses circumferentially, but the overlying epithelium typically remains intact. Perforation is rare but may occur. Corneal hydrops has been reported, which may present as a clear intracorneal pocket of aqueous rather than stromal clouding.<sup>64</sup>

Irregular corneal astigmatism from progressive flattening of the vertical meridian and high against-the-rule astigmatism is characteristic. Initial conservative management includes the use of rigid gas-permeable contact lenses. Rarely, Terrien's degeneration may present as a pseudo-ptyerygium with a broad, flat, leading edge that arises in an oblique axis. Underlying corneal thinning should be monitored carefully. Intraocular lenses have been placed successfully through the furrow.

## Diagnosis

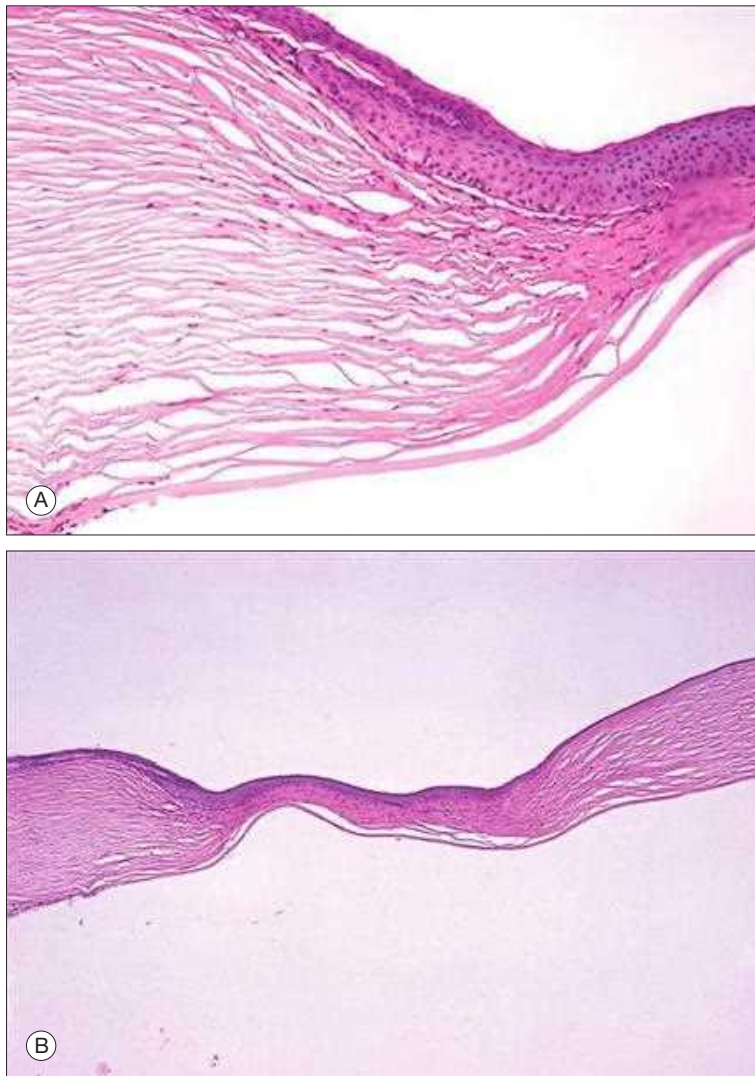
Terrien's marginal degeneration is distinguished from other peripheral corneal thinning disorders by the lack of inflammation, presence of superficial vascularization, advancing linear deposition of lipid, lack of epithelial defect, and slow progressive course. Collagen vascular disease should be ruled out. No known systemic disorders occur with Terrien's marginal degeneration.

## Differential Diagnosis

The differential diagnosis of Terrien's marginal degeneration is outlined in Box 4.17.5. Terrien's generally is easy to distinguish from Mooren's ulcer because usually no pain or inflammation occurs. The epithelium is intact, and no overhanging edge exists. Marginal furrow degeneration is bilateral and avascular, with only minimal, if any, thinning.

## Pathology

Bowman's membrane is typically absent or has degenerated (Fig. 4.17.10). Thinning and occasional breaks in Descemet's membrane may be seen. Subepithelial fibrillar collagen degeneration has been demonstrated by



**Fig. 4.17.10 Terrien's Degeneration.** (A) Histological section shows limbus on the left (iris not present) and central cornea to the right. (B) Note the marked stromal thinning, thickened epithelium, and loss of Bowman's membrane on the limbal side.

#### BOX 4.17.5 Differential Diagnosis of Terrien's Marginal Degeneration

- Marginal furrow degeneration
- Dellen
- Collagen vascular disease
- Pellucid marginal degeneration
- Sclerokeratitis
- Keratoconjunctivitis sicca
- Staphylococcal marginal keratitis
- Infectious corneal ulcer

light microscopy, and an unknown stromal material in phagocytic cells has been demonstrated by electron microscopy.<sup>63</sup>

### Treatment

Usually no treatment is required, unless perforation or impending perforation occurs. Severe astigmatism may be managed with spectacles or rigid contact lenses. More severe thinning may require crescentic, full-thickness, or lamellar keratoplasty.<sup>65</sup> Eccentric, full-thickness grafts have been performed, with an increase in graft rejection. Recently, case reports have been published in which corneal collagen cross-linking has been used to halt progression and even reverse some of the degenerative changes seen in the condition.<sup>66</sup>

### Course and Outcome

Most patients who have Terrien's degeneration do not progress to corneal perforation and can be managed successfully with glasses or rigid contact



**Fig. 4.17.11** Patient with lax eyelid syndrome (LES)

lenses. Because Terrien's degeneration typically lacks an associated epithelial defect, the risk of infectious keratitis and acute corneal thinning is low.

## LAX EYELID CONDITION, LAX EYELID SYNDROME, AND FLOPPY EYELID SYNDROME

### Epidemiology and Pathogenesis

The term “floppy eyelid syndrome” (FES) was first used in 1981 to describe the association of rubbery, lax upper eyelids with tarsal papillary conjunctivitis seen in young obese men.<sup>67</sup> In 1994, Van den Bosch and Lemji proposed a new classification system to include three related conditions: (1) lax eyelid condition (LEC), describing patients with laxity of the eyelids in patients of any age without conjunctivitis, and not necessarily obese (Figs. 4.17.11 and 4.17.12); (2) lax eyelid syndrome (LES), in patients with LEC who also had chronic conjunctivitis; and (3) floppy eyelid syndrome (FES), in patients who had LES and were obese.<sup>68,69</sup> Eyelid laxity is actually a very common, but overlooked, clinical finding. Ansari reported a high prevalence (54%) of eyelid laxity in the upper or lower eyelids in a veteran's administration population associated with significant ocular surface morbidity.<sup>70</sup>

Obstructive sleep apnea (OSA) is highly prevalent, affecting 34% of men and 17% of women.<sup>71</sup> OSA is a significant public health problem that has remained undiagnosed in 82% of patients and is responsible for \$115 billion dollars in healthcare expenditures annually in the United States.<sup>72</sup> Woog first reported the association between OSA and FES in 1990, with multiple subsequent studies supporting this association.<sup>73–80</sup> Chambe et al. showed that LEC/FES was observed in 15.8% of patients without OSA, 25.8% of patients with OSA, and 40% of patients with severe OSA defined as the apnea-hypopnea index (AHI) score > 30.<sup>77</sup> In another study that included 89 patients with OSA, 16% were found to have FES, and 60.67% were found to have increased eyelid laxity.<sup>79</sup> Additionally, Acar et al. studied 51 patients and monitored the effect of positive airway pressure on clinical symptoms of FES. A significant improvement occurred in FES with



positive airway pressure.<sup>78</sup> A positive correlation between the severity of FES and the severity of OSA has also been reported (Table 4.17.2).<sup>77,78</sup> Robert also reported that LEC itself is strongly associated with OSA.<sup>81</sup>

The pathology of FES was first reported by Netland et al. in 1994, and these authors demonstrated a decreased concentration of elastin in the tarsal plate of patients with FES.<sup>82</sup> This observation was later corroborated by Schlötzer-Schrehardt et al., who demonstrated papillary hyperplasia, keratinization, and subepithelial infiltrate of the tarsal conjunctiva, as well as co-localization of elastin loss with increased presence of matrix metalloproteinase, particularly MMP-7 and MMP-9, in the tarsal conjunctiva and near the ciliary roots, accounting for the clinical sign of lash ptosis (Figs. 4.17.13 and 4.17.14).<sup>83</sup> Ischemia–reperfusion injury has been proposed as the most likely mechanism in LEC.

TABLE 4.17.2 Clinical Findings in Patient With Lax Eyelids and Obstructive Sleep Apnea					
Clinical Finding	Control No OSA	Mild OSA	Moderate OSA	Severe OSA	Sig ( <i>P</i> < .05)
FES	23.1%	41.7%	66.7%	74.6%	<i>P</i> < .01
OSDI	12.57 +/- 17.64	22.90 +/- 16.78	45.94 +/- 22.03	56.68 +/- 22.5	<i>P</i> < .01
Schirmer (mm)	10.76 +/- 3.58	9.83 +/- 2.53	7.73 +/- 2.42	6.97 +/- 2.15	<i>P</i> < .01
TBUT (seconds)	10.53 +/- 3.64	9.46 +/- 2.40	7.29 +/- 2.13	6.82 +/- 2.20	<i>P</i> < .01
Corneal Stain	0.26 +/- 0.60	0.40 +/- 0.71	0.98 +/- 0.72	1.14 +/- 0.90	<i>P</i> < .01

FES, floppy eyelid syndrome; OSA, obstructive sleep apnea; OSDI, ocular surface disease index; TBUT, tear break-up time.



Fig. 4.17.12 Patient with lax eyelid condition (LEC)

The pathophysiology of OSA is complex and incompletely understood.<sup>84</sup> A systemic elastin dysfunction may account for the multisystem changes reportedly associated with OSA. Sériès et al. demonstrated elastin changes in soft palate specimens from patients with OSA undergoing uvulopalatopharyngoplasty (UPPP).<sup>85</sup> Ryan et al. demonstrated selective activation of inflammatory cytokines in an in vitro model of intermittent hypoxia.<sup>86</sup> They further demonstrated that circulating tumor necrosis factor alpha (TNF-α) levels were higher in patients with OSA (2.56 pg/mL; interquartile range [IQR] 2.01–3.42 pg/mL) than in control subjects (1.25 pg/mL; IQR 0.94–1.87; *P* < .001) but normalized with continuous positive airway pressure (CPAP) therapy (1.24 pg/mL; IQR 0.78–2.35 pg/mL; *P* < .002). Circulating neutrophil levels were higher in patients with OSA than in control subjects. Taban et al. found elevated plasma leptin levels in patients with LES. Leptin was proposed to trigger the inflammatory cascade by up-regulating MMP-9, resulting in breakdown of elastin.<sup>87</sup>

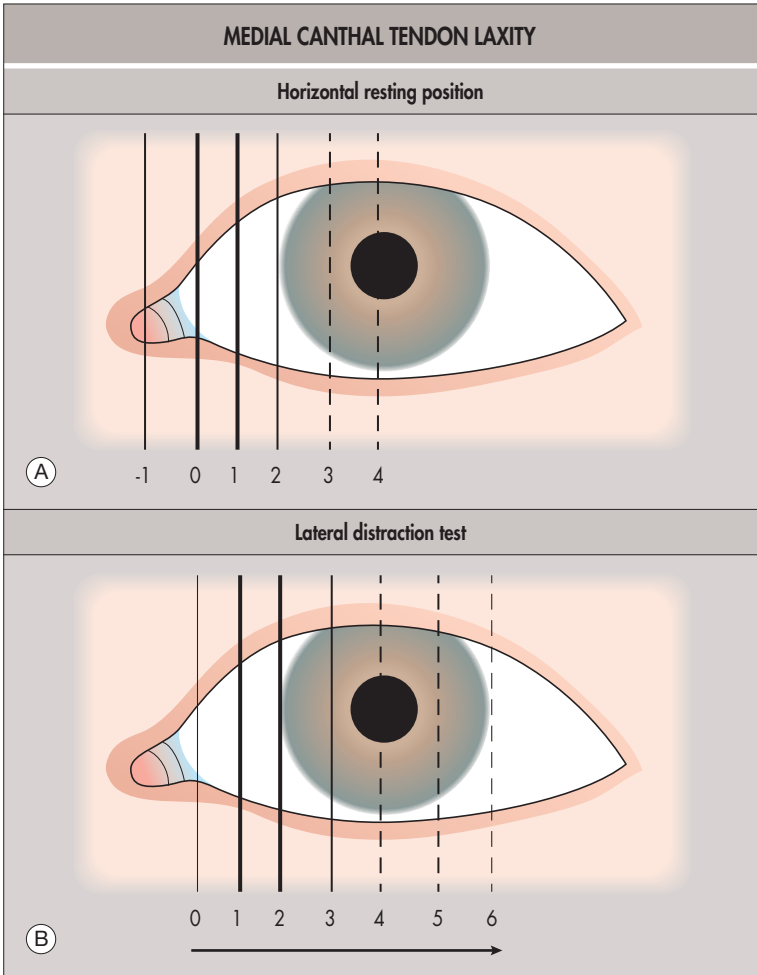


Fig. 4.17.13 Clinical grading system for lax eyelids. (From Olver J, Sathia PJ, Wright M. Lower eyelid medial canthal tendon laxity. *Ophthalmology* 2001;108(12):2321–5.)

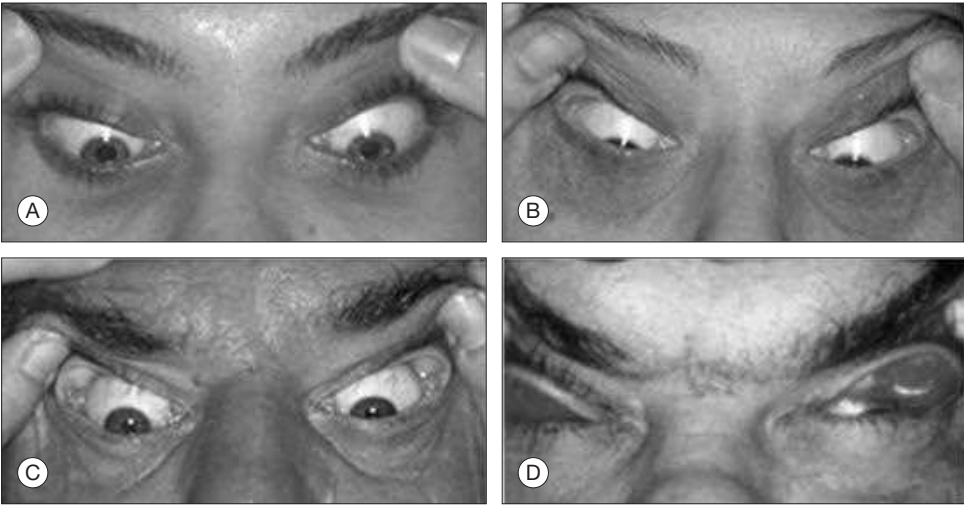


Fig. 4.17.14 Clinical grading system for lax eyelids. (From Liu DT, Di Pascuale MA, Sawai J, Gao Y, Tseng SCG. Tear film dynamics in floppy eyelid syndrome. *Invest Ophthalmol Vis Sci* 2005;46(4):1188–94.)



Nadeem identified multiple circulating inflammatory factors associated with OSA, including CRP, TNF- $\alpha$ , ICAM, IL-6, IL-8, VCAM, and selectins.<sup>88</sup> Becker reported the elevation of MMP-9 in the tear film of patients with OSA.<sup>89</sup>

## Ocular Manifestations

FES has been associated with a variety of anterior and posterior segment conditions. Anterior ocular findings include keratoconus, ptosis, eyelash ptosis, meibomianitis, blepharitis, and ocular surface disorders including superficial punctate keratitis and chronic conjunctivitis.<sup>90</sup> Patients with FES may present with a variety of symptoms including eye irritation, redness, discharge, pain, swelling of the eyelids, and foreign body sensation.<sup>91</sup> In addition, patients with LEC tend to have a more reactive ocular surface, probably as a result of increased concentration of MMPs, particularly MMP-7 and MMP-9 in the conjunctival epithelium, and also in the tear film.<sup>89</sup> The presence of an increase in MMPs may predispose patients with FES to develop more severe manifestations of a wide variety of ocular surface diseases, including DED; phlyctenular disease; superior limbic keratoconjunctivitis; neurotrophic keratitis; and many other noninfectious ocular inflammatory diseases.

Because of the strong association between LEC and OSA, the diagnosis of FES becomes a critical risk factor for a wide variety of posterior segment neurovascular ocular diseases as well.<sup>77</sup> These include retinal vascular occlusion,<sup>92</sup> nonarteritic anterior ischemic optic neuropathy,<sup>93,94</sup> and glaucoma.<sup>95–98</sup> Kremmer reported a halting of progressive field loss following CPAP treatment in a patient with low-tension glaucoma.<sup>99</sup> OSA and FES should be considered risk factors for those patients, and OSA should be a considered a potential modifiable factor, in addition to IOP, for the development and progression of glaucoma.<sup>100</sup> A positive family history in these patients with OSA can be elicited as well.

## Diagnosis

Several methods exist for diagnosing the presence and severity of lid laxity. Olver et al. described two methods of grading medial canthal tendon laxity.<sup>101</sup> They described the horizontal resting position method, which grades the severity of lid laxity based on the resting position of the lower punctum (Fig. 4.17.15). Normal, or grade 0, was defined as the location of the lower punctum just medial to a vertical line made perpendicular to the upper punctum. Grading ranged from –1 to 6 based on the extent of displacement of the lower punctum at rest. Olver et al. also used the lateral distraction method, which grades the severity of lid laxity on the basis of displacement of the lower punctum laterally from resting position with minimal pressure. They used several anatomical landmarks to describe the degree of lateral displacement including the plica semilunaris, medial corneal limbus, visual axis, and lateral corneal limbus.

Beis et al. defined hyperelasticity as upper lid eversion resulting in exposure of the tarsal conjunctiva for 3 seconds with the eyes in the inferior gaze position.<sup>102</sup> They then separated the severity of FES (LEC) into stages 1 and stage 2, with stage 1 describing tarsal conjunctival exposure lasting less than 6 seconds in the inferior gaze positioning and stage 2 describing exposure for greater than 6 seconds.

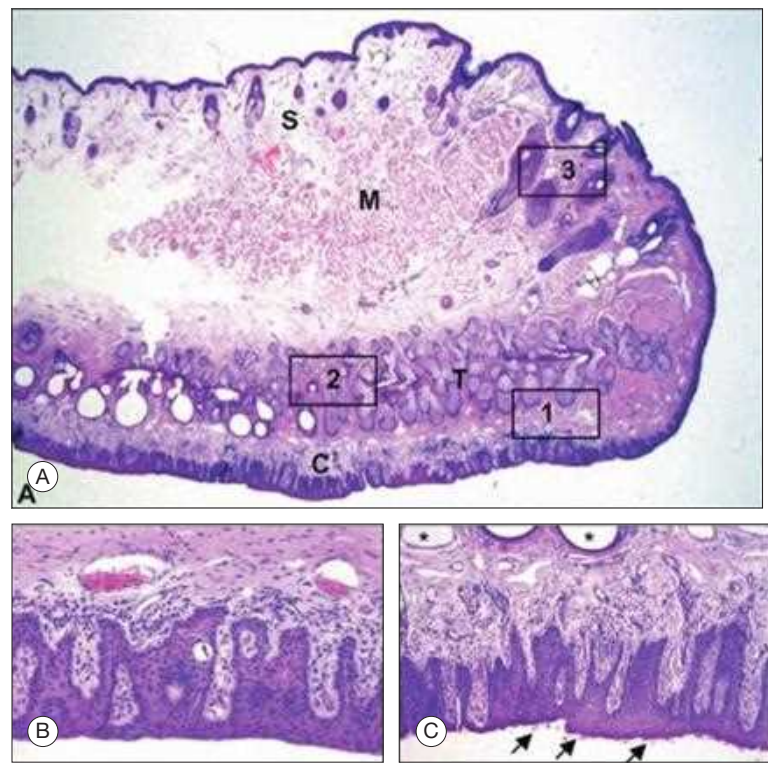
Liu et al. separated the severity of FES (LEC) into grade 0 to grade 3 (Fig. 4.17.16).<sup>103</sup> Grade 0 referred to no visibility of the upper eyelid tarsal conjunctiva with eversion and, thus, no floppy eyelid. Grade 1 or mild FES (LEC) described exposure of less than one third of the tarsal conjunctiva. Grade 2 or moderate FES (LEC) included exposure of one third to one half of the tarsal conjunctiva. Grade 3 or severe FES was described as more than one half of the tarsal conjunctiva exposed.

Finally, Robert et al. defined the vertical hyperlaxity of the eyelids as the maximal distance between the palpebral rim and the center of the pupil in primary position after manual traction on the eyelid.<sup>81</sup> They also noted the presence of spontaneous tarsal eversion.

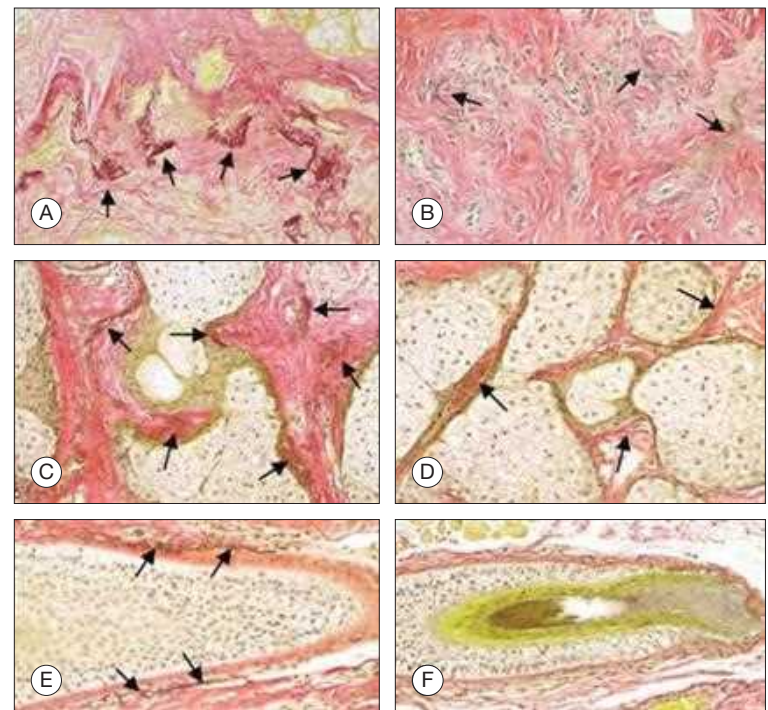
In a general ophthalmology practice, however, most cases of LEC/FES probably are overlooked. This reflects the national statistics of 80% of patients with OSA being undiagnosed. Bouchard et al. supported this conclusion and reported the diagnosis of LEC in only 4% of the 11975 patients with OSA in an academic institution who were seen in the eye clinic over a 5-year period.<sup>100</sup>

## Differential Diagnosis

Because the diagnosis of LEC often is missed, a large population of patients with mild to moderate LEC and LES (with elevated MMP in their tear



**Fig. 4.17.15** Histopathology of eyelid (hematoxylin and eosin stain) (From Schlötzer-Schrehardt U, Stojkovic M, Hofmann-Rummelt C, Cursiefen C, Kruse FE, Holbach LM. The pathogenesis of floppy eyelid syndrome involvement of matrix metalloproteinases in elastic fiber degradation. *Ophthalmology* 2005;112(4):694–704.)



**Fig. 4.17.16** Elastin changes in lax eyelids (Von Gieson stain). (From Schlötzer-Schrehardt U, Stojkovic M, Hofmann-Rummelt C, Cursiefen C, Kruse FE, Holbach LM. The pathogenesis of floppy eyelid syndrome involvement of matrix metalloproteinases in elastic fiber degradation. *Ophthalmology* 2005;112(4):694–704.)

film) has been managed with treatment for DED, with over-the-counter artificial teardrops. In some cases, tear production is decreased, but many have normal tear production and are unresponsive to topical lubricants. Some patients with LES, as in Acar's study, are treated for their associated chronic papillary conjunctivitis, without identifying the eyelid laxity. Associated findings of blepharoptosis, lash ptosis, and ectropion, as well as the meibomianitis that often accompanies the LEC, can be managed separately.<sup>90</sup> Dermatochalasis can mask the LEC as well. Nocturnal lagophthalmos can also be managed.

## Systemic Associations

As mentioned previously, OSA is strongly associated with eyelid laxity. OSA is defined as greater than five apnea/hypopnea events per hour, and severity is graded as mild, moderate, or severe. The respiratory disturbance index (RDI) measures the number of events per hour. The history of snoring and daytime fatigue as well as lax eyelids should prompt suspicion of sleep apnea. Not all patients with OSA have daytime sleepiness and are described as having OSA. Most patients do not remember waking at night during the apneic episode, which makes the diagnosis more difficult. Apnea results in peripheral vasoconstriction and then regional vasodilation of the cerebral and myocardial circulation. Postapneic hyperventilation leads to hypocapnia and peripheral vasodilation. Lack of subsequent vasodilation in the ophthalmic vessels in glaucomatous eyes could then lead to a cerebrovascular “steal” from the blood flow to the optic nerve head. Hypercapnia also increases intracranial pressure and causes metabolic stress and acidosis. As a result of chronic intermittent hypoxia, the increase in sympathetic tone in OSA associated with intermittent hypoxic episodes is thought to result in endothelial damage.<sup>84,86,88</sup> OSA affects the vascular endothelium through oxidative stress, inflammation, atherosclerosis and a decreases in nitric oxide.<sup>84</sup> The vasoconstrictor, endothelin-1 has been shown to upregulate in OSA and in NTG. OSA then has a role in vascular regulation.

OSA has been associated with increasing risk of neurovascular disease (diabetes), including pulmonary, cardiovascular (atherosclerosis, heart disease, peripheral neuropathy), and cerebrovascular disease (stroke, cognitive decline, depression, headache, and nonarteritic ischemic optic neuropathy).<sup>104,105</sup> OSAS also is associated with pulmonary hypertension, myocardial infarction, cardiac arrhythmia, congestive heart failure, stroke, cardiac related mortality, and all may cause mortality.<sup>106</sup>

## Pathology

The pathology of LEC involves a decreased concentration of elastin colocalized with MMP in the tarsal plate (see Fig. 4.17.12).<sup>82,83</sup>

The pathophysiology of FES has been thought to result from a process of ischemia–reperfusion injury from the pressure of the globe onto the eyeball while sleeping. Indeed, the nocturnal eversion of the eyelid with contact of the eyeball and tarsal conjunctiva has been thought to account for the chronic conjunctivitis.<sup>91</sup> Additional hypothesis includes a systemic elastin dysfunction.<sup>84–89</sup>

## TREATMENT

There is a wide variety of eyelid, tear film, conjunctival, corneal, and ocular surface changes that are associated with LES. The eyelid changes include (1) lax eyelids, (2) blepharoptosis, (3) ectropion, (4) lagophthalmos, (5) eyelash ptosis, (4) meibomianitis, and (5) infestation by *Demodex brevis*.<sup>90</sup> Infrared thermography demonstrates increased blood flow to the eyelids and perioral region.<sup>103</sup> Management of eyelid laxity depends on the severity of the disease. For mild disease an eye shield at bedtime might be helpful. Most of these patients, however, use a CPAP machine at night, which precludes the use of a shield. The CPAP device may result in worsening ocular symptoms. For more severe disease, treatment approaches include full thickness upper eyelid wedge resection, and lateral tarsal strip.<sup>107</sup>

The tear film changes include lipid tear deficiency, decreased BUT, and MMP-9 elevation with associated punctate keratopathy (see Table 4.17.2). Most patients also have meibomian gland dysfunction and may benefit from oral omega-3 fatty acids.<sup>108</sup> Short-term topical corticosteroid use and

topical lubricants and gels and ointments at bedtime may be of some benefit.

Conjunctival changes include chronic papillary conjunctivitis associated with nocturnal lid eversion and metalloproteinase elevation. Management of the ocular surface as well as therapeutic bandage with contact lens wear may be tried.

Corneal and ocular surface disease associations include (1) keratoconus, (2) corneal scarring, (3) corneal neovascularization, (4) filamentary keratitis, (5) corneal erosion, (6) microbial keratitis, and (7) corneal thinning/melting.<sup>90</sup> Association with keratoconus is well known and should be suspected in these patients and managed appropriately. Chronic ocular surface disease associated with LES can result in corneal scarring, neovascularization, and microbial keratitis.

Finally, in addition to managing the above eyelid and ocular surface diseases, one of the most important recommendations for ophthalmologists is to identify the patients at risk for OSA and refer them for a sleep study. Evaluation of all patients with complaints of chronic irritation should include a careful evaluation of the eyelid laxity including distraction test of both the upper and lower lids as well as tarsal conjunctival inflammation. Patients with complaints of chronic irritation with a normal Schirmer's score and who are unresponsive to frequent topical preservative-free, teardrops should suggest a diagnosis other than aqueous tear deficiency (caused by *Demodex*, lax eyelids, allergic conjunctivitis). Identification of lax eyelids should prompt an evaluation of sleep apnea and the many associated ocular (and systemic) neurovascular diseases associated with sleep apnea (glaucoma, ischemic optic neuropathy, papilledema, retinal vein occlusion). A careful snoring history needs to be obtained from both the patient and partner as a key element for the diagnosis of sleep apnea and lax eyelid condition (LEC).<sup>106,109</sup> A history of snoring and daytime fatigue as well as lax eyelids should prompt suspicion of sleep apnea.<sup>109,110</sup> STOP-BANG or Berlin Questionnaires validated for diagnosing OSA should also be administered (Video 4.17.1).



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## Keratoconus and Other Ectasias

Joel Sugar, Debora E. Garcia-Zaliskak

4.18

**Definition:** Corneal ectasia is a group of disorders affecting the shape of the cornea and include keratoconus, pellucid marginal corneal degeneration, post-refractive surgery corneal steepening, and keratoglobus.

**Key Features**

- Usually bilateral, although often asymmetric.
- Isolated to cornea.
- Noninflammatory.

**Associated Features**

- Obesity.
- Sleep apnea.
- Down syndrome.
- Atopic disease.

**KERATOCONUS**

Keratoconus is a disorder characterized by progressive corneal steepening, most typically inferior to the center of the cornea, with eventual corneal thinning, induced myopia, and both regular and irregular astigmatism.

**Epidemiology and Pathogenesis**

The pathogenesis of keratoconus is not fully understood, although both genetic and environmental processes are likely to be involved. Keratoconus is probably not a single disorder but, rather, a phenotypic expression of several possible causes.

A hallmark of keratoconus is stromal thinning, which may be related to alterations in enzyme levels in the cornea, causing stromal degradation. This is supported by multiple studies suggesting increased levels of degradative lysosomal enzymes and decreased levels of inhibitors of proteolytic enzymes in corneal epithelium.<sup>1,2</sup> These findings are consistent with the observation of increased collagenolytic and gelatinolytic activity in keratoconic cells.<sup>3,4</sup>

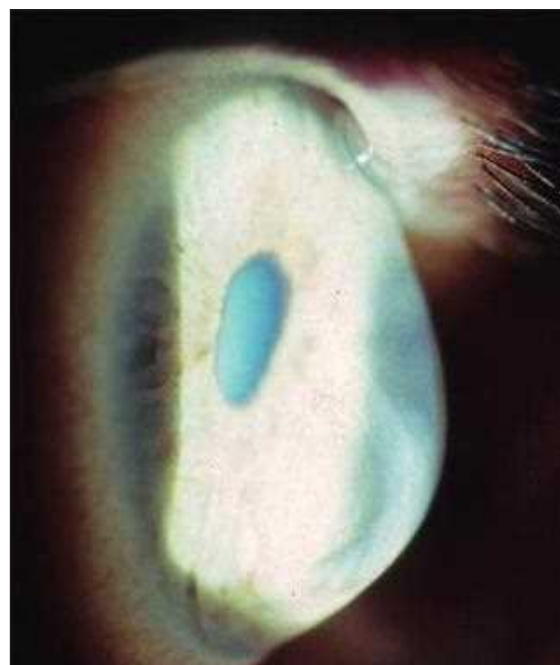
Increased apoptosis of stromal keratocytes has been reported in keratoconus, as suggested by confocal microscopy.<sup>5,6</sup> It is postulated that this loss of keratocytes results in a decrease in collagen and extracellular matrix production, leading to reduced stromal mass. Other investigators have suggested that abnormalities in corneal collagen and its cross-linking may be the cause of keratoconus.<sup>7</sup>

Eye rubbing is strongly associated with the development of keratoconus. The mechanism by which eye rubbing contributes to keratoconus is not completely understood, but it may be related to mechanical epithelial trauma, triggering a wound-healing response that leads to keratocyte apoptosis. Other factors, such as slippage of collagen fibrils and a decrease in ground substance viscosity, may play a role.<sup>8</sup> The cytokine interleukin-6 has been suggested as a mediator of eye rubbing and stromal degradation.<sup>9</sup>

The prevalence of keratoconus in the general population varies in different series. A recent study that evaluated 4.4 million patients from a mandatory health insurance database found the estimated prevalence of keratoconus in the general population to be 1 out of 375 persons.<sup>10</sup>

**Ocular Manifestations**

Manifestations of keratoconus include steepening of the cornea, especially inferiorly (Fig. 4.18.1), thinning of the corneal apex, scarring at the level of

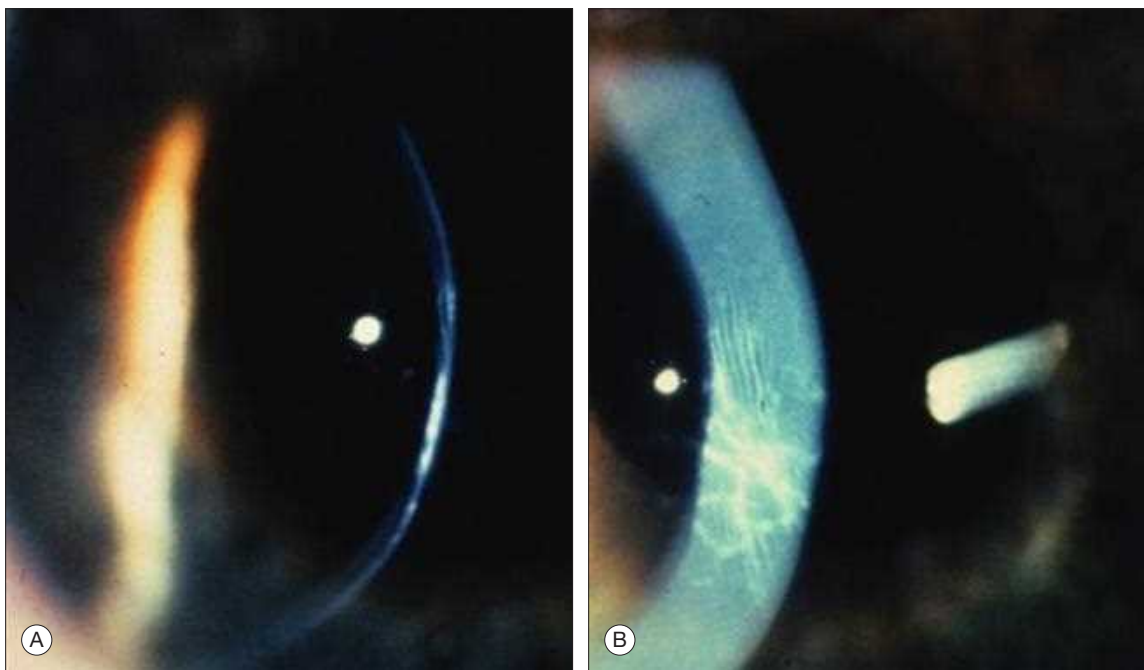


**Fig. 4.18.1**  
Characteristic conical steepening of the cornea in keratoconus.

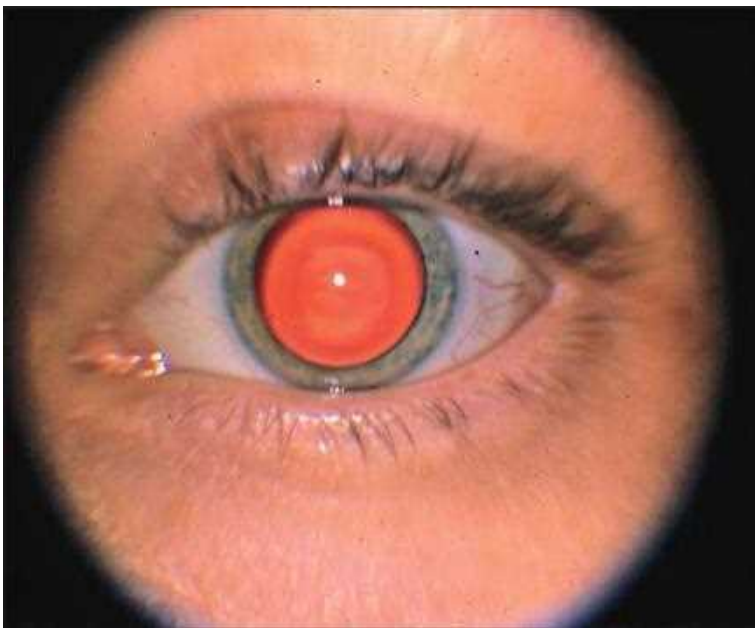
Bowman's layer, and deep stromal stress lines that clear when pressure is applied to the globe. A ring of iron deposition (Fleischer's ring) (Fig. 4.18.2) can accumulate in the epithelium at the base of the cone. Steepening of the cornea leads to clinical signs which include protrusion of the lower eyelid on downgaze (Munson's sign), focusing of a light beam shone from temporally across the cornea in an arrowhead pattern at the nasal limbus (Rizutti's sign), and a dark reflex in the area of the cone on observation of the cornea with the pupil dilated using a direct ophthalmoscope set on plano (Charleaux's sign) (Fig. 4.18.3). In addition, a scissoring reflex can be found on retinoscopy. In some patients who have keratoconus, especially if associated with trisomy 21 (Down syndrome), acute corneal hydrops may occur, in which an abrupt rupture of Descemet's membrane results in acute overhydration of the cornea and accumulation of lakes of fluid within the corneal stroma. Over time, endothelial cells spread over the posterior stromal defect to lay down new Descemet's membrane and recompensate the cornea (Fig. 4.18.4).

**Diagnosis**

Topography and tomography are useful to confirm the diagnosis of keratoconus and, in some cases, even to make the diagnosis of subtle cases without clinical manifestations (see Fig. 4.18.3). Both placido disc and rotating Scheimpflug camera systems for assessing corneal curvature are reliable in distinguishing keratoconic eyes from normal eyes, although there may be differences in posterior elevation measurements between the two systems.<sup>11</sup> The Rabinowitz criteria can be used for the diagnosis of keratoconus, and they include K greater than +47.20 diopters (D), inferior-versus-superior corneal dioptric asymmetry value greater than +1.40 D, KISA% greater than 60%, which is suggestive of the disease, whereas more than 100% strongly suggests keratoconus, and a pachymetry/asymmetry index of less than 105. KISA% index quantifies the topographical features seen in keratoconus. It includes the K-value, the inferior-superior dioptric asymmetry, and the AST index, which quantifies the degree of regular corneal astigmatism.<sup>12</sup>



**Fig. 4.18.2 Severe Apical Thinning in a Cornea With Keratoconus.** A broader slit-beam view of the same cornea (B) reveals extensive stromal apical scarring and linear breaks in Bowman's layer.



**Fig. 4.18.3** Charleaux's sign in keratoconus, delineating the extent of the cone.

Such analyses have been used to demonstrate that keratoconus is almost always a bilateral disease, even when not evident in the fellow eye as seen under at the slit lamp.

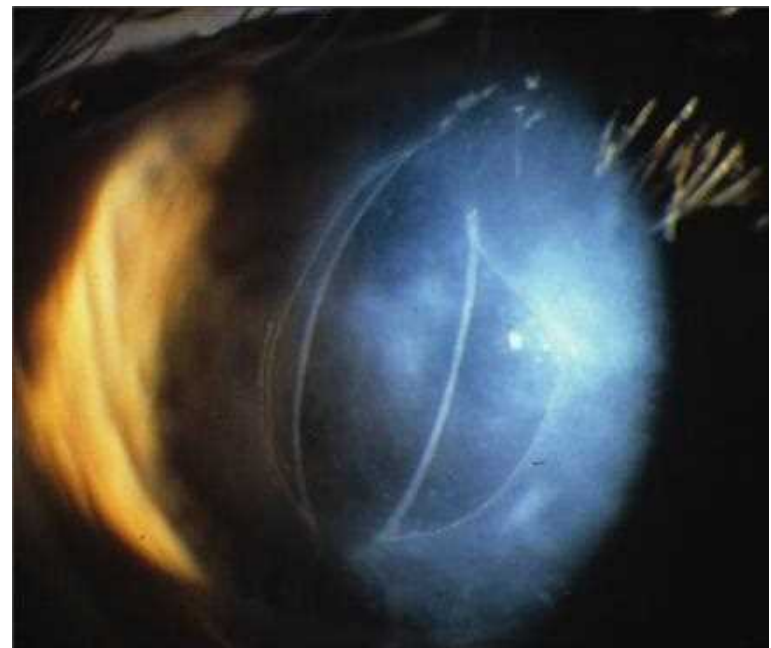
The inheritance pattern of keratoconus is incompletely defined. In the past, it was believed that more than 90% of cases were sporadic. With the advent of videokeratography to assess family members, however, pedigrees have been analyzed. These studies show corneal changes consistent with keratoconus in some asymptomatic family members, which suggests an autosomal dominant pattern of inheritance.<sup>13</sup>

### Differential Diagnosis

The differential diagnosis of keratoconus includes pellucid marginal corneal degeneration, post-refractive surgery corneal ectasia, posttraumatic corneal ectasia, protrusion of the cornea after corneal thinning from ulceration, and keratoglobus.

### Systemic Associations

A number of systemic and ocular disorders have been described in association with keratoconus. Conditions found to have increased odds of keratoconus include sleep apnea, asthma, and Down syndrome. Interestingly, patients with diabetes mellitus and collagen vascular disease



**Fig. 4.18.4 Massive Hydrops in Keratoconus.** Note the large tear in Descemet's membrane.

have been found to have lower odds of keratoconus, and no association has been found between keratoconus and allergic rhinitis, mitral valve disorder, aortic aneurysm, or depression.<sup>14</sup> Other systemic associations include Ehlers–Danlos, Marfan's, Cruzon's, and Apert's syndromes. Ocular-associated disorders include Leber's congenital amaurosis, retinitis pigmentosa, and retinopathy of prematurity. Fuchs' dystrophy and posterior polymorphous dystrophy have been reported as well.

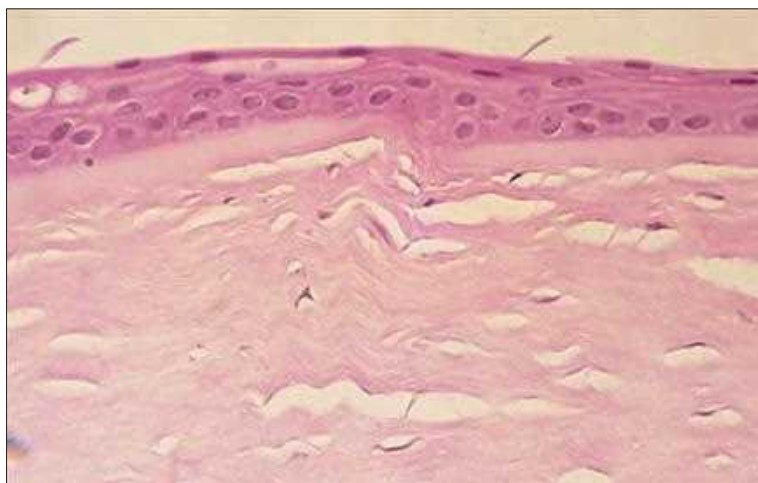
### Pathology

Histopathology shows irregular epithelium and breaks in Bowman's layer with fibrosis filling in the breaks and extending beneath the epithelium (Fig. 4.18.5), and central corneal thinning. With hydrops, breaks at the level of Descemet's membrane are seen with inward curling of the membrane, which is otherwise normal. Electron microscopy shows decreased thickness of the cornea with fewer lamellae. The collagen fibrils in the lamellae are thinned mildly, and the space between fibrils is decreased.<sup>15,16</sup>

### Treatment

Treatment consists of spectacles for myopic astigmatism and then rigid contact lenses or scleral lenses once spectacle-corrected visual acuity





**Fig. 4.18.5 Keratoconus.** Breaks in Bowman's layer, with fibrosis that extends beneath the epithelium, can be seen. The stroma shows scarring.

(SCVA) becomes inadequate. When contact lenses fail, surgical treatment is indicated. In one series, the reasons for penetrating keratoplasty were contact lens intolerance (83%), frequent contact lens displacement (8.5%), and unsatisfactory visual acuity despite good fit of contact lenses (8.5%).<sup>17</sup>

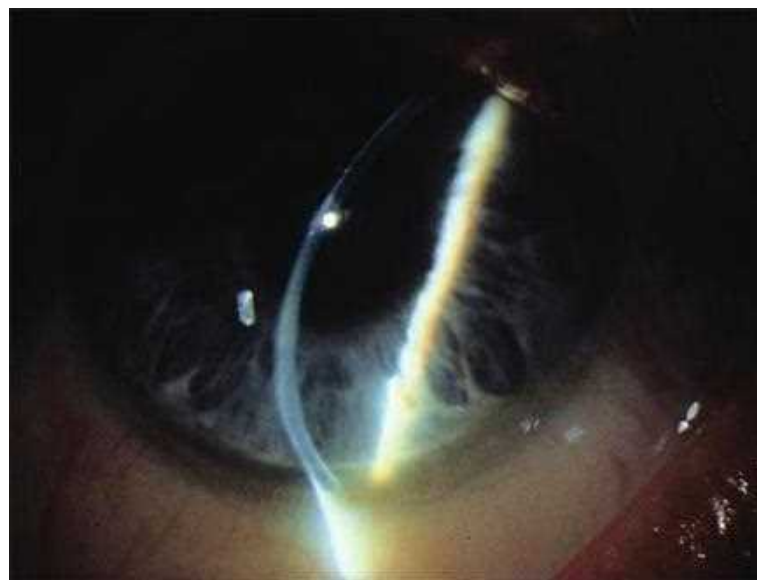
Standard surgical treatment consists of deep anterior lamellar keratoplasty (DALK) or penetrating keratoplasty (PKP). Keratoconus accounted for 14.8% of all penetrating keratoplasty and 38.3% of all DALK carried out in the United States in 2015.<sup>18</sup> At the time of keratoplasty, decreasing the donor/recipient size disparity reduces postkeratoplasty myopia.<sup>19</sup> Primary advantages of DALK over PKP include increased structural integrity and reduced risk of graft rejection. Some surgical techniques, such as the big-bubble technique, have reduced surgical operating time, though it remains challenging to perform, especially for inexperienced surgeons.<sup>20</sup> Bowman's layer graft is another surgical technique in the treatment of keratoconus. It was shown to be beneficial in a small series, where reduction and stabilization of corneal ectasia were achieved in eyes with progressive, advanced keratoconus.<sup>21</sup>

Intracorneal ring segments, first described for keratoconus in 2000,<sup>22</sup> have been shown in several studies to be successful in reducing myopia and astigmatism and improving SCVA.<sup>23</sup> The ring segments can be inserted into the stroma either via mechanical dissection or femtosecond laser assistance. Currently Intacs (Addition Technology, Sunnyvale, CA) is the only intrastromal corneal ring segment approved in the United States.

Another less invasive technique that was approved by the Food and Drug Administration (FDA) in the United States in August 2016 is combined riboflavin–ultraviolet A rays (UVA) corneal cross-linking. This procedure, first described in 1998,<sup>24</sup> consists of photopolymerization of corneal stroma by combining riboflavin (photosensitizing substance) with UVA. This process increases corneal rigidity and thus reduces the likelihood of further ectasia. Cross-linking is indicated in patients with documented progressive corneal ectasia. Contraindications include corneal thickness less than 400 microns (although use of hypotonic solutions may allow swelling to greater than this level prior to treatment), prior herpetic infection, concurrent infection, severe corneal scarring, history of poor epithelial wound healing, severe ocular surface disease, and autoimmune disorders.<sup>25</sup> Various protocols with different treatment and epithelium handling are under ongoing evaluation. Currently, the only FDA-approved protocol in the United States is the “epithelium off” protocol, where the cornea is treated after epithelial removal, but “transepithelial” corneal cross-linking continues to be studied and refined.<sup>26–28</sup>

## Course and Outcome

The natural course of untreated keratoconus can be unpredictable, although progressive myopia, irregular astigmatism, and corneal scarring are typical. It is widely estimated that 10%–20% of patients with keratoconus undergo keratoplasty, although a recent report found as much as a 25% reduction in the performance of keratoplasty since corneal cross-linking began to be used.<sup>29</sup> Keratoplasty outcomes in terms of graft clarity and improved vision are excellent, although residual astigmatism and myopia remain problematic. Recurrence of keratoconus after keratoplasty may rarely occur, although thinning and ectasia at the inferior host-graft junction is not uncommon 15 or more years after keratoplasty. Some authors



**Fig. 4.18.6 Pellucid Marginal Corneal Degeneration.** The point of greatest protrusion is just above the area of maximal thinning (located inferiorly).

have postulated that recurrence could be related to incomplete excision of the cone at the time of surgery, unrecognized keratoconus in the corneal donor, or host cellular activity that causes changes in the donor corneal material.<sup>30</sup>

In one study on the long-term outcomes of intracorneal ring segments, with 17 eyes and 5-year follow-up, Intacs placement reduced mean spherical equivalent refractive error from  $-5.54 \pm 5.02$  D to  $-3.02 \pm 2.65$  D ( $P = .01$ ), reduced mean keratometry from  $49.59 \pm 5.10$  D to  $48.02 \pm 4.99$  D ( $P = .009$ ), and improved uncorrected visual acuity in 77% of patients.<sup>31</sup> Complications of Intacs include infection, corneal melt, and ring extrusion. One study showed significant postoperative problems in 30% of Intacs with thinning and ring exposure.<sup>32</sup>

Results of long-term follow-up of corneal cross-linking are promising. Data from the Siena Eye Cross Study in Italy revealed a mean hyperopic shift in spherical equivalent of +2.15 D and a mean reduction in keratometry of +2.26 D on 4-year follow-up of 44 patients.<sup>33</sup> Complications include temporary stromal edema, temporary or permanent corneal haze, corneal scarring, sterile infiltrates, infectious keratitis, and diffuse lamellar keratitis.<sup>34–38</sup>

Both intracorneal ring segments and corneal cross-linking are most likely to be beneficial in patients with mild to moderate keratoconus without corneal scarring; in these patients, stabilization of keratoconus may obviate or delay the need for keratoplasty. More advanced cases typically need keratoplasty for optimal visual outcome.

## PELLUCID CORNEAL DEGENERATION

Pellucid marginal corneal degeneration appears to be a variant of keratoconus, with some different clinical features. Corneal thinning and protrusion are seen in the inferior peripheral cornea; the thinning begins 1–2 mm inside the inferior limbus in a horizontal oval band approximately 2 mm in radial extent and 6–8 mm in horizontal extent (Fig. 4.18.6). The involved area is clear, and usually no iron line occurs central to it. Hydrops may occur. The central cornea is regular, but usually with marked against-the-rule astigmatism. Some patients who have pellucid may have more typical central corneal changes of keratoconus, as may family members, although the inheritance of pellucid is not clear. Pathology appears to be the same as in keratoconus. Treatment, as for keratoconus, consists of spectacles or contact lenses. When these modalities are insufficient, results are best found with large, eccentric keratoplasty. Outcomes of keratoplasty in pellucid marginal degeneration are poorer than in keratoconus because of the more peripheral location of corneal thinning.

## KERATOGLOBUS

### Epidemiology and Pathogenesis

At least two forms of keratoglobus appear to exist: (1) a congenital or juvenile form and (2) an acquired adult form. The acquired form may be an

end-stage form of keratoconus—patients have been described with initial keratoconus followed by later keratoglobus—or acquired keratoglobus may be seen with no known prior keratoconus. The congenital form appears to be part of at least two different autosomal recessive syndromes. One is Ehlers–Danlos syndrome type VI. Another clinically similar syndrome, but with normal lysyl hydroxylase activity, is brittle corneal syndrome with associated blue sclera and red hair, which mimics Ehlers–Danlos syndrome type VI.<sup>39</sup>

## Ocular Manifestations

Keratoglobus is a disorder characterized by the presence of limbus-to-limbus corneal thinning with globular corneal protrusion. The thinning is usually greatest in the corneal periphery or midperiphery. Hydrops may occur, and perforations may result from relatively minor trauma. In Ehlers–Danlos syndrome type VI, patients have diffuse corneal thinning with corneal rupture spontaneously or after minor trauma, and corneal hydrops is common. Blue sclerae are present. These patients may have systemic connective tissue abnormalities as well, with hyperextensible joints, bone anomalies, and hearing loss.<sup>39</sup> A defect in lysyl hydroxylase activity is present.

## Pathology

Pathology of acquired keratoglobus is similar to that of keratoconus, whereas congenital keratoglobus shows an absence of Bowman's membrane, stromal disorganization, and thickening of Descemet's membrane with breaks.<sup>40</sup>

## Treatment

Treatment includes protection from trauma. Outcomes of penetrating keratoplasty are typically poor because of severe host peripheral thinning. Lamellar epikeratoplasty has been used successfully to reinforce thin corneas and, in some cases, to improve vision.<sup>41</sup> For acquired keratoglobus, large penetrating keratoplasty may be successful.

## POSTERIOR KERATOCONUS

*Posterior keratoconus* refers to a congenital corneal anomaly in which the posterior corneal surface protrudes into the stroma, which usually occurs in a localized area, but may be more diffuse. This disorder usually is sporadic, unilateral, and nonprogressive. Bilateral and familial cases do occur but are less frequent. The anterior corneal contour is often affected minimally, although anterior protrusion and even a surrounding iron line have been described. Frequently, scarring occurs in the stroma anterior to the Descemet's bulge. On pathological examination, scarring at the level of Bowman's membrane is seen and thinning of Descemet's membrane with excrescences has been reported variably.<sup>42,43</sup> Descemet's membrane changes and congenital nature of this disorder suggest that it is a variant

of corneal mesenchymal dysgenesis. Treatment usually is not necessary, although occasionally keratoplasty is indicated.

## POST-REFRACTIVE SURGERY CORNEAL ECTASIA

Corneal ectasia is an uncommon yet serious complication that can occur after refractive surgery. Its prevalence has been reported to be 0.04%–0.6%, although some believe this is an underestimation. Ectasia is thought to be a consequence of disrupting the biomechanical integrity of the cornea below a certain threshold. The FDA's current guidelines prohibit leaving less than 250  $\mu\text{m}$  of untouched tissue, but most refractive surgeons prefer to leave 300  $\mu\text{m}$  or more.<sup>44</sup> Risk factors for ectasia include an abnormal preoperative corneal topography, >40% of tissue altered, a low preoperative corneal thickness, high myopia, and younger age.<sup>44,45</sup>

Corneal cross-linking has currently emerged as a proposed treatment to not only treat but also, ideally, prevent corneal ectasia that occurs after refractive surgery. A recent study from Japan found no case of post-LASIK ectasia in 673 eyes, with follow-up ranging from 3 months up 3.5 years. Given the prevalence of ectasia, as stated above, this may or may not be clinically significant, but more studies should be performed for further evaluation.<sup>46</sup>

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## Anterior Corneal Dystrophies

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4.19

**Definition:** Bilateral disorders, most of which are inherited, in which an abnormal substance accumulates primarily in the corneal epithelium.

**Key Features**

- Typically bilateral.
- Progressive.
- Involvement is anterior to corneal stroma.

**Associated Features**

- Many are associated with recurrent erosion syndrome.
- Not associated with systemic disease, with rare exceptions.

**INTRODUCTION**

In general, most corneal dystrophies are autosomal dominant, bilateral disorders that primarily affect one or more layers of an otherwise normal cornea, progress slowly after their appearance in the first or second decade, and are not associated with any systemic disease. Historically, corneal dystrophies were categorized by the involved corneal layer. The distinctive clinical appearance of most corneal dystrophies allows accurate diagnosis based on clinical grounds. Transmission electron microscopy is the most accurate method for histopathological diagnosis.<sup>1</sup> Genetic studies on corneal dystrophies, however, also provide insight at a basic molecular level and are assisting in refining the classification systems. Several corneal dystrophies are closely related at the molecular level with different phenotypes resulting from mutations within the same gene. For example, the *BIGH3* gene on chromosome 5q31 is associated with granular corneal dystrophy (types I, II, and III), lattice corneal dystrophy (types I, IIIA, IIIA-like, and IV), and corneal dystrophy of Bowman's layer (types I and II).<sup>2</sup>

The anterior corneal dystrophies involve Bowman's layer and involve the epithelium as well. Some also may involve the anterior stroma. This categorization, however, is arbitrary because many of the stromal dystrophies also involve Bowman's layer and the epithelium. The genetic understanding of these disorders makes this classification even less appropriate, and many of these conditions will ultimately be better classified and named by their specific biochemical defects (Table 4.20.1).<sup>3</sup>

**ANTERIOR BASEMENT MEMBRANE DYSTROPHY****Introduction**

Anterior basement membrane dystrophy (ABMD), also termed *epithelial basement membrane dystrophy* (EBMD), *map-dot-fingerprint corneal dystrophy*, and *Cogan's microcystic dystrophy*, is the most common anterior corneal dystrophy.<sup>1</sup>

**Epidemiology and Pathogenesis**

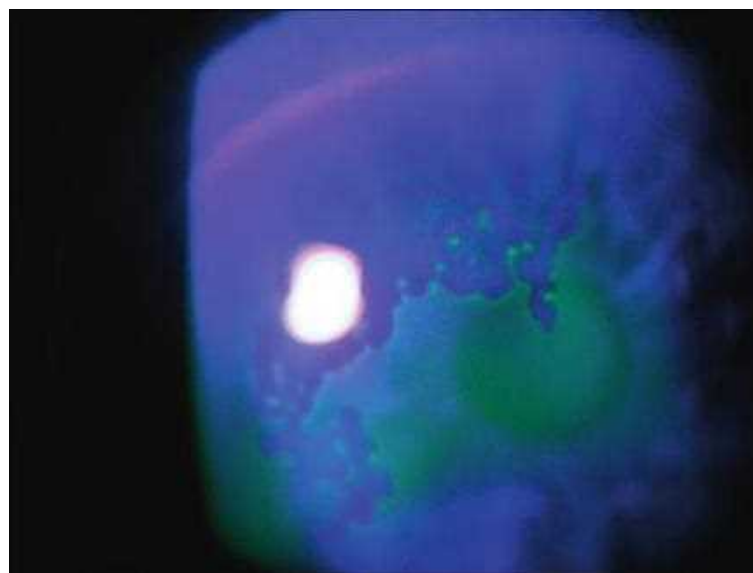
ABMD has been reported to occur in approximately 3%–6% of the general population but is much more common over age 40 years.<sup>4,5</sup> Familial patterns have been described for ABMD,<sup>4</sup> but many patients with the disorder will not have any known family history, which has caused some debate as to whether ABMD is actually a corneal dystrophy or a degenerative change.<sup>3</sup> Point mutations in the *TGFBI/BIGH3* gene have been reported in two families showing autosomal dominant inheritance.<sup>6</sup>

**Ocular Manifestations**

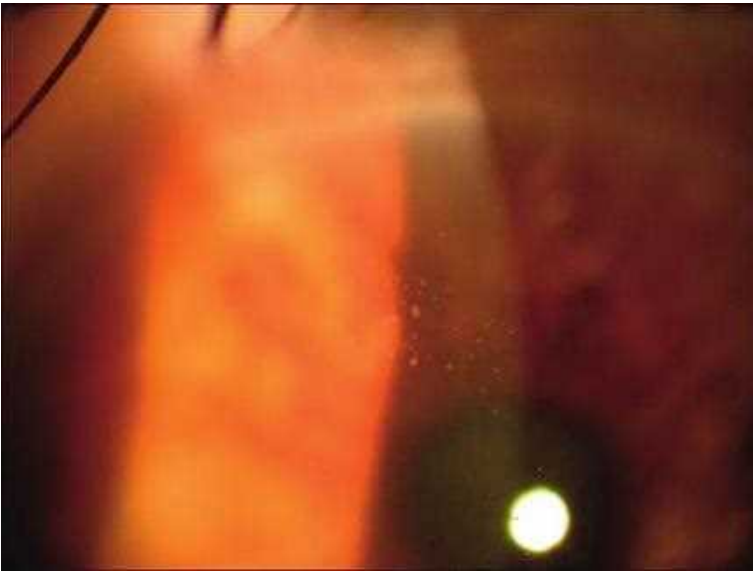
The most common clinical manifestations of ABMD are recurrent erosion syndrome (RES) and blurry or distorted vision. Most patients with RES describe mild pain on awakening, subsiding within minutes to hours, but larger erosions can cause severe pain, which may take hours to days to resolve. Patients also note blurred vision or occasionally monocular diplopia or image ghosting. Although ABMD is often thought to be the most common cause for RES, other conditions (including trauma), can cause RES.<sup>7–9</sup> In some cases, both entities are present, and the diagnosis of ABMD is made by carefully examining the unaffected eye after trauma. Patients with ABMD and a history of a traumatic abrasion are even more likely to develop RES. The clinical symptoms of ABMD overlap considerably with recurrent erosions secondary to trauma. In both conditions, recurrent erosions are felt to be secondary to friability of the superficial epithelium caused by poor adhesion of epithelial cells to each other and to the underlying basement membrane.<sup>10,11</sup>

In patients with blurred or distorted vision, which is thought to be related to central ABMD changes, corneal topography can be very helpful in identifying irregular astigmatism as the source of the visual problem. In addition, a trial with a soft bandage contact lens can be a helpful diagnostic or therapeutic tool.

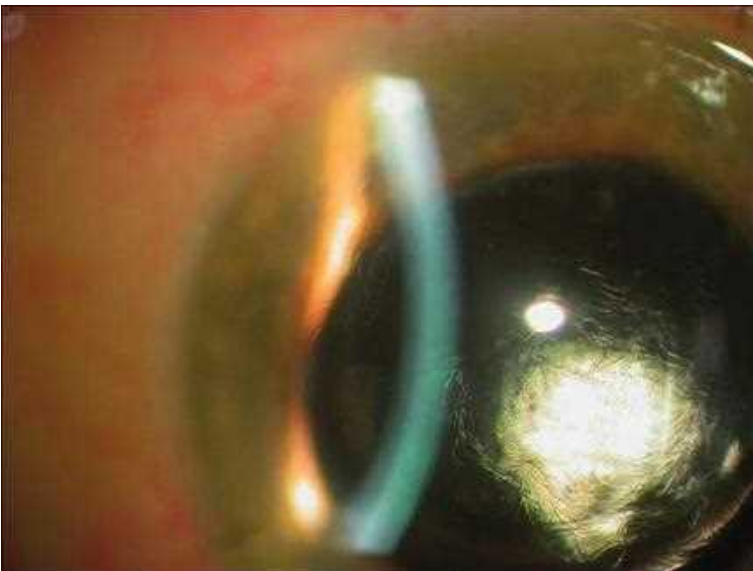
ABMD is characterized by several changes apparent in the anterior cornea on slit-lamp examination. They often are seen best with a dilated pupil and retroillumination. Cases may be subtle and can be detected by looking for negative staining using cobalt blue filter after the application of fluorescein (Fig. 4.19.1). Corneal findings seen with ABMD include intra-epithelial microcysts (dots) (Fig. 4.19.2), map-like grayish patches, and fingerprint parallel lines (Fig. 4.19.3).<sup>12–14</sup> The condition is referred to as Cogan's microcystic dystrophy when only microcysts are present. Confocal microscopy is helpful in corneas with a history of erosions that appear to be normal on clinical examination. With confocal microscopy, corneas with recurrent erosions or ABMD showed deposits in basal epithelial cells, subbasal microfolds and streaks, damaged subbasal nerves, or altered morphology of the anterior stroma.<sup>15,16</sup>



**Fig. 4.19.1** Area of epithelial thickening, demonstrating negative staining, in a patient with anterior basement membrane dystrophy. (Courtesy Anthony J. Aldave, MD.)



**Fig. 4.19.2** Opaque epithelial cysts in a patient with epithelial basement membrane dystrophy. (Courtesy Anthony J. Aldave, MD.)



**Fig. 4.19.3** Prominent epithelial map lines in a patient with epithelial basement membrane dystrophy. (Courtesy Anthony J. Aldave, MD.)

## Pathology

The clinical appearance of ABMD corresponds well with the pathology. Specimens from affected patients show protrusions of sheets (maps) or rows of thickened basement membrane (fingerprints) into the superficial epithelium as well as mounds of thickened basement membrane beneath the epithelium. Microcysts of degenerated cellular material accumulate within the epithelium (dots). A bilaminar subepithelial layer of fibrogranular material often occurs.<sup>1,10,11</sup>

## Treatment

The majority of patients with recurrent corneal erosions will respond to conventional forms of therapy, such as topical lubricants, patching, debridement, or bandage soft contact lenses.<sup>17</sup> Topical hyperosmotic solutions are well tolerated and appear to be effective in treating recurrent corneal erosion in some cases.<sup>18</sup> Therapy with a combination of medications that inhibit metalloproteinase-9 (topical corticosteroid and oral doxycycline) may produce rapid resolution and help prevent further recurrence in cases unresponsive to conventional therapies.<sup>19</sup>

In some cases, surgical intervention will be required. Anterior stromal micropuncture, superficial keratectomy, excimer laser ablation (phototherapeutic keratectomy [PTK]), and diamond burr (DB) superficial keratectomy have all been used.<sup>8</sup> Anterior stromal puncture was the first to be described, and presumably stimulates more secure epithelial adhesion

to the underlying stroma.<sup>17</sup> The use of 23- or 25-gauge needles instead of 30-gauge needles may decrease the risk of corneal perforation.<sup>20</sup> Micropuncture should be used with caution for erosions in the visual axis because central corneal scarring can lead to decreased vision.

PTK is a safe and effective procedure for recurrent corneal erosions (trauma and ABMD) refractory to conventional treatment as well as to treat visually significant ABMD.<sup>21–25</sup> In the great majority of patients, visual fluctuation and monocular diplopia or “ghost images” resolved.<sup>21–24,26</sup> A hyperopic shift can be an adverse side effect in some individual cases.<sup>19,24</sup> It is possible to combine PTK with PRK to manage the hyperopic shift in select patients.<sup>27–29</sup> ABMD has been reported as a risk for increasing complication rates after laser-assisted in situ keratomileusis (LASIK) including epithelial defects and epithelial ingrowth, so these patients may be better candidates for photorefractive keratectomy (PRK).<sup>30</sup>

DB superficial keratectomy appears to be an effective and safe method of treating recurrent erosions (both posttraumatic and ABMD). Little refractive shift occurs with this method.<sup>31,32</sup> As an alternative to DB, an Amoils epithelial scrubber may be used to debride the epithelium and buff Bowman's layer.<sup>33</sup> The DB procedure is simple, office-based, and inexpensive, so it may be the preferred technique in some settings.<sup>34</sup>

## MEESMANN'S EPITHELIAL DYSTROPHY

Meesmann's epithelial dystrophy is a rare, bilateral condition confined to the corneal epithelium. It is an autosomal dominant disorder that leads to fragility of the anterior corneal epithelium. It has been linked to mutations in locus 12q13 (KRT3) and 17q12 (KRT12) that are specifically expressed in the epithelium.<sup>35–38</sup>

Symmetrical intraepithelial microcysts appear in the first few years of life and are visible only at the slit lamp. They are concentrated within the visual axis and midperiphery. They are seen best with indirect illumination or retroillumination. Typically, patients are either asymptomatic or report mild symptoms, including recurrent erosions or minimal loss of visual acuity. These symptoms usually can be treated with topical lubricants only. Surgical intervention is rarely needed.

Histological examination shows two characteristic findings in the corneal epithelium: (1) intracellular “peculiar substance” and (2) intraepithelial microcysts containing cellular debris.<sup>39–41</sup> The epithelial cells are rich in glycogen and many contain the fibrogranular “peculiar substance,” possibly derived from tonofilaments.<sup>31,32</sup> Moreover, a nonspecific thickening of the epithelial basement membrane occurs without any apparent modification of Bowman's layer or superficial stroma.<sup>39–41</sup>

## REIS-BÜCKLER DYSTROPHY

### Introduction

“True” Reis-Bückler dystrophy, also known as *corneal dystrophy of Bowman's layer type I* (CDB I) or granular dystrophy type III, is discussed here.

### Epidemiology and Pathogenesis

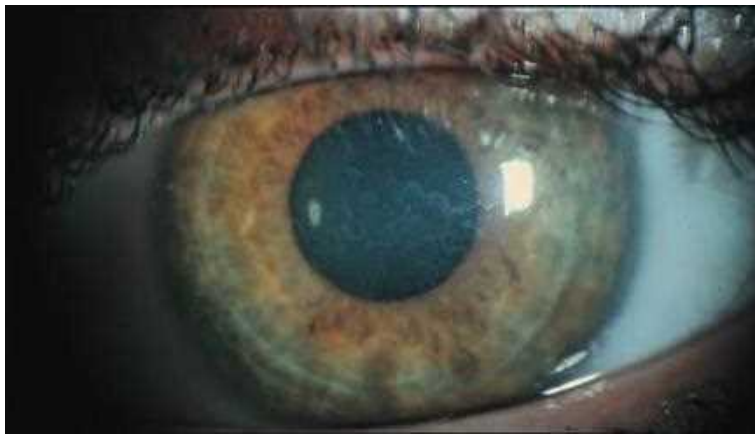
Reis-Bückler dystrophy has an autosomal dominant inheritance and has been linked to a specific defect in the keratoprotein gene on chromosome 5q31. An arginine replaced by a glycine at codon 555 has been found in families with this disorder, although other defects have been found in other families.<sup>42,43</sup> No systemic associations are known. The diagnosis is made on the basis of clinical appearance, although differentiation from honeycomb dystrophy often is difficult.

### Ocular Manifestations

Reis-Bückler dystrophy is characterized by recurrent, painful, corneal epithelial erosions that often begin in the first 1–2 years of life. Minimal corneal changes are seen at first, but then ring and map-like opacities appear at the level of Bowman's membrane; these become denser and more irregular over time (Fig. 4.19.4). By the second or third decade of life, the painful erosions diminish as corneal sensitivity decreases, but the increasing fibrosis results in visual difficulty.

### Pathology

Pathology shows eosinophilic and fibrotic material beneath the corneal epithelium and within the anterior stroma, with destruction of Bowman's membrane. The material is somewhat granular in appearance. Electron



**Fig. 4.19.4 Reis–Bückler Corneal Dystrophy.** Note the irregular opacities at the level of Bowman's layer.

microscopy shows rod-shaped bodies that replace Bowman's layer and lie between epithelial cells. These pathological findings are the same as those seen in superficial granular dystrophy (granular dystrophy type III).

### Treatment

Treatment of Reis–Bückler dystrophy is symptomatic for the recurrent erosions. Superficial keratectomy, either by mechanical stripping or by excimer laser ablation, is the appropriate treatment for the visual disturbance. Recurrence may be relatively rapid and keratoplasty may become necessary after multiple treatments.

### THIEL–BEHNKE DYSTROPHY

Also known as *honeycomb dystrophy*, *Waardenburg and Jonkers dystrophy*, or *corneal dystrophy of Bowman's membrane II* (CDB II), Thiel–Behnke dystrophy often is confused in the literature with Reis–Bückler dystrophy. Patients have recurrent erosions, although less severe than those associated with Reis–Bückler dystrophy. A reticular array of anterior stromal opacities develops and elevates the corneal epithelium in a “saw-tooth”

pattern. The disorder is inherited as an autosomal dominant disorder. A defect has been found in the keratoepithelin gene.<sup>44</sup>

In one family, a defect was found on chromosome 10q24. No known associated systemic abnormality exists. Histopathology shows wavy, sub-epithelial fibrosis with disruption of Bowman's layer and epithelial basement membrane. Electron microscopy reveals that curly collagen filaments replace Bowman's layer.<sup>45</sup> Treatment is the same as that for Reis–Bückler dystrophy, namely, superficial keratectomy or excimer ablation. Keratoplasty may become necessary after multiple recurrences.

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# Stromal Corneal Dystrophies

Joel Sugar, Praneetha Thulasi

4.20

**Definition:** An inherited, bilateral disorder in which an abnormal substance accumulates in the cornea.

**Key Features**

- Characteristically bilateral.
- Progressive.
- Isolated to the cornea.

**Associated Features**

- Usually autosomal dominant.
- Not associated with systemic disease, with rare exceptions.

INTRODUCTION

Corneal dystrophy is classically bilateral, progressive, and isolated to the cornea. The disorder is generally inherited, usually in a dominant fashion, and often appears clinically to involve only one layer of the cornea. With the progressive identification of genes involved in these entities, a better pathophysiological understanding and ultimately better treatment will be developed. Epithelial and endothelial dystrophies are discussed in their respective chapters.

The stromal dystrophies are classified as such because they appear to accumulate material predominantly in the stroma. As was noted in Chapter 4.19 this categorization is, however, arbitrary because many of the stromal dystrophies also involve Bowman’s layer and the epithelium. The genetic understanding of these disorders makes this classification even less appropriate. Many of these conditions ultimately will be classified and named by their specific biochemical defects (Table 4.20.1). The classification of corneal dystrophies has recently been reviewed in 2015 and standardized by an international committee and published as “The International Classification of Corneal Dystrophies (IC3D).”<sup>1</sup>

GELATINOUS DROP-LIKE DYSTROPHY

Gelatinous drop-like dystrophy was previously categorized as stromal but is now considered an epithelial/subepithelial dystrophy, as described in the most recent IC3D classification.

LATTICE DYSTROPHY TYPE I

Genetics

This disorder is autosomal dominant, with mutation in the transforming growth factor- $\beta$ -induced (*TGFBI*) gene, resulting in abnormal

keratoepithelin production at locus 5q31. The most common mutation is at codon 124, where arginine is replaced by cysteine.

Ocular Manifestations

Rod-like glassy opacities appear in the anterior stroma in the first or second decade and become denser over time, resulting in linear, often branching opacities (Figs. 4.20.1 and 4.20.2). These opacities are most dense anteriorly and centrally, with a clear zone in the periphery. The lines are relatively fine, as opposed to the more ropy opacities seen in lattice dystrophy type III. Although this disorder is bilateral, it can be asymmetrical.

Clinical Presentation

Patients often present in their first and second decades with pain and decreased vision. Recurrent erosions are common and, over time, can lead to anterior stromal haze that can limit vision. Patients often need corneal transplantation by their fourth decade.



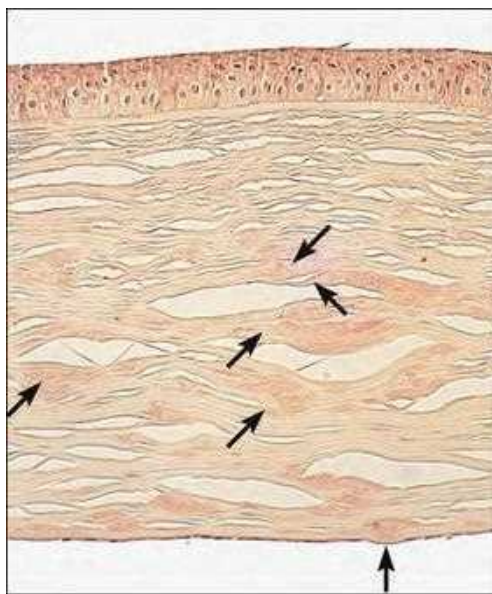
**Fig. 4.20.1 Lattice Dystrophy Type I.** This patient has very fine, rod-like opacities in the anterior stroma.



**Fig. 4.20.2 Lattice Dystrophy Type I.** Denser, ropier opacities than those shown in Fig. 4.20.1.

**TABLE 4.20.1** Corneal Dystrophies Due to Keratoepithelin Gene Defects

Dystrophy	Defect
Reis-Bückler’s	Arg555Gly, Arg124Leu, Arg555Gln
Thiel-Behnke	Arg124Leu (other families chromosome 10)
Lattice I	Arg124Lys
Lattice IIIA	Arg124Thr, Pro501Thr
Lattice IV	Leu527Arg
Granular I	Arg555Trp, Arg124Ser
Granular II (Avellino)	Arg124His



**Fig. 4.20.3 Lattice Dystrophy Type I.** Histopathology using Congo red stain shows the amyloid accumulations throughout the stroma (arrows).

## Pathology

Histopathologically, dense deposits are seen in the stroma. These stain with Congo red, periodic acid–Schiff (PAS), and Masson's trichrome (Fig. 4.20.3). Dichroism and birefringence are seen with polarized light and fluorescence is seen with thioflavin-T. All of these findings are characteristic for amyloid, a  $\beta$ -pleated protein structure. The amyloid appears to be distinct from that seen in lattice dystrophy type II.<sup>2</sup> Descemet's membrane and the endothelium are normal. Electron microscopy shows extracellular masses of fine, electron-dense randomly aligned fibrils characteristic of amyloid protein.<sup>3</sup>

## Treatment

Initial treatment consists of soft contact lenses for corneal epithelial erosions. Phototherapeutic keratectomy may be a good option to treat anterior visually significant deposits, although epithelial healing may be delayed, and recurrences may occur.<sup>4</sup> When visual acuity decreases significantly, deep anterior lamellar keratoplasty (DALK) is the procedure of choice because it has a benefit over penetrating keratoplasty (PKP) in minimizing the risk of rejection.<sup>5</sup> Epithelial cells are thought to be the source of these deposits, and although PKP has not shown statistically significant results, presence of transplanted limbal stem cells may have fewer recurrences.<sup>6</sup> Recently, investigators have been studying the efficacy of fibronectin drops after corneal epithelium debridement in improving visual acuity in this condition.<sup>7</sup>

## SYSTEMIC AMYLOIDOSIS WITH CORNEAL LATTICE

### Genetics

Locus 9q34 mutation in gelsolin protein is involved in actin modulation.

### Ocular Manifestations

Often classified as lattice dystrophy type II, this is part of the systemic disorder familial amyloid polyneuropathy type IV (Finnish type), also known as Meretoja's syndrome. In this disorder, fine lattice lines extend to the limbus and are not related to corneal nerves, although the sub-basal nerve density is reduced.<sup>8</sup> Patients may have increased risk of glaucoma and also can present with facial weakness with lid lag.

Systemic associations include multiple cranial neuropathies and systemic amyloid deposition.

### Patient Presentation

Patients often present with this condition during routine examinations. Visual disturbance is less compared with that in lattice dystrophy type I, and recurrent erosions are less frequent. Patients also can present with lid lag and corneal exposure.



**Fig. 4.20.4 Granular Dystrophy.** Note the more crumb-like opacities in this patient who has sufficient clear cornea to have normal acuity.

## Pathology

The pathology is similar to that of lattice dystrophy type I.

## Treatment

Treatment, if necessary, is the same as for lattice dystrophy type I, although additional consideration must be given to the risk of corneal exposure from facial neuropathy. Animal studies on gene silencing therapy hold promise.<sup>9</sup>

## Other Lattice Dystrophies

Multiple subtypes of lattice dystrophy have been described based on genotypical and phenotypical variations, especially as the genetics of those with atypical features are further explored. Lattice dystrophy types III, I/III, and IV and the polymorphic variant have delayed onset at age greater than 40 years and have thicker, ropy lattice lines.<sup>10,11</sup> Type IIIA has identical changes but has more recurrent erosions.<sup>12</sup> Many of these variants are geographically restricted.

## GRANULAR CORNEAL DYSTROPHY TYPE I

### Genetics

This disorder is autosomal dominant, with mutation in the *TGFBI* gene at locus 5q31.

### Ocular Manifestation

Previously called *Groenouw's dystrophy type I*, granular corneal dystrophy is characterized by the presence of discrete opacities in the corneal stroma that do not extend to the limbus, and the intervening stroma is clear. The opacities have irregular crumb-like or flake-like shapes and are whitish or slightly glassy in appearance (Fig. 4.20.4). The pattern within a given family appears to be consistent. No systemic associations are known.

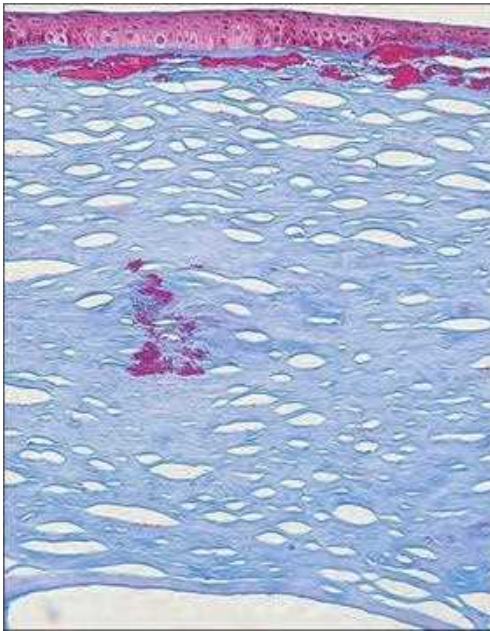
### Patient Presentation

Many patients have no symptoms, whereas some patients develop recurrent erosions. In the fifth decade or later, some patients develop visual difficulties as the opacities become prominent in the superficial stroma. Anterior stromal opacities tend to be much more visually significant than posterior stromal opacities.

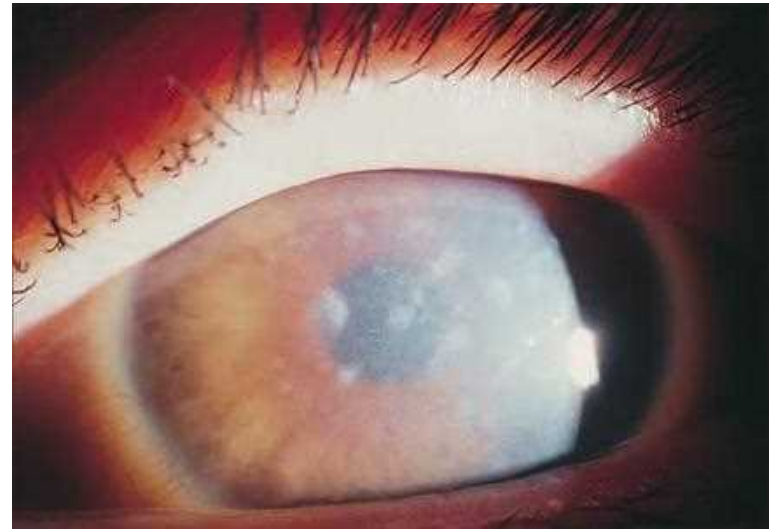
## Pathology

Histopathological findings show red staining (Fig. 4.20.5) with Masson's trichrome stain without Congo red staining. Electron microscopy shows electron-dense, rod-like deposits and microfibrils, which are present in keratocytes as well as epithelial cells.<sup>13</sup> The material is thought to be phospholipid.





**Fig. 4.20.5 Granular Corneal Dystrophy.** Masson's trichrome staining shows accumulation of hyaline material in the corneal stroma and beneath the epithelium.



**Fig. 4.20.6 Macular Corneal Dystrophy.** Note the stromal haze between the denser macular opacities in this 40-year-old woman.

## Treatment

Because the superficial deposits are often the most visually significant, vision often improves with excimer ablation and does not impair future keratoplasty.<sup>14,15</sup> Patients who require keratoplasty do well, and DALK is the procedure of choice.<sup>16</sup> Granules do recur superficially in the graft, at times in a swirling pattern that suggests the epithelium is the source of the deposits.<sup>16</sup> There are a few case reports of concurrent limbal stem cell transplantations with improved long-term outcomes.<sup>17</sup>

## GRANULAR CORNEAL DYSTROPHY TYPE 2

A dystrophy that combines features of both granular and lattice dystrophies has been described, with the majority of the original patients coming from the Avellino region of Italy. This is also referred to as *Avellino granular dystrophy*.

## Genetics

This disorder is autosomal dominant, with mutation in the *TGFBI* gene at locus 5q31.

## Ocular Manifestations

Patients have granular deposits in the anterior stroma along with lattice-like lines deeper within the stroma. These lines rarely cross and are whiter than lattice corneal dystrophy. A gray subepithelial haze may develop centrally after repeat corneal erosions and can affect visual acuity.

## Patient Presentation

Similar to granular corneal dystrophy type I, patients often present with decreased vision over time and may have epithelial erosions. Homozygotes have worse symptoms compared with heterozygotes.<sup>18,19</sup>

## Pathology

Histopathology shows superficial, discrete, red granular deposits with Masson's trichrome stain, as well as mid-to-deep stromal fusiform deposits with the typical Congo red and other stains characteristic of lattice dystrophy type I.<sup>20</sup>

## Treatment

Treatment is the same as for granular and lattice dystrophies. These individuals, even heterozygotes, are at high risk of aggressive recurrence of deposits predominantly in the interface if they undergo laser in situ keratomileusis (LASIK).<sup>21-23</sup> Although surface ablation by itself can lead to mild exacerbation, it may improve vision and delay corneal transplantation, with heterozygotes doing better than homozygotes.<sup>24</sup>

## MACULAR CORNEAL DYSTROPHY

In macular corneal dystrophy, three types have been defined on the basis of immunoreactivity to specific markers of antigenic keratan sulfates (AgKS). In type I, there is no AgKS reactivity in the cornea or in the serum. In type IA, the keratocytes manifest AgKS reactivity, but neither the serum nor the extracellular material in the cornea does.<sup>25</sup> In type II, all the abnormal deposits in the cornea as well as the serum have positive AgKS reactivity. Clinically and histopathologically, types I and II are indistinguishable.<sup>26</sup>

## Genetics

This disorder is autosomal recessive, with mutations in the *CHST6* gene at locus 16q22, leading to abnormal keratan sulfate.<sup>27</sup>

## Ocular Manifestations

Faint anterior stromal white opacities are seen early in life, often in the first decade. The opacities progress over time and a grainy, ground-glass haze becomes evident between the opacities and then throughout the stroma from limbus to limbus, down to Descemet's membrane. Over time, the cornea thins,<sup>28</sup> and the endothelium may develop guttae, although endothelial decompensation is rare (Fig. 4.20.6).

Although abnormalities in keratan sulfate in the blood and in cartilage have been reported, no systemic clinical abnormalities have been found in patients who have macular corneal dystrophy.

## Patient Presentation

Patients often present with decreased vision and photophobia in their second and third decades. They also may have recurrent erosions and decreased corneal sensitivity.

## PATHOLOGY

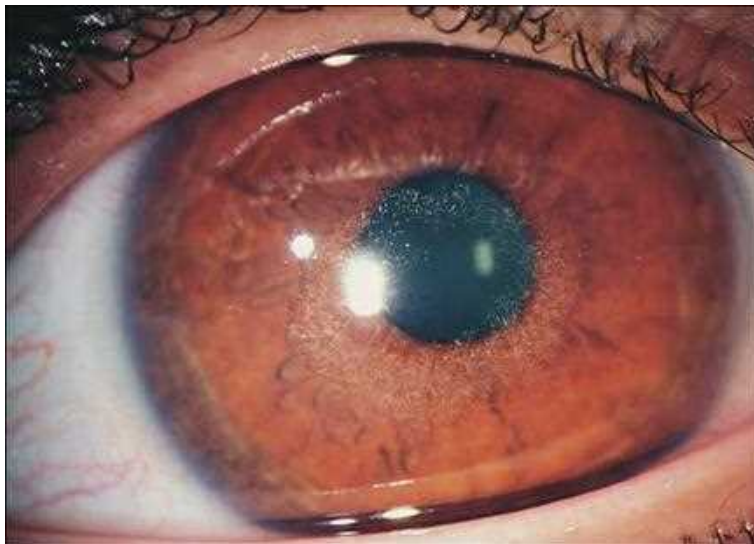
Pathology shows glycosaminoglycan (GAG) accumulation within and outside stromal keratocytes, beneath the corneal epithelium, and within corneal endothelial cells. This is evident with Alcian blue, colloidal iron (Fig. 4.20.7), and PAS staining. Electron microscopy shows intracytoplasmic vacuoles that contain GAGs, and the extracellular matrix contains fibrillogranular GAGs.<sup>29</sup>

## Treatment

Treatment consists of corneal transplantation and has good outcomes. In those without apparent endothelial involvement, DALK has shown comparable results to PKP in multiple studies at up to 5 years of follow-up.<sup>30-32</sup> Although PKP has a higher risk of rejection, DALK has a higher risk of endothelial failure. Higher rates of intraoperative perforations and need for conversion to PKP have been reported. Phototherapeutic keratectomy can improve vision for a short period but there is a high risk of recurrence.<sup>33</sup>



**Fig. 4.20.7 Macular Corneal Dystrophy.** Colloidal iron shows accumulation of glycosaminoglycan at all levels of the cornea.



**Fig. 4.20.8 Schnyder's Crystalline Dystrophy.** This patient has a paracentral ring of crystals. (Courtesy Frederick Brightbill, MD.)

Determining absence of endothelial involvement at the time of surgery remains a challenge. Recurrence in grafts is infrequent.

## SCHNYDER'S CORNEAL DYSTROPHY

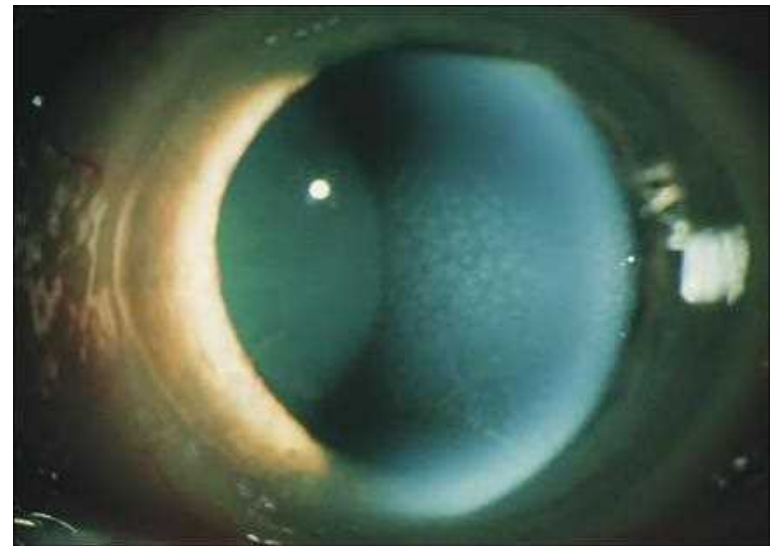
### Genetics

This disorder is autosomal dominant, with mutation in the UBIA phenyltransferase domain containing 1 (*UBIAD1*) gene at locus 1p36 and is involved in the synthesis of vitamin K<sub>2</sub>.

### Ocular Manifestations

Schnyder's corneal dystrophy is an autosomal dominant disorder with variable phenotypical expression. Younger patients present with central corneal opacity with or without central subepithelial corneal crystals (Fig. 4.20.8). With advancing age, arcus lipoides and more diffuse stromal haze may emerge. In up to 50% of patients, however, even in those from the same family, such crystals may not be evident. Weiss called this *Schnyder's crystalline dystrophy sine crystals*.<sup>34</sup>

Systemic hypercholesterolemia is frequent both in affected and unaffected family members.<sup>35</sup> Genu valgum (knock-knees) is rarely associated.<sup>36</sup>



**Fig. 4.20.9 Findings Typical of Central Cloudy Dystrophy (Posterior Crocodile Shagreen).** Such patients are almost always asymptomatic.

## Patient Presentations

Patients complain of severe photophobia. They often can have decreased corneal sensation and may retain much better scotopic vision than photopic vision.

## Pathology

Histopathology shows oil red O–positive material throughout the stroma, which is more prominent peripherally, in Bowman's membrane, and just anterior to Descemet's membrane. If a surgeon suspects Schnyder's corneal dystrophy, it is advisable to send fresh tissue that has not been preserved. Electron microscopy shows membrane-bound intracellular and extracellular vacuoles that contain electron-dense materials throughout the stroma and cholesterol clefts that may be seen in the anterior stroma.<sup>37</sup> The accumulated material appears to be phospholipid with esterified and unesterified cholesterol.

## Treatment

Treatment consists of DALK when the acuity declines sufficiently.<sup>38</sup> Phototherapeutic keratectomy may be beneficial in some patients.<sup>39</sup> Corneal erosions may result in better vision after their resolution because of decreased number of superficial crystals.<sup>40</sup>

## CENTRAL CLOUDY DYSTROPHY

### Genetics

This disorder is autosomal dominant, with no genetic abnormality.

### Ocular Manifestations

Central cloudy dystrophy, also known as *central cloudy dystrophy of François*, has the same clinical appearance as Vogt's posterior crocodile shagreen, with the exception being that central cloudy dystrophy appears to be dominantly inherited, whereas posterior crocodile shagreen appears to be sporadic. These disorders have central corneal haze in a mosaic pattern like that on crocodile skin and involves the posterior stroma (Fig. 4.20.9).

## Patient Presentations

Patients often are asymptomatic.

## Pathology

Histopathology shows a "saw-tooth" disarray of the corneal stromal lamellae.<sup>41</sup> Electron microscopy shows extracellular vacuoles, some containing fibrillogranular material and electron-dense deposits.<sup>42</sup>



## Treatment

No treatment is necessary.

## FLECK DYSTROPHY

Fleck dystrophy is also referred to as *speckle dystrophy*, *François–Neeten’s dystrophy*, or *cornea en moucheté*.

## Genetics

This disorder is autosomal dominant, with mutation in the phosphoinositide kinase FYVE finger containing gene at locus 2q34.

## Ocular Manifestations

Patients have discrete, small, white-to-gray opacities, which may be solid in appearance or have clear centers, scattered throughout the stroma. The corneal epithelium and endothelium are uninvolved.

## Patient Presentation

Most patients are asymptomatic, although the occasional patient may be photophobic.

## Pathology

Histopathology shows distension of some keratocytes with membrane-bound vacuoles containing GAGs (staining with Alcian blue and colloidal iron) and complex lipids (staining with oil red O and Sudan black).<sup>43</sup> The epithelium and the endothelium are normal. Electron microscopy shows membrane-based inclusions with delicate granular material in some keratocytes.<sup>44</sup>

## Treatment

No treatment is necessary.

## POSTERIOR AMORPHOUS CORNEAL DYSTROPHY

## Genetics

This disorder is autosomal dominant, with deletion of chromosome 12q21.33-q22 coding for four small leucine-rich proteoglycans<sup>45</sup> that are thought to play roles in collagen fibrillogenesis and matrix assembly.

## Ocular Manifestations

Posterior amorphous corneal dystrophy is a rare disorder, dominantly inherited, and defined by the presence of central and peripheral, deep corneal, gray, broad sheets of opacification.<sup>46</sup> Those with centrop peripheral changes were flat and hypermetropic, whereas those with less severe peripheral form were less hypermetropic and had keratometry readings above 41.<sup>47</sup> Iridocorneal adhesions have been reported.<sup>48</sup> The disorder appears to be nonprogressive, which has prompted the recommendation that this entity be considered a dysgenesis rather than a dystrophy.<sup>49</sup>

## Patient Presentation

Patients often present in their first decade, but vision is minimally affected.

## Pathology

Histopathological evaluation has shown irregular disorganization of the corneal lamellae anterior to Descemet’s membrane, with lipid deposition in the cytoplasm of some keratocytes.<sup>50</sup> Electron microscopy shows abnormal keratocytes and abnormally oriented collagen fibers, with disorganization of the posterior stromal lamellae.<sup>50</sup> A report described a case where subepithelial deposits and a thick collagenous layer posterior to Descemet’s membrane were found.<sup>51</sup>

## Treatment

No treatment is necessary.

## CONGENITAL STROMAL CORNEAL DYSTROPHY

Congenital stromal corneal dystrophy is present at birth and nonprogressive, so it better fits the category of congenital anomalies. Nonetheless, it is referred to as a dystrophy and resembles many of the other dystrophies.

## Genetics

This disorder is autosomal dominant, with a truncating mutation in the decorin (*DCN*) gene at locus 12q21.

## Ocular Manifestations

Congenital hereditary stromal dystrophy is a very rare disorder that is characterized by the presence of bilateral feathery or flaky, white, diffuse stromal clouding, most prominent in the central cornea. The corneal epithelium is normal, and no corneal edema occurs. The opacification is present at birth and is nonprogressive. Without treatment, visual acuity is reduced significantly, and nystagmus may ensue.

## Differential Diagnosis

The differential diagnosis includes congenital corneal edema (from congenital hereditary endothelial dystrophy), congenital glaucoma, and posterior polymorphous dystrophy. The absence of epithelial edema and the presence of normal corneal thickness and intraocular pressure, however, exclude these. Corneal haze from metabolic disorders usually is less evident at birth, increases over time, and is associated with systemic findings. In congenital stromal corneal dystrophy, no known systemic abnormalities have been found.

## Pathology

Histopathology reveals normal epithelium and Bowman’s layer, whereas the stroma shows separation of lamellae with layers of normal fibrillar arrangement separated by loosely packed layers of irregular and amorphous arrayed collagen, shown to be accumulated decorin material.<sup>52</sup> The collagen fibrils are about half the normal diameter. The normally banded anterior portion of Descemet’s membrane lacks bandings, but the posterior portion of Descemet’s membrane and the endothelium are normal.<sup>53</sup>

## Treatment

Treatment consists of DALK, usually with good outcomes.

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## Diseases of the Corneal Endothelium

4.21

Noel Rosado-Adames, Natalie A. Afshari

**Definition:** Diseases affecting the innermost layer of the cornea, which is in charge of regulating the hydration state of the corneal stroma.

## Key Features

- Bilateral presentation.
- Corneal clarity affected (variable degree).
- Hereditary pattern.

## Associated Features

- Key clinical features on slit-lamp examination.
- Severe cases usually require corneal transplantation.

## INTRODUCTION

The effects of external trauma and of ophthalmic and systemic disease on human corneal endothelium are best understood by first reviewing the anatomy and physiology of the adult human endothelium. A comprehensive review of this material can be found in Chapter 4.1.

## FUCHS' DYSTROPHY

## Introduction

Fuchs' endothelial corneal dystrophy (FD) is a bilateral, noninflammatory, progressive loss of endothelial cells that results in corneal edema and reduction of vision. Its key features include the presence of central guttae, folds in Descemet's membrane, stromal edema, and microcystic epithelial edema. Corneal endothelial degeneration is the primary defect that leads to the development of corneal edema. Associated features include prominent corneal nerves, stromal opacification, recurrent corneal erosions, female gender predominance, and familial predisposition.

## Epidemiology and Pathogenesis

FD is the most common corneal dystrophy to require keratoplasty, accounting for approximately 3.1% of all penetrating keratoplasties (PKPs) and 47.1% of all endothelial keratoplasties in the United States in 2015.<sup>1</sup> The genetic basis of FD is complex and heterogeneous, demonstrating variable expressivity and incomplete penetrance.<sup>2</sup> FD is likely to be complex in etiology, with genetic as well as environmental factors playing a role in its pathogenesis.<sup>3</sup> A significant variation occurs in expressivity between males and females, with a 3–4:1 female/male ratio recorded at the time of keratoplasty.<sup>4</sup> It is equally common among white and black patients who undergo keratoplasty but is relatively rare in Asian patients.<sup>5</sup>

Development of guttae and the onset of symptoms are more common in middle age.<sup>6</sup> Patients with FD are believed to have an increased incidence of open-angle glaucoma.<sup>7</sup> Short axial length, shallow anterior chamber, and angle-closure glaucoma also have been seen in conjunction with FD.<sup>8</sup> FD has been associated with keratoconus.<sup>9–11</sup> The progressive loss of endothelial cell function is primary in nature rather than secondary to any alteration in aqueous humor flow rate<sup>12</sup> or constituency.<sup>13</sup> Endothelial dysfunction is mainly a result of a reduction in sodium, potassium–adenosine

triphosphatase ( $\text{Na}^+, \text{K}^+$ -ATPase) pump activity,<sup>14</sup> which leads to a reduction in ion flux across the endothelium.<sup>11</sup> Molecular biological studies of corneal buttons from patients with FD suggest that apoptosis may play an important role in endothelial cell degeneration.<sup>15</sup> Recent studies have demonstrated an oxidant–antioxidant imbalance in FD cells, which, in turn, leads to oxidative DNA damage and apoptosis.<sup>16</sup>

Several genetic loci have been identified in patients with FD.<sup>3</sup> The first genetic locus was mapped to chromosome 13, called *Fuchs' corneal dystrophy locus 1* (FCD1).<sup>17</sup> Subsequently, three other loci, FCD2,<sup>18</sup> FCD3,<sup>19</sup> and FCD4,<sup>20</sup> were mapped to chromosomes 18, 5, and 9, respectively. Additionally, other reports have provided evidence for potential linkage to chromosomes 1, 7, 15, 17, and X by genome-wide linkage analysis.<sup>21</sup>

Multiple causal genetic mutations have been linked to FD. Mutations in the ion cotransporter encoded by the *SLC4A11* gene, also associated with congenital hereditary endothelial dystrophy, have been linked to the development of FD.<sup>22,23</sup> Additionally, mutations in the transcription factor *TCF8* gene, also associated with posterior polymorphous corneal dystrophy, have been identified in patients with FD.<sup>20</sup> A third causal gene for FD, *LOXHD1*, was identified on chromosome 18.<sup>24</sup> This gene has been associated with the development of progressive hearing loss in humans.

A strong association has been discovered between FD and trinucleotide repeats (TNRs) in the transcription factor 4 (*TCF4*) gene in chromosome 18.<sup>25–28</sup> This gene encodes the E2-2 transcription factor, which is involved in cellular growth and differentiation.<sup>25</sup> Expansion of TNR lead to messenger RNA (mRNA) missplicing, which leads to RNA toxicity.<sup>26</sup> TNR expansion in *TCF4* of more than 50 is highly specific for FD.<sup>27</sup> Changes to the endothelial barrier function, a known event in the development of FD, was identified as a key biological process influenced by the missplicing events.<sup>28</sup>

Mutations in the gene *COL8A2* that codes for the  $\alpha_2$ -chain of type VIII collagen have been reported in patients with an early onset endothelial dystrophy that was previously considered an early form of FD.<sup>29</sup> Recent studies suggest that the endothelial dystrophy linked to mutations in *COL8A2* represents a disease that is phenotypically distinct from FD.<sup>2</sup>

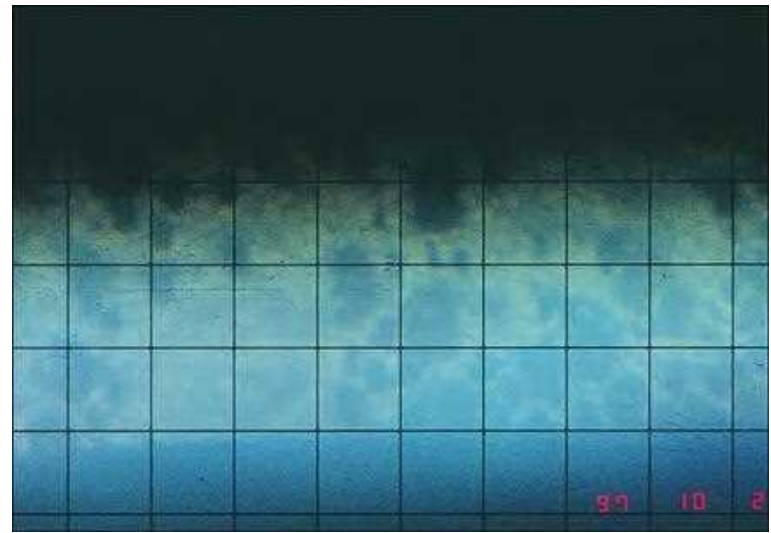
## Ocular Manifestations

The earliest slit-lamp finding in FD is the presence of focal excrescences of extracellular matrix in Descemet's membrane, called guttae (cornea guttata). In the earliest stages of this disease, the guttae first emerge in the central corneal endothelium (Fig. 4.21.1). Guttae are not specific to FD and may be seen in asymptomatic patients and in the setting of both uveitis and nonspecific superficial keratopathies. Up to 11% of eyes in patients older than age 50 years have guttae.<sup>30</sup> Pathologically identical lesions in peripheral Descemet's membrane are known as Hassall–Henle warts and are part of the normal aging process (see Chapter 4.22).

The guttae initially appear on specular reflection as scattered, discrete, isolated dark structures, smaller than an individual endothelial cell.<sup>31</sup> An associated fine pigment dusting may be observed within the central endothelium. At this stage, referred to as *stage 1*, the patient's vision usually is normal, and the stroma and epithelium are uninvolved.<sup>3,30</sup> Over time, these individual excrescences increase in number, enlarge, and fuse with adjacent guttae to disrupt the normal endothelial monolayer's specular reflection.<sup>31</sup> This produces a roughened surface with a specular reflection similar to beaten metal in appearance. Eventually, this process expands from the center of the cornea to involve the corneal periphery. As the disorder progresses, the endothelial monolayer becomes attenuated in thickness, with an increase in average cell size (polymegathism), a decrease in the percentage of hexagonal shaped cells, and an increase in the coefficient of variation in cell size (pleomorphism). In the last stages of the dystrophy, effacement of the endothelium results in overlying stromal edema. At this



**Fig. 4.21.1** Slit-Lamp View of Fuchs' Dystrophy (FD). Note the guttae on the image of the endothelium reflected on the speculum.



**Fig. 4.21.2** Specular Photomicrograph of Fuchs' Dystrophy (FD). Note dark areas that represent guttae adjacent to areas of enlarged endothelial cells. (Spacing of grid 0.1 mm.)

point, the endothelium becomes more difficult to observe using conventional specular microscopy, but it may still be visualized using confocal microscopy.<sup>31</sup>

As endothelial function progressively declines, the fluid accumulated in the stroma during nighttime lid closure is removed at a reduced rate, which results in significant stromal edema upon awakening.<sup>32</sup> This heralds the onset of *stage 2*.<sup>3,30</sup> Patients note blurred vision, glare, and colored halos around lights. Initially, the stromal edema is localized in front of Descemet's and behind Bowman's membrane.<sup>33</sup> Eventually, the entire stroma swells, taking on a ground-glass appearance. With the increase in corneal thickness, the posterior stroma and Descemet's membrane are thrown into folds. Vision at this time is variable.

With progressive endothelial dysfunction, bulk fluid flow across the cornea results in microcystic and bullous epithelial edema. This development represents *stage 3* of the disease.<sup>3,30</sup> With involvement of the epithelial layer, the optical quality of the tear-air interface is severely degraded, which produces a profound reduction in vision. With the onset of epithelial edema, basal adhesion complexes become disrupted to produce recurrent corneal erosions. As a slit-lamp marker of recurrent epithelial sloughing, duplication of basement layers occurs, which creates fingerprint and map changes.

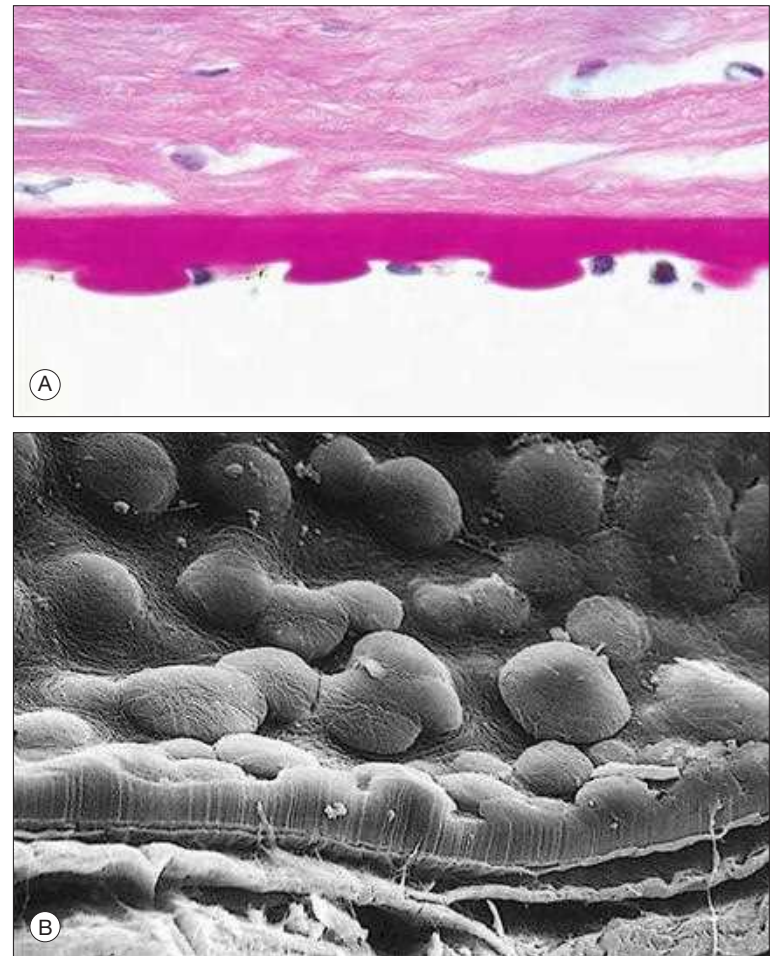
If erosions are prominent, a vascular pannus between epithelium and Bowman's membrane may be induced and results in an anterior stromal haze, with further reduction in vision, representing *stage 4* of the disease.<sup>3</sup> However, the associated secondary fibrotic layer produced within the pannus often reduces or eliminates the painful recurrent epithelial erosions experienced by the patient. With the increase in stromal edema, glycosaminoglycans elute from the stroma,<sup>34</sup> causing disorganization of the collagen fibrils, which contributes to additional stromal opacification.

## Diagnosis and Ancillary Testing

The earliest observable change suggestive of FD is the presence of guttae on slit-lamp examination (see Fig. 4.21.1). Specular microscopy provides endothelial cell counts, as well as a photographic record that can be a useful educational aid for the patient (Fig. 4.21.2). Subtle stromal edema can be observed using sclerotic scatter techniques. Corneal pachymetry documents increased corneal thickness. As the disease progresses, more obvious signs may develop, which include folds in Descemet's membrane, stromal haze, microcystic and bullous epithelial edema, subepithelial fibrosis, and pannus formation. When corneal opacification precludes specular microscopy, confocal microscopy can be used to image the endothelium and obtain reliable endothelial cell counts.<sup>31,32</sup>

## Differential Diagnosis

Differential diagnosis includes posterior polymorphous corneal dystrophy, congenital hereditary endothelial dystrophy, aphakic or pseudo-phakic bullous keratopathy, and Hassall-Henle bodies. No associated systemic diseases exist.<sup>3,30</sup>



**Fig. 4.21.3** Characteristic Wart-Like Bumps Present Within Descemet's Membrane. (A) Periodic acid-Schiff stain. (B) Scanning electron microscopy shows this better. (Courtesy Dr. R. C. Eagle, Jr.)

## Pathology

Light microscopy findings include a thickened Descemet's membrane, which may be laminated in appearance with buried guttae, guttae on the surface, or devoid of guttae but thickened (Fig. 4.21.3).<sup>4</sup> The endothelial layer is attenuated. Electron microscopy in FD shows characteristic thickening of Descemet's membrane caused by the deposition of an additional posterior banded layer (PBL), posterior to the posterior nonbanded layer. The PBL is markedly thickened and contains abnormally deposited



collagen and the classic posterior excrescences, guttae.<sup>3</sup> The production of this morphologically abnormal Descemet's membrane serves as a marker for a dysfunctional endothelium.<sup>35</sup>

## Treatment

Early stages of the disease may be managed medically, temporizing the need for a keratoplasty. Medical management includes the use of hypertonic solutions or ointments and decreasing ambient humidity. If intraocular pressure (IOP) is above 20 mm Hg (2.67 kPa), attempts to lower it may reduce the force that drives fluid into the stroma. Treatment measures for painful erosions include hypertonics, bandage contact lenses, anterior stromal puncture, and conjunctival flaps.

With progressive corneal edema refractory to medical management, keratoplasty usually is offered. PKP was traditionally performed for the treatment of advanced cases.<sup>36</sup> If the patient shows signs of visually significant cataracts, keratoplasty may be combined with cataract extraction.<sup>37</sup> In recent years, endothelial keratoplasty, including Descemet's stripping automated endothelial keratoplasty (DSAEK or DSEK) and Descemet's membrane endothelial keratoplasty (DMEK), has been performed as an alternative to conventional full-thickness corneal transplantation for the treatment of endothelial disorders.<sup>38–42</sup> In fact, endothelial keratoplasties represented 92% of the total keratoplasties performed in 2015 in patients with FD.<sup>1</sup> The DSAEK procedure involves replacing the diseased endothelium and deep stroma with a posterior lamellar disc of tissue, including donor corneal endothelium, Descemet's membrane, and posterior corneal stroma. DMEK involves replacing the diseased tissue with just the donor endothelium and Descemet's membrane. Both DSAEK and DMEK have been demonstrated to be superior to PKP in terms of earlier visual recovery, postoperative refractive outcomes, wound- and suture-related complications, and intraoperative and late suprachoroidal hemorrhage risk.<sup>40,43</sup> Studies have reported faster visual rehabilitation and better best corrected visual acuity with DMEK compared with DSAEK.<sup>44</sup> With DMEK, patients also had a lower rate of endothelial rejection (1%) at 2 years compared with DSAEK (9%) and PKP (17 %).<sup>45</sup>

## Course and Outcome

Long-term outcomes of patients with FD undergoing PKP have shown that graft clarity approached 90%, and approximately 60% of patients achieved 20/40 (6/12) or better visual acuity 5 years after transplantation.<sup>35</sup> Results after DSAEK have shown that average best-corrected visual acuity (BCVA; mean 9 months after surgery) ranged from 20/34 to 20/66.<sup>40</sup> One year after DMEK surgery, patients had an average BCVA of 20/24, with 98% of patients achieving 20/30 or better.<sup>46</sup> Reports of graft survival rates at 5 years for DMEK and DSAEK were similar to those reported for PKP in patients with FD (95%, 95%, and 93% respectively).<sup>41,47</sup>

## CONGENITAL HEREDITARY ENDOTHELIAL DYSTROPHY

### Introduction

First described by Maumenee<sup>48</sup> in 1960, congenital hereditary endothelial dystrophy (CHED) is but one of the many causes of bilateral corneal clouding in full-term infants and usually requires keratoplasty. Key features of this autosomal dominant or recessive condition are a corneal thickness 2–3 times normal, normal IOP, and normal corneal diameter. Associated features are corneal pannus, nystagmus, and esotropia.

### Epidemiology and Pathogenesis

Prevalence, incidence, and gender distribution for this disorder are unknown. The onset is usually at birth in a term infant; corneal clouding may be maximal at birth or progress over a period of years. Family pedigree studies support that autosomal dominant (CHED1) and recessive (CHED2) forms exist, as well as sporadic occurrences. Autosomal recessive inheritance is associated with bilateral corneal edema without photophobia but with nystagmus that is present at birth.<sup>49</sup> Autosomal dominant inheritance is associated with the progressive onset of corneal edema 1–2 years post partum with photophobia but without nystagmus.<sup>49</sup> Autosomal dominant and autosomal recessive forms of CHED have been linked to chromosome 20, mapped to the loci 20p11.2-q11.2 and 20p13, respectively.<sup>50</sup> Mutations in the *SLC4A11* gene in chromosome 20 have been highly associated with the

development of autosomal recessive CHED.<sup>50</sup> A related X-linked endothelial dystrophy has been described in males that clinically resembles CHED very closely.<sup>51</sup>

CHED is believed to result from abnormal neural crest cell terminal induction during the late term to perinatal period. At this time, failure to complete final differentiation of the endothelial monolayer occurs, which results in a dysfunctional endothelium.<sup>52</sup> This dysfunctional endothelium is believed to have faulty growth regulation mechanisms that lead to accumulation of a functionally abnormal and structurally exaggerated form of posterior nonbanded Descemet's membrane.<sup>53</sup>

## Ocular Manifestations

The usual presentation is bilateral, symmetrically edematous, cloudy corneas evident at birth or early in the postnatal period.<sup>49</sup> Examination reveals the corneas to have a diffuse gray-blue, ground-glass coloring.<sup>49</sup> Corneal thickness is 2–3 times normal and often greater than 1 mm centrally. Both IOP and horizontal corneal diameter are normal. Rarely, CHED is associated with glaucoma and should be considered if corneal opacification fails to resolve after normalization of IOP.<sup>54</sup>

Closer examination reveals the texture of the epithelial surface to be irregular, with a diffuse pigskin-like roughness.<sup>49</sup> Occasionally, discrete white dots may be seen in the stroma. In areas where stromal opacification is less dense, Descemet's membrane appears gray, and on specular reflection may have a *peau d'orange* texture.<sup>49</sup> The endothelial layer may or may not be visualized. A fine corneal pannus may be seen, as well as low-grade inflammation.

## Diagnosis

A tentative diagnosis usually is possible when examination under anesthesia demonstrates typical bilateral stromal opacification, gross corneal thickening, normal horizontal diameter, normal IOP, and absence of breaks in Descemet's membrane.

## Differential Diagnosis

Differential diagnosis includes congenital glaucoma without buphthalmos, posterior polymorphous corneal dystrophy, macular stromal dystrophy, mucopolysaccharidosis, intra-uterine infection, and birth trauma from forceps. Harboyan's syndrome is an entity defined as CHED accompanied by progressive, sensorineural hearing loss.<sup>55,56</sup> This disorder has been linked to the *SLC4A11* gene mutation.<sup>56</sup>

## Pathology

Light microscopy shows epithelial atrophy with basal cell hydrops, subepithelial calcification or fibrosis, patchy loss of Bowman's membrane, and variable vascularization or spheroidal degeneration of the stroma.<sup>53</sup> Descemet's membrane is thickened, often with discrete laminations. The endothelial layer is attenuated.<sup>53</sup>

## Treatment

If the edema is stationary and mild, use of hypertonics and desiccating measures may be employed. Usually, however, these patients require keratoplasty because of the bilateral nature of the corneal edema. Keratoplasty in infants and children is a high-risk procedure and is technically difficult, and the long-term prognosis for graft clarity is worse than it is for adults. No definitive clinical guidelines have emerged with regard to the timing of surgical intervention, as a result of significant heterogeneity in disease severity, follow-up periods, and patient ages at both diagnosis and surgery, among the few published studies.<sup>57</sup> Delayed PKP (after age 12 years) may offer better graft outcomes and visual prognosis in patients with CHED, even in the presence of nystagmus, according to a publication.<sup>58</sup> DSAEK has been performed in recent years as a therapeutic alternative for CHED. DSAEK performed in eyes with CHED has allowed rapid restoration of corneal clarity while minimizing intraoperative and postoperative complications normally associated with pediatric PKP.<sup>59</sup>

The decision regarding surgery may be difficult because despite significant corneal haze and absence of a red reflex, patients often seem to see much better than expected.<sup>60</sup> If patients maintain good fixation with normal alignment, surgery may be delayed; loss of fixation or development of nystagmus may lead to earlier intervention.<sup>60</sup>

## Course and Outcome

In one large study, during a mean follow-up period of over 70 months, 69% of eyes retained full graft clarity. Postoperative visual acuity improvement of 1 or more Snellen lines was seen in 5 of 10 eyes in which the patients were old enough for accurate assessment of visual acuity; however, just four of these 10 eyes attained a visual acuity of 20/200 or better.<sup>61</sup> First graft survival rates range from 25% at 3 months in earlier studies to 62%–90% at 2–3 years in more recent series.<sup>57,60,61</sup>

Results from a small series of patients older than age 12 months who underwent DSAEK revealed that BCVA of 20/40 or better was achieved in 8 of the 9 patients, and visual acuity of 20/70 was achieved in the remaining patient. In the infant group, the three patients who had DSAEK were able to “fix and follow” after the procedure.<sup>59</sup>

## POSTERIOR POLYMORPHOUS CORNEAL DYSTROPHY

### Introduction

First described in 1916 by Koeppe, this rare dystrophy has a clinical spectrum that ranges from congenital corneal edema to late-onset corneal edema in middle age. Many cases are subclinical—the majority of patients have good vision and only subtle slit-lamp and specular micrographic abnormalities. Posterior polymorphous corneal dystrophy (PPCD) is a bilateral autosomal dominant disorder characterized by polymorphic posterior corneal surface irregularities with variable degrees of corneal decompensation. Key features consist of the following:

- Vesicular, curvilinear, and placoid irregularities found on slit-lamp examination
- Rounded dark areas with central cell detail that produce a doughnut-like pattern on specular microscopy
- Epithelial-like transformation of endothelium on histological examination
- Reduced vision from the corneal edema.

Associated features are iridocorneal adhesions, peripheral anterior synchiae, glaucoma, and a tendency to recur in graft patients. Some of these features overlap with iridocorneal endothelial (ICE) syndrome, Peters' anomaly, and Axenfeld–Rieger syndrome, suggesting that PPCD may be part of a broader spectrum of disorders united by abnormalities of terminal neural crest cell differentiation.<sup>62,63</sup> PPCD associated with posterior amyloid degeneration of the cornea, keratoconus, and Alport's syndrome has been reported.<sup>62,64,65</sup>

### Epidemiology and Pathogenesis

The prevalence of this rare disorder in the general population is unknown. This autosomal dominant condition presents with variable genetic penetrance and expressivity.<sup>66,67</sup> PPCD has been linked to three chromosomal loci: (1) PPCD1 (OMIM 122000) on chromosome 20p11.2-q11.2; (2) PPCD2 (OMIM 609140) on chromosome 1p34.3–p32.3; and (3) PPCD3 (OMIM 609141) on chromosome 10p11.2.<sup>67</sup> Specific genes at each locus have been identified, but there is some controversy regarding the role of these genes in the pathogenesis of this condition.<sup>68–74</sup> Mutations in the homeobox gene *VSX1* in PPCD1 were demonstrated in PPCD families,<sup>69,70</sup> but other studies did not replicate these results.<sup>70,71</sup> Reports have associated the *COL8A2* gene within the PPCD2 locus, coding for the  $\alpha_2$ -chain of type VIII collagen, with PPCD,<sup>29,74</sup> as well as contributing to the pathogenesis of an early-onset endothelial corneal dystrophy. The contribution of this gene has been questioned as additional studies have failed to identify similar mutations within analyzed PPCD cohorts.<sup>74–76</sup> Studies investigating a candidate gene at the PPCD3 locus demonstrated disease-causing mutations in the zinc finger E-box binding homeobox 1 gene *ZEB1*, previously known as *TCF8*.<sup>77–81</sup> The *ZEB1* gene has the strongest association to PPCD based on linkage, association, and familial segregation analyses.<sup>81</sup>

The pathogenesis of PPCD is attributed to focal metaplasia of endothelial cells into a population of aberrant keratinized epithelial-like cells.<sup>62,65</sup> Immunohistochemical analyses of these transformed cells show that they contain antigens and cytokeratins that usually are associated with epithelial cells.<sup>82</sup> The transformation of a single-cell layer of endothelium into a multilayered epithelium-like tissue is believed to be responsible for the loss of stromal deturgescence, the observed specular microscopic patterns, and the tendency toward synechiae formation.



**Fig. 4.21.4** Slit-lamp appearance of vesicles in posterior polymorphous dystrophy. Note the small vesicular lesions on retroillumination. (Courtesy Dr. Richard Yee.)

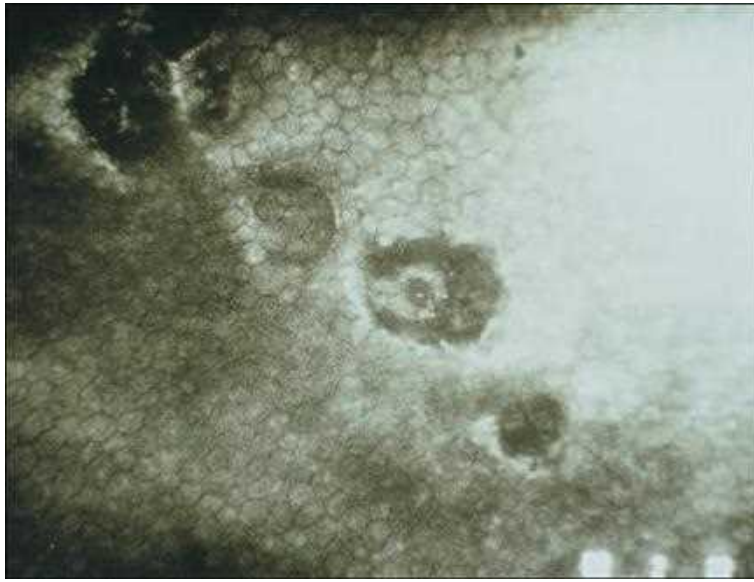


**Fig. 4.21.5** Slit-Lamp Appearance of the Band Form of Posterior Polymorphous Dystrophy. Note the vertical serpentine band. (Courtesy Dr. Richard Yee.)

### Ocular Manifestations

The most common finding is isolated vesicles bilaterally, which appear as circular or oval transparent cysts with a gray halo, diameters in the range of 0.2–1 mm, at the level of Descemet's membrane, best viewed by retroillumination with a widely dilated pupil (Fig. 4.21.4).<sup>83,84</sup> The cysts may be few or many, widely separated or clustered close together to create confluent geographical patches. Less common are band-shaped or “snail track” areas, which typically have scalloped edges and are about 1 mm across (Fig. 4.21.5).<sup>83</sup> Their length can range from 2–10 mm.<sup>84</sup> In both vesicular and band presentations, the overlying stroma and epithelium are uninvolved, and vision is normal. The least common slit-lamp finding is placoid or diffuse endothelial involvement.<sup>83</sup> Patients who have placoid-type PPCD often present with reduced vision. Specular microscopy of the presenting lesions shows them to be sharply demarcated from uninvolved endothelium. In this presentation, Descemet's membrane and the posterior stroma are hazy, and usually areas of corneal edema and iridocorneal adhesions occur.<sup>84</sup>

On specular microscopy, the vesicles appear as circular dark rings around a lighter, although mottled, center in which cellular detail is evident.<sup>83–87</sup> These vesicles represent steep-sided, shallow depressions in the endothelium<sup>83</sup>; the steep sides correspond to the peripheral dark ring seen on specular reflection, and the depressed center corresponds to the lighter, mottled central portion (Fig. 4.21.6). Specular microscopy of the band-shaped areas shows them to be composed of a chain of overlapping vesicles, which create a shallow trench with scalloped borders



**Fig. 4.21.6 Specular Photomicrograph of Vesicles in Posterior Polymorphous Dystrophy.** Note the doughnut-like appearance of the vesicles. (Courtesy Dr. Richard Yee.)

that represent the edges of individual vesicles that have fused.<sup>83</sup> Patients with PPCD may exhibit broad-based iridocorneal adhesions and peripheral anterior synechiae. These most often are seen in corneas with placoid areas of involvement.<sup>84</sup> Elevation of IOP refractory to medical measures is common in these patients. All patients who have PPCD have reduced endothelial cell counts compared with age-matched controls.<sup>83,85</sup>

## Diagnosis

The majority of patients are diagnosed with use of the slit lamp that helps visualize vesicular, band-like, or placoid areas on the posterior corneal surface. The diagnosis of PPCD in patients with corneal edema of unknown cause is based on light and electron microscopy of the excised buttons obtained during keratoplasty.

## Differential Diagnosis

Differential diagnosis includes tears in Descemet's membrane, interstitial keratitis, FD, and ICE syndrome (discussed in detail in Chapter 10.20). As in PPCD, endothelial cells in ICE syndrome may show epithelial characteristics, leading to speculation that they represent a spectrum of the same disease.<sup>63</sup> No systemic associations exist except for rare reports of PPCD associated with Alport's syndrome.

## Pathology

Light microscopy shows pits in the posterior corneal surface, which correspond to the vesicles seen on slit-lamp examination. Descemet's membrane in these areas is attenuated, and the endothelium may be multilayered.<sup>86,87</sup> In other areas, Descemet's membrane appears multilayered, of variable thickness, and with attenuation or loss of endothelium. Discontinuities in Descemet's membrane with anterior migration of cells to form slit-like structures or clefts in pre-Descemet's stroma have been described.<sup>64</sup> Scanning electron microscopy of keratoplasty buttons may show a striking

juxtaposition of normal-appearing endothelial cells adjacent to epithelial cell-like areas that show myriad surface microvilli.<sup>86,87</sup> Transmission electron microscopy shows multilayered cells that contain numerous desmosomes and intracytoplasmic filaments.<sup>86,87</sup> Cell culture studies demonstrate features similar to cultured epithelial cell lines.<sup>87</sup>

## Treatment

The majority of patients require no treatment; those with corneal opacification are offered keratoplasty. Traditionally, penetrating keratoplasty was performed in this group of patients. Recent reports have shown the implementation of endothelial keratoplasty with positive results.<sup>88,89</sup>

## Course and Outcome

In the majority of patients, PPCD is believed to be a nonprogressive type of dystrophy, usually without vision impairment. Those patients who require keratoplasty appear to be at risk for recurrence of this dystrophy in the grafted cornea,<sup>90-92</sup> as well as for the development of glaucoma.<sup>87</sup> It is thought that the genesis of this behavior is the epithelial-like transformation and subsequent migration of host endothelium, which causes the endothelium to encroach on the donor corneal tissue and host angle structures.<sup>87</sup>

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# Corneal Degenerations

Maria A. Woodward, Shahzad I. Mian, Alan Sugar

# 4.22

**Definition:** Secondary deterioration or deposition in the cornea, distinct from dystrophies.

## Key Features

- Common.
- Bilateral usually.
- Typically does not affect vision.

## Associated Features

- Increased prevalence with age.
- Often associated with chronic light exposure.
- May occur after inflammation.
- Not inherited.

## INTRODUCTION

Degenerations of the cornea are common conditions that, in most cases, have relatively little effect on ocular function and vision. These conditions occur with increasing age, as a result of past inflammation, and with long-term toxic effects of environmental exposure. Unlike corneal dystrophies, corneal degenerations are not inherited, may be unilateral or bilateral, and often are associated with corneal vascularization. Degenerations tend to involve the peripheral cornea and may overlap the limbus and conjunctiva.

The conditions that occur in the corneal periphery are discussed first, followed by the conditions that occur more centrally. This is an arbitrary division as many conditions, such as spheroidal degeneration or band keratopathy, can be found in either or both locations.

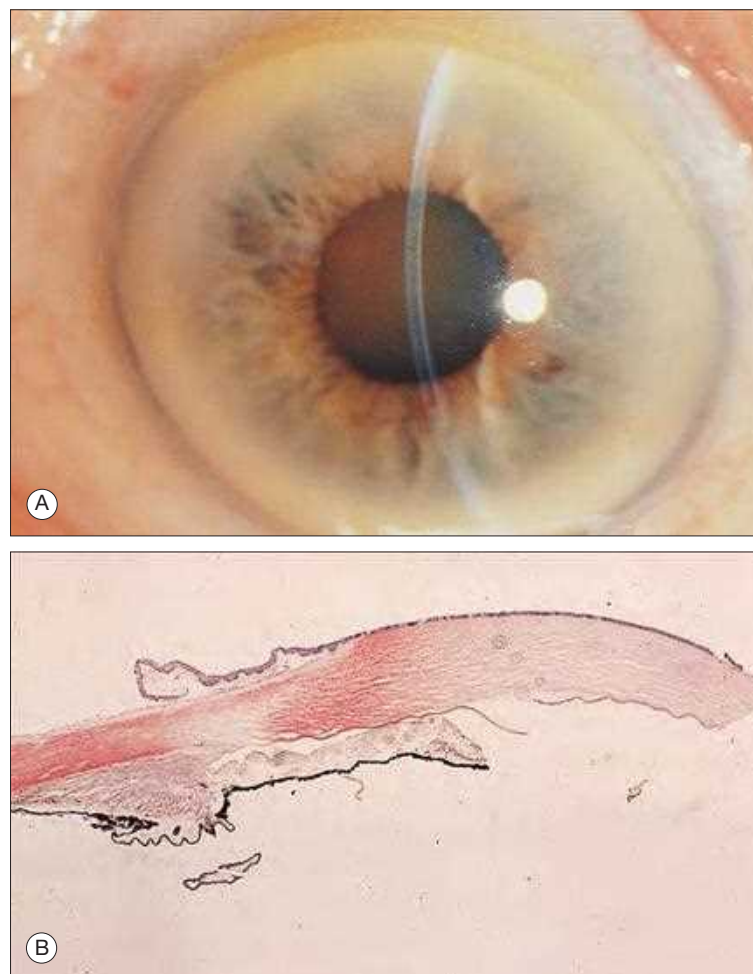
## CORNEAL ARCUS (ARCUS SENILIS)

Corneal arcus presents as a gray-to-white, occasionally yellow, band of peripheral corneal opacification. It consists of fine dots, has a clear zone (clear interval of Vogt) between it and the limbus, and has a diffuse central border with a sharper peripheral border (Fig. 4.22.1). It begins superiorly and inferiorly and spreads to involve the entire periphery. Deposits begin in the deep stroma with progression to involve the superficial stroma. Arcus is almost always bilateral but can be asymmetric in unilateral carotid vascular disease (decreased arcus) or chronic ocular hypotony (increased arcus).<sup>1</sup>

Arcus is the most common corneal degeneration. In men, the frequency increases with age and occurs in essentially all men older than 80 years of age. The presentation is delayed by 10 years in women.<sup>1</sup>

Arcus deposits consist of extracellular corticosteroid esters of lipoproteins, mostly of low density. Lipid material leaks from limbal capillaries with central flow being limited because of a functional barrier to the flow of large molecules in the cornea.<sup>2,3</sup>

Strong evidence exists for an association with increased plasma cholesterol and low-density lipoprotein cholesterol, particularly when it occurs in men younger than 50 years (arcus juvenilis). Men with arcus juvenilis have a fourfold increased relative risk of mortality from coronary heart disease and cardiovascular disease. Arcus in young men, therefore, is a useful clinical indication for the need for lipid and cardiovascular evaluation.<sup>4</sup> Young patients who have arcus have an increased risk for type



**Fig. 4.22.1 Arcus Senilis.** (A) Corneal arcus in an older man. (B) Histological section shows that the lipid is concentrated in the anterior and posterior stroma as two red triangles, apex to apex, with the bases being Bowman's and Descemet's membranes, both of which are infiltrated heavily by fat (red staining), as is the sclera.

IIa dyslipoproteinemia but a decreased risk for type IV.<sup>5</sup> In older patients, arcus does not correlate with mortality.<sup>6</sup>

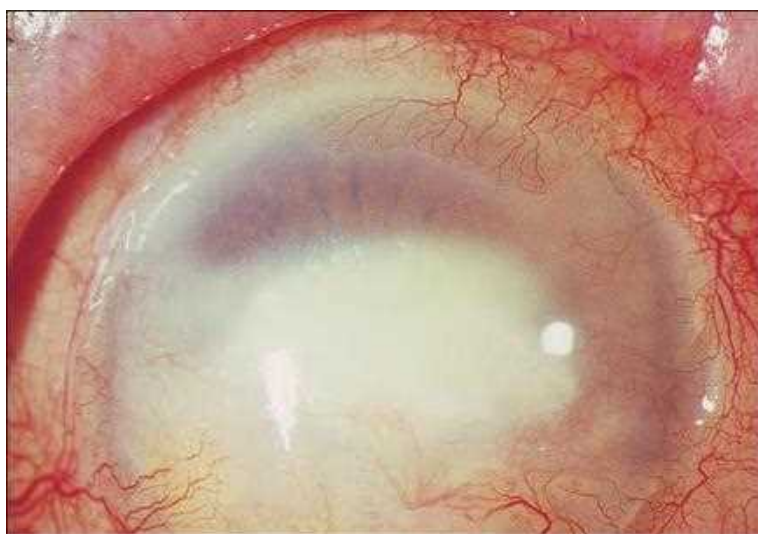
## LIPID KERATOPATHY

Lipid keratopathy may be peripheral, central, or diffuse and is similar in appearance to arcus. It occurs mainly in a secondary form, but rarely may be seen in a primary form. Primary lipid keratopathy has features of a corneal dystrophy, is usually bilateral, and the central lipid, often with cholesterol crystals, may severely decrease vision.<sup>7</sup>

Secondary lipid keratopathy appears as a white or yellow stromal deposit separated by a narrow, clear zone from corneal stromal neovascularization<sup>8</sup> (Fig. 4.22.2). It often is denser than arcus and may appear as a circular deposit at the end of long-standing stromal vessels. It can follow corneal edema, as in hydrops.<sup>9</sup> Histological evaluation shows that the material consists of intra- and extracellular lipids.<sup>10</sup>

Lipid deposition may occur secondary to systemic lipid processing disorders. Defects in esterification of cholesterol and in lipoprotein scavenging have been implicated in lecithin cholesterol acetyltransferase (LCAT)





**Fig. 4.22.2 Dense Lipid Keratopathy.** Note the central and peripheral lipid deposits that followed zoster keratitis with vascularization.



**Fig. 4.22.3 Vogt's Limbal Girdle.** The fimbriated peripheral corneal opacity is visible in the 9 o'clock position (arrow).

deficiency, Fish-eye disease, and Tangier disease. Disorders of high-density lipoprotein function appear to allow accumulation of cholesterol centrally within the cornea.<sup>1</sup>

### VOGT'S WHITE LIMBAL GIRDLE

Vogt<sup>11</sup> was the first to describe two types of limbal girdle—white, arc-like opacities in the cornea central to the limbus in the 3 o'clock and 9 o'clock positions. Type I is a mild, early form of calcific band keratopathy. Type II lacks a peripheral clear zone and consists of fine, white radial lines, located nasally more often than temporally (Fig. 4.22.3). The prevalence of this condition increases with age to essentially 100% in those older than 80 years of age.<sup>12</sup>

Histologically, Vogt's limbal girdle type II is made up of hyperelastotic and hyaline deposits peripheral to Bowman's layer, similar to those seen in a pingueculum and pterygium.

### SENILE CORNEAL FURROW DEGENERATION

Furrow degeneration is a painless bilateral thinning of peripheral cornea. A peripheral corneal furrow can occur between corneal arcus and the limbus in older adults.<sup>11</sup> Often the clear area may appear to be furrowed, but it was considered to be falsely thinned by Vogt.<sup>11,13</sup> Rarely, true thinning with no inflammation, vascularization, or induced corneal astigmatism can occur in this region. Furrow degeneration does not require any therapy, but the location and degree of thinning should be evaluated when considering location for cataract incisions.

## TERRIEN'S MARGINAL CORNEAL DEGENERATION

This condition is described in Chapter 4.17.

### PERIPHERAL CORNEAL GUTTAE

The corneal endothelium undergoes degeneration with age, as manifested by a decreasing endothelial cell density<sup>14</sup> and thickening of the posterior, nonbanded layer of Descemet's membrane.<sup>15</sup> Degenerating endothelial cells produce localized nodular thickening of Descemet's membrane, known as *guttae*. The relationship of central guttae to Fuchs' corneal endothelial dystrophy (FD) is discussed elsewhere (see Chapter 4.21). Peripheral guttae, known as Hassall–Henle warts, are visible in normal adult corneas and are thought to be truly degenerative and unrelated to FD. They are not associated with functional corneal changes.

### CALCIFIC BAND KERATOPATHY

Band keratopathy is a common corneal degeneration that can occur at any age, presenting in the central or peripheral cornea. It most commonly occurs secondary to chronic corneal diseases, particularly uveitis, advanced glaucoma, keratitis, or trauma; primary idiopathic forms rarely occur. Band keratopathy can present secondarily with elevated serum calcium or phosphate in systemic diseases, including sarcoidosis, hyperparathyroidism, vitamin D toxicity, metastatic neoplasm to bone, and chronic renal failure with secondary hyperparathyroidism. Researchers have described a toxic form resulting from mercurial preservatives in pilocarpine and an acute form after intracameral tissue plasminogen activator injection.<sup>16</sup> In children, band keratopathy may be the presenting sign of chronic uveitis as a result of juvenile idiopathic arthritis. Band keratopathy may occur after localized corneal damage from intraocular silicone oil and phosphate forms of corticosteroids.<sup>17,18</sup>

Histologically, calcium is deposited as the hydroxyapatite salt in the epithelial basement membrane, basal epithelium, Bowman's layer,<sup>19</sup> and anterior stroma. The mechanism of calcium deposition in the cornea is unknown but occurs primarily in the exposed area of the cornea. Deposition of calcium may result from the precipitate tears leave when they evaporate or because the exposed cornea is at a lower pH than other areas.<sup>19</sup> The most severely affected areas are the middle and inferior thirds of the cornea, which are the areas of greatest exposure to the atmosphere.

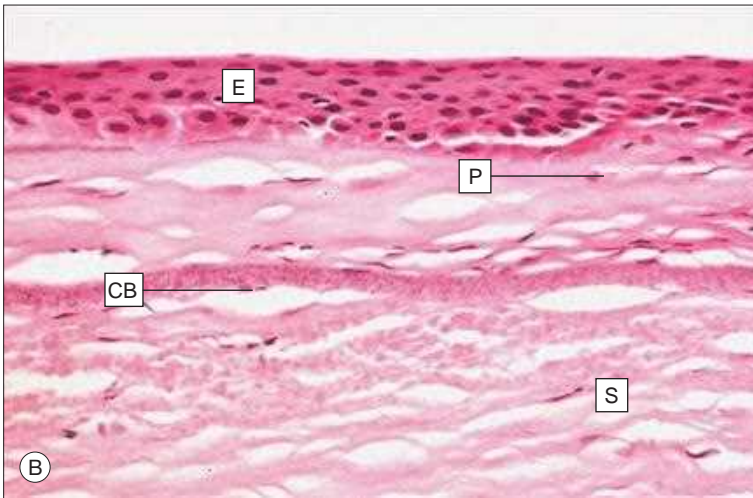
Corneal calcium deposits as a horizontal band and begins near the corneal periphery (Fig. 4.22.4). As the deposits move centrally, the band has clear void circles where Bowman's layer is traversed by nerve endings. The deposits begin as a gray haze and can become densely white with a rough, pebbly surface.

Patients can have symptoms of pain, foreign body sensation, recurrent corneal erosions, and decreased vision. The rate of development and progression of disease is variable.<sup>20</sup> If band keratopathy causes persistent pain or decreased vision, corneal surgery is indicated. The surgery involves removing the epithelium over the deposits, applying 0.05 mol/L disodium ethylenediaminetetraacetic acid to chelate the calcium and dissolve it, and using a brush or surgical blade to remove remaining calcium.<sup>21</sup> The process can take a few minutes to an hour, depending on the density of the calcium. Excimer laser phototherapeutic keratectomy also may be used to remove the calcium deposits.<sup>22</sup>

### SPHEROIDAL DEGENERATION

Spheroidal degeneration may occur in the cornea or the conjunctiva. Other names for this degeneration include climatic droplet keratopathy, hyaline degeneration, and local designations, such as Labrador keratopathy.<sup>23,24</sup> Spheroidal degeneration occurs as a primary corneal form, a secondary corneal form, and a conjunctival form. The frequency of this degeneration increases with age and varies with geographical location—occurring most often in areas that have high sunlight exposure (snow or sand) and high winds. It is twice as prevalent in men as in women. The prevalence varies from 6% in England to greater than 60% in Labrador. It is thought to be a result of ultraviolet light exposure and may be associated with blue-light exposure.<sup>25,26</sup> Other risk factors are drying of the cornea and repeated corneal trauma. Secondary forms can occur with corneal scars, lattice dystrophy, and glaucoma.

Spheroidal degeneration presents as fine droplets, yellow or golden in color, beneath the epithelium (Fig. 4.22.5). The droplets appear oily, although they are not composed of lipid. In the primary form, droplets



**Fig. 4.22.4 Band Keratopathy.** (A) Calcium deposits in the cornea of a 13-year-old with juvenile rheumatoid arthritis. (B) A fibrous pannus (P) is present between the epithelium (E) and a calcified Bowman's membrane (CB). Some deposit is also present in the anterior corneal stroma (S).

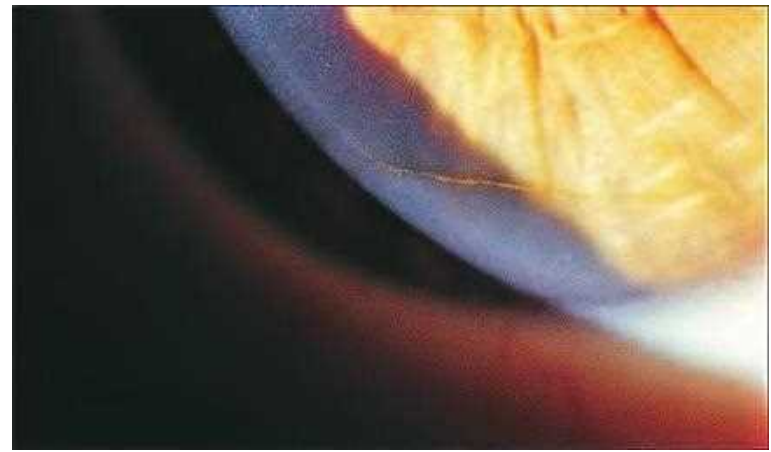


**Fig. 4.22.5 Spheroidal Degeneration.** Central spheroidal droplets in the cornea of an eye that is blind as a result of glaucoma.

begin peripherally and advance centrally between the palpebral fissures. As the condition advances, the droplets become larger, more nodular, and more opaque lifting the central corneal epithelium. Three stages of the primary form have been described:

- Grade I—fine shiny droplets are present only peripherally without symptoms.
- Grade II—the central cornea is involved and vision  $\geq 20/100$  (6/30).
- Grade III—there are large corneal nodules and vision  $\geq 20/200$  (6/60).

These forms are always bilateral. Grade III disease may be rapidly progressive and lead to corneal ulceration with secondary bacterial infection.<sup>27</sup>



**Fig. 4.22.6 Hudson–Stähli Line.** Thin horizontal brown line in inferior cornea of a healthy 57-year-old male. (Courtesy the photography department, WK Kellogg Eye Center, University of Michigan.)

Histologically, deposits appear as extracellular amorphous globules, which may coalesce in Bowman's layer and spill over to anterior stroma. These globules consist of a protein material with elastotic features, as in pingueculae. The source of the protein is unknown, but it has been postulated to result from the action of ultraviolet light on proteins from limbal vessels.<sup>23,28</sup>

The majority of cases of spheroidal degeneration are asymptomatic. Patients with visual loss may be treated with superficial keratectomy and, when necessary, lamellar or penetrating keratoplasty.

## IRON DEPOSITION

Iron deposition occurs in the corneal epithelium in several clinical situations. The prototype is the Hudson–Stähli line, which is located at the junction of the middle and lower thirds of the cornea (Fig. 4.22.6). It is yellow-brown in color, curves downward at its center, and is usually about 0.5 mm wide and 1–2 mm long. It is seen most clearly in blue light as a black line. Similar iron deposition occurs in keratoconus at the base of the cone (Fleischer's ring), around filtering blebs (Ferry's line), central to a pterygium (Stocker's line), around Salzmann's nodules, within the margin of corneal grafts, between radial keratotomy scars, and following laser in situ keratomileusis (LASIK) or intrastromal corneal ring placement.<sup>29,30</sup> The source of the iron is unknown but most likely comes from the tear film. It is postulated that altered tear flow secondary to distorted corneal shape is a factor in the formation of these lines and that epithelial migration patterns affect the shape of the Hudson–Stähli line.

Histologically, the iron is deposited intracellularly in corneal epithelial cells as a ferritin-like material, possibly hemosiderin.<sup>31</sup> Iron lines do not affect vision or cause any symptoms and thus require no treatment.

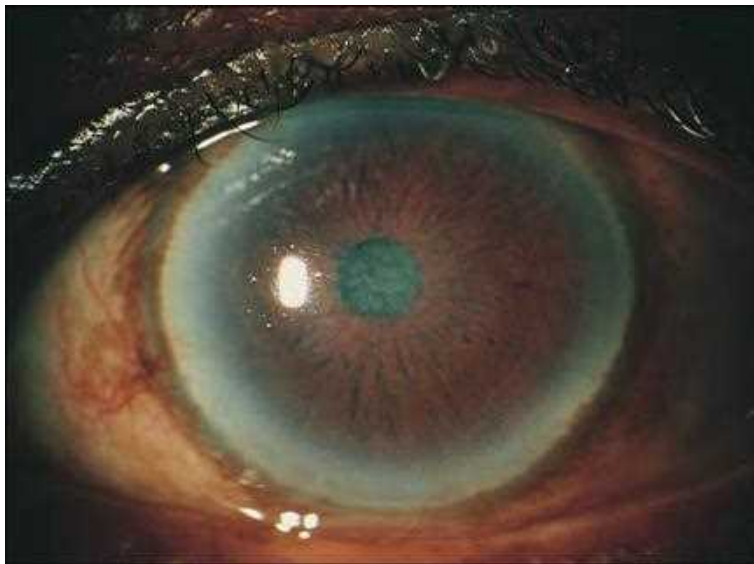
Coats' white ring is an iron deposition that occurs in the anterior portion of Bowman's layer. It appears as a tiny ring of white dots, most often inferiorly, and is asymptomatic.<sup>32</sup> It is thought to result from previous iron deposition by a corneal foreign body.

## CROCODILE SHAGREEN

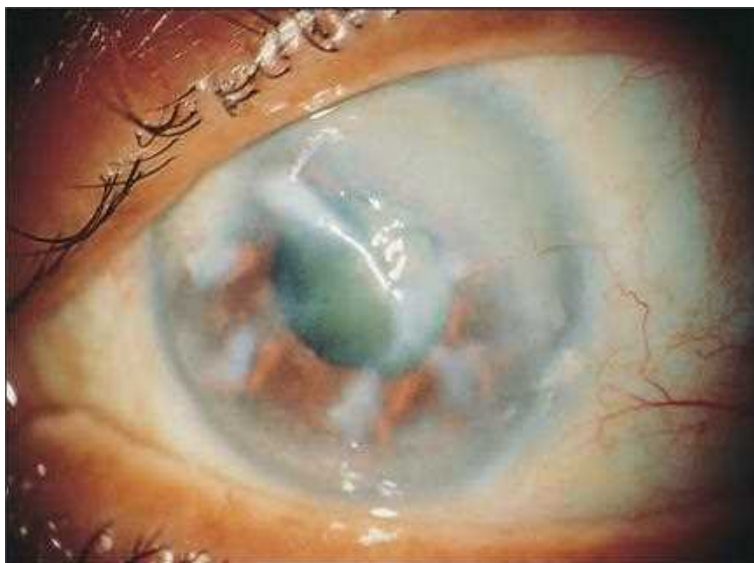
Crocodile shagreen appears as anterior or posterior polygonal opacities in the corneal stroma that occur as a consequence of aging. Crocodile shagreen was first described by Vogt.<sup>11</sup> The pattern resembles that of crocodile skin and is thought to be related to the oblique insertion of the collagen lamellae that constitute the corneal stroma<sup>33,34</sup> (Fig. 4.22.7). In vivo confocal microscopy demonstrates the mosaic pattern of the collagen lamella.<sup>35</sup> Crocodile shagreen is a very common, although frequently subtle, finding in older patients. The anterior form is more common than the posterior form, with the opacities in posterior crocodile shagreen presenting more peripherally and, thus, may be indistinguishable from corneal arcus.

Familial forms of posterior crocodile shagreen have been described in a dominant juvenile form and in a form associated with X-linked megalocornea. Central cloudy dystrophy of François appears to be similar and is likely not a true dystrophy (see Chapter 4.20).





**Fig. 4.22.7 Posterior Crocodile Shagreen.** A mottled, gray pattern is visible in the central cornea.



**Fig. 4.22.8 Salzmann's Nodular Degeneration.** Severe corneal involvement in an elderly woman.

## CORNEA FARINATA

First described by Vogt, cornea farinata occurs in the corneas of older patients, is without symptoms, and is recognized as an incidental finding.<sup>11</sup> The corneal opacities in this condition are fine, dust-like dots of white or gray color in the deep central stroma, just anterior to Descemet's layer.<sup>36</sup> The Latin word *farinata*, meaning "like wheat flour," refers to the appearance of the dots. The bilateral deposits are best visualized by slit-lamp retroillumination. The cause of the condition is unknown. The histology suggests that the deposits may be composed of lipofuscin in stromal keratocytes.<sup>37</sup>

## SALZMANN'S CORNEAL DEGENERATION

Salzmann's corneal degeneration may occur at any age but is primarily a condition of older adults. It has been associated with phlyctenular keratitis, interstitial keratitis, vernal keratitis, trachoma, or Thygeson's superficial punctate keratitis. It also occurs with no history of prior corneal disease. It typically develops several decades after previous keratitis. It may be unilateral or bilateral and occurs more often in women than in men.

Salzmann's corneal degeneration appears as white-to-gray or light-blue nodules that elevate the epithelium in the superficial corneal stroma (Fig. 4.22.8). The nodules may be single or in clusters, often at the edge of old corneal scars. Each nodule is about 0.5–2 mm in diameter, not vascularized, and separated from other nodules by clear cornea. The onset of the lesions is gradual, over many years, during which time they increase in both size and number.<sup>38</sup> They may decrease vision by encroaching upon



**Fig. 4.22.9 Corneal Keloid Recurrence.** A central, elevated, fibrous opacity is present centrally. The photo was taken 6 months after superficial keratectomy for the original lesion.

the central cornea or by altering the corneal shape. They may be associated with recurrent corneal erosions.<sup>39</sup>

Histologically, thinned epithelium overlies hyalinized avascular collagen. Bowman's layer is damaged or focally absent and replaced by material that is similar to basement membrane.<sup>40</sup> Usually, evidence of old keratitis is seen in the surrounding stroma. In vivo confocal microscopy studies show irregular epithelium and activated keratocytes in the area of the nodule.<sup>41,42</sup> Many patients who have peripheral nodules are asymptomatic and require no treatment. If vision is altered or if recurrent erosions are frequent, the nodules may be removed by peeling from the underlying stroma or excimer laser phototherapeutic keratectomy.<sup>23</sup> Recurrences have been found after all forms of treatment.<sup>43</sup>

## CORNEAL KELOIDS

Corneal keloids are uncommon and result from progressive growth of fibrous tissue on the cornea that outgrows the original boundaries. They typically appear months or years following trauma, surgery, or inflammatory processes. The appearance is consistent with an elevated gray-white mass involving the entire stroma or isolated nodules (Fig. 4.22.9).

Histologically, poorly arranged collagen fibers, myofibroblasts, and blood vessels are noted in early stages. In later stages, compaction of collagen and reduction in vascularity and cellularity occurs. Significant keloids may be treated with superficial keratectomy, lamellar keratoplasty, or penetrating keratoplasty.<sup>44,45</sup>

## CORNEAL AMYLOID DEGENERATION

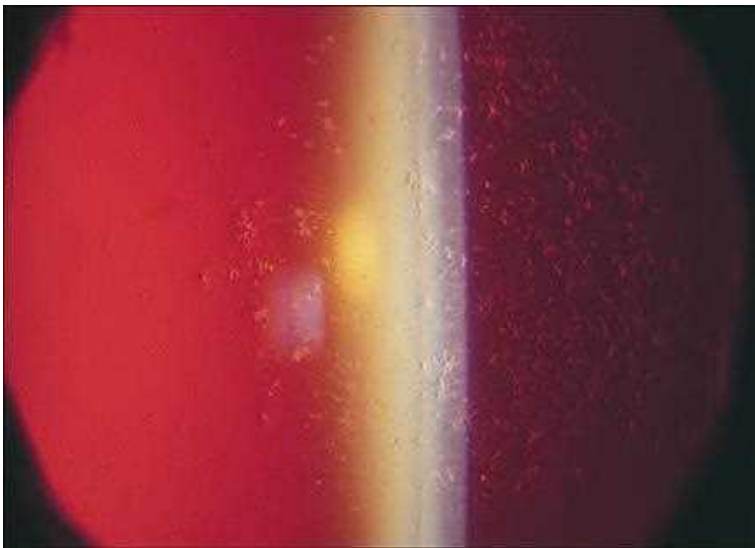
Amyloid is a group of hyaline proteins deposited in tissues in a variety of systemic and localized conditions. Familial localized amyloidosis is seen in the cornea as lattice, Avellino's, and gelatinous drop-like corneal dystrophies.

The degenerative forms of amyloid seen in the cornea and conjunctiva are secondary, localized, and nonfamilial. These occur as nonspecific corneal deposits that follow corneal trauma, keratitis, or chronic intraocular inflammation. Usually, they are diagnosed with histopathology after removal of nonspecific corneal opacities.<sup>46</sup>

A specific form of corneal amyloid degeneration has been described as polymorphic amyloid degeneration.<sup>47</sup> It is characterized by the presence of deep central corneal stromal glass-like deposits that often indent Descemet's layer (Fig. 4.22.10). They are bilateral, generally occur after age 50 years, and do not affect vision. Histologically, they appear similar to lattice dystrophy deposits composed of amyloid. The cause is unknown.

Another stromal deposition with features of both spheroidal degeneration and amyloid deposition has been called *climatic proteoglycan stromal keratopathy*.<sup>48</sup> This has been described in Saudi Arabian patients with risk factors similar to those of spheroidal degeneration. The patients have bilateral, horizontal, oval, central anterior stromal, ground-glass haze that consists of both proteoglycan and amyloid on histopathology. This condition does not usually affect vision.<sup>48</sup>





**Fig. 4.22.10 Polymorphic Amyloid Degeneration.** Glassy, fine deep corneal deposits in the central cornea of an older woman.

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# Dry Eye Disease

Michael H. Goldstein, Naveen K. Rao

# 4.23

**Definition:** A multifactorial disease of the ocular surface characterized by deficient tear production and/or excessive tear evaporation, leading to loss of homeostasis of the tear film.

## Key Features

- Symptoms: ocular and conjunctival irritation.
- Ocular surface disruption.

## Associated Features

- Possible autoimmune disease (i.e., Sjögren's syndrome).
- Possible conjunctival or lid abnormalities.
- Blurred or unstable vision.

## INTRODUCTION

Dry eye disease (DED), also known as dry eye syndrome (DES) or keratoconjunctivitis sicca (KCS), is characterized by ocular irritation and visual disturbance resulting from alterations of the tear film and ocular surface.<sup>1-10</sup> The effects of DED can vary from minor inconvenience to rare sight-threatening complications. Although the diagnosis of DED traditionally has focused on inadequate secretion or aqueous tear deficiency, the tear film is a complex and delicately balanced unit dependent on the normal function of several distinct components.<sup>10-13</sup> Current treatment is heavily weighted toward supplementation, stimulation, preservation of aqueous tears, or treatment of ocular surface inflammation, which is satisfactory for many patients. DED, however, often involves multiple deficiency states, which, when disregarded, can result in treatment failure and frustration for both the patient and the physician. Currently, a large unmet need still exists for better treatment options for patients with DED.

## EPIDEMIOLOGY

Estimating the prevalence of DED is complicated by the absence of consensus on a single reliable diagnostic test. Several population-based epidemiological studies have utilized questionnaires to assess prevalence of dry eye symptoms. American and Australian studies have revealed a prevalence of 5%–16%, whereas Asian studies have revealed a higher prevalence of approximately 27%–33%.<sup>14-25</sup>

## PATHOGENESIS

### Normal Physiology

The stratified tear film is composed of mucin, aqueous, and lipid components. The mucin layer consists of high-molecular-weight glycoproteins closely adherent to an inherently hydrophobic surface epithelium and its glycocalyx. Mucin provides a smooth, hydrophilic surface permitting even distribution of the overlying aqueous layer. Its primary source is conjunctival goblet cells with a small contribution from surface epithelial cells.<sup>26,27</sup> Comprising the largest volume of the tear film, the aqueous is secreted by the main lacrimal gland, the accessory glands of Krause and Wolfring, and, minimally, a transudate of the conjunctival vessels and cornea. Consisting primarily of water, it also contains electrolytes (sodium [Na], potassium [K], chloride [Cl]) and proteins, including epidermal growth factor, immunoglobulins (IgA, IgG, IgM), lactoferrin, lysozyme, and other cytokines.<sup>28,29</sup> These components likely play both a protective and a homeostatic role for the ocular surface. Last, meibomian glands (MGs) secrete a lipid layer,

containing chiefly sterol esters and wax monoesters.<sup>3,30</sup> Although only 0.1- $\mu$ m thick, the lipid layer serves to stabilize the tear film by increasing surface tension and retarding evaporation.

The tear layer maintains a smooth surface for optical clarity, lubricates to facilitate eyelid blink, and offers protection against ocular infection.<sup>11</sup> Average tear flow is about 1.2- $\mu$ m/minute.<sup>31</sup> Blinking serves to periodically distribute tears evenly over the ocular surface and encourages both secretion and mechanical drainage of tears through the lacrimal drainage system. Regulation likely involves both neuronal and hormonal pathways. Direct innervation of the lacrimal gland, MGs, and goblet cells has been demonstrated, with M3 class cholinergic receptors predominating in the lacrimal gland.<sup>32</sup> Although estrogen has little effect on tear secretion, it may have a supportive role on the ocular surface.<sup>33</sup> Androgens appear to have a positive effect on the secretion of both aqueous and lipid tears.<sup>34,35</sup>

## Pathophysiology

Reduced aqueous tear flow and increased evaporation of the aqueous component of tears leads to hyperosmolarity. Tear hyperosmolarity damages the ocular surface epithelium and sets off a cascade of inflammatory pathways that leads to apoptotic cell death, loss of goblet cells, and deficient mucus production, with resultant tear film instability. Tear film instability, in turn, leads to increased evaporation. Implicated cytokines include mitogen-activated protein (MAP) kinases, nuclear factor- $\kappa$ B (NF- $\kappa$ B), interleukin-1 (IL-1), tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), and matrix metalloproteinases (MMP-9, in particular).<sup>36-38</sup> In the early stages of DED, inflammation and mechanical irritation stimulates reflex secretion from the lacrimal gland and increased blink rate. Over time, damage to the ocular surface leads to reduction in corneal sensation and impaired reflex tearing.<sup>10</sup> In advanced cases, chronic conjunctival damage can lead to metaplasia and keratinization.

## Diagnosis and Classification

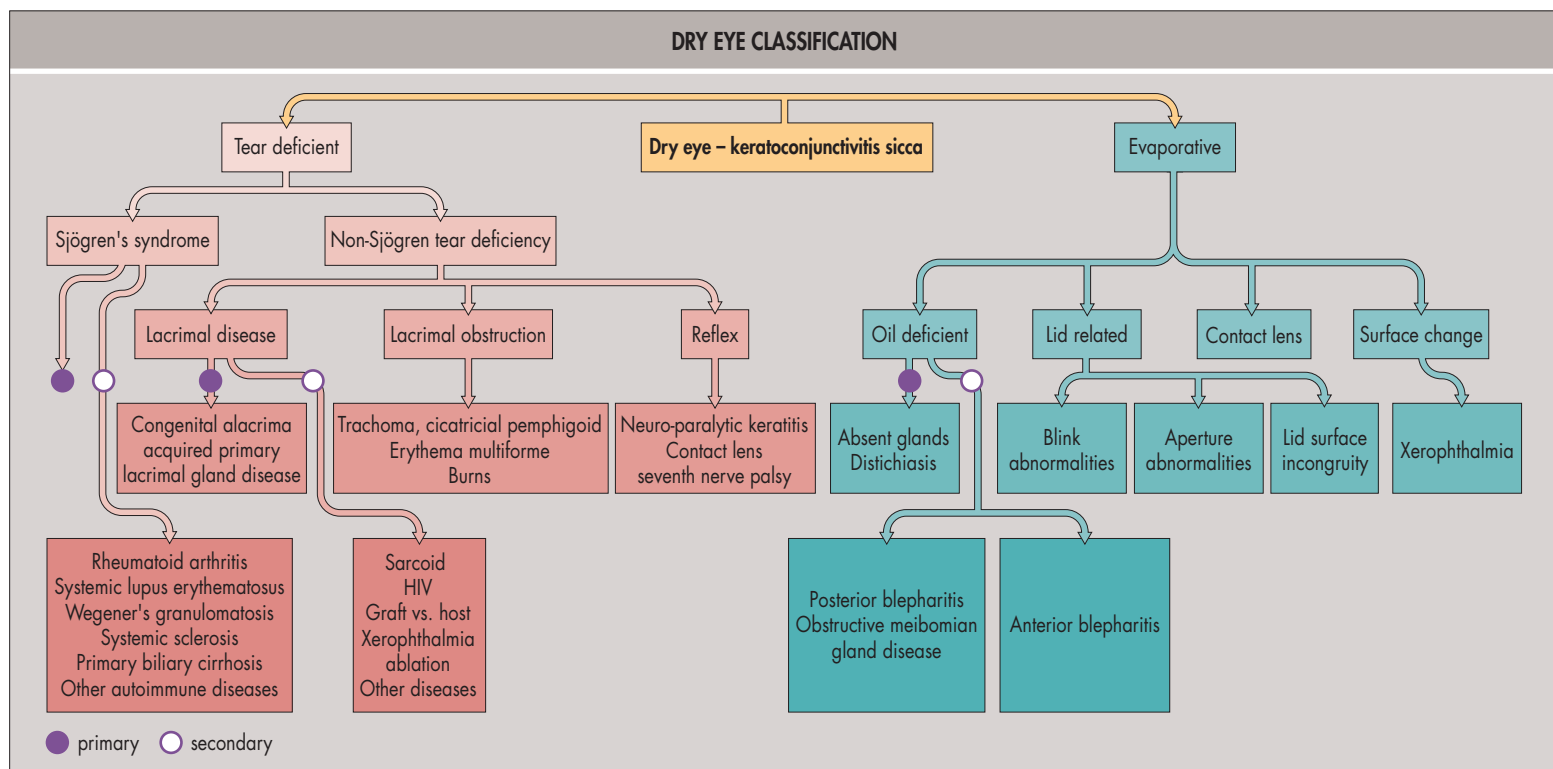
The 2017 report for the International Dry Eye Workshop (DEWS II) was a 2-year effort with 12 subcommittees made up of 150 experts from 23 countries. The DEWS II report updated the definition of dry eye as follows: "Dry eye is a multifactorial disease of the ocular surface characterized by a loss of homeostasis of the tear film, and accompanied by ocular symptoms, in which tear film instability and hyperosmolarity, ocular surface inflammation and damage, and neurosensory abnormalities play etiological roles."<sup>39</sup> The new definition emphasizes the multifactorial nature of DED, where loss of homeostasis of the tear film is the central pathophysiological concept. It also recognizes the role of neurosensory abnormalities in the development of DED. This definition continues to incorporate concepts introduced in the first DEWS report that DED results in ocular discomfort, visual disturbance, and tear film instability with potential damage to the ocular surface.<sup>10</sup> This definition encompasses all the clinical entities associated with systemic disease, as well as idiopathic DED.

A classification system algorithm for dry eye is depicted in Fig. 4.23.1. The effect of the environment on an individual's risk of developing dry eye also is considered. Low blink rate,<sup>40,41</sup> wide lid aperture,<sup>42-44</sup> aging,<sup>45-47</sup> low androgen levels,<sup>48,49</sup> high estrogen levels,<sup>50,51</sup> and systemic drugs affect the so-called milieu interieur.<sup>10</sup> Low relative humidity, air conditioning, air travel,<sup>52</sup> high wind velocity, and other occupational environmental factors, such as video display terminal use<sup>53</sup> affect the so-called milieu exterieur.<sup>10</sup>

## Aqueous Tear-Deficient Dry Eye

Sjögren described KCS in 1933.<sup>54</sup> Consequently, defective lacrimal tear secretion is subdivided into non-Sjögren's tear deficiency (NSTD) and





**Fig. 4.23.1** Dry eye disease classification. (With permission from Lemp MA. The 1998 Castroviejo Lecture. New strategies in the treatment of dry-eye states. *Cornea* 1999;18:625–32.)

Sjögren's syndrome tear deficiency (SSTD). NSTD has no association with systemic autoimmune disease, which is a cardinal feature of SSTD.

### Non-Sjögren's Tear Deficiency

NSTD can occur from primary lacrimal gland deficiencies, secondary lacrimal gland deficiencies, obstruction of lacrimal gland ducts, or reflex hyposcretion.<sup>10</sup> Primary lacrimal gland deficiencies include age-related DED, congenital alacrima, and familial dysautonomia (Riley–Day syndrome). The most common form of NSTD is age-related DED, which is associated with ductal and interacinar fibrosis and obstruction within the lacrimal gland, possibly as a result of low-grade chronic inflammation.<sup>55–57</sup> Congenital alacrima is a rare cause of DED in youth, resulting from primarily absent or hypoplastic lacrimal glands. Familial dysautonomia is an autosomal recessive multisystem disorder, in which generalized pain insensitivity accompanies absence of both emotional and reflex tearing. Defective sympathetic and parasympathetic innervation of the lacrimal gland and defective sensory innervation of the ocular surface occur.<sup>10</sup>

Secondary lacrimal gland deficiency from infiltration and damage to the lacrimal gland in benign lymphoepithelial lesion of Godwin ("Mikulicz's disease"), lymphoma, sarcoidosis, hemochromatosis, amyloidosis, human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS), and graft-versus-host disease all can result in DED.<sup>58–61</sup> Surgical or radiation-induced destruction or denervation of lacrimal tissue can result in secondary lacrimal deficiency.<sup>58</sup> Secondary obstruction of the lacrimal gland ducts can occur with trachoma,<sup>61</sup> ocular cicatricial pemphigoid, mucous membrane pemphigoid,<sup>62–64</sup> erythema multiforme/Stevens–Johnson syndrome,<sup>65</sup> chemical burns, and thermal burns.<sup>66</sup>

Reflex hyposcretion of tears can be conceptually divided into reflex sensory block (damage to the afferent arm) and reflex motor block (damage to the efferent, or secretomotor arm). Reflex sensory block occurs with any reduction in ocular surface sensation and leads to decreased reflex-induced lacrimal secretion and decreased blink rate, which increases tear evaporation.<sup>10,67</sup> Causes of decreased ocular surface sensation leading to dry eye include topical anesthetic use,<sup>68</sup> contact lens wear,<sup>69,70</sup> diabetes mellitus,<sup>17,71–74</sup> aging, and neurotrophic keratitis.

As shown by studies utilizing topical anesthesia, interruption of the afferent stimulus of tear production, or sensory loss (denervation), results in decreased tear secretion and reduced blink rate.<sup>68,75</sup> Damage to afferent sensory fibers occurs after incisional corneal surgery (penetrating or anterior lamellar keratoplasty, radial keratotomy, and limbal cataract incision) and after damage to the first division of the trigeminal ganglion from trauma, tumor, and herpes simplex or zoster, resulting in reduced tear production. Laser-assisted in situ keratomileusis (LASIK) and photorefractive

**TABLE 4.23.1** Medications Associated With Dry Eye Disease

Mechanism of Action	Class	Medications
Anticholinergic	Antimuscarinics	Tolterodine tartrate (Detrol) Scopolamine
	Antihistamines (sedating compounds are associated with greater dryness)	Chlorpheniramine (Chlor-Trimeton) Diphenhydramine (Benadryl) Promethazine (Phenergan)
	Antiparkinsonian	Benzotropine (Cogentin) Trihexyphenidyl (Artane)
	Antidepressants	Amitriptyline (Elavil)
	MAO inhibitors	Nortriptyline (Pamelor) Imipramine (Tofranil) Doxepin (Sinequan) Phenelzine
	Antipsychotics	Chlorpromazine (Thorazine) Thioridazine (Mellaril) Fluphenazine (Prolixin)
Antiadrenergic	Alpha-agonists	Clonidine (Catapres)
	Beta-blockers	Methyldopa (Aldomet) Propranolol (Inderal) Metoprolol (Lopressor)
Diuretic	Thiazide	Hydrochlorothiazide
Other	Nonsteroidal anti-inflammatory drugs	Ibuprofen (Advil) Naproxen (Naprosyn, Aleve)
	Cannabinoids	Marijuana

keratectomy resulting in decreased corneal sensation and blink rate are recognized as precipitating causes of dry eye.<sup>67,76–79</sup> Systemic medications are a common source for the inhibition of efferent lacrimal gland stimulation through anticholinergic activity or decreased secretion through systemic dehydration (Table 4.23.1).<sup>80</sup> Although DED has been reported in association with menopause, estrogen supplementation has not been shown to have a beneficial effect.<sup>50,81</sup> Alterations in other hormones, especially androgens, which also are reduced during menopause, have been implicated.

### Sjögren's Syndrome Tear Deficiency

Sjögren's syndrome is a clinical condition of aqueous tear deficiency combined with dry mouth. The syndrome is classified as primary (patients

without a defined connective tissue disease) or secondary (patients who have a confirmed connective tissue disease).<sup>82–84</sup> Primary SSTD refers to aqueous tear deficiency combined with symptoms of dry mouth, presence of autoantibodies to Ro(SSA) or La(SSB) antigens, decreased salivary secretion, and presence of lymphocytic foci on minor salivary gland biopsy. Secondary SSTD is associated with rheumatoid arthritis, systemic lupus erythematosus, polyarteritis nodosa, Wegener's granulomatosis, systemic sclerosis, primary biliary cirrhosis, and mixed connective tissue disease.<sup>10,83</sup> Both subtypes of SSTD feature progressive lymphocytic infiltration of the lacrimal and salivary glands and can be associated with severe and painful ocular and oral discomfort. The pathogenesis of the tear deficit in SSTD is infiltration of the lacrimal gland by B and CD4 lymphocytes (with some CD8 lymphocytes) and by plasma cells, with subsequent fibrosis.

Revised American-European consensus diagnostic and classification criteria for Sjögren's syndrome were published in 2002.<sup>83</sup> One point is given for at least one positive response or positive result in each of the following categories:

- **Ocular symptoms**—daily dry eye symptoms for more than 3 months, ocular irritation, use of artificial tears more than three times per day.
- **Oral symptoms**—daily dry mouth symptoms for more than 3 months, presence of swollen salivary glands, frequent drinking of liquids to aid in swallowing.
- **Ocular signs**—Schirmer's test I (without anesthetic)  $\leq 5$  mm in 5 minutes, Rose Bengal score  $\geq 4$  according to the van Bijsterveld scoring system.
- **Histopathology**—biopsy of minor salivary gland showing inflammation with lymphocytic foci.
- **Oral signs**—reduced salivary flow  $\leq 1.5$  mL in 5 minutes, parotid sialography showing salivary duct dilation without obstruction, salivary scintigraphy showing signs of decreased saliva production.
- **Autoantibodies**—presence of anti-Ro(SSA) antibody, presence of anti-La(SSB) antibody.

For a diagnosis of primary Sjögren's syndrome, either four of the six categories (including either histopathology or autoantibodies) or three of the four objective categories (ocular signs, histopathology, oral signs, and autoantibodies) must be met. For diagnosis of secondary Sjögren's syndrome, in patients with a defined connective tissue disease, the presence of one symptom (ocular or oral) plus two of the three objective categories (ocular signs, histopathology, and oral signs) must be met.

## Evaporative Dry Eye Disease

Excessive evaporation that occurs in specific periocular disorders can cause dry eye disease with or without concurrent aqueous tear deficiency. Evaporation leads to both loss of tear volume and a disproportionate loss of water, resulting in tear hyperosmolarity. Environmental conditions such as high altitude, dryness, or extreme heat accelerate evaporative tear loss even in normal eyes. Causes of evaporative DED can be intrinsic (disease affecting lid structures or dynamics) or extrinsic.<sup>10</sup>

## Meibomian Gland Disease and Blepharitis

Meibomian gland dysfunction (MGD) leads to both decreased secretion and abnormal composition of the tear film lipid layer. The abnormal composition leads to MG blockage and reduced effectiveness in the tear film. The resulting ocular surface and eyelid inflammation perpetuates a cycle of inflammation, scarring, hyperkeratosis, stenosis, and further MGD.

Often associated, bacterial colonization by normal lid commensals (*Staphylococcus aureus*, *Propionibacterium acnes*, and coagulase-negative staphylococci) acts directly by altering secreted lipids and indirectly by causing inflammation. Esters and lipases produced by these commensals act on secreted lipids in the tear film, producing soaps that manifest as "meibomian foam."<sup>85,86</sup> An association also is seen with dermatological conditions, such as seborrheic dermatitis, atopic dermatitis, and acne rosacea, a disorder resulting in vascular dilation, telangiectasias, and plugging of sebaceous glands of both facial and eyelid skin. Secondary MGD can occur with use of 13-*cis* retinoic acid (isotretinoin) for treatment of acne,<sup>87–89</sup> ingestion of polychlorinated biphenyls in contaminated cooking oil,<sup>90–92</sup> and with cicatricial changes in conditions, such as chemical/thermal burns, trachoma, pemphigoid, erythema multiforme/Stevens-Johnson syndrome, acne rosacea, vernal keratoconjunctivitis, and atopic keratoconjunctivitis.<sup>10</sup> In simple MGD, the MG orifices remain anterior to the mucocutaneous junction, whereas in cicatricial MGD, MG orifices are drawn posteriorly onto the lid and tarsal mucosa.

## Exposure

Excessive exposure of the ocular surface leads to increased evaporative loss of tears; thus, any disorder that results in increased ocular exposure can cause evaporative DED. Psychological, psychiatric, mechanical, neurological, or traumatic impairment of eyelid function may result in impaired or reduced blinking, lagophthalmos, or an increased palpebral fissure width, resulting in an evaporative dry eye. Evaporative DED can be seen in thyroid eye disease secondary to proptosis or lid retraction.

## Mucin Deficiency

Local conjunctival damage from cicatrizing disease or surgical trauma results not only in aqueous tear deficiency but also in depopulation of mucin-producing goblet cells and creation of anatomical abnormalities of the conjunctiva leading to improper tear distribution. Although uncommon in incidence, trachoma, pemphigoid, erythema multiforme/Stevens-Johnson syndrome, and chemical and thermal burns can result in severe DED characteristically resistant to aqueous tear replacement therapy.

## Extrinsic Causes

Vitamin A deficiency can result in extensive goblet cell loss and dysfunction, leading to an unstable tear film and severe DED (xerophthalmia).<sup>93–96</sup> Preservatives in many eyedrops (especially benzalkonium chloride) can lead to ocular surface toxicity and a dry-eye state that may be reversible if eyedrops are switched to nonpreserved formulations. Contact lens wear is commonly associated with DED symptoms. Pre-lens tear film thinning time and pre-lens lipid layer thickness is reduced in contact lens wearers with DED symptoms, and may lead to higher evaporative loss.<sup>97</sup> Ocular allergies can cause a variety of corneal and conjunctival irregularities with decrease in tear film stability and consequent DED.

## OCULAR MANIFESTATIONS

Regardless of the cause, most forms of DED share similar symptoms, interpalpebral surface damage, tear instability, and tear hyperosmolarity. Typical complaints include burning, itching, foreign body sensation, stinging, dryness, photophobia, ocular fatigue, and redness. Although symptoms usually are nonspecific, careful attention to details will help refine the diagnosis.

Patients commonly describe a diurnal pattern of aqueous tear deficiency with progression of symptoms over the day and decompensation in particular environmental conditions, such as low humidity in airline cabins, climate control, and the use of video display terminals.<sup>53,98</sup> Conversely, nighttime exposure, floppy eyelid syndrome, and inflammatory conditions often present with worst discomfort upon awakening.

MGD creates an unstable tear film resulting in intermittent visual blurring and a gritty or sandy sensation. DED in diabetes and other corneal neuropathies may exhibit little or no discomfort and create high risk for keratolysis.

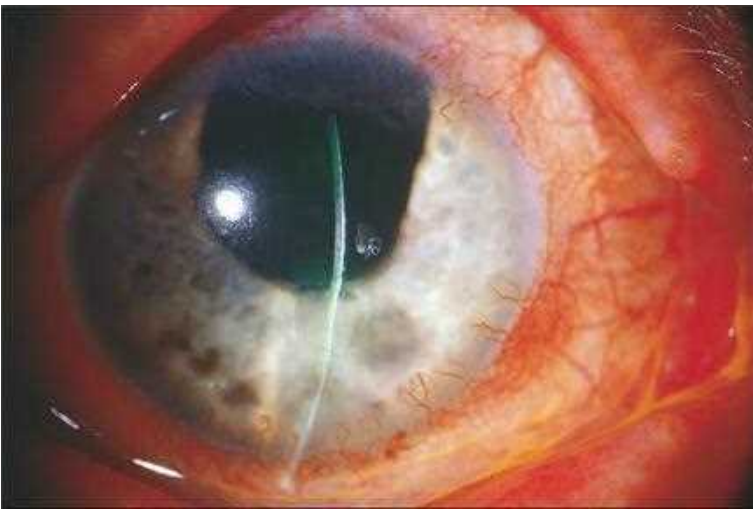
Common signs of DED include conjunctival injection, decreased tear meniscus, photophobia, increased tear debris, and loss of corneal sheen found more commonly in the exposed interpalpebral fissure. Paradoxical epiphora in DED is usually a result of reflex tearing. Greater risk for external infections exists secondary to decreased tear turnover and desiccation of the surface epithelium. Instability of the surface epithelium and disordered mucin production may lead to painful and recurrent filamentary keratitis. Although keratinization may occur uncommonly in chronic DED, vitamin A deficiency also should be suspected.

Patients who have SSTD tend to have more severe symptoms and more serious findings compared with NSTD patients. Sterile ulceration of the cornea in SSTD can be peripheral or paracentral; both thinning and perforation of these ulcers can occur (Fig. 4.23.2). Acute lacrimal enlargement may be seen in SSTD but should be differentiated from benign lymphoepithelial lesion of Godwin (Mikulicz's disease), which results from infiltration of the gland without surface findings.<sup>99</sup>

## DIAGNOSIS AND ANCILLARY TESTING

### Diagnostic Dye Evaluation

Fluorescein is a large molecule unable to traverse normal corneal epithelial tight junctions. In advanced DED, these junctions are disrupted, allowing characteristic diffuse subepithelial or punctate staining. Rose Bengal stain,



**Fig. 4.23.2** Patient (age 73 years) with rheumatoid arthritis and secondary Sjögren's disease.



**Fig. 4.23.3** Dry eye disease with Rose Bengal staining.

a derivative of fluorescein, in a 1% solution or impregnated strips, stains devitalized epithelial cells (Fig. 4.23.3).<sup>100</sup> Alternatively, lissamine green stains for cell death or degeneration, as well as cell-to-cell junction disruption, but does not irritate the eye.<sup>101</sup>

## Tear Film Stability

Tear film instability may be a result of either tear deficiency or evaporative DED. In the tear break-up time (TBUT) test, described by Norn and revised by Lemp and Holly, fluorescein dye is instilled and the time interval is measured between a complete blink to the first appearance of a dry spot in the precorneal tear film.<sup>102</sup> TBUTs shorter than 10 seconds indicate tear film instability.

## Measurement of Tear Production

The most common means of measuring tear production has been Schirmer's test, the details of which were first published in 1903.<sup>103</sup> Jones later advocated the use of topical anesthesia combined with a Schirmer's test strip for 5 minutes to reduce the stimulating effect of the filter paper strip—the “basal” tear secretion test.<sup>104</sup> Inconsistencies in its application limit repeatability in DED, but it still enjoys widespread use.<sup>105</sup> With these caveats in mind, the following general guidelines are recommended (when topical anesthesia is used): a 5-minute test that results in less than 5 mm of wetting confirms the clinical diagnosis of DED, and a result of 6–10 mm of wetting suggests DED.<sup>106</sup>

Hamano et al. developed the phenol red thread test to obviate the disadvantages of Schirmer's test by eliminating the need for anesthesia.<sup>107</sup> Three millimeters of a fine dye-impregnated 75-mm cotton thread is placed under the lateral one fifth of the inferior palpebral lid margin for

15 seconds; alkalinity changes its color to bright orange from tear contact. Asian populations show a lessened wet-length response with diminishing racial differences with advancing age.<sup>108</sup>

Hyperosmolarity is a common endpoint for all DED. Its measurement can be a sensitive and specific indicator.<sup>106</sup> Its use had previously been limited to specialized research centers because of the need for expensive equipment, but commercially available devices may now make this test more widely used in the clinic. Researchers also have sampled tears or ocular surface cells looking for inflammatory biomarkers, such as IL-1, IL-17, MMP-9, interferon- $\gamma$  (IFN- $\gamma$ ) and human leukocyte antigen–antigen D-related (HLA-DR). A qualitative commercial test currently is available to sample ocular surface tears for MMP-9 in the clinic. Other rarely performed tests for reduced tear function include fluorophotometry for decreased protein content, lysozyme levels, ocular ferning, impression cytology, and lactoferrin assays. Noninvasive imaging of the tear film using meniscometry, lipid layer interferometry, high-speed videography, optical coherence tomography, and confocal microscopy has been advocated as well.<sup>109–113</sup>

## Other Tests

Corneal sensation may be qualitatively assessed with a cotton wisp, but quantification requires an instrument, such as the Cochet–Bonnet aesthesiometer. The tear clearance test measures tear turnover with serial tear collection after instillation of a standardized volume of dye.<sup>105,114</sup> Serological tests, traditionally including antinuclear, anti-Ro, and anti-La antibodies, should be performed in patients suspected of having autoimmune DED. A recently launched commercial diagnostic test combines traditional biomarkers with novel, proprietary biomarkers to create a more accurate diagnostic test for patients suspected of having Sjögren's syndrome. A definitive diagnosis of Sjögren's syndrome requires minor salivary or, rarely, lacrimal gland biopsy.

Neither clinical presentation nor individual ancillary tests alone are sufficient for an accurate diagnosis of DED. Because of the therapeutic importance of appropriate categorization of patients, Pflugfelder et al. combined standard subjective examination with ancillary tests in the evaluation of patients with SSTD, NSTD, inflammatory MGD, and atrophic MGD.<sup>115</sup> Clinically important results were identified and compiled into an algorithm that helps differentiate patients with DED by using available tests (Fig. 4.23.4).

## TREATMENT

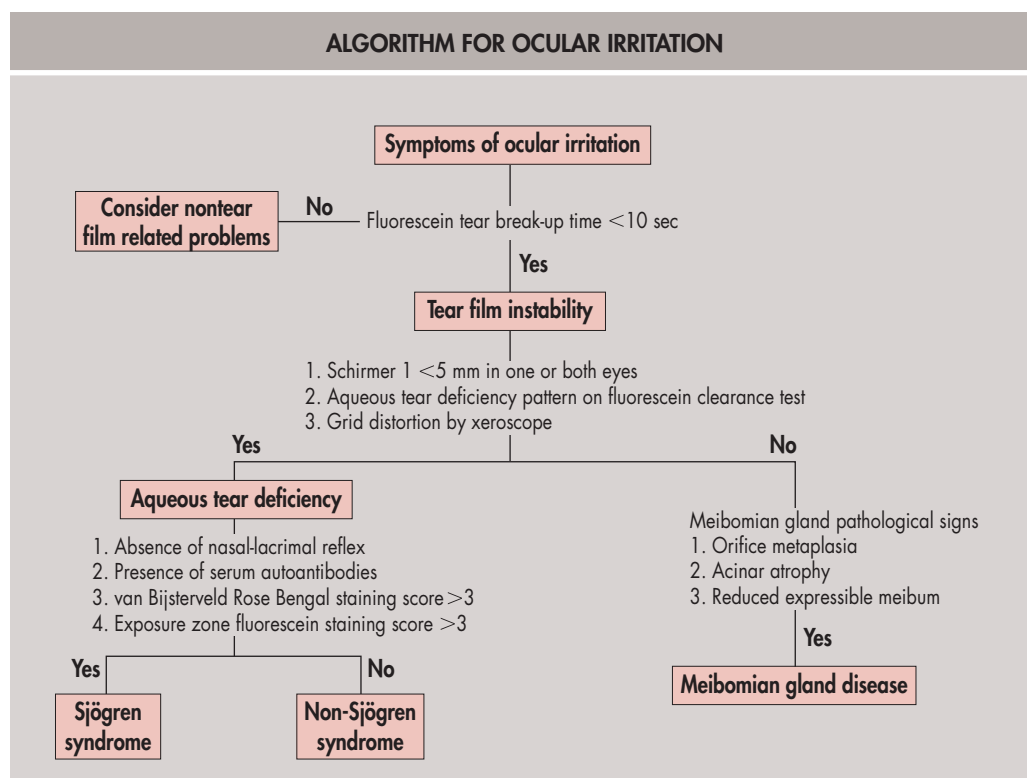
Significant advances have been made in treating the many facets of DED, but it remains a disorder of long-term maintenance rather than permanent cure. Current therapy focuses on restoring a normal ocular surface through tear supplementation as well as inhibition of aberrant inflammation seen in chronic DED. Since the tear film is a highly integrated unit, addressing each component is central to the successful treatment of DED.

## Aqueous Tear Deficiency

As the first line of treatment, artificial tears increase available tears and, through dilution, reduce tear hyperosmolarity. Commercial artificial tears differ in electrolyte composition, thickening agents (methylcellulose, hydroxypropyl methylcellulose, polyvinyl alcohol), physiological buffering, tonicity, and preservative system. Individual patient preferences involve such disparate concerns as cost, comfort, visual blurring, and ease of use. Preserved tears (i.e., benzalkonium chloride) can be toxic in moderate or severe DED, are poorly tolerated, and harmful. For patients with significant DED, single-dose, nonpreserved tear preparations are the mainstay of therapy with bottled tear products a reasonable alternative when preserved with relatively nontoxic compounds. These less toxic preservatives include polyquaternium-1, sodium chlorite, and sodium perborate.<sup>116</sup> Some artificial tear preparations are formulated to be hypo-osmotic, with the goal of balancing the hyperosmolarity of the tear film in DED. Artificial tear ointments are effective for longer-lasting control of symptoms, especially during sleep, but visual blurring limits their daytime usefulness. In addition, some ointments contain lanolin and parabens, which can be poorly tolerated by patients with severe DED. Autologous serum tears contain trophic factors and other proteins useful in ocular surface maintenance.<sup>116</sup> These can be useful as a preservative-free, biological tear substitute, but their preparation is labor intensive.

Punctal occlusion retards tear drainage, thereby increasing tear volume on the ocular surface and lowering tear osmolarity. Occlusion may be





**Fig. 4.23.4** Diagnostic algorithm for ocular irritation. (With permission from Pflugfelder SC, Tseng SC, Sanabria O, et al. Evaluation of subjective assessments and objective diagnostic tests for diagnosing tear-film disorders known to cause ocular irritation. *Cornea* 1998;17:38–56.)

achieved irreversibly by cauterization or semi-permanently with the use of nonabsorbable plugs. Occlusion with collagen plugs provides temporary relief (3 days to 6 months) and may identify those at risk for epiphora prior to permanent occlusion. Epiphora in the setting of one functional punctum is uncommon.

Secretagogues, agents that stimulate lacrimal gland secretion, require functional glandular tissue. Oral pilocarpine (Salagen) and cevimeline (Evovac) are M3 cholinergic agonists approved for use in dry mouth that also stimulate tear secretion.<sup>32,117,118</sup> Their effect tends to be greater in oral dryness rather than ocular dryness. Systemic cholinergic side effects, such as sweating reduce patients' acceptance. Various nutritional supplements are also touted for DED but without clear confirmation of their efficacy.

## Evaporative Dry Eye Disease

Primary treatment of MGD involves improving the quality and quantity of native MG secretions. Lid hygiene, in the form of warm compresses and lid massage, is effective in improving MG secretion. Several techniques, including the Lipiflow System, have been developed to help with expression of meibomian glands. Lid scrubs with dilute detergents decrease the seborrheic or bacterial load, thereby breaking the proinflammatory cycle of MGD. Systemic tetracyclines have been shown to decrease local inflammation and improve MG function after several weeks. The antibacterial effect also contributes to a decrease in meibomian lipid breakdown products in the tear film. Topical erythromycin or azithromycin applied to the eyelid margins are alternatives for patients who are unable to tolerate tetracycline derivatives. A number of lipid-like tear substitutes have become commercially available, which have been used with some success.<sup>119</sup>

Correction of eyelid abnormalities that increase exposure of the ocular surface, such as lower lid ptosis and lagophthalmos, can stabilize a decompensated ocular surface. In severe cases, a partial or complete tarsorrhaphy or a conjunctival flap may be necessary to prevent decompensation of the cornea. The use of humidifiers, moisture chambers, glasses, or goggles increases periorbital humidity and decreases surface evaporative pressure. New high-*Dk* (oxygen permeability), high-water-content contact lenses and new polymer lenses, accompanied by proper tear supplementation and hygiene, are effective in treating patients with DED with poor corneal wetting. In patients with severe DED, scleral contact lenses can promote lubrication and slow evaporation of tears from the ocular surface.

## Ocular Surface Inflammation

A common endpoint of all treatments of DED is not only prevention of ocular surface inflammation and its consequential cellular changes but

also restoration of the ocular surface. DED-induced ocular surface inflammation disrupts the epithelial and mucin layers, further exacerbating tear film breakdown. Suppression of inflammation creates a supportive environment for reversal of DED-induced cellular changes.<sup>120,121</sup> Topical cyclosporine A has been shown to increase tear production in a subset of patients through inhibition of lacrimal gland inflammation and suppression of DED-induced ocular surface inflammation.<sup>122–124</sup>

Lifitegrast 0.05% is the drug most recently (July 11, 2016) approved by the U.S. Food and Drug Administration to address DED and is the only therapy approved to treat both the signs and symptoms of DED. Lifitegrast is a topical anti-inflammatory drug that blocks the binding of intercellular adhesion molecule-1 (ICAM-1) to lymphocyte function associated antigen-1 (LFA-1) on the T-cell surface. Lifitegrast decreases inflammation by inhibiting T-cell recruitment and activation.<sup>125,126</sup>

Judicious use of low-dose topical corticosteroids has been shown to reduce inflammation and allow normal reparative mechanisms to restore the natural equilibrium of the ocular surface.<sup>127,128</sup> Use of topical corticosteroids in DED currently is limited because of concerns about adverse events with chronic use, such as glaucoma and cataract. Control of these reactive epithelial changes restores normal cell morphology, cell-to-cell interactions, and critical mucin production and clearly has a role in the global treatment of all forms of DED.

Essential fatty acids cannot be synthesized by humans and must be consumed in the diet. The typical Western diet contains a ratio of omega-6 to omega-3 fatty acids of approximately 25:1.<sup>114</sup> Omega-6 fatty acids are precursors to arachidonic acid and proinflammatory molecules, including prostaglandin E2 and leukotriene B4. Omega-3 fatty acids inhibit synthesis of these inflammatory mediators and decrease production of IL-1 and TNF- $\alpha$ .<sup>129,130</sup> Supplementing the diet with omega-3 fatty acids has been shown to decrease both signs and symptoms of DED.<sup>131</sup> Omega-3 fatty acids include eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA), and alpha-linolenic acid (ALA). EPA and DHA are believed to be primarily responsible for the beneficial health effects of omega-3 fatty acids. Fish oil contains high levels of EPA and DHA, and flaxseed oil contains high levels of ALA. Although ALA is converted by the body into EPA and DHA, this process is not efficient; much higher quantities of flaxseed oil must therefore be consumed to achieve equivalent EPA and DHA levels from smaller quantities of fish oil.<sup>132,133</sup>

A number of drugs (mostly topical and a few systemic) are currently being evaluated in clinical trials aimed at providing new treatment options for patients with DED.<sup>134,135</sup> Success with this research should provide patients with many more treatment options in the future and has the potential to improve quality of life for patients suffering from DED.<sup>136</sup>

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# Complications of Contact Lens Wear

Joshua S. Agranat, Deborah S. Jacobs

# 4.24

**Definition:** Inflammatory, metabolic, mechanical, or infectious events that are associated with contact lens use.

## Key Features

- Overall safety record of contact lenses is excellent.
- Low-Dk lenses, overnight wear, and poor lens care practices are modifiable risk factors for the development of contact lens–related problems.
- Patient education remains an important avenue for prevention of complications of contact lens wear.

## INTRODUCTION

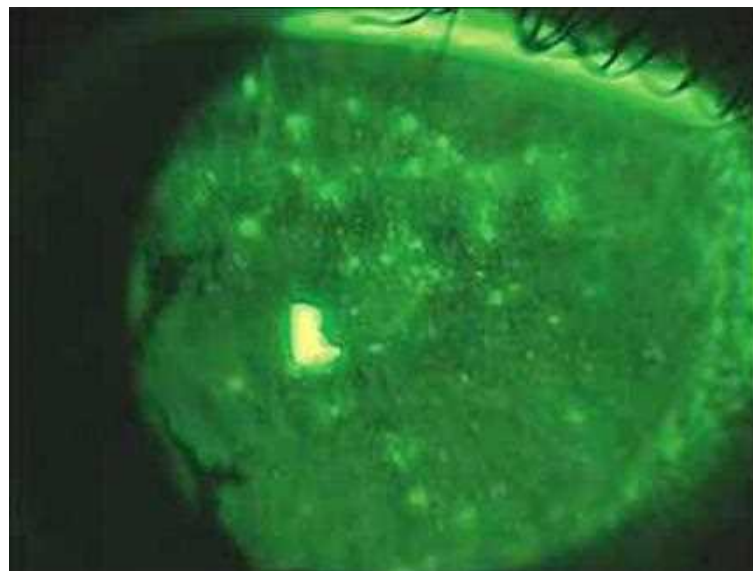
In the United States, an estimated 40.9 million adults wear contact lenses, and nearly one third of them have experienced a contact lens–related complication requiring a visit to their doctors.<sup>1</sup> Although many contact lenses are managed by optometrists and opticians, some complications threaten sight and the long-term health of the eye, which makes it important that ophthalmologists are well informed about this problem.<sup>2–4</sup> This chapter will discuss toxic and allergic reactions, conditions reflecting metabolic challenge, corneal inflammatory events (CIEs), and microbial keratitis (MK). The long-term sequelae of these contact lens–related complications range from mild, self-limiting disease to vision loss even with proper treatment. Problems related to fit, comfort, and tolerance, including lens warpage, tight lens, dry eye, deposits, and mucin balls, are outside the scope of this chapter.

## TOXIC, ALLERGIC AND MECHANICAL REACTIONS

### Solutions

Toxic or allergic conjunctivitis may be caused by some components of the lens care system. The agents frequently responsible for toxic or allergic reactions are preservatives, disinfectants, surfactant and enzyme cleaners, and concentrated hydrogen peroxide. Allergic reactions are hypersensitivity reactions that occur after repeated exposure to the sensitizing antigen. In the past, thimerosal was a common offender, but sorbate and benzalkonium chloride are likely causes now.<sup>5</sup>

Patients with a toxic reaction experience immediate ocular discomfort and conjunctival injection with lens insertion. Toxic conjunctivitis can occur the first time the solution is used or may result from a buildup of the toxic component in the hydrogel material. Typically, patients have used the care system for 1 month or longer before symptoms of conjunctival injection and irritation develop. On examination, conjunctival hyperemia, follicles, superficial punctate keratitis, scattered fine infiltrates, and superior limbic keratoconjunctivitis may be seen (Fig. 4.24.1). Discontinuation of the solution results in resolution of symptoms, but if the symptoms and signs are severe, a short course of topical corticosteroids may be needed. When resuming lens wear, wearers of hydrogel lenses should replace their lenses, which may have absorbed the offending agent, but wearers of rigid gas-permeable (RGP) lenses may use the same lenses if they are thoroughly cleaned and rinsed. Incorrect use of solutions and cleaners can contribute to toxic reactions, especially with incomplete rinsing of surfactant cleaners or failure to neutralize peroxide solutions. Environmental chemical exposure, such as cosmetics and hair sprays, may also lead to toxic or allergic reactions when they contaminate lenses. Patients can be



**Fig. 4.24.1** This photo with fluorescein and cobalt lighting shows a diffuse superficial keratitis typical of solution toxicity.

switched to care systems with different preservatives or to daily disposable lenses to avoid solutions altogether.

There have been case reports of severe toxic reactions to contact lens use that resemble central toxic keratopathy syndrome—a constellation of corneal thinning and flattening, hyperopic shift, and marked stromal “mud crack” central opacity.<sup>6,7</sup> Treatment includes removal of the offending chemicals; use of preservative-free solutions; topical corticosteroid, if inflammation is severe; and a change to more frequent lens replacement and/or alternative lens material and care system.

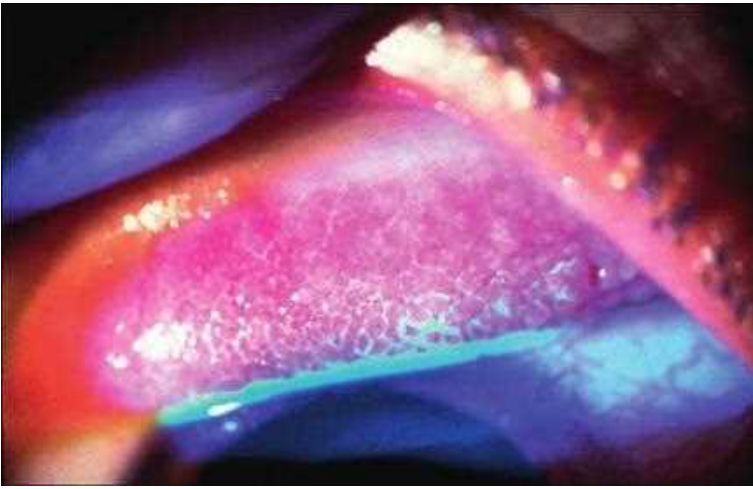
### Giant Papillary Conjunctivitis

Giant papillary conjunctivitis (GPC), sometimes called *contact lens papillary conjunctivitis* (CLPC), was first reported in the 1970s and is thought to be a result of both mechanical irritation and immunological stimulation.<sup>8–11</sup> It is believed that a cell-mediated reaction to the antigens deposited on contact lenses causes trauma to the tarsal conjunctiva, exposing the antigens to the ocular immune system and initiating the reaction.<sup>9,12,13</sup> It should be noted that GPC has also been reported in those who do not wear contact lenses as a result of other causes of mechanical irritation, such as exposed sutures, extruded scleral buckles, foreign bodies, cyanoacrylate glue, ocular prostheses, and filtering blebs.<sup>14</sup> GPC is characterized by itching, burning, increased mucus production, foreign-body sensation, and papillae on the upper tarsus ranging from 0.3–2 mm<sup>14</sup> (Figs. 4.24.2, 4.24.3, 4.24.4). It is the most common complication of contact lens use.<sup>15</sup> Patients typically report increased deposits on lenses, which may be visible on examination. Papillae are a late finding and are not necessary for diagnosis.

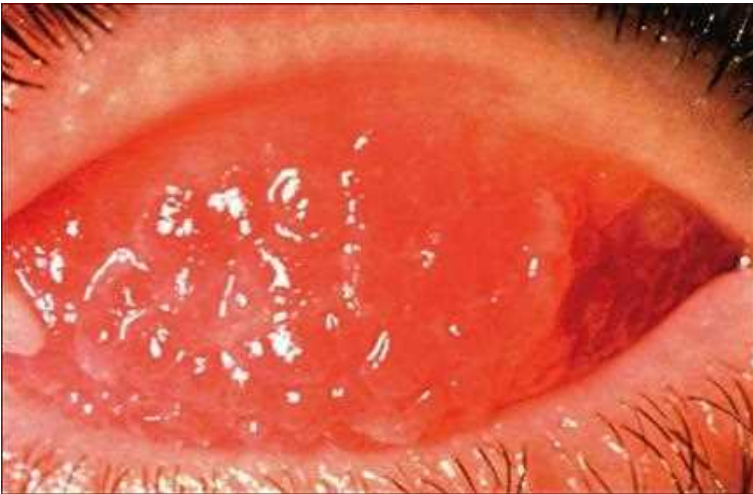
Factors associated with GPC include duration of wear, hygiene, history of atopy/environmental allergy, and the fall and spring seasons.<sup>15–18</sup> Lens cornea fit, bacterial bioburden, history of adverse ocular events, race, and gender are not associated with GPC.<sup>19,20</sup>

The initial treatment for GPC is removal of the inflammatory stimulus via cessation of contact lens wear for 2–4 weeks. When resuming use, it may be helpful to decrease wear time, institute more frequent lens replacement, optimize lens hygiene with goal of reducing deposits, or prescribe a new lens material or design. Limited wear of daily disposable lenses is a

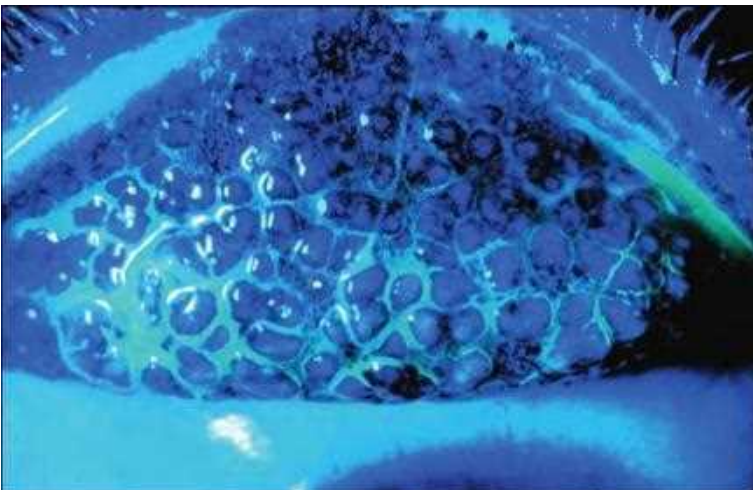




**Fig. 4.24.2** Early to moderate giant papillary conjunctivitis, highlighted with fluorescein dye.

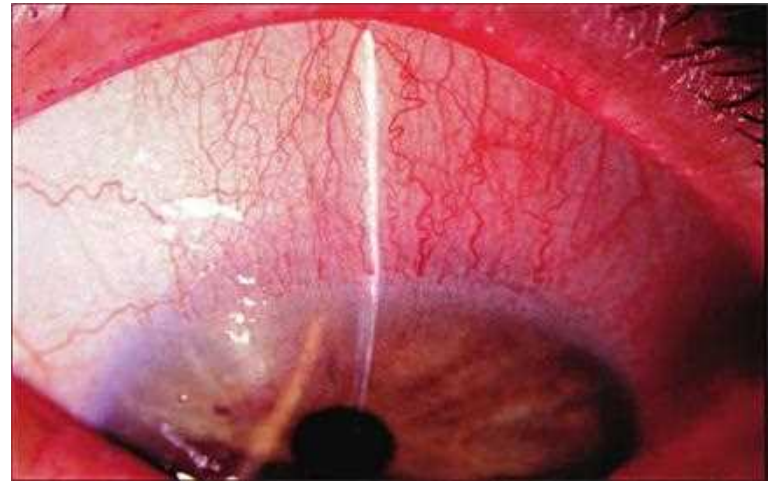


**Fig. 4.24.3** As giant papillary conjunctivitis progresses, the papillae can grow to greater than 1 mm in size, and advanced lid changes may not resolve completely with treatment.



**Fig. 4.24.4** The use of fluorescein dye highlights the large papillae in this patient with advanced giant papillary conjunctivitis.

good way of reintroducing lens wear while minimizing antigen presentation. Adjunctive therapies for severe cases include topical mast cell stabilizers, used as initial treatment and for suppressive maintenance, and pulse regimen of topical corticosteroid, with appropriate monitoring. The role of topical immunomodulators, such as tacrolimus, has been reported.<sup>21</sup> GPC is not vision threatening, and with proper management, resolution of redness and discharge is typically expected within 1–2 weeks. When inflammation is severe or long-standing, the papillae may remain.



**Fig. 4.24.5** Conjunctival injection, corneal pannus, and punctate keratitis seen in contact lens–induced superior limbic keratoconjunctivitis.

### Superior Limbic Keratoconjunctivitis

Contact lens wear has been associated with injection and fluorescein staining of the superior bulbar conjunctiva, termed *superior limbic keratoconjunctivitis* (SLK). Patients may experience tearing, burning, foreign body sensation, and lens intolerance. The appearance is similar to idiopathic SLK described by Theodore in 1963,<sup>22</sup> which, interestingly, is sometimes treated with therapeutic lenses.<sup>23</sup> SLK in contact lens wearers has been associated with preservatives in contact lens solutions, but mechanical irritation from poor-fitting contact lenses may also be a factor.

In contact lens–associated SLK, the superior corneal epithelium is irregular with a micropannus and punctate staining (Fig. 4.24.5). A papillary reaction is often present on the superior tarsal conjunctiva, but the papillae tend to be smaller than those seen in GPC. Discontinuation of lens wear and topical lubrication is generally effective, but resolution may take weeks or months. Punctal occlusion may aid in resolution of symptoms.<sup>24</sup> Patients can return to lens wear after being refitted with new lenses and switching to hydrogen peroxide disinfection, and nonpreserved saline daily disposable lenses are another option for SLK patients.

## CONDITIONS REFLECTING METABOLIC CHALLENGE

### Corneal Hypoxia and Edema

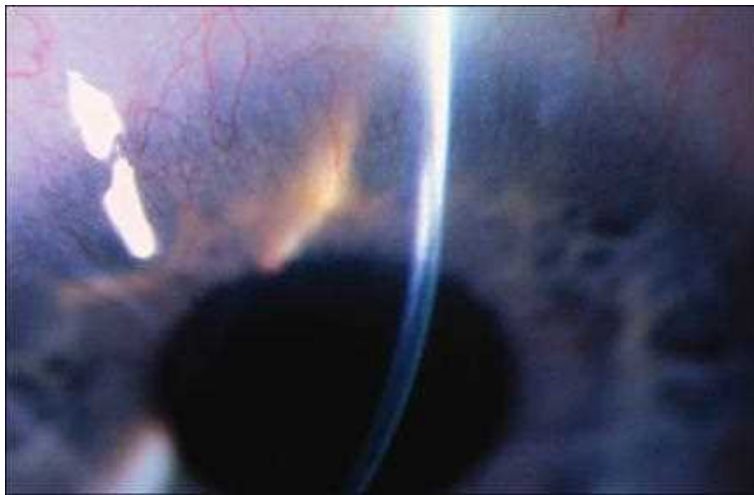
Contact lenses create a physical barrier that impairs the cornea's natural ability to harvest oxygen from the atmosphere and may lead to corneal hypoxia. With continued hypoxia, cell death occurs, leading to erosions or necrosis and desquamation and causing decreased vision, pain, tearing, and photoallodynia.<sup>25</sup> Chronic low-grade hypoxia causes subtle changes in corneal physiology and structure. Examination findings may include central epithelial microcysts and edema ("Sattler's veil"), neovascularization (Fig. 4.24.6), stromal thickening and striae, and endothelial blebs<sup>26</sup> (Fig. 4.24.7). The corneal edema can fluctuate throughout the day, typically being worse in the morning. Lens wear should be discontinued until the edema resolves and then a high-Dk lens should be substituted.<sup>25,27</sup>

### Neovascularization

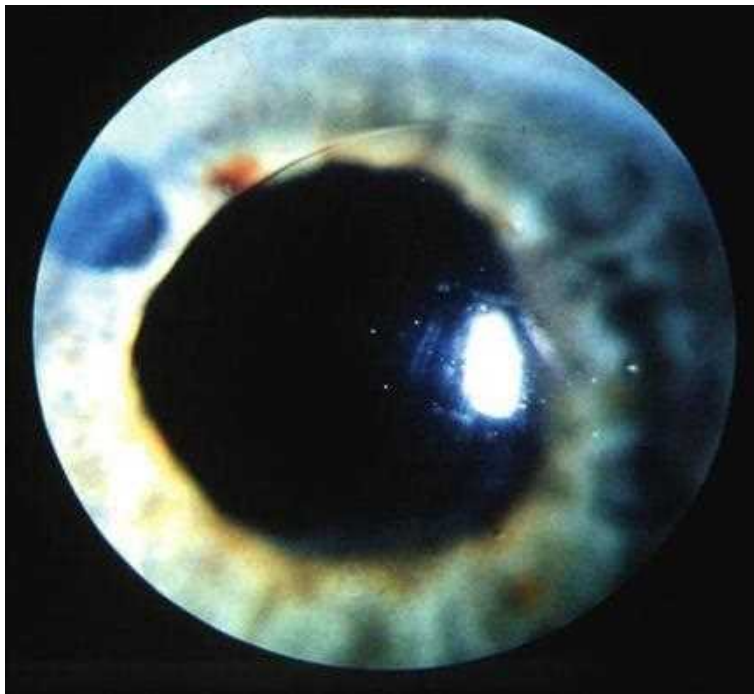
As previously mentioned, chronic low-grade hypoxia can cause corneal neovascularization. Hypoxia results in the accumulation of lactic acid and carbon dioxide, which stimulates vascular ingrowth<sup>26,28</sup> and hypoxic dilation of limbal vessels.<sup>29</sup> Although typically associated with low-Dk hydrogel lenses, neovascularization may also be seen with poorly fit RGP lenses because of chronic irritation, such as in vascularized limbal keratitis (VLK). VLK lesions appear as an elevated, opaque mass at the limbal–epithelial junction with superficial and deep vascularization.<sup>30</sup>

Superficial neovascular changes (pannus) are common in patients wearing soft, low-Dk lenses, and may be acceptable if the pannus is stable and it extends less than 1.5 mm onto the cornea. This superficial neovascularization is likely caused by angiogenic factors released in response to chronic limbal trauma and hypoxia. Vascular ingrowth into the corneal





**Fig. 4.24.6** Chronic hypoxia associated with contact lens wear can lead to corneal neovascularization.



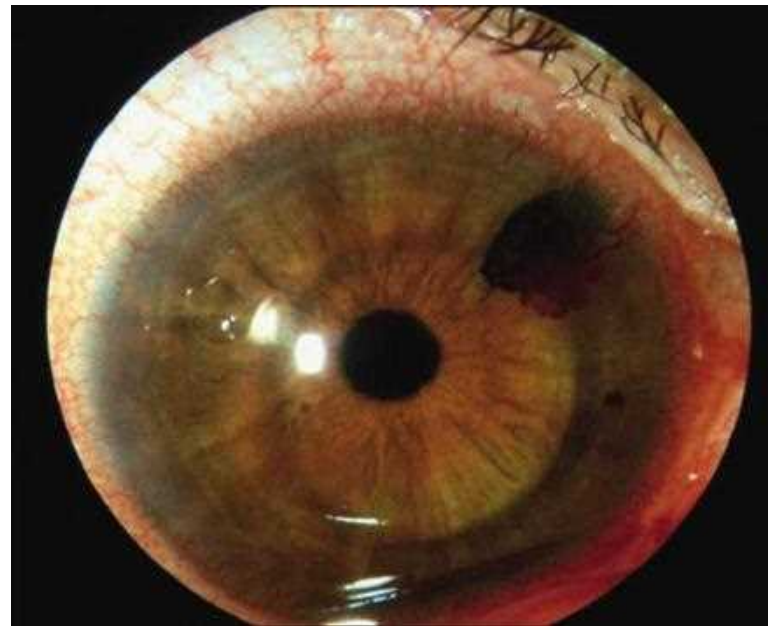
**Fig. 4.24.7** Stromal thickening and faint endothelial striae are seen in a patient with chronic stromal edema.

stroma is more worrisome because these vessels can lead to lipid exudation, scarring, and intracorneal hemorrhages (Fig. 4.24.8). Stromal neovascular changes or superficial neovascularization that extends more than 2 mm onto the cornea should be considered abnormal and unacceptable. When the patient is refitted with high-Dk lenses, reduction of the abnormal vessels and limbal erythema is expected.<sup>31-33</sup>

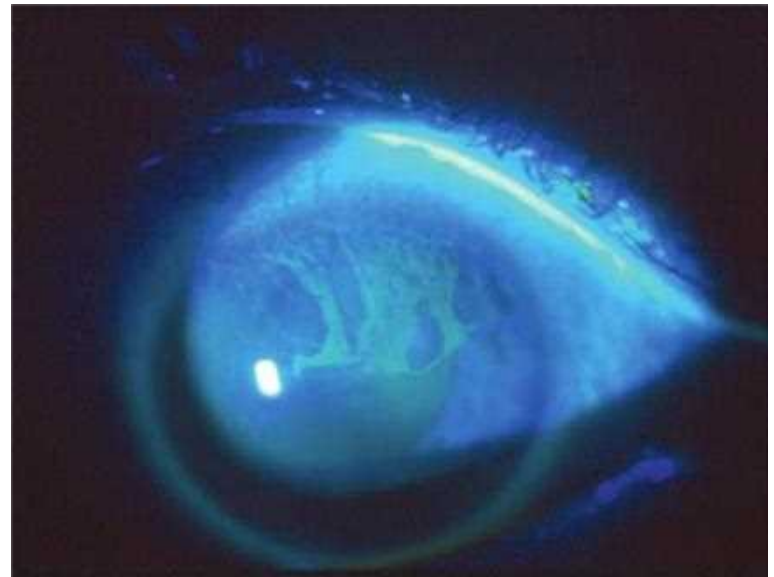
### Limbal Stem Cell Deficiency

Limbal stem cell deficiency (LSCD) is caused by the loss of function of corneal epithelial cell precursors. Contact lens-associated LSCD was first referred to as *contact lens-induced keratopathy* (CLIK), in which the keratoconjunctivitis progressed to diffuse corneal scarring and vascularization, sometimes requiring penetrating keratoplasty.<sup>34</sup> Bowman's membrane is damaged and replaced by fibrous scar tissue with deep stromal vascularization<sup>35</sup> (Fig. 4.24.9).

The clinical picture of contact lens-induced LSCD is typically milder than other causes of LSCD as evidenced by the finding that 71.4% of patients with contact lens-induced LSCD are asymptomatic.<sup>36</sup> The slit-lamp exam in contact lens-induced LSCD demonstrates whorl-like epitheliopathy, conjunctivalization of the cornea, absence of palisades of Vogt, and late fluorescein staining.<sup>37</sup> As the disease progresses, findings include pannus, epithelial defects, scarring, and vision loss.<sup>38</sup> Treatment of contact



**Fig. 4.24.8** Corneal neovascularization can, on rare occasion, lead to an intrastromal hemorrhage, seen at the 2 o'clock position in this patient.



**Fig. 4.24.9** Contact lens-induced keratopathy (CLIK) progresses to diffuse corneal scarring and vascularization, seen in this view with areas of superior thickening, fibrosis, and neovascularization.

lens-induced LSCD depends largely on the severity of disease. Initial medical treatment includes discontinuation of wear and optimization of the tear film and ocular surface via a combination of artificial tears, topical corticosteroid, topical cyclosporine, topical vitamin A, punctal occlusion, and oral doxycycline.<sup>39,40</sup> If maximal medical therapy fails, surgical options include mechanical removal of conjunctivalized corneal epithelium, amniotic membrane transplantation, and limbal autograft or allogeneic transplantation.<sup>41-44</sup>

### Abrasions

Corneal abrasions are epithelial defects caused by trauma to the ocular surface. Abrasions frequently occur with contact lens use during the insertion or removal process and are caused by fingernails or the lens itself. Abrasions allow bacteria access to the corneal stroma, and therefore careful evaluation for MK is warranted when there is an abrasion in the context of contact lens wear. In the setting of contact lens use, recommended treatment of corneal abrasion is a broad-spectrum antibiotic, such as a fluoroquinolone or aminoglycoside, which offers prophylaxis against *Pseudomonas*. Patching and topical corticosteroids have no proven benefit and should not be used in contact lens-associated corneal abrasions.<sup>45-47</sup>

## CORNEAL INFLAMMATORY EVENTS AND MICROBIAL KERATITIS

There is lack of standardization in the literature and discourse surrounding corneal opacities with or without an overlying defect.<sup>48–50</sup> It is common for the terms *ulcer*, *infiltrate*, *sterile infiltrate*, *presumed microbial keratitis*, and so on to be used imprecisely; the authors of this chapter will therefore use a classification system first proposed by Efron et al.<sup>51</sup> This system separates the spectrum of clinical findings into two distinct entities: CIEs and MK.

CIEs include an epithelial or subepithelial infiltrate, with or without an epithelial defect, which improves in the absence of treatment and typically does not cause scarring. Treatment of CIEs may be hastened by antibiotics and/or corticosteroids. However, MK is an epithelial defect with stromal involvement or tissue loss (also referred to as “crater”), typically leaves a scar, has a presumed or confirmed pathogen and requires intensive treatment with antimicrobials. It is acceptable to use the term “ulcer” when referring to MK but not to CIEs.

### The Role of Lens Care Systems

For several years, multipurpose solutions (MPSs) have been the most popular lens care products.<sup>52</sup> They may contain surfactant cleaners, disinfecting agents, preservatives, and polymers or conditioners to make the contact lens more comfortable. The disinfecting component must contain antimicrobial agents sufficient to destroy micro-organisms. Despite approval by the U.S. Food and Drug Administration (FDA) and the popularity of MPS solutions, recent outbreaks of MK have focused attention on lens care. Studies also suggest other problems with MPS care systems because some solutions can, in fact, increase the binding of *Pseudomonas* to epithelial cells and decrease the rate of epithelial cell exfoliation.<sup>53</sup> Polyhexamethylene biguanide (PHMB)-based systems used with FDA group II lenses (high water, nonionic) resulted in increased corneal staining, and biguanides used with group IV lenses (high water, ionic) also increased staining and decreased biocide efficacy.<sup>54,55</sup> Lens wearers with solution-associated corneal staining were significantly more likely to develop corneal infiltrates.<sup>56</sup> In general, hydrogen peroxide care systems appear to have the best profile for disinfection of lenses and the lowest incidence of CIEs and corneal staining.<sup>57</sup>

In addition, lens handling greatly increases the incidence of lens contamination, with more than half the lenses removed aseptically from the eye showing microbial contamination. Studies have shown that greater than 50% of lens cases are contaminated. All types of care solutions can become contaminated, including up to 30% of preserved solutions.<sup>58</sup> Not surprisingly, those who wear contact lenses infrequently had a higher contamination rate. Rinsing lenses with saline or MPS appears to be effective in reducing contamination.<sup>59</sup> Use of daily disposable lenses is a way to avoid contamination and is associated with lower complication rates compared with other modes of daily soft lens wear.<sup>60</sup>

### Corneal Inflammatory Events

Contact lens-related CIEs range from small, asymptomatic lesions to large opacities that obscure vision. The opaque lesions are caused by polymorphonuclear and mononuclear leukocyte recruitment to the cornea and are likely host response to commensal organisms or lens-related bacteria.<sup>29,61</sup> Bacteria can form a biofilm on the surface of the lens or the lens case, and one study found that more than 70% of the risk for CIEs was related to the exposure to the lens biofilm.<sup>62</sup> Multiple other causes, including hypoxia, retrolental debris, and staphylococcal immune complexes, have been proposed and investigated.<sup>63–66</sup> The epithelium is usually intact but may show overlying superficial punctate keratitis, and the anterior chamber shows only minimal reaction.<sup>67–69</sup> Symptoms typically include irritation, pain, foreign body sensation, photolodnyia, and tearing.

The true incidence and significance of peripheral infiltrates is an area of ongoing study and debate. Sankaridurg et al. found that 1.6% of asymptomatic patients with no history of contact lens wear had corneal infiltrates at the start of a study comparing spectacle wear and daily disposable lenses. Asymptomatic infiltrates were seen in spectacle wearers at a rate of 11.3 events per 100 years of wear compared with 20.5 events per 100 years in wearers of daily disposable lenses. The daily disposable group had 2.5 symptomatic peripheral ulcers events, but no events were noted in the spectacle group.<sup>70</sup> Several other studies have reported the incidence of sterile peripheral infiltrates in users of extended-wear disposable lenses to be equal to or higher than daily wear.<sup>71–73</sup>

A large study of 6245 lens wearers found lens-related CIE in 159 patients (2.5%). Risk factors included age  $\leq 25$  years or less and greater than 50 years; refractive error greater than +5.00 diopters (D); smoking; and failure to maintain prescribed wear schedule.<sup>74</sup> Further, a meta-analysis of published and presented studies (1991–2006) found a twofold higher risk for CIEs in users of SH lenses worn for up to 30 days compared with low-Dk extended-wear lenses worn for 7 days. However, it was not clear if the increased risk was related to the lens material or the wear schedule.<sup>75</sup>

The Moorfields Eye Hospital (London, UK) compared daily disposable, silicone hydrogel, and planned replacement lenses and found a significantly reduced risk of toxic/hypersensitivity reactions, papillary conjunctivitis, and metabolic disorders for daily disposables but an increased risk of sterile keratitis and mechanical disorders. Silicone hydrogels did not cause hypoxic complications but had an increased risk of sterile keratitis, mechanical disorders, and nonulcerative complications compared to conventional soft lenses.<sup>75</sup> Risk factors for CIEs included overnight wear, more days of lens wear per week, poor hand hygiene, smoking, and inexperience with use. The authors concluded neither daily disposable lenses nor silicone hydrogels reduced the overall risk of acute nonulcerative events.<sup>75</sup> Corneal scrape and cultures can be obtained to evaluate for infectious etiologies and should especially be acquired if the infiltrate increases, vision is affected, or if the infiltrate is large ( $>1$  mm).<sup>76</sup> However, it is difficult to rely only on culture data to guide clinical decision making. Reported cultures of “obvious” MK are positive 43%–86% of the time, yet one study of “sterile” peripheral infiltrates found positive cultures in 50% of the subset of patients.<sup>77–80</sup> Many clinicians believe that small peripheral infiltrates do not require cultures, but cultures on organisms have been performed, particularly if an epithelial defect is present.<sup>73,76</sup> When organisms are recovered, they tend to be less virulent than those associated with central ulcers. The most common isolate is staphylococcus spp., but even in the face of positive culture results, many authors believe that peripheral infiltrates are inflammatory because microorganisms are not recovered in most studies, and infiltrates often resolve with corticosteroid therapy alone.<sup>76,81</sup>

Discontinuation of lens wear is the first step in the treatment of CIEs. Depending on location and size of the infiltrate and the capacity for monitoring additional treatment options include topical, broad-spectrum antibiotics, topical corticosteroids, or a combination of the two. The clinical appearance can change rapidly, and most patients are seen in 24 hours with modification of therapy, as needed. After resolution, assessment of the patient's wear and replacement schedules, as well as their care regimen, should be made. Extended wear should be discouraged. Reduction of bioburden at the lid margins<sup>82</sup> and in lens cases, as well as a switch to daily disposable or hydrogen peroxide care system, should be considered.<sup>57</sup>

### Microbial Keratitis

Although the overall incidence is low, contact lens wear is now considered the major risk factor for MK, with about 65% of all new ulcers related to contact lens use.<sup>83,84</sup> MK can be sight threatening because of corneal scarring and is therefore important to differentiate early-stage MK from CIEs so as to not delay treatment.

The most important risk factor for MK is overnight or extended lens use,<sup>2,3,71,85–87</sup> followed by poor lens/lens case disinfection, smoking, lower socioeconomic class, and failure to wash hands.<sup>3,88–90</sup> It is surprising that the surge in disposable single-use contact lenses has not decreased the rates of MK; however, there has been a decrease in vision loss caused by MK in daily contact lens wearers.<sup>91</sup> Stapleton reported a higher incidence rate of MK with silicone hydrogel (SH) contact lenses compared to daily disposable, and higher rates of MK when SH contact lenses were worn overnight compared with conventional hydrogels.<sup>92</sup> Overall, daily disposable lenses are associated with less severe MK and are less likely to cause vision-impairing central MK.

Findings associated with MK include positive corneal culture results, continuous pain after discontinuation of wear, photolodnyia, purulent discharge (Fig. 4.24.10), conjunctival injection, epithelial staining, anterior chamber reaction<sup>67</sup> and corneal edema that surrounds an infiltrate. Stromal opacities in MK are usually larger than 1.5 mm and have overlying epithelial defect and purulent discharge. Multiple studies have demonstrated that pathogenic microorganisms, especially *Pseudomonas* spp., fungi, *Acanthamoeba*, and *Nocardia*, are the main causes and determinants of outcome in MK.<sup>93–101</sup>

Lee et al. found that Gram-positive bacteria are more prevalent in MK, whereas Gram-negative bacteria are more virulent.<sup>102</sup>

When MK ulcers are suspected, scraping, culture, and Gram staining must be performed. The solutions and the lens case should be





**Fig. 4.24.10** This *Fusarium* ulcer occurred in a contact lens wearer using the lens solution brand ReNu with MoistureLoc, which was subsequently withdrawn from the market.

sampled as well, if possible. Aggressive therapy with broad-spectrum, topical fortified antibiotics should be initiated immediately. A combination broad-spectrum regimen that includes either cefazolin or vancomycin and tobramycin or gentamicin is recommended. In less severe cases, aggressive broad-spectrum monotherapy with a fluoroquinolone is often effective.<sup>103</sup> Delay in treatment of more than 12 hours increase the risk of vision loss.<sup>101</sup> The Steroids for Corneal Ulcers Trial (SCUT) identified that adjunctive topical corticosteroids may be associated with improved outcomes in bacterial MK not caused by *Nocardia* spp. and that the worst ulcers benefit the most from corticosteroid application.<sup>104</sup> However, as will be mentioned later, misdiagnosis in the context of corticosteroid use can be vision threatening because corticosteroids worsen nonbacterial keratitis, such as that caused by herpes simplex virus, fungal keratitis, and *Acanthamoeba* keratitis.

Careful follow-up and adjustment of therapy, based on identification of the organism, sensitivity testing, and clinical response, are essential. Unfortunately, MK often causes corneal scarring and decreased acuity because these lesions are often centrally located; up to 25% of patients are left with best-corrected visual acuity of less than 20/200.<sup>105</sup> Patients may require corneal transplantation or RGP lens to improve acuity.

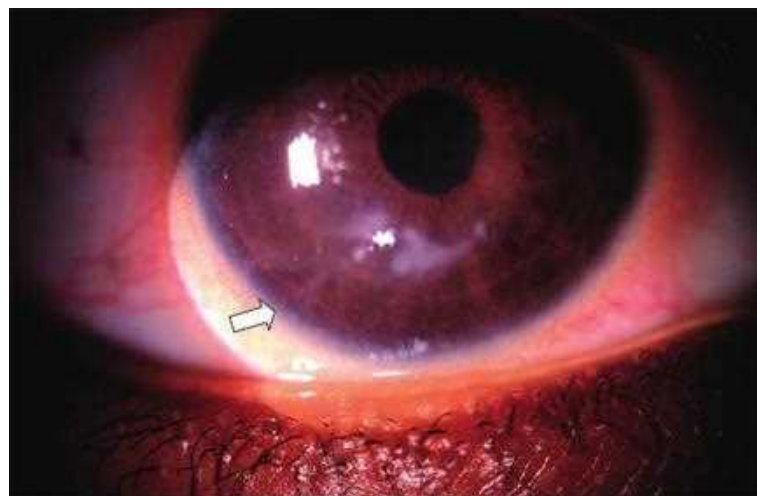
## Fungal Keratitis

Historically, fungal infections are a rare cause of contact lens–induced MK. However, the incidence of fungal keratitis is increasing, and the increase has resulted from contact lens–associated filamentary fungal infections.<sup>106</sup> All types of contact lenses, including daily disposables, have been associated with fungal keratitis.<sup>107</sup> *Candida* spp. are the most common non-filamentous isolates, and *Aspergillus* and *Fusarium* lead the filamentous causes.<sup>108</sup>

Patients present with decreased vision, injection, and pain that may be severe. Early filamentous infections have a feathery appearance at the edges and may be less dense than those seen with bacterial MK. There may be a frank epithelial defect, and the anterior chamber reaction may be mild or severe, even forming a hypopyon. MK caused by yeast infections are typically more localized, with a small epithelial defect overlying an infiltrate. Fungal MK may be slowly progressive, often delaying correct diagnosis.

Culture and Gram staining of corneal scrapings should be performed if fungal keratitis is suspected. Cultures of the solutions, lenses, and lens cases are also advised. Unlike suspected bacterial infections, which are often treated empirically pending culture results, treatment for fungal keratitis does not typically begin until confirmation with positive culture results, scrapings, confocal microscopy, or (occasionally) a corneal biopsy.

The Mycotic Ulcer Treatment Trial (MUTT) demonstrated level 1 evidence that topical natamycin is superior to topical voriconazole in the treatment of fungal keratitis, especially in cases of *Fusarium* keratitis.<sup>109</sup> Systemic voriconazole in combination with topical treatment is used in severe cases. Interestingly, some fungal keratitis associated with soft contact lens wear can resolve with topical fluoroquinolone treatment; it is postulated that fluoroquinolones augment the innate immune response.<sup>110</sup>



**Fig. 4.24.11** Patients with *Acanthamoeba* keratitis often show radial keratoneuritis (arrow) with infiltration along the corneal nerves.

## Acanthamoeba Keratitis

*Acanthamoeba* is a protozoa found in fresh water and soil and the majority of cases of *Acanthamoeba* keratitis are associated with contact lenses. The key risk factors for *Acanthamoeba* infection involve poor hygiene practices, including using tap water or saline to rinse or store lenses, swimming in fresh water while wearing contact lenses, and using hydrogen peroxide instead of multipurpose solution.<sup>111</sup> However, other studies have indicated that hydrogen peroxide is a superior lens disinfectant solution.<sup>112</sup> Overall, it has been estimated that over 80% of *Acanthamoeba* infections could be prevented with proper lens disinfectant systems.<sup>113–115</sup>

*Acanthamoeba* keratitis should be suspected in all contact lens wearers who experience foreign body sensation; severe pain out of proportion to clinical examination findings; lid edema; lack of improvement with antibiotics, antivirals, or corticosteroids; and epithelial findings, including punctate epithelial erosions, ring-shaped infiltrates, and pseudo-dendritic lesions<sup>116</sup> (Fig. 4.24.11). If a patient presents with an isolated ring-shaped corneal infiltrate and *Acanthamoeba* is not found, consideration should be given to unrelated causes, such as anesthetic abuse or a type 3 response to endotoxin (e.g., Wessely immune rings).

Definitive diagnosis entails corneal scrapings and cultures, although there is a role for preliminary confocal microscopy.<sup>117</sup> The lesion may be confused with fungal, bacterial, or herpetic keratitis, and this often leads to delay in diagnosis and treatment. Even if promptly diagnosed, vision loss may result because there is no optimal treatment for this condition that causes amebic encystation and medication resistance.

Treatment is amebicidal therapy with propamidine isethionate 0.1% and PHMB 0.02%, for months.<sup>118–121</sup> Use of topical corticosteroid can have detrimental effects on visual outcome, but its use can be considered after initiation of modern antimicrobial therapy.<sup>122</sup> Penetrating keratoplasty is often required, but infection may recur in the graft, necessitating enucleation.<sup>123–125</sup> Considering the virulence of the organism and its resistance to treatment, it is critical that proper lens hygiene is emphasized to prevent *Acanthamoeba* infection. Daily disposable lenses may be the best option for patients who exhibit less than optimal adherence to sanitation measures.

## UNSUPERVISED LENS WEAR

Unsupervised lens wear occurs when individuals inexperienced with contact lens use obtain lenses without a prescription and from unlicensed sellers. No individualized fitting occurs, and no instruction is given on any aspect of lens wear or care. These lenses are typically plano lenses worn to change the color of the eye or for some dramatic effect. The sale of these “black market” lenses occurs at unlikely locations, such as convenience stores, nail salons, beauty parlors, theatrical supply houses, flea markets, and even street vendors. These lenses also are available from Internet suppliers, some of whom advertise that no prescription is needed. The typical customer is a young person; the risks may be compounded by overnight wear of these lenses and sharing and swapping of lenses. As these lenses gained popularity, eye care professionals have started to see more cases with such problems as infectious keratitis, which sometimes result in loss of vision, hospitalization, and the need for penetrating keratoplasty.<sup>126–128</sup> In



2005, plano, or decorative, lenses were classified as medical devices requiring a prescription as a result of significant effort by professional eye care organizations and individuals and concern shared by the FDA.<sup>129</sup>

Unsupervised lens wear also occurs with prescription lenses, now readily available from alternative lens sellers. Despite the legal requirement for a valid contact lens prescription, some wearers are able to obtain contact lenses for extended periods without regular eye examinations. If a lens wearer has no acute problem requiring immediate attention, it is only at the yearly examination that eye care professionals can examine the patient for subtle signs of lens problems, review wearing and replacement schedules, and ensure that the patient is using an appropriate lens care system. In contact lens care, if there is no immediate consequence to deviation from recommended practices, a slow drift away from good lens care can occur. In 2006, the FDA issued guidelines emphasizing the importance of professional advice, valid contact lens prescriptions, and continuing professional care. FDA guidelines succinctly state: "Because of these risks, contact lenses, including decorative contact lenses that are noncorrective, are not safe for use except under the supervision of a practitioner licensed by law to direct the use of such devices."<sup>130</sup>

## FDA AND CDC RECOMMENDATIONS

The recommendations of the FDA and the Centers for Disease Control and Prevention for contact lens safety are summarized below and can be found at [www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/HomeHealthandConsumer/ConsumerProducts/ContactLenses/](http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/HomeHealthandConsumer/ConsumerProducts/ContactLenses/) and [www.cdc.gov/contactlenses/](http://www.cdc.gov/contactlenses/).

- Follow the recommended wear schedule. Do not substitute sterile saline solutions with multipurpose solutions.
- Rub and rinse your contact lenses as directed by your eye care professional.
- Do not "top off" the solutions in your case. Always discard all of the left-over contact lens solution after each use. Never reuse any lens solution.
- Clean, rinse, and air-dry your lens case each time lenses are removed.
- Do not expose your contact lenses to any water: tap, bottled, distilled, lake, or ocean water.
- Contact your eye care professional if you experience any symptoms of eye irritation or infection.

## CONCLUSIONS

The overall safety profile of contact lenses is excellent, but wearers are at increased risk for both non-sight-threatening and blinding complications.

Appropriate lens selection and patient education regarding lens hygiene can reduce complications. Public health initiatives may be required to reduce unsupervised lens wear. Regular monitoring by an eye care provider are critical to primary and secondary prevention. In the event of a contact lens-related complication, prompt referral, early diagnosis, and proper treatment typically result in good visual outcomes and allow continuation of contact lens wear.

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Corneal and External Eye Manifestations of Systemic Disease

4.25

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**Definition:** Disorders with corneal, external, and other anterior segment manifestations of systemic diseases and syndromes.

Key Feature

- External and anterior segment ocular anomalies as well as systemic abnormalities.

Associated Feature

- Usually genetic defect with multisystem clinical findings.

INTRODUCTION

As is broadly evident in multiple other ocular and orbital tissues, systemic disorders commonly exhibit ocular manifestations. Because of the multiplicity and complexity of these disorders, this chapter presents these associations largely in tabular form. Where known, the causative genetic loci and resultant metabolic defects are specified. Finally, as many disorders are genetically heterogeneous, only the more commonly associated genetic loci are listed.

CONGENITAL DISORDERS

Congenital disorders are nonmetabolic disorders present at birth that have generalized systemic features as well as ocular anterior segment abnormalities. These groupings are arbitrary and may change as genetic information allows for more specific categorizations. Some craniofacial malformation syndromes with associated anterior ocular findings are given in Table 4.25.1. Given the severity of these disorders, management is multidisciplinary and requires a team approach by ophthalmologists, facial plastic surgeons, neurosurgeons, and others.<sup>1–11</sup>

CHROMOSOMAL DISORDERS

Syndromes consequent to chromosomal disorders are defined by their abnormal genetic loci (Table 4.25.2). With rapid advances in molecular genetics, more thorough understanding of relevant regulatory or other gene mechanisms involved will allow for better interpretation of their widespread, multisystemic (also see Section I: Genetics). A striking finding is that different chromosomal defects may lead to similar phenotypic abnormalities.<sup>12–16</sup>

INHERITED CONNECTIVE TISSUE DISORDERS

The inherited connective tissue disorders are striking in their musculoskeletal manifestations and often serious in their visceral involvements

TABLE 4.25.1 Craniofacial Malformation Syndromes With Corneal Manifestations

Syndrome	Protein Defect	Gene Locus	Ocular Manifestations	Systemic Manifestations
Crouzon’s, Apert’s, and Pfeiffer’s	Fibroblast growth factor receptor-2	10q26 <sup>1</sup>	Shallow orbits, decreased motility, secondary corneal exposure	Craniofacial malformation and syndactyly (Apert’s)
Meyer–Schwickerath (oculodentodigital dysplasia)	Connexin43 (Cx43) or gap junction alpha 1 gene ( <i>GJA1</i> )	6q22–q24	Microphthalmos, microcornea, narrow palpebral fissures, blue sclera	Syndactyly, dysplastic tooth enamel and microcephaly
Goldenhar’s (oculoauriculovertebral dysplasia)			Limbal dermoids, microphthalmos, anophthalmos, lid notching, blepharophimosis	Facial asymmetry, vertebral anomalies, ear deformities, mandibular hypoplasia
Hallermann–Streiff	Connexin43	6q22–24	Microphthalmos, spontaneously resorbing cataracts, macular pigment changes, Coats’ disease	Facial malformation, hypoplastic mandible, short stature, skin atrophy

TABLE 4.25.2 Chromosomal Disorders With Corneal Manifestations

Genetic Findings	Ocular Manifestations	Systemic Manifestations
13q deletion	Hypertelorism, ptosis, epicanthal folds, microphthalmos, retinoblastoma	Growth retardation, microcephaly, facial malformation, absent thumbs
18p deletion	Ptosis, epicanthal folds, hypertelorism, corneal opacity, keratoconus, microphthalmos, strabismus	Brachycephaly, growth retardation, mental retardation
18q deletion	Hypertelorism, epicanthal folds, nystagmus, corneal opacity, microphthalmos, corneal staphyloma, microcornea	Growth retardation, mental retardation, facial malformation, microcephaly, prostate cancer, hearing loss, endocrine disorders
4p deletion (Wolf–Hirschhorn syndrome)	Hypertelorism, ptosis, microphthalmos, strabismus, cataract	Growth retardation, microcephaly, micrognathia, hypotonia seizures, epilepsy
Turner’s syndrome (45×0)	Ptosis, epicanthal folds, strabismus, rarely microcornea, blue sclera, corneal opacity	Female, short stature, webbed neck, hearing loss
Trisomy 13 (Patau’s syndrome)	Microphthalmos, corneal opacity, Peters’ anomaly, cataract, retinal dysplasia (Fig. 4.25.1)	Microcephaly, cleft lip and palate, low-set ears
Trisomy 18 (Edwards’ syndrome)	Corneal opacity, ptosis, hypertelorism, epicanthal folds, microphthalmos, colobomas, cataract, retinal dysplasia	Low birth weight; failure to thrive; brain hypoplasia; cardiac, gastrointestinal, renal, and musculoskeletal anomalies
Trisomy 21 (Down syndrome)	Shortened, slanted palpebral fissure, neonatal ectropion, later trichiasis and entropion, keratoconus, cataract	Cardiac defects, mental retardation, short stature, characteristic facies
Partial trisomy 22 (cat’s eye syndrome)	Microphthalmos, hypertelorism, colobomas	Mental retardation, microcephaly, cardiac anomalies, ear anomalies, anal atresia



**Fig. 4.25.1 Trisomy 13.** (A) Inferior nasal iris coloboma and leukocoria are present. (B) Light microscopy discloses ciliary body coloboma filled with mesenchymal tissue containing cartilage (C); note the retinal dysplasia (R). (Generally, in trisomy 13, cartilage is present in eyes less than 10 mm in size.) (C) Karyotype shows extra chromosome in group 13 (arrow). (A, Courtesy Shaffer DB. In: Yanoff M, Fine BS, editors. *Ocular pathology*, 4th ed. London, UK: Mosby; 1996. C, Courtesy Drs. B. S. Emanuel and W. J. Mellman.)

TABLE 4.25.3 Inherited Connective Tissue Disorders With Corneal Manifestations				
Disease	Biochemical Defect	Gene Locus	Ocular Manifestations	Systemic Manifestations
Marfan's syndrome	Fibrillin-I gene mutations ( <i>FBN1</i> )	15q21.1	Megalocornea, lens subluxation, high myopia, retinal detachment, microspherophakia	Long extremities, lax joints, aortic/mitral dilatation, aortic dissection
Osteogenesis imperfecta	Type I procollagen COL1A1 COL1A2	17q21.31–q22.7q22.1	Blue sclera, keratoconus, megalocornea, optic nerve compression	Bone deformities, recurrent fractures, otosclerosis, dental anomalies
Ehlers–Danlos syndrome type VIA	Lysyl hydroxylase	1p36.3–p36.2	Blue sclera, keratoconus, keratoglobus, lens subluxation, myopia, floppy eyelids, ocular fragility to trauma	Skin stretching, scarring joint hypermobility, scoliosis, tissue fragility
Ehlers–Danlos syndrome type VIB	Normal lysyl hydroxylase	Unknown	Same as VIA	Same as VIA

TABLE 4.25.4 Disorders of Protein and Amino Acid Metabolism						
Disorder	Enzyme Deficiency	Gene Locus	Metabolite Accumulated	Mode of Inheritance	Ocular Manifestations	Systemic Manifestations
Cystinosis	Probable defect of lysosomal cysteine transport protein	17p13 <i>CTNS</i> gene	Cystine	Autosomal recessive	All forms: conjunctival and corneal cystine crystals deposition, band keratopathy, blepharospasm, photophobia Infantile and adolescent forms: retinal abnormalities, occasional macular changes (Fig. 4.25.2)	Infantile form (90%): renal failure, death Adolescent form (5%): renal failure, skeletal deformities Adult form or ocular cystinosis (5%): no renal failure, nonnephropathic ocular form
Tyrosinemia <sup>a</sup> type II (tyrosinosis, Richner–Hanhart syndrome)	Tyrosine transaminase deficiency	16q22.1–22.3	Tyrosine	Autosomal recessive	Dendritiform corneal epithelial changes (branches or snowflake opacities), red eye, photophobia	Palmar–plantar hyperkeratosis, mental retardation, growth retardation, epilepsy
Alkaptonuria	Homogentisate-1, 2-dioxygenase	3q21–q23	Homogentisic acid	Autosomal recessive	Pigmentation (ochronosis) of sclera near insertion of horizontal rectus muscles, “oil-droplet” opacities in limbal corneal epithelium and Bowman’s layer, pigmented pingueculae	Joint pain and stiffness
Wilson’s disease	Defective excretion of copper from hepatic lysosomes	13q14.3–q21.1 ( <i>ATP7B</i> gene)	Copper	Autosomal recessive	Kayser–Fleischer ring, “sunflower” cataract (Fig. 4.25.3)	Liver dysfunction, spasticity, behavior disturbance, nephrotic syndrome
Lattice dystrophy type II (Meretoja’s syndrome)	Gelsolin gene defect (G654A–Finnish type) or G654T (Danish type)	9q32–34	Amyloid	Autosomal dominant	Lattice dystrophy, dry eye, light sensitivity, ptosis, glaucoma	Progressive cranial neuropathy, facial paralysis, cardiac disease

(Table 4.25.3). More detailed discussions on this topic are featured elsewhere (also see Chapters 4.3, 4.19, and 4.20).<sup>17–22</sup>

## METABOLIC DISORDERS

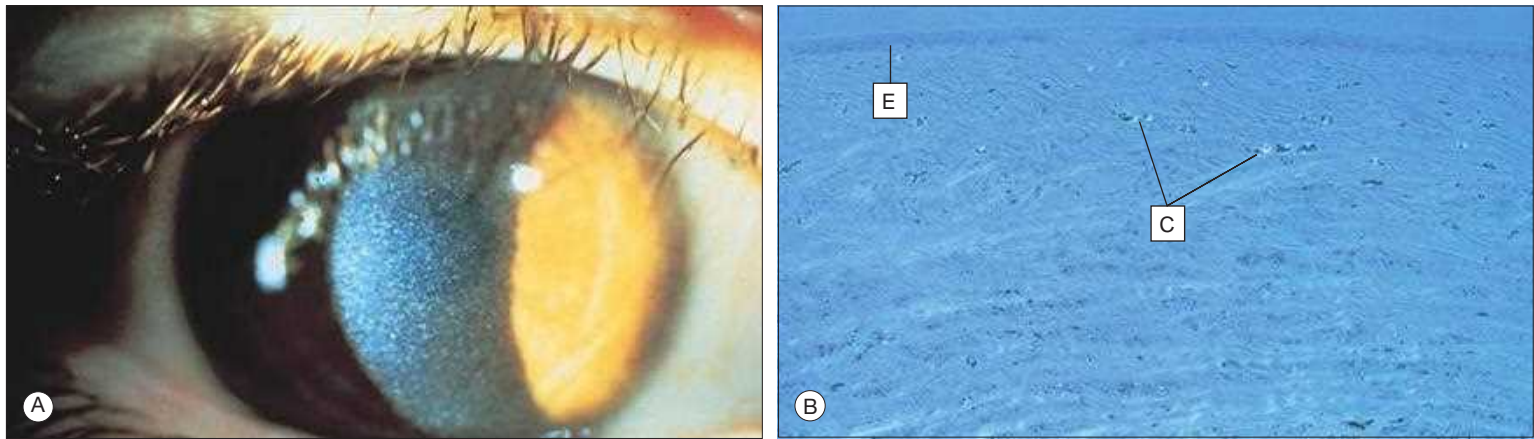
Numerous inherited metabolic disorders affect the eye. Frequently autosomal recessive, these disorders are often consequent to a defect or reduction of a single lysosomal enzyme (hence the broad term *lysosomal storage diseases* [LSDs]) resulting in accumulation of metabolites in multiple affected tissues. For many disorders, the specific genetic defect has been identified, and for some (notably Fabry’s disease) synthesis of the defective enzyme has facilitated enzyme replacement therapy. In contrast to most corneal dystrophies, corneas affected by metabolic disorders demonstrate abnormality in multiple cell types, affect the peripheral cornea as well as the central cornea, and may be progressive.

## Protein and Amino Acid Metabolic Disorders

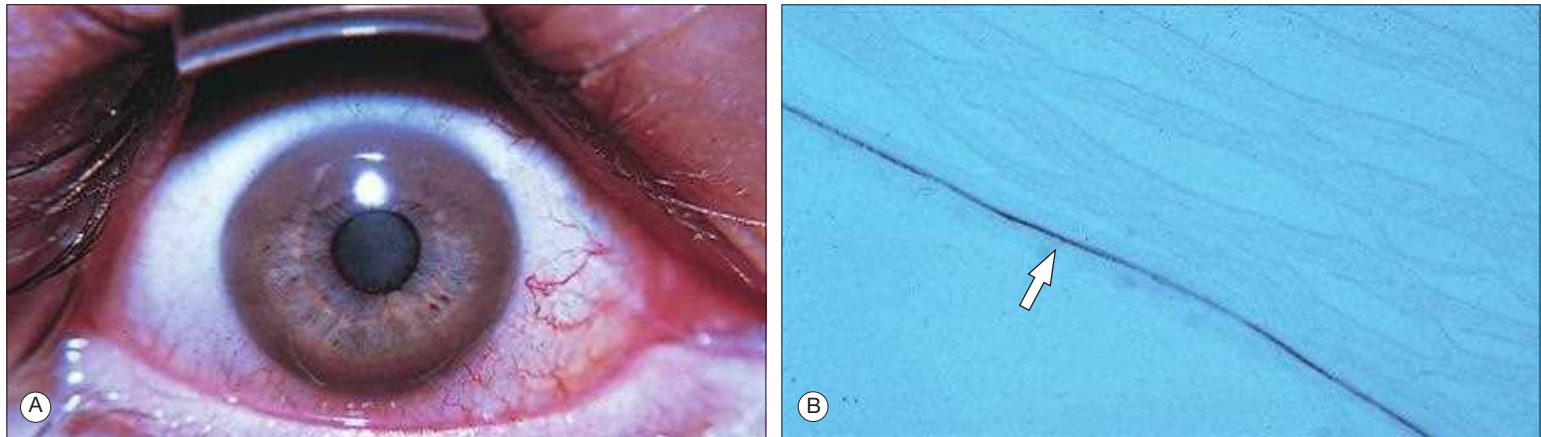
As specified in Table 4.25.4, the accumulated metabolites are sometimes amenable to treatment. For cystinosis, therapy is accomplished with oral cysteamine.<sup>23–27</sup> In tyrosinemia, dietary therapy (avoiding phenylalanine and tyrosine) keeps tyrosine levels controlled.<sup>28,29</sup> Vitamin C and nitisnone may be effective for alkaptonuria.<sup>30,31</sup> Chelation therapies to reduce elevated ceruloplasmin levels in Wilson’s disease utilize D-penicillamine and trientine.<sup>32–36</sup>

## Mucopolysaccharidoses

The mucopolysaccharidoses (MPSs) comprise the quintessential LSDs because their hydrolytic enzyme defects result in progressive intralysosomal (and eventual extracellular) storage of mucopolysaccharides (more



**Fig. 4.25.2 Cystinosis.** (A) Myriad tiny opacities are highly reflective. (B) Light microscopy of unstained corneal section viewed with polarization demonstrates birefringent cystine crystals (C); E, epithelium. (A, Courtesy Shaffer DB. In: Yanoff M, Fine BS, editors. Ocular pathology, 4th ed. London, UK: Mosby; 1996.)



**Fig. 4.25.3 Wilson's Disease.** (A) Annular deposition (Kayser-Fleischer ring) of golden brown-appearing copper in the periphery of Descemet's membrane partially obstructs the view of the underlying iris. Disciform "sunflower" cataract is also present. (B) Light microscopy of unstained section shows copper deposition (arrow) in the inner portion of peripheral Descemet's membrane. (Modified from Tso MOM, Fine BS, Thorpe HE. Kayser-Fleischer ring and associated cataract in Wilson's disease. *Am J Ophthalmol* 1975;79:479-88.)

properly termed *glycosaminoglycans*) (Table 4.25.5), often with variably profound skeletal and mental consequences. Corneal clouding in varying degrees and patterns, as well as retinal pigmentary degenerations, are the hallmarks of MPS disorders caused by accumulation of heparan, keratan, and dermatan sulfates.<sup>37-52</sup>

## Sphingolipidoses

Also considered LSDs, the sphingolipidoses arise from dysfunction of catabolic enzymes, with consequent accumulation of sphingolipids (Table 4.25.6).<sup>53-59</sup> Notable among sphingolipidoses are Tay-Sachs and Niemann-Pick diseases, which are not included as they lack major anterior segment manifestations.

## Dyslipoproteinemias

The dyslipoproteinemias (Table 4.25.7) comprise a somewhat diverse group of disorders resulting from the multiplicity of lipid metabolic processes and pathways. In the anterior eye, they variably manifest as eyelid xanthelasma, corneal arcus, and corneal clouding.<sup>60-66</sup>

## Mucopolysaccharidoses

The mucopolysaccharidoses (Table 4.25.8) are LSDs whose enzyme defects occur at the intersection of both glycoprotein and glycolipid metabolic pathways.

Hence the accumulation of oligosaccharides and gangliosides result in alterations common to both mucopolysaccharidoses and sphingolipidoses.<sup>67-70</sup>

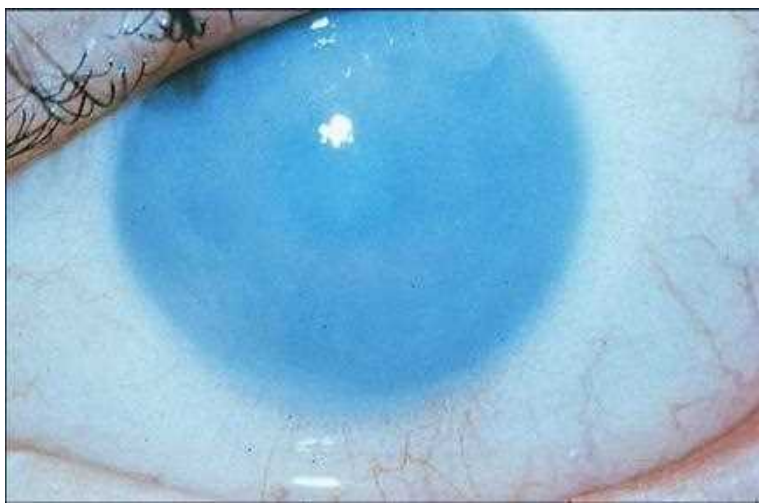
## OTHER OCULOSYSTEMIC DISORDERS

Apart from the above specified disorders, numerous other systemic diseases have ocular manifestations, and they may be grouped accordingly. Thus corneorenal syndromes are a disparate group of disorders in which corneal abnormalities combine with renal disease (Table 4.25.9).<sup>71-79</sup> Corneohepatic syndromes are less common (Table 4.25.10).<sup>80-83</sup> Oculocutaneous disorders are numerous, and here only the more prominent are specified (Table 4.25.11).<sup>84,85</sup>

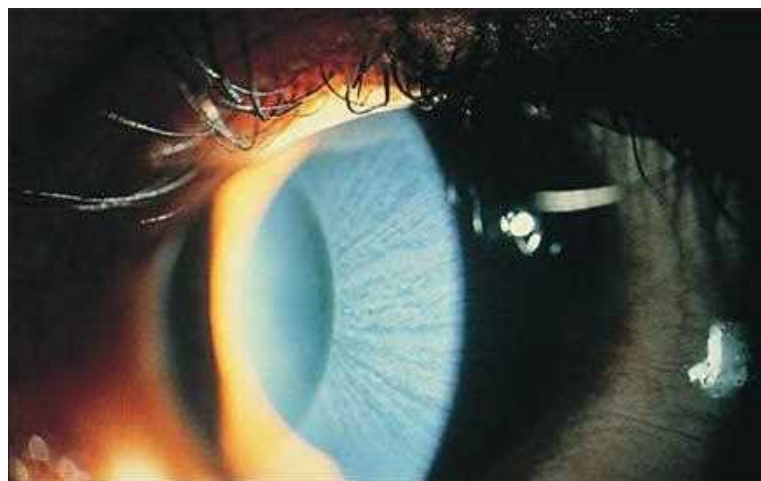
## CONCLUSIONS

This largely tabular overview of systemic diseases with corneal, external, and other anterior segment involvements emphasizes broad manifestations of specific diseases and thus the critical importance of evaluating and managing the whole patient and not overfocusing on the eye alone. As understanding of the basic disease mechanisms increases, new therapeutic interventions will be instituted. One such current strategy includes enzyme replacement therapy, as for example, alpha-L-iduronidase infusions have benefited the mobility of children with MPS type I,<sup>39</sup> and alpha-galactosidase has helped alleviate clinical symptoms in patients with Fabry's disease.<sup>72</sup>





**Fig. 4.25.4 Mucopolysaccharidosis.** In Hurler–Scheie syndrome (MPS I-H/S) the cornea is diffusely clouded. (Courtesy Shaffer DB. In: Yanoff M, Fine BS, editors. Ocular pathology, 4th ed. London, UK: Mosby; 1996.)



**Fig. 4.25.5 Fabry's Disease.** Verticillate changes radiate in the superficial cornea of a female carrier.

**TABLE 4.25.5 Mucopolysaccharidoses (MPS)**

Disorder	Enzyme Deficiency	Metabolite Accumulated	Mode of Inheritance	Gene Locus	Ocular Manifestations	Systemic Manifestations
Mucopolysaccharidosis I-H (Hurler)	$\alpha$ -L-Iduronidase ( <i>IDUA</i> gene)	Heparan sulfate Dermatan sulfate Glycosaminoglycans (GAGs)	Autosomal recessive	4p16.3	Corneal clouding, pigmentary retinopathy, optic atrophy, trabecular involvement	Gargoyle facies, mental retardation, dwarfism, skeletal dysplasia, valvular heart disease, hepatosplenomegaly
Mucopolysaccharidosis I-S (Scheie's, previously MPS V)	$\alpha$ -L-Iduronidase	Heparan sulfate Dermatan sulfate	Autosomal recessive	4p16.3	Corneal clouding, pigmentary retinopathy, optic atrophy, glaucoma	Coarse facies, claw-like hands, aortic valve disease
Mucopolysaccharidosis I-H/S (Hurler–Scheie; Fig. 4.25.4)	$\alpha$ -L-Iduronidase	Heparan sulfate Dermatan sulfate	Autosomal recessive	4p16.3	Corneal clouding, pigmentary retinopathy, optic atrophy	More severe than I-S, less severe than I-H
MPS II (Hunter's)	Iduronate sulfate sulfatase (iduronate sulfatase)	Heparan sulfate Dermatan sulfate	X-linked recessive	Xq28	Rare corneal clouding, pigmentary retinopathy, optic atrophy	Similar to I-H with less bony deformity
MPS III (Sanfilippo's)	Variable, depending on type	Heparan sulfate	Autosomal recessive	17q25.3 17q21.1 12q14 Chr #14	All forms: clinically clear cornea, occasional slit-lamp corneal opacities pigmentary retinopathy, optic atrophy	All forms: mild dysmorphism, progressive dementia, hearing loss, behavior issues
MPS IV (Morquio's)	A: galactose-6-sulfatase B: $\beta$ -galactosidase	Keratan sulfate, chondroitin-6 sulfate	Autosomal recessive Autosomal recessive	16q24.3 3p21.33	Corneal clouding, optic atrophy	Severe bony deformity, aortic valve disease, normal intelligence
MPS VI (Maroteaux–Lamy)	N-acetylgalactosamine-4-sulfatase	Dermatan sulfate	Autosomal recessive	5q11–q13	Corneal clouding, optic atrophy	Similar to I-H, but normal intellect
MPS VII (Sly's)	$\beta$ -glucuronidase	Dermatan sulfate Heparan sulfate	Autosomal recessive	7q21.1	Corneal clouding	Similar to I-H

**TABLE 4.25.6 The Sphingolipidoses**

Disorder	Enzyme Deficiency	Gene Locus	Metabolite Accumulated	Mode of Inheritance	Ocular Manifestations	Systemic Manifestations
GM <sub>2</sub> gangliosidosis II (Sandhoff's disease)	Hexosaminidase B, HEX B chain	5q13	Ganglioside GM <sub>2</sub>	Autosomal recessive	Membrane-bound vacuoles within corneal keratocytes, cherry-red macula	Psychomotor retardation, hepatosplenomegaly, Mongolian spots (unusual)
Metachromatic leukodystrophy (Austin's juvenile form)	Arylsulfatase A isozymes	22q13.31-qter	Sulfatide	Autosomal recessive	Corneal clouding	Mental retardation, seizures
Fabry's disease	$\alpha$ -Galactosidase A	Xq22	Ceramide trihexoside	X-linked recessive	Conjunctival and retinal vascular tortuosity, anterior subcapsular lens opacities, oculomotor abnormalities, cornea verticillata (Fig. 4.25.5)	Renal failure, peripheral neuropathy, hypo/hyperhidrosis, hypoacusis
Gaucher's disease	Glucocerebrosidase	1q21	Glucocerebrosidase	Autosomal recessive	Prominent pinguiculae, white corneal epithelial deposits, vitreous opacities, paramacular gray ring	Hepatosplenomegaly, bone pain, anemia

TABLE 4.25.7 The Dyslipoproteinemias

Disorder	Deficiency	Gene Locus	Metabolite Accumulated	Mode of Inheritance	Ocular Manifestations	Systemic Manifestations
Lecithin–cholesterol acyltransferase (LCAT) deficiency	Lecithin–cholesterol acyltransferase	16q22.1	Free cholesterol	Autosomal recessive	Dense peripheral arcus, gray dots in central stroma, no visual changes	Atherosclerosis, xanthomas, premature coronary artery disease, hepatosplenomegaly, anemia, renal insufficiency
Fish eye disease (high-density lipoprotein lecithin–cholesterol acyltransferase)	α-Lecithin–cholesterol acyltransferase	16q22.1	Triglycerides, very low density lipoproteins (VLDL); low-density lipoproteins (LDL)	Autosomal dominant	Progressive corneal clouding, increased corneal thickness	None
Tangier’s disease (analphalipoproteinemia)	High-density lipoprotein	9q22–q31 (ABCA1 gene)	Triglycerides; low levels of high-density lipoproteins (HDL), cholesterol and phospholipids	Autosomal recessive	Fine dot corneal clouding, severe visual loss, incomplete eyelid closure, ectropion, no arcus	Lymphadenopathy hepatosplenomegaly, coronary artery disease
Hyperlipoproteinemia I (hyperchylomicronemia)	Lipoprotein lipase	8p22	Triglycerides, chylomicrons	Autosomal recessive	Lipemia retinalis, palpebral eruptive xanthomata	Xanthomas
Hyperlipoproteinemia II, hyper-β-lipoproteinemia IIA, hyper-β-lipoproteinemia IIb	LDL receptor (type IIa); defective lipid metabolism in type IIb	19p13 (type IIa); 1q21-23 (type IIb); others	Type IIa: LDL, cholesterol Type IIb: LDL, VLDL, cholesterol, triglycerides	Autosomal dominant	Both forms: corneal arcus, conjunctival xanthomata, xanthelasma	Coronary artery disease
Hyperlipoproteinemia III (dys-β-lipoproteinemia; broad β-disease)	Abnormality in apolipoprotein E	19q13.2	VLDL remnants, cholesterol, triglycerides	Autosomal recessive with pseudo-dominance	Arcus, xanthelasma, lipemia retinalis	Peripheral vascular disease, diabetes mellitus
Hyperlipoproteinemia IV (hyperpre-β-lipoproteinemia)	Lipoprotein lipase; apolipoprotein A	15q11-13; 21q11; others	Triglycerides, VLDL	Autosomal dominant	Arcus, xanthelasma, lipemia, retinalis	Vascular disease, diabetes mellitus
Hyperlipoproteinemia V (hyperprelipoproteinemia and hyperchylomicronemia)	Apolipoprotein A	11q23	VLDL, chylomicrons	Uncertain	Lipemia retinalis, no arcus	Xanthomas, hepatosplenomegaly

TABLE 4.25.8 Mucopolidoses (MI)

Disorder	Enzyme Deficiency	Gene Locus	Metabolite Accumulated	Mode of Inheritance	Ocular Manifestations	Systemic Manifestations
ML I (dysmorphic sialidosis, Spranger’s syndrome)	Glycoprotein sialidase (neuraminidase I)	6p.21.3	Sialyl-oligosaccharides	Autosomal recessive	Macular cherry-red spot, tortuous retinal and conjunctival vessels, spoke-like lens opacities, progressive corneal clouding	Coarse facies, hearing loss, normal IQ
ML II (I-cell disease)	GluNac-I-phosphotransferase	4q21–q23	Increased plasma lysosomal hydrolases	Autosomal recessive	Small orbits, hypoplastic supraorbital ridges and prominent eyes, glaucoma, megalocornea, corneal clouding	MPS I-H facies, mental retardation
ML III (pseudo-Hurler’s polydystrophy)	GluNac-I-phosphotransferase	4q21–q23	Increased plasma lysosomal hydrolases	Autosomal recessive	Corneal clouding	Milder growth and mental retardation
ML IV (Berman’s syndrome)	Possible ganglioside sialidase	19p13.3–p13.2	Sialogangliosides	Autosomal recessive	Corneal clouding retinal degeneration	Slowed psychomotor development
Galactosialidosis (Goldberg’s syndrome)	β-Galactosidase Neuraminidase	20q13.1	Sialyl-oligosaccharides	Autosomal recessive	Macular cherry-red spot, diffuse mild corneal clouding, conjunctival telangiectases	Seizures, mental retardation, hearing loss, hemangiomas

TABLE 4.25.9 Corneorenal Syndromes

Syndrome	Gene Locus	Ocular Manifestations	Systemic Manifestations
Alport’s	Xq22.3 COL4A5 2q36–q37 COL4A3-COL4A4	Posterior polymorphous corneal dystrophy, juvenile arcus, pigment dispersion, lenticonus, retinal pigmentary changes	Renal failure, hearing loss, lamellated glomerular basement membrane
Cystinosis	17p13	(See Fig. 4.25.2)	Infantile form: renal failure, death Intermediate form: renal failure Adult form: no renal failure
Fabry’s disease	Xq22	(See Fig. 4.25.5) (See Table 4.25.6)	Renal failure, peripheral neuropathy, angiokeratomas
Lowe’s syndrome (oculocerebrorenal)	Xq26.1	Corneal keloids, glaucoma, congenital cataracts	Mental retardation, amino acid urea, tubular acidosis, angiokeratomas, muscle hypotonia, subcutaneous nodules, arthropathy
Wegener’s granulomatosis	Nongenetic	Marginal keratitis, orbital disease, scleritis, episcleritis	Granulomatous vasculitis of lungs, kidneys, nasopharynx
WAGR	11p13	Superficial corneal opacity and vascularization, aniridia, glaucoma, foveal hypoplasia, optic nerve hypoplasia	Wilms’ tumor, mental retardation, craniofacial anomalies, growth retardation
Zellweger’s	2p15(PEX 13)1q2212p 13.3 (PEX 5) 7q21–q22(PEX1) 6q23–q24	Axenfeld’s anomaly, corneal clouding, glaucoma, retinal degeneration	Craniofacial anomalies, hypotonia seizures, retardation, hepatic degeneration, cystic kidneys, cardiac defects, early death

WAGR, Wilms’ tumor, aniridia, genital anomalies, and mental retardation.

TABLE 4.25.10 Corneohepatic Syndromes			
Syndrome	Gene Locus	Ocular Manifestations	Systemic Manifestations
Wilson's disease	13q14.3–21.1	Kayser–Fleisher ring (see Fig. 4.25.3)	Liver dysfunction; neurological dysfunction with dysarthria, spasticity, behavior disturbances
Zellweger's syndrome	7q21–q22	(See Table 4.25.9)	(See Table 4.25.9)
Alagille's syndrome	20p11.2–p12	Posterior embryotoxon, anterior chamber anomalies, eccentric or ectopic pupils, chorioretinal atrophy, retinal pigment clumping	Cholestatic liver disease, structural heart defects, butterfly vertebrae

TABLE 4.25.11 Oculocutaneous Disorders				
Syndrome	Protein Defect	Gene Locus	Ocular Manifestations	Cutaneous/Systemic Manifestations
Basal cell nevus syndrome	PTCH1 protein	9q22.3, 9q31, 1p32	Multiple basal cell carcinomas of the eyelid, hypertelorism	Multiple basal cell carcinomas, jaw cysts, bony anomalies
Xeroderma pigmentosum (seven types, A–G, plus variant type V)	Nucleotide excision repair (NER) enzymes (types A–G); DNA polymerase (type V)	9q22, 2q21, 3p25, 19q13, 11p12, 16p13, 13q33, 6p21	Lid neoplasms, conjunctival and corneal neoplasia, corneal exposure, drying	Basal cell carcinoma, squamous cell carcinomas, and malignant melanomas develop in sun-exposed areas
Ichthyosis (multiple types)	Filaggrin (ichthyosis vulgaris); others	1q21(vulgaris),12q11–q13, 14q11.2, X922.32, 19p 12–q12	Eyelid and lash scaling (all types), ectropion with corneal exposure (lamellar ichthyosis)	Scaly skin
Keratitis–ichthyosis–deafness syndrome	Connexin-26	13q11-12	Keratoconjunctivitis with corneal pannus formation	Ichthyosis, deafness
Ectrodactyly–ectodermal dysplasia–clefting	TP63 (p63 gene)	3q27-28	Dysplasia of meibomian glands, blepharitis, corneal pannus formation, corneal scarring	Lobster-claw deformity of hands and feet, ectodermal dysplasia, cleft lip and palate

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# Acid and Alkali Burns

Naveen K. Rao, Michael H. Goldstein

# 4.26

**Definition:** Chemical exposure to the eye resulting in trauma ranging from mild irritation to severe damage of the ocular surface and anterior segment with permanent vision loss.

## Key Features

- Alkali burns typically are more severe than acid burns.
- Acute management directed at eliminating the causative agent.
- Initial evaluation includes assessment of degree of corneal epithelial injury, corneal opacity, and limbal ischemia.

## Associated Feature

- Limbal stem cell deficiency, corneal opacification, corneal perforation, glaucoma, symblepharon, cicatricial entropion, trichiasis, fibrovascular pannus.

## INTRODUCTION

Chemical exposure to the eye can result in trauma ranging from mild irritation to severe damage of the ocular surface and anterior segment with permanent vision loss. Chemical burns constitute 77%–18% of all ocular trauma.<sup>1,4</sup> The majority of victims are young men.<sup>5–7</sup> Injuries usually are caused by accidents at work or home but also may be deliberately caused by assault.<sup>5–9</sup> Many victims report not wearing proper eye protection at the time of the injury.<sup>7</sup> In the household setting, numerous chemicals exist in the form of solutions in automobile batteries, pool cleaners, detergents, ammonia, bleach, and drain cleaners. Although most injuries caused by these are mild with minimal sequelae, but in severe cases, management can be a challenge (Fig. 4.26.1).

## ALKALI INJURIES

Alkali injuries occur more frequently and are more severe than acid injuries.<sup>1,5–8</sup> Alkalis penetrate more readily into the eye compared with acids,

damaging the stroma and the endothelium, as well as intraocular structures, such as the iris, lens, and ciliary body. Common causes of alkali injury include ammonia ( $\text{NH}_3$ ), lye ( $\text{NaOH}$ ), lime ( $\text{CaOH}_2$ ), potassium hydroxide ( $\text{KOH}$ ), and magnesium hydroxide ( $\text{Mg(OH)}_2$ ).<sup>5,7,10,11</sup> Lime, found in cement and plaster, is the most common cause of alkali injury. Damage from lime injury is limited, however, because of the precipitation of calcium soaps that limit further penetration. Lye and ammonia are associated with the most severe alkali injuries. Ammonia can be detected in the anterior chamber with a rise in aqueous humor pH within seconds of exposure.<sup>12,13</sup> Irreversible intraocular damage has been noted to occur at aqueous pH levels of 11.5 or greater.<sup>14</sup>

## ACID INJURIES

Acids cause superficial damage but generally cause less severe ocular injury than alkalis, as the immediate precipitation of epithelial proteins offers some protection by acting as a barrier to intraocular penetration.<sup>15</sup> Very strong or concentrated acids, however, can penetrate the eye just as readily as alkaline solutions. Sulfuric ( $\text{H}_2\text{SO}_4$ ), sulfurous ( $\text{H}_2\text{SO}_3$ ), hydrochloric ( $\text{HCl}$ ), nitric ( $\text{HNO}_3$ ), acetic ( $\text{CH}_3\text{COOH}$ ), formic ( $\text{CH}_2\text{O}_2$ ), and hydrofluoric ( $\text{HF}$ ) acids are frequent causes of acid burns.<sup>10</sup> The most common cause is sulfuric acid, which is found in industrial cleaners and automobile batteries. Hydrofluoric acid causes the most serious acid injuries because of its low molecular weight, which allows easier stromal penetration.<sup>16</sup> The injury may be compounded by thermal burns from heat generated by the acid's reaction with water on the tear film.<sup>11</sup>

## PATHOPHYSIOLOGY

The severity of ocular injury from alkali or acid is related to the type of chemical, the concentration of the solution, the surface area of contact, the duration of exposure, and the degree of penetration. The hydroxyl ion ( $\text{OH}^-$ ) of alkaline solutions saponifies fatty acids in cell membranes leading to cell lysis, with subsequent hydrolysis and denaturation of proteoglycans and stromal collagen.<sup>17,18</sup> The hydrogen ion ( $\text{H}^+$ ) of acidic solutions alters the pH, whereas the anion causes protein binding and precipitation in the corneal epithelium and superficial stroma.<sup>19</sup> This protein precipitation produces the typical ground-glass appearance of the epithelium and acts as a barrier to further penetration. If penetration of either alkali or acid occurs, the hydration of glycosaminoglycans leads to loss of stromal clarity. Loss of proteoglycans from the stroma results in shrinkage of collagen and can lead to an acute rise in intraocular pressure (IOP) as a result of distortion of the trabecular meshwork.<sup>20</sup> The release of prostaglandins also contributes to the rise in IOP following alkali and acid injuries.<sup>19,21,22</sup> Chemical penetration into the eye may acutely damage stromal keratocytes, stromal nerve endings, corneal endothelium, iris, trabecular meshwork, and ciliary body.<sup>17,19</sup>

In addition to corneal and intraocular injury, chemical burns result in damage to the conjunctiva, limbus, and eyelids.<sup>23</sup> Damage to palpebral and bulbar conjunctiva can lead to loss of goblet cells and chronic dry eye disease.<sup>17</sup> Ischemic necrosis of the conjunctiva causes loss of vascularization at the limbus and loss of limbal stem cells, as well as infiltration of leukocytes.<sup>17,19,24</sup> Damage to the corneal epithelium with injury solely to Bowman's layer and anterior stroma may lead to recurrent corneal erosions. Damage to the limbal stem cells, however, can result in persistent corneal epithelial defects, conjunctivalization of the cornea, presence of goblet cells within the corneal epithelium, and superficial and deep neovascularization.<sup>19,23</sup> Late sequelae of severe burns include cicatrization of the conjunctiva with symblepharon formation and entropion.<sup>19</sup> Coagulation of the posterior lid margin may cause posterior displacement of meibomian gland orifices with trichiasis.<sup>17</sup>



**Fig. 4.26.1** Complete corneal vascularization and opacification in patient with previous alkali injury. (Courtesy Anthony J. Aldave, MD.)



TABLE 4.26.1 Roper-Hall Classification

Grade	Prognosis	Conjunctival Involvement	Corneal Involvement
I	Good	None	Epithelial damage
II	Good	Less than 33% limbal ischemia	Stromal haze present but iris details visible
III	Guarded	33%–50% limbal ischemia	Total epithelial loss, stromal haze obscures iris details
IV	Poor	Greater than 50% limbal ischemia	Cornea opaque, iris and pupil obscured

From Roper-Hall MJ. Thermal and chemical burns. *Trans Ophthalmol Soc UK* 1965;85:631–53.

After a chemical burn, breakdown of the blood–aqueous barrier may result in a severe fibrinous inflammatory reaction. Damage to the ciliary body epithelium can cause decreased secretion of ascorbate, resulting in impaired keratocyte collagen synthesis and deficient stromal repair because ascorbate is a cofactor in the rate-limiting step in collagen synthesis.<sup>25</sup>

Within 12–24 hours of injury, conjunctival necrosis and hydrolysis of cellular and extracellular proteins produce chemotactic inflammatory mediators that stimulate the infiltration of the peripheral cornea with neutrophils.<sup>1,17,26</sup> The neutrophils potentiate surface inflammation and release a variety of degradative enzymes such as *N*-acetylglucosaminidase and cathepsin-D.<sup>24</sup> Damage to the corneal stroma is mediated by the interaction among keratocytes, epithelial cells, and neutrophils. Stromal repair is marked by a balance between collagen synthesis and degradation.<sup>27</sup> Keratocytes are multipotent cells capable of producing new type I collagen as well as type I collagenase, a matrix metalloproteinase (MMP).<sup>28</sup> MMPs are enzymes that can degrade matrix macromolecules, such as collagen. The three major groups of MMPs include collagenases, gelatinases, and stromelysins.<sup>27</sup> Keratocyte activity may be regulated by cytokines from epithelial cells, inflammatory cells, and other keratocytes. A close interaction exists between keratocytes and the overlying epithelial cells; type I collagenase production by keratocytes is both stimulated and inhibited by epithelial cytokines.<sup>29,30</sup>

## CLINICAL COURSE

McCulley divided the course of chemical injury into four distinct phases: immediate, acute (0–7 days), early reparative (7–21 days), and late reparative (after 21 days).<sup>16</sup> Clinical findings immediately following chemical exposure can be used to assess the severity and prognosis of the injury. The Roper-Hall classification system (Table 4.26.1) provides a prognostic guideline based on corneal appearance and extent of limbal ischemia.<sup>7,31,32</sup> In grade I injury, there is corneal epithelial damage, no corneal opacity, no limbal ischemia, and a good prognosis. In grade II injury, the cornea is hazy but iris details are visible. Ischemia involves less than one third of the limbus, and the prognosis is good. In grade III injury, there is total epithelial loss, stromal haze obscuring iris details, and ischemia of one third to one half of the limbus, and the prognosis is guarded. In grade IV injury, the cornea is opaque with no view of the iris or pupil, the ischemia is greater than one half of the limbus, and the prognosis is poor.

In the acute phase during the first week, grade I injuries heal, whereas in grade II injuries, corneal clarity is recovered slowly. Grade III and IV injuries have little or no re-epithelization, with no collagenolysis or vascularization. IOP may be elevated as a result of inflammation and mechanical distortion of the trabecular meshwork or decreased because of ciliary body damage.<sup>33</sup> During the early reparative phase, re-epithelization is completed in grade II injury, with clearing of opacification. In more severe cases, delayed or arrested re-epithelization may occur. Keratocyte proliferation occurs with production of collagen and collagenase, resulting in progressive thinning and potential for perforation.<sup>33</sup>

In the late reparative phase, re-epithelization patterns divide injured eyes into two groups. In the first group, epithelization is complete or is nearly complete, with sparing of limbal stem cells. Corneal anesthesia, goblet cell and mucin abnormalities, and irregular epithelial basement membrane regeneration may persist. In the second group, limbal stem cell damage is present, resulting in corneal re-epithelization by conjunctival epithelium. This group has the worst prognosis with severe ocular surface damage characterized by vascularization and scarring, goblet cell and mucin deficiency, and recurrent or persistent erosions.<sup>33</sup> Ocular surface abnormalities may be exacerbated by symblepharon formation, cicatricial entropion, and trichiasis.<sup>19,23</sup> A fibrovascular pannus results if ulceration does not occur, compromising visual rehabilitation.

TABLE 4.26.2 Dua Classification

Grade	Prognosis	Limbal Involvement	Conjunctival Involvement	Analog Scale
I	Very good	0 clock hours (none)	0% (none)	0.0%
II	Good	Less than 3 clock hours	<30%	0.1–3/1–29.9%
III	Good	3–6 clock hours	>30%–50%	3.1–6/31–50%
IV	Good to guarded	6–9 clock hours	>50%–75%	6.1–9/51%–75%
V	Guarded to poor	9–<12 clock hours	>75%–<100%	9.1–11.9/75.1–99.9%
VI	Very poor	12 clock hours (total)	100% (total)	12/100%

From Dua HS, King AJ, Joseph A. A new classification of ocular surface burns. *Br J Ophthalmol* 2001;85:1379–83.

In 2001, Dua proposed a new classification system (Table 4.26.2) accounting for more recent advances in surgical treatment of ocular surface burns and the resultant limbal stem cell deficiency.<sup>34</sup> This system is based on clock hours of limbal involvement and percentage of total bulbar conjunctival involvement, and unlike the Roper-Hall classification system, is not based on the degree of corneal stromal haze.<sup>34,35</sup> The Dua classification system subdivides grade IV Roper-Hall injuries into three additional categories (grades IV, V, and VI) and provides more up-to-date prognostic information for the most severe ocular surface burns.<sup>34–37</sup> It also includes an analog scale, which allows for more nuanced and flexible recording of injury severity.<sup>37</sup>

## THERAPY

### Immediate Phase

Because the area and duration of contact determines the extent of subsequent injury and prognosis, immediate copious irrigation upon exposure is of paramount importance.<sup>12</sup> Irrigation should be continued for at least 15 minutes with at least 1 L of irrigant, until the pH of the ocular surface reaches neutrality. Currently available solutions include normal saline, borate-buffered saline, balanced salt solution, phosphate-buffered saline, lactated Ringer’s, and amphoteric solutions that aim to chelate acids and alkalis and create a reverse osmotic gradient to draw chemicals out of the cornea.<sup>12,38,39</sup> Some authors discourage the use of phosphate-buffered saline, which may lead to precipitation of calcium in the corneal stroma.<sup>39</sup> Borate-buffered saline and amphoteric solutions were found to be most effective in reducing aqueous humor pH after an alkali burn.<sup>38,39</sup> Normal saline and tap water were found to be intermediately effective, and phosphate buffered saline and lactated Ringer’s were found to have the least effective buffering capacity.<sup>39,40</sup> If access to commercial irrigating solutions is not immediately available, tap water should be used despite the fact that it is hypo-osmolar and may contribute to corneal edema.<sup>12</sup> If an acid burn is suspected, a base should never be used for irrigation in an effort to neutralize the acid. A retained reservoir of chemical in the fornices should be suspected if neutrality cannot be achieved, especially with exposure to lime, which can be embedded in the fornices and the upper tarsal conjunctiva.<sup>33</sup> Eversion of the lids and removal of particulate matter should be performed; a cotton-tipped applicator soaked in ethylenediaminetetraacetic acid 1% may help with the removal of stubborn lime particles.<sup>41</sup> Necrotic corneal and conjunctival tissues should be debrided to promote re-epithelization because this debris provides a stimulus for continued inflammation with recruitment of neutrophils and mucous membrane pemphigoid production.<sup>41</sup>

### Acute and Reparative Phases

After irrigation, all efforts should be made to promote epithelial wound healing, prevent infection, reduce inflammation, minimize ulceration, and control intraocular pressure. Topical antibiotics should be used if there is any corneal or conjunctival epithelial defect. Topical and systemic ocular hypotensive medications may be needed. Better outcomes can be expected with prompt re-epithelization, while delayed or absent re-epithelization may require surgical intervention. Bandage contact lenses or amniotic membrane transplantation may be used to promote epithelial healing.<sup>35,36</sup> Intensive topical corticosteroid therapy every 1–2 hours in the first 1–2 weeks decreases the inflammatory response that can delay epithelial migration, and thus helps enhance re-epithelization in the early phases of injury.<sup>7,42</sup> Corticosteroid use in the first 10 days of injury has no adverse effect on outcome with little risk of sterile ulceration.<sup>43</sup> Prolonged use of

corticosteroids, however, can be deleterious since corticosteroids can blunt stromal wound repair by decreasing keratocyte migration and collagen synthesis.<sup>44</sup> Beyond 2 weeks at the peak of the early reparative phase, suppression of keratocyte collagen production by continued use of corticosteroids may offset the benefits of inflammatory suppression and lead to stromal ulceration.<sup>44,45</sup> Corticosteroid use should, therefore, be stressed in the first 2 weeks with subsequent taper as dictated by clinical examination. Medroxyprogesterone 1% is a synthetic progestogenic corticosteroid that has weaker anti-inflammatory activity compared with corticosteroids. Medroxyprogesterone inhibits collagenase, but unlike corticosteroids, it minimally suppresses stromal wound repair.<sup>44</sup> As such, medroxyprogesterone can be substituted for corticosteroid after 10–14 days if worsening ulceration is of concern.

Topical ascorbate 10% drops every 2 hours, topical citrate 10% drops every 2 hours, and systemic ascorbate (2000 mg per day in divided doses) restore levels depleted from the aqueous following alkali injury.<sup>7</sup> Ascorbate is a cofactor in the rate-limiting step of collagen synthesis and has been shown to decrease the incidence of stromal ulceration.<sup>46</sup> Citrate is a calcium chelator that decreases intracellular calcium levels of neutrophils and thus impairs chemotaxis, phagocytosis, and release of lysosomal enzymes.<sup>47</sup> Applied topically, citrate has been shown to reduce corneal ulceration and perforation.<sup>48</sup> Tetracyclines have been shown to offer protection against collagenolytic degradation. Proposed mechanisms for inhibition of mucous membrane pemphigoid include suppression of neutrophil collagenase and epithelial gelatinase gene expression, inhibition of  $\alpha_1$ -antitrypsin degradation, and scavenging of reactive oxygen species.<sup>27</sup> Autologous serum tears may also be a useful adjunct medical therapy. Topical amniotic membrane suspension drops have been shown to speed epithelial healing in animal models.<sup>49</sup> Topical and subconjunctival bevacizumab as well as subconjunctival triamcinolone have been reported to decrease corneal neovascularization after alkali burns in animals.<sup>50,51</sup>

## Surgical Therapy

Surgical interventions that may help stabilize the ocular surface after severe chemical injury include tarsorrhaphy to promote epithelial healing, superficial keratectomy to remove localized corneal pannus from focal limbal stem cell deficiency, limbal stem cell transplantation for diffuse limbal stem cell deficiency, and amniotic membrane transplantation. Tenoplasty and amniotic membrane transplantation are additional strategies to aid epithelial healing. Tenoplasty attempts to re-establish vascularity to ischemic areas of the limbus and to promote re-epithelization.<sup>52</sup> In this procedure, all necrotic conjunctival and episcleral tissues are excised, Tenon's capsule is bluntly dissected, and the resultant flap with its preserved blood supply is advanced to the limbus. Limbal stem cell transplantation is covered in Chapter 4.30.

The amniotic membrane is the innermost layer of the placenta and consists of a stromal matrix, a thick basement membrane, and a single epithelial layer. Amniotic membrane transplantation (AMT) has been found to reduce proteolytic activity, increase goblet cell density, and down-regulate conjunctival and corneal fibroblasts.<sup>53–56</sup> These actions are beneficial in restoring the ocular surface, especially in Roper-Hall grades II and III chemical burns, and may be considered in the acute or reparative phases.<sup>56,57</sup> Success of AMT in the treatment of grade IV injury may be limited because of stem cell loss and ischemia; when used in conjunction with limbal stem cell transplantation, however, AMT may provide a substrate for stem cell proliferation and re-epithelization.<sup>53,57–60</sup> The amniotic membrane has been shown in some studies to promote more rapid corneal re-epithelization and to reduce ocular surface inflammation, vascularization, and scarring. Other studies, however, show similar epithelial healing times and similar long-term outcomes whether or not AMT was performed.<sup>36,61</sup> If surgical amniotic membrane placement in the operating

room is either not possible or impractical, a sutureless cryopreserved amniotic membrane patch is commercially available preloaded in a symblepharon ring and can be easily inserted in the office or at the bedside.<sup>62</sup> Freeze-dried amniotic membrane preparations also are available and can be placed on the cornea under a bandage contact lens.

Penetrating keratoplasty (PKP) and deep anterior lamellar keratoplasty (DALK) for visual rehabilitation after chemical injury can be fraught with complications. Prognosis is poor in the setting of glaucoma, hypotony, limbal stem cell dysfunction, conjunctival cicatrization, entropion, and trichiasis.<sup>19</sup> If intraocular complications are minimized in the setting of an optimized ocular surface and limited deep stromal vessels, PKP or DALK may be performed with favorable results. A large-diameter PKP with or without donor limbal tissue may be considered in the acute and chronic setting.<sup>63–65</sup> Corneal transplantation provides tectonic support in the event of an impending perforation, and the limbal stem cells of the donor address ocular surface issues.<sup>63,64</sup> Staged surgery with limbal stem cell transplantation followed by PKP at least 6 weeks later has been shown to significantly decrease the likelihood of corneal graft failure.<sup>66</sup> When it is not possible to rehabilitate the ocular surface adequately, keratoprosthesis surgery may be considered.

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# Corneal Surgery

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# 4.27

**Definition:** Corneal procedures performed to either restore vision or restore globe integrity.

## Key Features

- Careful preoperative preparation and planning are critical to success.
- Understand intraoperative and postoperative complications and management.

## Associated Feature

- Be alert to the signs and symptoms of graft rejection.

## KERATOPLASTY

### Introduction

The successful outcomes enjoyed by patients who undergo modern penetrating keratoplasty (PKP) and lamellar keratoplasty are the result of advances in technology and surgical techniques.

### Historical Review

Corneal grafting techniques were pioneered by ophthalmologists, such as Reisinger,<sup>1</sup> von Hippel,<sup>2</sup> and Elschmig.<sup>3</sup> Today keratoplasty is the most common and successful human transplantation procedure, with over 45 000 corneal transplantations performed in the United States each year.<sup>4</sup> The number of PKP decreased to less than 20 000 in the year 2014, and the number of endothelial keratoplasty (EKP) increased to over 25 000 in that same year.<sup>4</sup> Optical results have improved significantly as a consequence of advances in tissue selection and preservation, techniques, trephines, and management of postoperative astigmatism.

Lamellar grafts date back to 1886 when von Hippel<sup>2</sup> successfully performed the first lamellar grafting in a human. Lamellar techniques have revolutionized the treatment of corneal diseases by offering such advantages as faster visual recovery, less postoperative astigmatism, and decreased risk of suture-related complications compared with PKP. Because “selective keratoplasty” replaces only the diseased tissue, the risk of graft rejection is theoretically lower. EKP now has become the standard of care for endothelial diseases.

### Anesthesia

Corneal transplantation may be performed under cover of regional or general anesthesia, depending on patient preference and cooperation. Typically, local anesthesia entails peribulbar or retrobulbar injection of lidocaine 2%, bupivacaine 0.75%, and hyaluronidase. A lid block may be employed to prevent squeezing.

### Specific Techniques

#### Penetrating Keratoplasty

PKP involves full-thickness replacement of corneal tissue with a healthy donor graft.

#### Preoperative Evaluation and Diagnostic Approach

PKP may be used to provide tectonic support (as in corneal thinning or perforation) and to improve visual outcomes (as in the replacement of

an opaque or irregular cornea). Indications for PKP include keratoconus; previous graft failure or rejection; full-thickness or deep corneal scars; Fuchs’ endothelial dystrophy; pseudo-phakic or aphakic bullous keratopathy; chemical burn; corneal ulcer; corneal dystrophy and degeneration; herpetic keratitis; trauma; or any other causes of corneal decompensation. Conditions with primarily posterior pathologies, such as Fuchs’ endothelial dystrophy and pseudo-phakic or aphakic bullous keratopathy, now are commonly treated with EKP. The rate of success of PKP is excellent, but the long-term risk of graft rejection increases significantly with active or recurrent infection, inflammation, corneal neovascularization, previous graft rejection, and each subsequent penetrating graft.

It is important to perform a careful preoperative evaluation and have a thorough discussion with patients about the surgery, visual expectation, possible complications, and the long postoperative course. The recipient must be prepared for the lifelong care required. In general, important considerations for the preoperative evaluation for PKP are as follows:

- Visual potential must be evaluated.
- Ocular surface must be optimized before a planned PKP. Conditions that may affect the ocular surface include rosacea, dry eyes, blepharitis, trichiasis, exposure keratopathy, ectropion, and entropion.
- Intraocular pressure (IOP) must be controlled adequately prior to surgery.
- Ocular inflammation must be recognized and treated.
- Previous corneal diseases and vascularization must be considered. A history of herpetic keratitis significantly reduces the chance of graft success because of several factors, including recurrent disease in the graft, neovascularization, trabeculitis with increased IOP, and persistent inflammation that may induce rejection.

#### Donor Selection

The Eye Bank Association of America has developed a set of criteria for donor corneas.<sup>5,6</sup> Contraindications for the use of donor tissue for PKP include the following:

- Death as a result of an unknown cause.
- Central nervous system diseases, such as Creutzfeldt–Jakob disease, subacute sclerosing panencephalitis, rubella, Reye’s syndrome, rabies, meningitis, and infectious encephalitis.
- Systemic infections, such as human immunodeficiency virus (HIV) infection, hepatitis viruses B and C infection, septicemia, syphilis, Ebola, and infective endocarditis, as well as other relevant communicable diseases, such as West Nile virus, vaccinia virus, or Zika virus infections.
- Leukemia or actively disseminated lymphomas.
- History of melanoma with known metastatic disease.
- Eye diseases, such as retinoblastoma, malignant tumors of the anterior segment, and active ocular inflammation (e.g., uveitis, scleritis, retinitis, and choroiditis).
- Prior ocular surgery, including refractive procedures. (Eyes with previous laser photorefractive surgery may be used for tectonic grafts and posterior lamellar procedures, and pseudo-phakic eyes and eyes that have undergone glaucoma filtration surgery may be used if they meet endothelial criteria by specular microscopy.)
- Congenital or acquired anterior segment abnormalities, such as corneal scars, keratoconus or Fuchs’ endothelial dystrophy, or associated conditions, such as Down syndrome (for penetrating or anterior lamellar keratoplasty).

Prior to PKP, the donor’s history and blood must be evaluated for communicable diseases, and donor tissues are inspected by the surgeon with the slit lamp.

### Surgical Techniques

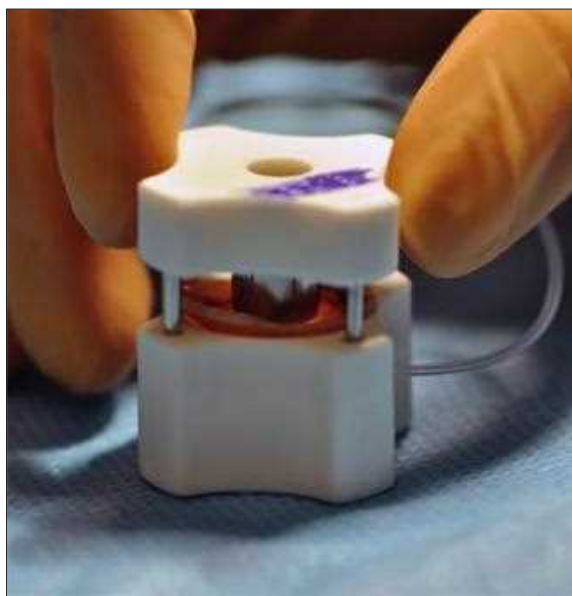
Adequate decompression of the globe is ensured prior to PKP because excessive preoperative IOP may increase the risk of expulsive choroidal hemorrhage. Intravenous mannitol or mechanical ocular decompression can be considered to reduce IOP. Miotics are placed preoperatively to protect the lens during surgery unless lenticular surgery also is planned. Scleral supporting (Flieringa) rings may be used principally in aphakic eyes or young patients.

The size of the graft is determined on the basis of the location of the pathology and on clinical judgment. The donor tissue usually is 0.25 mm larger in diameter compared with the recipient tissue. In certain circumstances, a larger (0.5 mm) donor may be considered in an aphakic eye to induce myopia, or a same-size donor button, such as in a recipient with keratoconus, may be chosen to reduce myopia. The visual axis of the recipient cornea is marked with a marking pen. An inked radial keratotomy marker may be used to mark the peripheral cornea. A donor corneal button is punched. In the United States, the most commonly used trephine is the Barron Donor Cornea Punch (Fig. 4.27.1). The donor is cut from endothelium to the epithelium. The donor also may be cut from the epithelium to the endothelium by using an artificial anterior chamber and then by using the same technique described for the recipient cornea. This has the theoretical advantage of both the donor and the recipient being cut in the same fashion with the same type of blade, which reduces donor–recipient disparity and potentially reduces astigmatism.

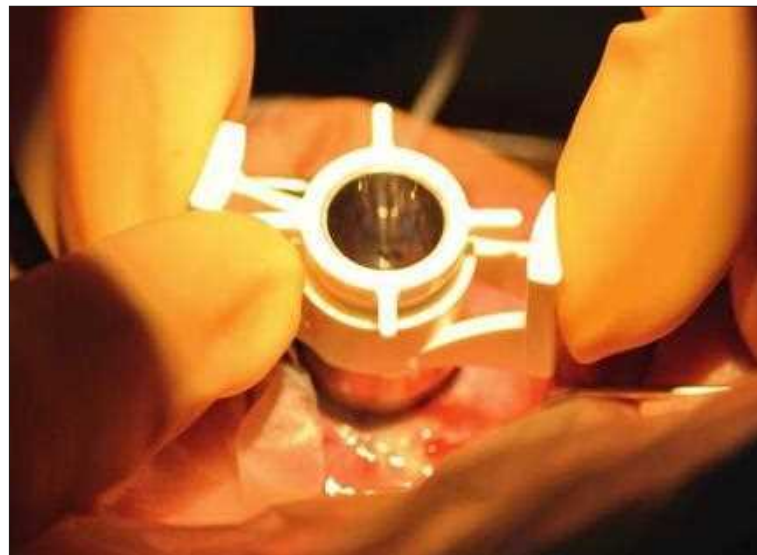
The recipient cornea may be cut using a variety of trephines, such as the Hessburg–Barron suction trephine (Fig. 4.27.2), Hanna trephine, or Castroviejo trephine. More recently, the use of the femtosecond laser to cut the recipient cornea has been described.<sup>7</sup> Excision of the host corneal button may be performed via partial-thickness trephination followed by a controlled entry into the anterior chamber using a No. 75 blade, or via a continued trephination that is stopped as soon as aqueous egress shows the anterior chamber has been entered. If viscoelastic was not placed into

the anterior chamber prior to host trephination, it may be placed to protect intraocular structures. The recipient button is then excised using forceps and corneal scissors (Fig. 4.27.3). The edge of the recipient bed is made perpendicular for optimal graft–host apposition.

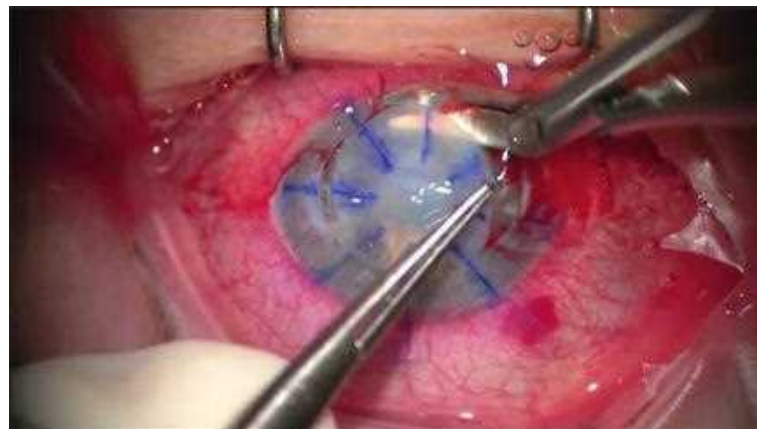
If the patient requires concurrent cataract extraction, intraocular lens (IOL) explantation, iridectomy, anterior vitrectomy, or a secondary IOL, this may be done prior to trephination if visualization allows. Because the diseased cornea precludes adequate visualization in many cases, an “open sky” technique is utilized after trephination (Fig. 4.27.4). In cases of emergent grafting, such as in the setting of an active infectious process, uncontrolled inflammatory disease, or a recent perforation, an iridectomy is performed to avoid pupillary block.



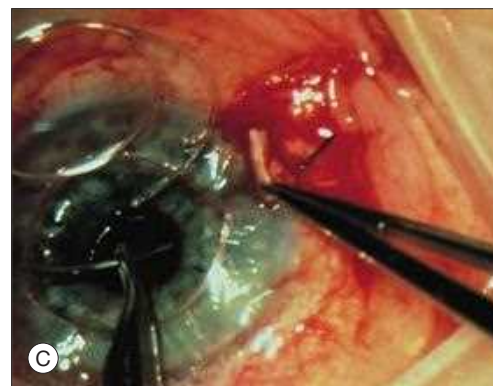
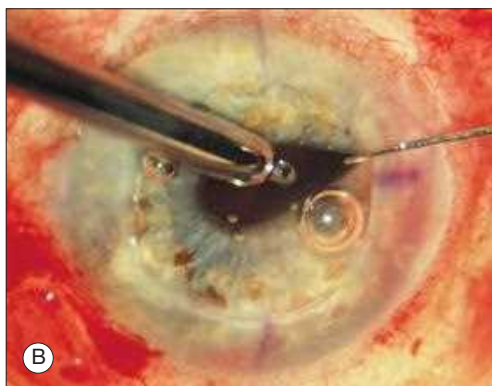
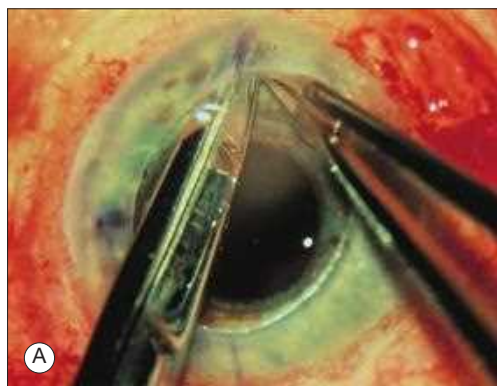
**Fig. 4.27.1 The Corneal Donor Button Is Cut.** A Barron donor cornea punch may be used to cut the donor tissue from the endothelial side.



**Fig. 4.27.2 Hessburg–Barron Vacuum Trephine.** A vacuum corneal trephine may be used to trephinate into the host cornea.

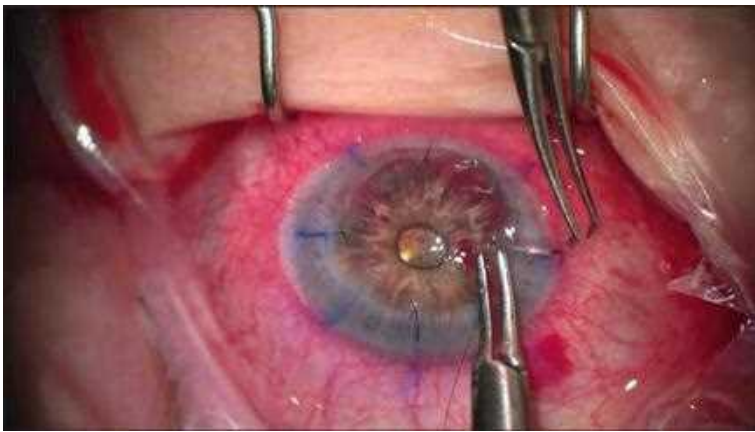


**Fig. 4.27.3 Excision of the Corneal Button.** The corneal button is removed completely using corneal scissors.

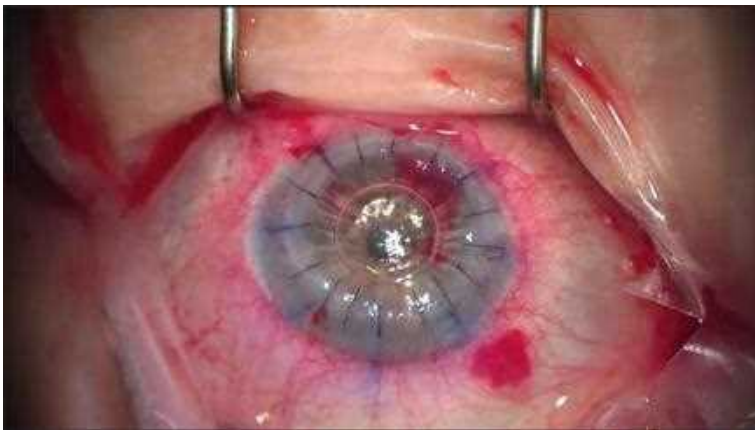


**Fig. 4.27.4 Replacement of Anterior Chamber Intraocular Lens.** (A) Care is taken when the anterior chamber haptics are removed, as they may become encysted in the peripheral iris and bleeding may occur on removal. (B) An anterior vitrectomy is performed—an iris hook may be used to improve visualization. (C) A 10-0 Prolene suture is passed beneath the iris, through the scleral sulcus and out through the previously prepared scleral flap. After the suture-supported lens is placed in the sulcus, the suture is tied to itself beneath the scleral flap. Alternatively, the knot may be rotated beneath the sclera. This is performed on both sides. (Courtesy Dr. W. W. Culbertson.)





**Fig. 4.27.5 The Corneal Button Is Placed.** Care is taken in the placement of cardinal sutures to ensure appropriate distribution.



**Fig. 4.27.6** Placement of 10-0 nylon interrupted sutures in a corneal transplant.

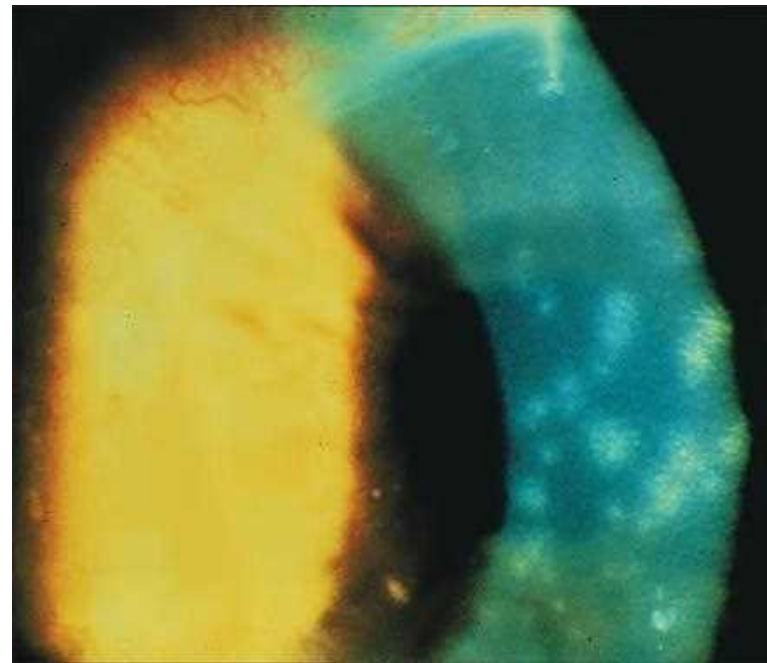
Viscoelastic may be placed in the anterior chamber, and the donor button then is placed over the recipient bed and sutured in place with four cardinal sutures (Fig. 4.27.5). Care is taken in the placement of the cardinal sutures, as proper tissue distribution is paramount. The depth of suture is 90% of the corneal thickness. The remaining sutures may be a combination of interrupted and running sutures or solely interrupted sutures (Fig. 4.27.6). Interrupted sutures are suited for vascularized or thinned cornea, as subsequent selective removal may be necessary to prevent the advancement of vessels or to control astigmatism. Running sutures have the advantage of speedy placement intraoperatively and better tension distribution but are more difficult to adjust. Prior to the placement of the final sutures, the viscoelastic material in the anterior chamber is removed. The running sutures may be adjusted intraoperatively by using a keratoscope. When the suturing is complete, all sutures are rotated such that the knots are buried within the stroma, and the security of the wound is tested for water tightness by using a combination of a surgical sponge and fluorescein.

### Complications and Postoperative Management

Intraoperative complications include poor graft centration, bleeding, damage to ocular structures (e.g., donor endothelium, iris, lens, or lens capsule), or expulsive suprachoroidal hemorrhage. During excision of the recipient button, it is imperative to continuously monitor the depth of the anterior chamber and the red reflex. A sudden shallowing of the anterior chamber or disappearance of the red reflex may signify an impending expulsive choroidal hemorrhage. Sealing of the globe can be accomplished quickly by a gloved finger over a partially excised host cornea or with placement of a donor cornea or temporary keratoprosthesis. The key management strategy is to close and repressurize the globe.

The success of PKP depends significantly on adequate postoperative care and management. The surgeon must be able to recognize and manage a variety of possible complications, such as wound leak, infection, glaucoma, and graft rejection or failure. The common postoperative complications and their management are discussed in the following subsections.

**Wound Leak.** A shallow anterior chamber in a soft globe the day after PKP may indicate a wound leak, which may need patching, aqueous



**Fig. 4.27.7** Subepithelial infiltrates secondary to subepithelial graft rejection. (Courtesy Dr. W. W. Culbertson.)

suppressant, lubrication, or bandage contact lenses. Resuturing of the wound may be required if the leak is significant.

**Flat Anterior Chamber With Increased Intraocular Pressure.** Flat anterior chamber with increased IOP may result from pupillary block, anterior rotation of the lens–iris diaphragm (as found in choroidal hemorrhage), choroidal effusion, or aqueous misdirection. The cause must be identified and treated.

**Endophthalmitis.** Postoperative endophthalmitis, a devastating complication, may result from a variety of factors, including contamination of donor tissue, prior infection in the host, or postoperative infection acquired through a wound leak.

**Persistent Epithelial Defect.** Epithelial defects that persist beyond 1–2 weeks occur more commonly in eyes that have ocular surface disorders, such as limbal stem cell deficiency, neurotrophic keratopathy, dry eye disease (DED), blepharitis, exposure keratopathy, and rosacea. Treatment includes frequent lubrication with preservative-free drops and lubricating ointment. Possible causes of ocular surface toxicity, such as topical eyedrops, must be eliminated or minimized. If the defect does not heal, ophthalmic blood derivatives, a tarsorrhaphy, or punctal occlusion may be necessary.

**Primary Graft Failure.** Primary graft failure (which is different from graft rejection) is recognized when significant edema of the donor tissue in a noninflamed eye is present on the first postoperative day and does not clear by 2–4 weeks. Primary graft failure may be attributed to either poor donor endothelial function or iatrogenic damage to the donor tissue during PKP. The graft is observed for several weeks. Graft failure should be differentiated from Descemet's membrane detachment. A regrant (either repeat PKP or EKP) is considered if the corneal edema fails to resolve.

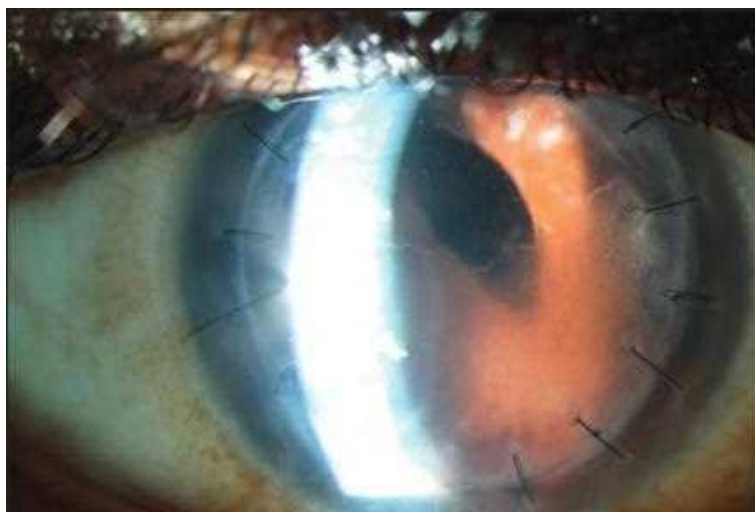
**Suture-Related Problems.** Loose or broken sutures must be removed to prevent associated infection or neovascularization, which can increase the likelihood of rejection.

**Graft Rejection.** Graft rejection remains the most common cause of graft failure. The overall incidence of endothelial graft rejection has been reported as 20%.<sup>8</sup> Symptoms include decreased vision, redness, photophobia, and pain; however, patients may experience as few as one or even none of these symptoms. Patients must be educated carefully about these symptoms and must be instructed to seek medical attention immediately should they occur.

Graft rejection may be divided anatomically into three categories:

- **Epithelial rejection**—may be recognized by observation of an epithelial line. This is seen early before the host epithelium replaces the donor epithelium.
- **Subepithelial rejection**—multiple subepithelial infiltrates limited to the corneal graft may be observed (Fig. 4.27.7).
- **Endothelial rejection** (the most severe type of rejection)—characterized by keratic precipitates, iritis, and corneal edema. A Khodadoust line





**Fig. 4.27.8 Graft Rejection.** Note the inflammatory precipitates and Khodadoust line secondary to endothelial rejection. (Courtesy Dr. A. Galor.)

may be seen, which represents the advancing front of the host's inflammatory cells against a receding front of donor endothelium (Fig. 4.27.8).

The treatment of graft rejection consists primarily of corticosteroids, usually in topical form. The frequency of the corticosteroid drops is increased to hourly or even more often in the case of endothelial graft rejection until the process is reversed. Subconjunctival or Subtenon's injection of corticosteroids may be used. Systemic corticosteroids (oral or intravenous) also may be utilized in severe cases. For patients with a history of multiple rejection episodes either in the current cornea or previous grafts, systemic immunomodulatory therapy may be considered.

**Treatment for Astigmatism.** Adequate control of postoperative astigmatism is vital to achieving the best-corrected visual acuity possible. Typically starting at 8–12 weeks after PKP, the patient is followed using serial corneal topography. Subsequently, interrupted sutures are removed selectively, and running sutures are adjusted, as necessary to reduce astigmatism.<sup>9</sup> Early suture removal may have a more significant effect on astigmatism, although care is required with regard to wound stability.

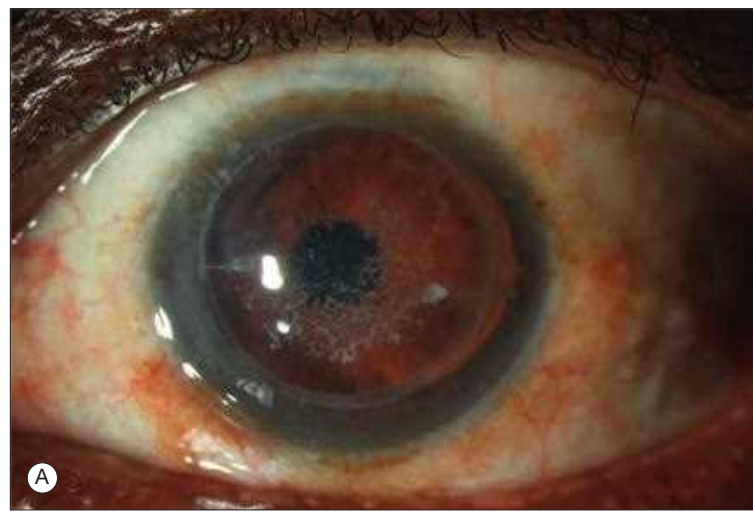
**Corneal Ulcers.** Patients who have undergone PKP are more susceptible to infectious keratitis. Such factors as loose sutures and persistent epithelial defects may contribute to the development of corneal ulcers.

**Recurrence of Diseases.** Various corneal dystrophies and infections may recur in grafts. Among the three most common stromal corneal dystrophies [macular, granular (Fig. 4.27.9), and lattice], lattice corneal dystrophy has the highest recurrence. In the setting of keratic precipitates on a graft in a patient who has a history of herpes simplex virus infection, it is sometimes difficult to distinguish recurrence of a disease from graft rejection. It is important, however, to make such a distinction as the treatment for a recurrence of herpes simplex virus (antiviral agent  $\pm$  corticosteroid) is different from treatment for rejection (corticosteroid alone). The observation of keratic precipitates and corneal edema confined only to the donor button may suggest graft rejection. Anterior chamber paracentesis and polymerase chain reaction analysis can aid in the diagnosis.

### Anterior Lamellar Keratoplasty

A concept that has gained popularity in the treatment of corneal disease is the selective removal of only the diseased tissue. Lamellar keratoplasty is a procedure in which a partial-thickness graft of donor tissue is used to provide tectonic stability or optical improvement.<sup>10</sup> A partial-thickness section of donor stroma or sclera may be used. Two types of lamellar keratoplasty exist: anterior lamellar keratoplasty (ALK) and posterior lamellar keratoplasty (also referred to as *endothelial keratoplasty*) (see Chapter 4.29).

In ALK, the transplanted tissue does not include corneal endothelium, thus avoiding endothelial rejection and allowing donor tissue to be obtained from older eyes. Indications for ALK mainly include anterior corneal pathology in which the posterior cornea is unaffected, such as keratoconus, anterior corneal scars, and corneal dystrophies limited to the stroma. Femtosecond lasers can aid in this procedure.<sup>11,12</sup> A subtype of ALK is deep anterior lamellar keratoplasty (DALK), in which the objective is to eliminate all of the host stromal tissue; this can be achieved through the use of manual dissection,<sup>13</sup> viscoelastic, or an air bubble,<sup>14</sup> to dissect the host's stromal–Descemet's membrane interface.



**Fig. 4.27.9 Recurrence of Granular Dystrophy in a Graft.** (A) Slit-lamp photograph of a granular dystrophy recurrence in a penetrating keratoplasty graft. (B) Anterior segment optical coherence tomography (AS-OCT) image of recurrence showing location on Bowman's layer. (Courtesy Dr. C. Karp.)

### Preoperative Evaluation and Diagnostic Approach

A tectonic graft is performed to reinforce areas of perforated or thinned cornea. Optical lamellar grafts are used to replace diseased anterior cornea to improve visual function and require that the posterior stroma of the recipient is healthy.

The rationale for a lamellar keratoplasty and the various surgical options must be thoroughly discussed with patients. Different modalities can be used to assess the depth of a scar, the adequacy of the planned remnant stromal bed, and the severity of endothelial disease, including topography, anterior segment optical coherence tomography (AS-OCT), and specular microscopy.

### Donor Selection

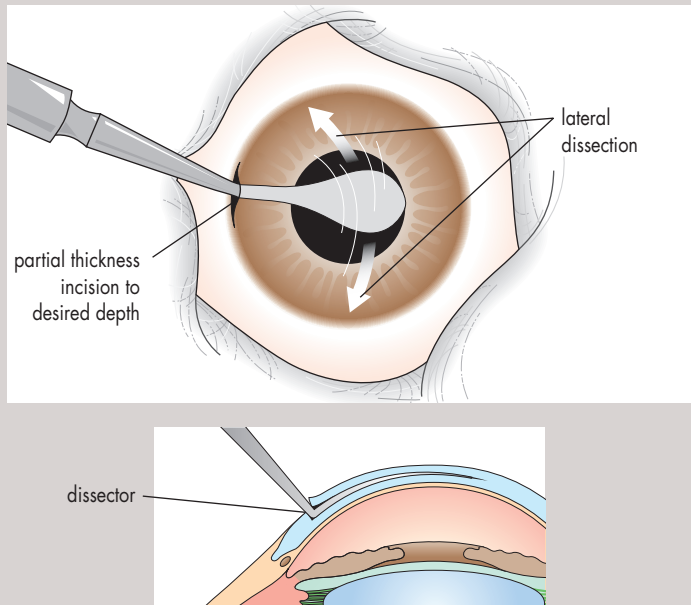
**Donor Preparation.** Criteria for donor tissue selection and screening are the same as those listed for PKP except that tissue with local eye disease affecting the corneal endothelium or previous ocular surgery that does not compromise the corneal stroma (e.g., a history of endothelial dystrophy or iritis) are acceptable.<sup>5</sup>

In ALK, a fresh or frozen whole donor eye or a corneoscleral donor and artificial anterior chamber may be used to fashion the anterior lamellar donor tissue. When done manually, an incision is made just inside the limbus of the donor cornea to reach the depth of the desired dissection. A Martinez dissector or a cyclodialysis spatula is used to extend the dissection plane within the corneal stroma and harvest the donor tissue (Fig. 4.27.10). The tissue harvested may be circular, annular, or any other shape, depending on the needs of the patient (Fig. 4.27.11). Both the cornea and the sclera may be used. Usually, the donor tissue is slightly oversized (0.25–0.5 mm) in width and thickness compared with the recipient bed.<sup>15,16</sup> Donor tissue suitable for PKP should be available in case of a large perforation that may occur in the lamellar dissection of the host tissue. Newer microkeratomes allow for more efficient host and donor dissection. In particular, the femtosecond laser has been helpful in performing lamellar keratoplasty.<sup>11</sup>

### Surgical Techniques

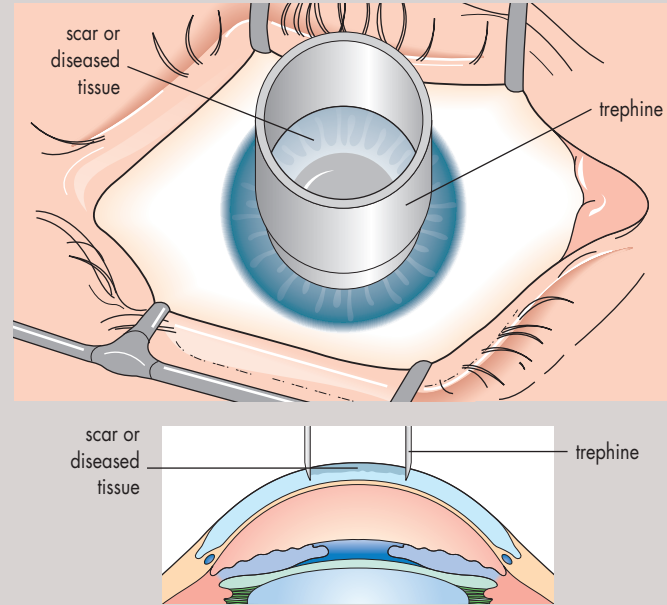
**Anterior Lamellar Dissection of the Host Tissue.** A measurement of the affected area is done, and this can be facilitated by OCT preoperatively. A trephine is used gently to mark the extent of graft needed. The surgeon may opt for a manual dissection of the host stroma or air-assisted dissection using the “big bubble” technique, as described by Anwar.<sup>17</sup> Irrespective of the technique chosen, the goal is to create a smooth, uniplanar recipient bed. Elimination of most or all of the host stroma will lead to better final

## SEPARATION OF CADAVERIC CORNEA



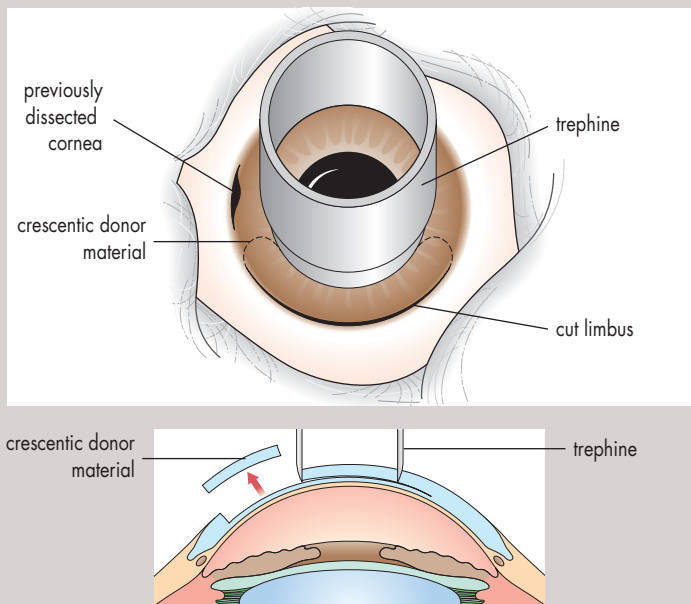
**Fig. 4.27.10 Separation of the Cadaveric Cornea.** A dissector, such as the Martinez dissector or a cyclodialysis spatula, is used to gently separate the cornea along the lamellar cleavage plane through the entire cornea.

## PARTIAL-THICKNESS TREPHINATION



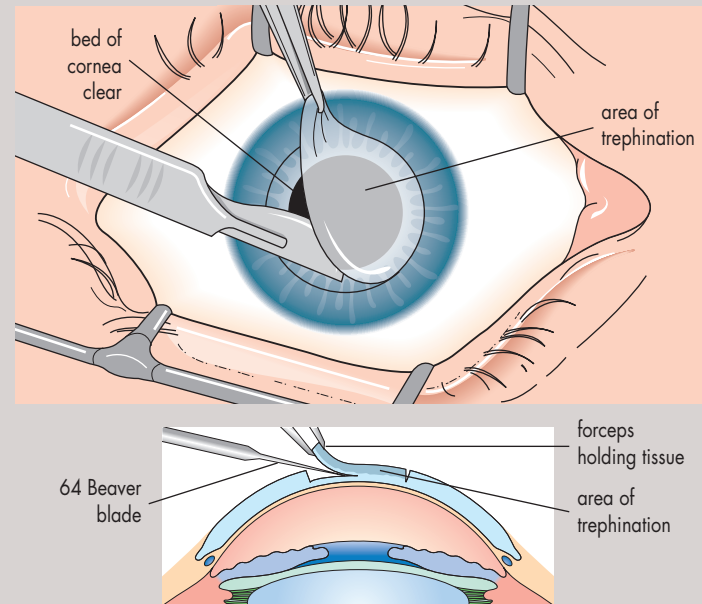
**Fig. 4.27.12 Partial-Thickness Trephination.** This is performed on the host in the desired location and to the desired depth. Care must be taken not to perforate the cornea.

## HORSESHOE OR ANNULAR LAMELLAR GRAFT



**Fig. 4.27.11 Donor Tissue Is Harvested.** A trephine is placed on the cadaveric globe in the size and shape desired. A horseshoe or annular lamellar graft is being harvested here. A combination of corneal and scleral tissue may be harvested to give a different tissue shape.

## DISSECTION OF DISEASED AREA



**Fig. 4.27.13 Dissection of the Diseased Area.** The diseased area in the host cornea is dissected gently to create a uniplanar, disease-free bed.

visual outcomes by eliminating stroma-to-stroma interface. If Descemet's membrane is violated, the procedure is then converted to a PKP, although conversion may be avoided in the setting of small perforations.

If a manual dissection is chosen, a partial-thickness trephination is performed until the desired depth of dissection is reached (Fig. 4.27.12). Alternatively, a microkeratome or femtosecond laser may be used for the host.<sup>11</sup> A blade is then used to extend the dissection plane along the entire host corneal tissue until the dissection of the host tissue is completed (Fig. 4.27.13). In manual ALK, the edge of the host bed should be undermined to create a horizontal groove using a Paufigue knife.<sup>16</sup> The donor lamella is placed on the recipient bed and secured with interrupted 10-0 nylon sutures (Fig. 4.27.14). The depth of the suture is about 90% of the corneal

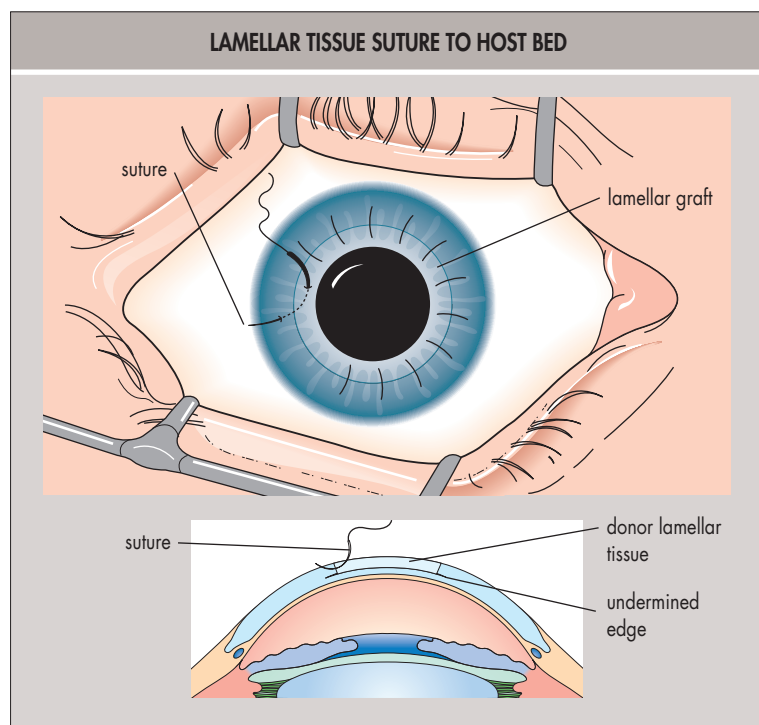
stromal depth. The donor tissue margins should not ride anteriorly to the rim of the recipient bed. At times, an anterior chamber paracentesis may become necessary before lamellar sutures are placed. ALK may be performed centrally or in the periphery for corneoscleral melts (Figs. 4.27.15 and 4.27.16).

In DALK, a deep anterior lamellar disc is trephined to about 80% total depth, or the femtosecond laser can be used for this part of the procedure.<sup>12</sup> A paracentesis can be done at this point to inject a small air bubble in the eye to improve visualization of the big bubble because it will push it to the periphery of the anterior chamber; a mild decrease in anterior chamber pressure will also decrease resistance to the big bubble. Some surgeons advocate debulking of the anterior half of the stroma before proceeding with air dissection, whereas others proceed directly with a 27-gauge needle or cannula (previously having created a track with a dissector) to the center



of the cornea (Fig. 4.27.17). Using a 5-cc syringe, air is applied firmly to create a bubble. Two types of bubbles have been described. A type 1 bubble occurs when the stroma is dissected at the level of pre-Descemet's layer; this yields a smaller bubble with greater structural integrity (higher bursting pressure). A type 2 bubble occurs when the cleavage happens between Descemet's and pre-Descemet's layers, producing a larger bubble with a thinner wall and a lower bursting pressure.

Viscoelastic material may then be injected into the space created by the air bubble to facilitate further separation of the layers. The deep stromal layers are excised, usually in quadrants (see Fig. 4.27.17). The intraoperative OCT can aid in determining dissection depth.<sup>18</sup> All viscoelastic material is removed to avoid a dual anterior chamber. A donor button, the same size as the trephination, is then placed after the removal of Descemet's membrane and the endothelium and secured using 10-0 nylon sutures.



**Fig. 4.27.14 The Lamellar Tissue Is Sutured to the Host Bed.** Suture placement is facilitated if the edge of the host bed is undermined. Traditionally, the graft is sutured with 10-0 nylon.

In femtosecond-assisted lamellar keratoplasty (FALK), the donor and recipient are cut with the femtosecond laser, and the donor lenticule can be placed without sutures on the recipient bed (Fig. 4.27.18). Only a bandage contact lens is used in cases when the residual stromal bed is thicker than 250 microns.<sup>11</sup>

### Complications and Postoperative Management

In general, anterior lamellar grafts can be very successful (see Figs. 4.27.15 and 4.27.16). Complications of ALK are less frequent or less severe in nature compared with those of PKP. Complications of lamellar graft include perforation of the recipient cornea, interface scarring and vascularization, persistent epithelial defect, inflammatory necrosis of the graft and graft melting, infection, astigmatism, and allograft rejection. Careful irrigation and cleaning of the host bed may reduce the incidence of complications. ALK has a significantly reduced incidence of allograft rejection because no transplantation of foreign endothelium is involved.

**Perforation of Descemet's Membrane.** This is a relatively common event early in the surgical learning curve. In small perforations, the case can proceed as planned, but the surgeon should leave a gas bubble (air or SF<sub>6</sub> 20%) in the eye to ensure that Descemet's membrane remains attached to the stroma. In larger perforations, a combination of gas and a pass-through suture may be necessary to anchor Descemet's membrane and avoid its retraction. In larger breaks, conversion to PKP may be required.

**Pseudo-Anterior Chamber.** A double anterior chamber may occur when an unrecognized Descemet's tear occurs, such as during suturing of the donor graft. Moreover, viscoelastic material has been implicated in certain cases. The dual chamber may resolve spontaneously, but most surgeons inject air or SF<sub>6</sub> 20% in the early postoperative period to enhance recovery times and potential endothelial cell loss.

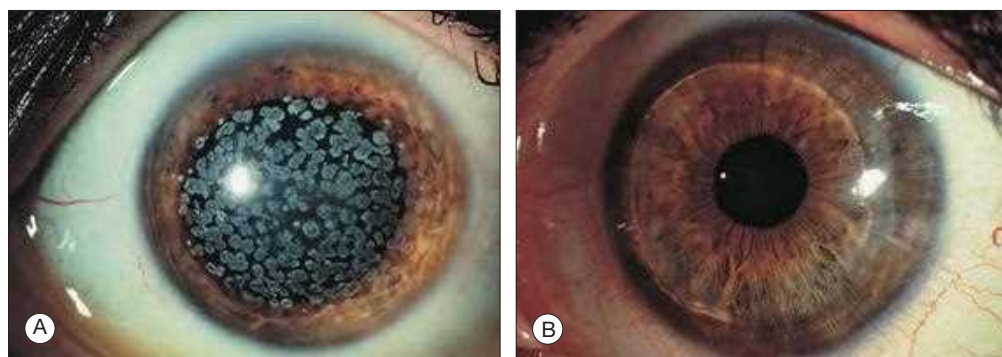
### Triple Procedure (Combined Procedure)

A *triple procedure* or *combined procedure* refers to keratoplasty, combined with cataract extraction and IOL implantation.

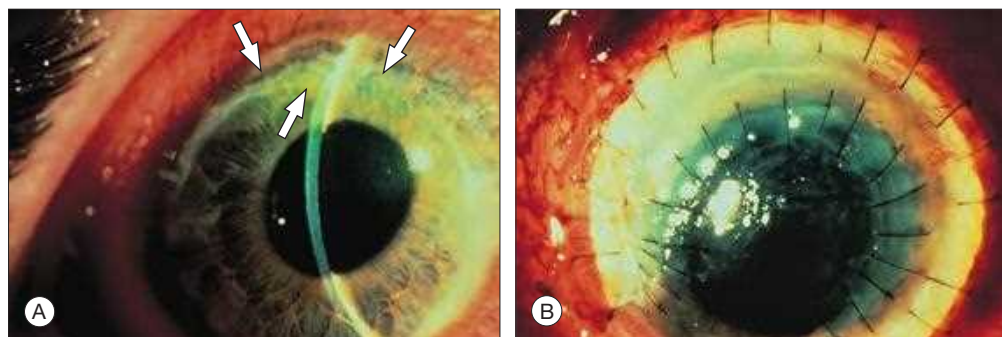
### Preoperative Evaluation and Diagnostic Approach

The triple procedure is indicated for patients with a visually significant cataract who also require corneal transplantation for visual rehabilitation. Triple procedures are increasingly being performed with the use of the DSAEK or DMEK technique for patients with endothelial disease. If visualization permits, cataract extraction may be performed in a closed system by using standard phacoemulsification techniques. The leading indication for a triple procedure is Fuchs' endothelial dystrophy and cataract, which accounts for up to 77% of eyes that require a triple procedure.<sup>19-21</sup>

Compared with PKP, a combined procedure requires the additional calculation of the power of the IOL. Different formulas, such as the Holladay or the Sanders-Retzlaff-Kraff formula (Eq. 4.27.1),<sup>22</sup> in which A is the

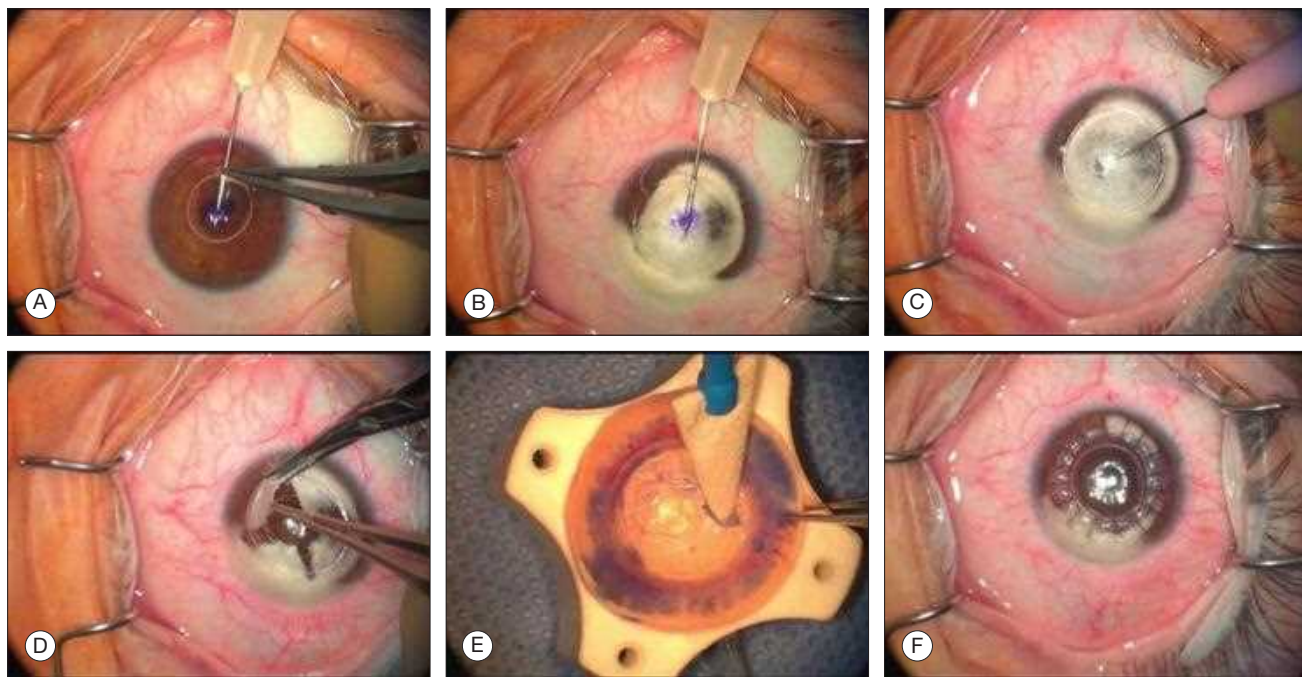


**Fig. 4.27.15 Lamellar Keratoplasty for Granular Dystrophy.** (A) Preoperative appearance of a patient who had granular dystrophy limited to the anterior cornea. (B) Postoperative appearance following manual lamellar keratoplasty. (Courtesy Dr W. W. Culbertson.)

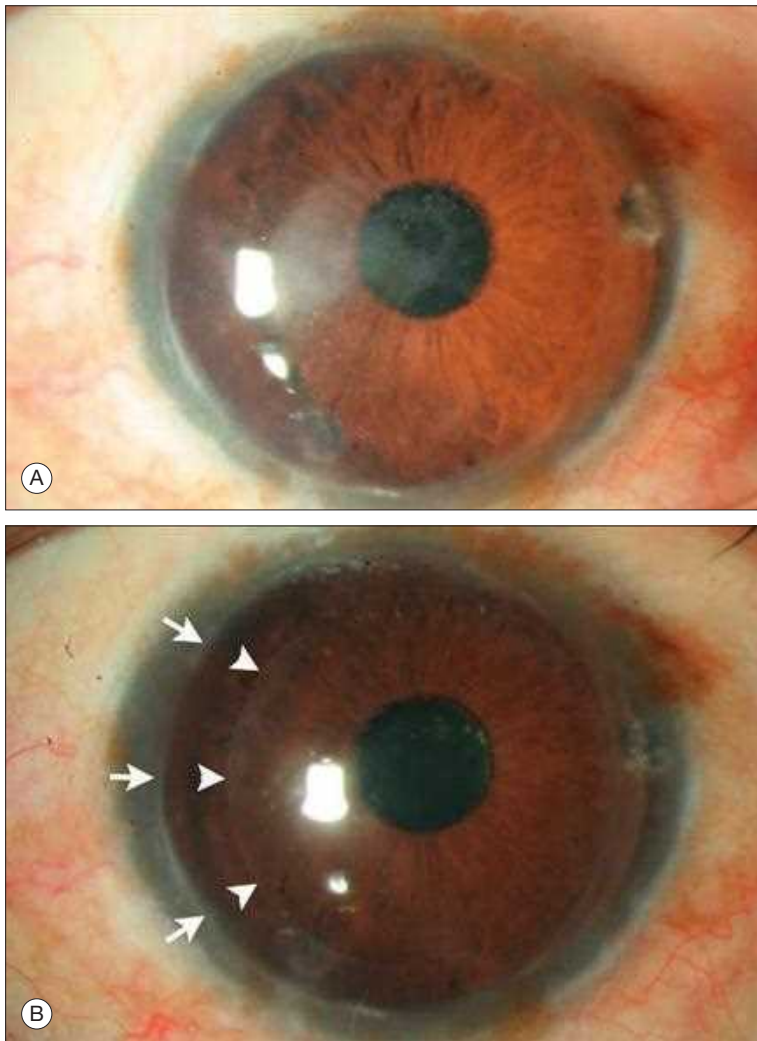


**Fig. 4.27.16 Lamellar Keratoplasty for Peripheral Corneal Melt and Perforation.** (A) Preoperative appearance of a patient who had a peripheral corneal melt and perforation (see arrows). (B) Postoperative appearance after the placement of a horseshoe corneoscleral lamellar graft. (Courtesy Dr W. W. Culbertson.)





**Fig. 4.27.17 Deep Anterior Lamellar Keratoplasty (DALK).** (A) After 80% trephination the 30-gauge needle is advanced until it reaches the center of the cornea. (B) Air is released firmly and steadily forming a big bubble, in this case a type 1 bubble was formed. (C) A “brave slash” is performed to access the bubble. (D) Dissection of the anterior lamella is performed until Descemet’s membrane is exposed. (E) The endothelium is removed from the donor cornea, then the donor cap is sutured to the host. (F) Final result. (Courtesy Dr. F. A. Valenzuela.)



**Fig. 4.27.18 Femtosecond-Assisted Lamellar Keratoplasty (FALK).** (A) Residual granular dystrophy and central corneal scar seen in a patient after corneal transplantation. When the dystrophy recurred, phototherapeutic keratectomy (PTK) had been performed on the PTK, which eliminated some of the granular deposits but caused some corneal haze. (B) After FALK—FALK was performed to remove the corneal haze and residual anterior granular deposits. FALK (arrowheads) was centered over the visual axis, not over the corneal graft (arrows). (Courtesy Dr. C. L. Karp.)

constant for an IOL,  $AL$  is the axial length, and  $K$  is the keratometric measurement. The determination of  $K$  varies from surgeon to surgeon. The authors typically advocate one of two alternative approaches, using either the average of the surgeon’s past postoperative keratometric readings associated with the surgical technique or the  $K$  readings from the contralateral eye. In the instances in which an over- or undersized graft is required,  $+1.00$ – $+2.00$  diopters (D) is subtracted from the IOL power for a 0.5-mm oversized graft or  $+1.00$ – $+2.00$  D is added to the IOL power for 0.5-mm undersizing.<sup>16</sup> Postoperative refractive targets must be adjusted in DSAEK or DMEK triple procedures, as there may be a hyperopic shift associated with these procedures.<sup>23</sup>

$$\text{IOL power} = A - 2.5AL - 0.9K \quad [\text{Equation 4.27.1}]$$

### Surgical Techniques

**Open Sky Cataract Extraction.** The detailed surgical technique for PKP is described above. Prior to the trephination of the recipient cornea, trypan blue may be considered for visual augmentation of the capsulotomy. After the recipient button has been excised, a capsulorrhexis, sufficiently large to allow subsequent expression of the lens nucleus, is performed. Caution is maintained during the capsulorrhexis because there is a tendency for the capsulotomy to extend peripherally, especially with increased posterior pressure.

After hydrodissection and mobilization of the lens nucleus, the lens is gently expressed. The remaining cortical material is removed carefully using an automated irrigation–aspiration instrument or a manual I/A, as the anterior and posterior capsules tend to collapse toward each other. The capsular bag is then inflated with viscoelastic material, and the appropriate posterior chamber IOL is inserted. The authors of this chapter prefer a rigid or a three-piece IOL in this scenario for increased stability because of anterior chamber fluctuations. If a posterior capsular tear and anterior prolapse of vitreous occur, a limited anterior vitrectomy is performed, and the IOL is inserted either into the ciliary sulcus and sutured to the iris or sclera or an open-loop anterior chamber IOL may be used. The remainder of the procedure for PKP is the same as described previously.

### Artificial Cornea (Keratoprosthesis)

Keratoprosthesis implantation is performed in patients in whom corneal transplantation is considered high risk, with a very high likelihood of graft failure, such as those with a history of multiple graft failures or deep neovascularization of the cornea.

#### Boston K-Pro

The Boston Keratoprosthesis (K-Pro) (formerly known as the *Dohlman–Doane Kpro*) has been under development since the 1960s. It received Food and Drug Administration (FDA) approval for commercialization in 1992. It is the most commonly used keratoprosthesis in the world.<sup>23</sup> The

keratoprosthesis is made of clear polymethyl methacrylate (PMMA) plastic and has two pieces that take the shape of a collar button. The device is inserted into a corneal graft, which is then transplanted into the recipient's cloudy cornea. There are two types of the Boston K-Pro: (1) type I, available in phakic and pseudo-phakic versions, is used in patients with an adequate ocular surface, and (2) type II, which is placed through the lids in patients with severe ocular surface disease.

### AlphaCor

The AlphaCor implant, approved by the FDA in 2003, is made of a flexible hydrogel material similar to a soft contact lens. It contains a central clear zone that provides refractive power and a peripheral skirt or rim made of a special material that encourages the eye to heal over the device. The device is available in two powers: one for aphakic and one for phakic patients. The two-stage surgery involves the initial implantation of the AlphaCor device into the cornea of the recipient and the creation of a protective conjunctival flap over the prosthesis. The subsequent removal of the flap allows light to pass through the central clear zone to restore vision.<sup>24</sup>

A retroprosthetic membrane can occur following implantation of any artificial cornea and can be removed by using a YAG (neodymium-doped yttrium aluminum garnet) laser, unless highly vascular. Migration of the AlphaCor under the lamellar flap can occur.

### Modified Osteo-Odonto-Keratoprosthesis

The osteo-odonto-keratoprosthesis (OOKP) was first described in Italy and documented in 1963 by Benedetto Strampelli and later modified by Giancarlo Falcinelli et al. for the treatment of bilateral corneal blindness in patients with end-stage ocular surface disorders. Falcinelli's group has completed more than 220 cases, with an anatomical success rate of 94% and a mean follow-up of 9.4 years.<sup>25</sup> The first modified OOKP (MOOKP) was performed in the United States in 2009.

The newer MOOKP consists of a cylindrical PMMA lens embedded within the patient's own tissue (heterotopic autograft of the patient's tooth root and alveolar bone). The complete implantation is a three-stage procedure. Initially, the lens, iris, and vitreous are removed from the eye. A portion of the tooth (preferably canine), bone, and periodontal complex is concurrently resected, typically with the assistance of an oral maxillofacial surgeon, and shaped into a thin rectangular lamina. Some surgeons advocate the procurement of the bone lamina from the tibia. The PMMA lens is mounted into the center of the lamina, and the complex is placed into a subcutaneous pocket. After 1–2 months, a patch of buccal mucosa is obtained and sutured over the scarred and vascularized ocular surface. Alternatively, the first two stages may be performed simultaneously. After a minimum period of 3 months, the lamina is retrieved from the subcutaneous pocket. After trephining appropriately into both the cornea and oral mucosa for the cylindrical lens, the prosthesis is then secured to the surface of the eye between the layers of the scarred cornea and buccal mucosa using absorbable suture (Fig. 4.27.19).<sup>25</sup>

Like any other type of keratoprosthesis, patients after MOOKP require lifelong follow-up. Early in the postoperative period, a need exists for topical broad spectrum antibiotics. Once the mucosa is healed, there is no need for chronic topical antibiotic treatment. Multiple complications can occur after MOOKP, including glaucoma, which is the most common cause for loss of vision after MOOKP. For this reason, patients need IOP estimation (by finger palpation of the globe) and optic nerve head evaluation at every visit.

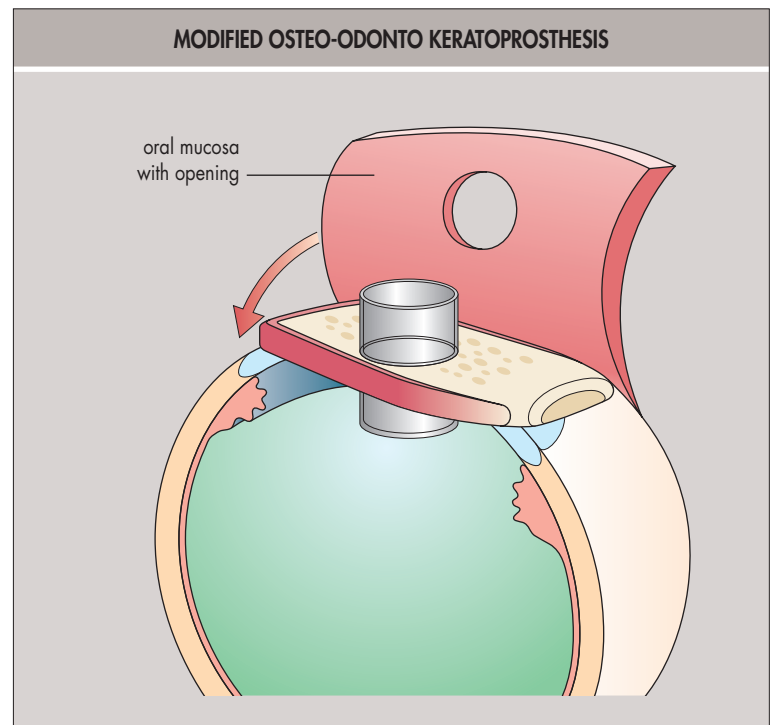
### Outcome

Corneal grafting techniques, such as PKP, ALK, and triple procedures, have become reliable and popular surgical techniques. Careful attention to preoperative evaluation, surgical techniques, and postoperative management will improve surgical outcome and patients' satisfaction.

## SUPERFICIAL CORNEAL PROCEDURES

### Historical Review

Superficial corneal procedures include corneal glue application (see Chapter 4.31), superficial keratectomy for anterior corneal degenerations and dystrophies, treatment of band keratopathy using ethylenediaminetetraacetic acid (EDTA; see Chapter 4.22), and corneal biopsy. With regard to superficial keratectomy for corneal dystrophies and other anterior pathologies, the advent of excimer laser phototherapeutic keratectomy (PTK) has become an effective alternative.



**Fig. 4.27.19 Modified Osteo-Odonto Keratoprosthesis (MOOKP).** Schematic drawing of the placement of the osteo-odonto-keratoprosthesis between the grafted buccal mucosa and the scarred and vascularized ocular surface. (Courtesy Sawatari S, Perez VL, Parel JM, et al. Oral and maxillofacial surgeons' role in the first successful modified osteo-odonto-keratoprosthesis performed in the United States. *J Oral Maxillofac Surg* 2011;69:1750–56, by kind permission.)

### Anesthesia

Superficial corneal procedures usually are performed under cover of topical anesthesia.

### Specific Techniques

#### Superficial Keratectomy

##### Preoperative Evaluation and Diagnostic Approach

Superficial keratectomy may be conducted either mechanically or with the excimer laser and consists of removal of pathological epithelial or subepithelial tissues. An AS-OCT may be helpful in delineating the depth of the corneal pathology. Indications include the following.<sup>17</sup>

- Anterior corneal dystrophies.
- Band keratopathy—often performed in conjunction with EDTA chelation.
- Superficial pannus or scar.
- Corneal dermoid, pterygium, or Salzmann's nodules.
- Excision of retained foreign bodies.

Superficial keratectomy also is used to obtain corneal tissue for microbiological or histological examination in the setting of infection or neoplasia.

#### Surgical Techniques

After the epithelium has been removed, the abnormal tissue is removed manually with a blade, a diamond burr, or the excimer laser. The corneal bed is left as smooth as possible. Bandage contact lenses or antibiotic ointment with a patch may be administered.

#### Complications and Postoperative Management

Bandage soft lenses, antibiotic drops, or aggressive lubrication should be continued until the corneal epithelium has healed. Oral analgesics are sometimes necessary to manage postoperative discomfort. Complications after superficial keratectomy include persistent epithelial defect, infection, and corneal scarring.

#### Corneal Biopsy

##### Preoperative Evaluation and Diagnostic Approach

Corneal biopsy is indicated in patients who have unresponsive and persistently culture-negative corneal ulcers.<sup>26</sup> Infections that arise from atypical mycobacteria, fungus, *Acanthamoeba*, and *Streptococcus viridans* with





**Fig. 4.27.20 Partial Trephination of the Cornea.** A 3-mm dermatological trephine is used to trephinate the cornea partially—both infected and noninfected cornea are straddled.



**Fig. 4.27.21** A blade is used to gently dissect the corneal tissue and removed with forceps.

associated crystalline keratopathy are examples of infectious disorders that may require corneal biopsy for definitive causative organism identification.

### Surgical Techniques

After topical anesthetic, a sterile, hand-held trephine (2–3 mm dermatological punch) is used at the slit lamp to achieve a partial-thickness trephination containing the pathological specimen. The size of the trephine depends on that of the lesion and the number of studies planned for the sample. The trephine is positioned to straddle the junction of diseased and normal corneal tissue (Fig. 4.27.20). After the partial-thickness trephination, the edge of the lesion, most easily in the area of healthy corneal tissue, is lifted using 0.12 forceps and dissected off the cornea using a blade (Fig. 4.27.21). The femtosecond laser also has been used to perform corneal biopsies.<sup>27</sup> The tissue is divided and sent for microbiological and histopathological evaluation.

### Complications and Postoperative Management

Complications can include perforation and postoperative secondary infection.

## Outcome

Eyes that undergo superficial corneal procedures, such as superficial keratectomy and corneal biopsy, generally heal well. The success of these techniques depends on the rate of re-epithelization and the underlying ocular surface pathology.

## PHOTOTHERAPEUTIC KERATECTOMY

The use of high-energy radiation of wavelength 193 nm is used to treat corneal pathology and smooth corneal surface irregularities. Laser energy emitted by the argon–fluoride (ArF) excimer laser for these purposes is referred to as PTK. The concept was first suggested by Trokel in 1983 and was approved by the FDA in 1995. PTK allows for the precise ablation of selected tissues in width and depth, leading to a regularization of the stromal bed. This can be used to treat anterior corneal pathology and thereby defer or eliminate the need for lamellar or penetrating keratoplasty.<sup>28</sup> Optimal results occur with pathology in the superficial 10%–20% of the cornea.<sup>29–33</sup>

## Preoperative Evaluation and Diagnostic Approach

Preoperative evaluation includes uncorrected visual acuity, best-corrected visual acuity by manifest refraction, hard contact lens refraction, pupil size measurements in ambient and near-dark lighting, slit-lamp biomicroscopy, dilated fundus examination, corneal topography, and wavefront analysis. The type of pathology and the proximity of the pathology to the pupillary center are documented, and the depth of pathology (as well as total corneal thickness) should be determined by AS-OCT. To plan the most effective procedure, determination of the pathology's ablation characteristics is necessary. The most common indications for PTK include recurrent erosion syndrome, anterior corneal dystrophies, superficial corneal scars, and Salzmann's nodules.<sup>29–32</sup>

Contraindications to PTK include severe keratoconjunctivitis sicca, uncontrolled uveitis, severe blepharitis, exposure keratopathy, and systemic immunosuppression. Moreover, PTK should be avoided in patients who have neurotrophic corneas (including previous herpes simplex or zoster keratitis or trigeminal nerve injury), collagen vascular disease, and diabetes because of potential problems with wound healing. Because of potential for microorganism spread during treatment, PTK should not be used for deep corneal scars or in active microbial keratitis, including infectious crystalline keratopathy.<sup>34,35</sup>

## Surgical Techniques

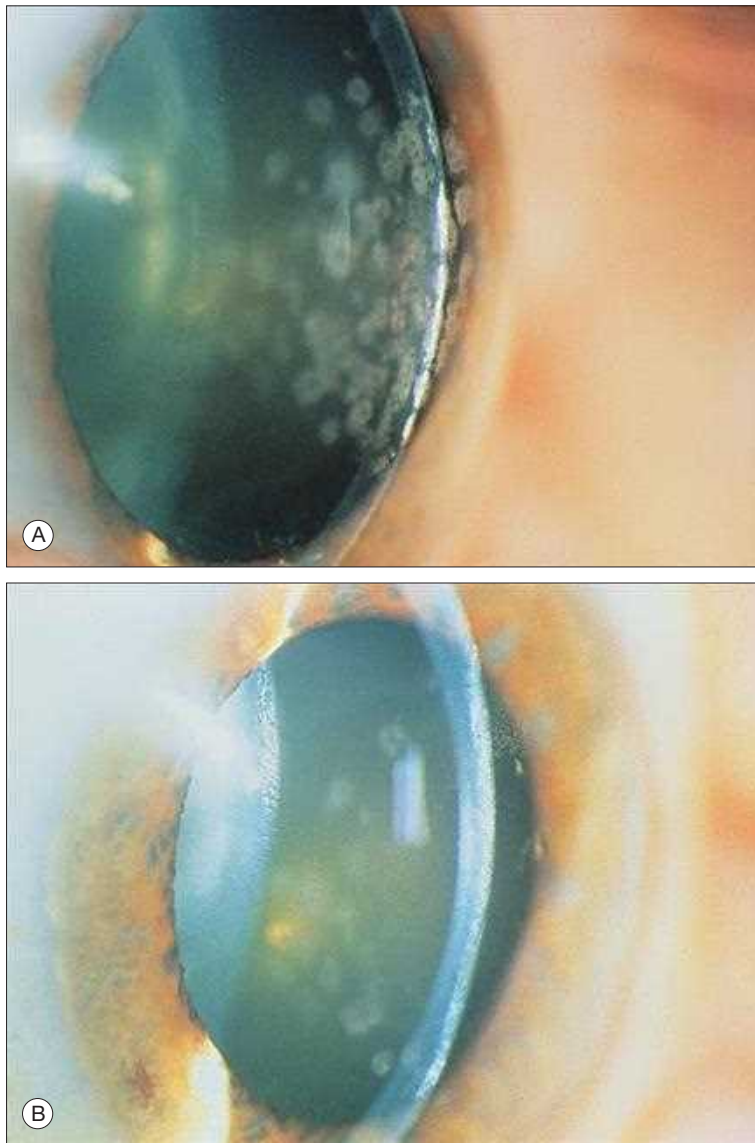
### Corneal Dystrophies, Scars, and Elevated Opacities

The goals of treatment of anterior stromal dystrophies are to ablate the confluent opacities in the visual axis and to remove the least amount of tissue possible to achieve the optimal visual outcome. Typically, the bulk of the lesions found in epithelial–stromal transforming growth factor- $\beta$ -induced dystrophies are located anteriorly (Fig. 4.27.22).<sup>36</sup> The middle and deep stroma often have fewer lesions with intervening clear stroma. Subsequently, deeper lesions are not ablated.<sup>37,38</sup>

Masking fluids are used to help fill in depressions and expose elevations of an irregular corneal surface by absorbing laser energy and thus shielding depressions. The most important principle is to use just enough masking fluid to cover the “valleys.” Carboxymethylcellulose 0.5% is of medium viscosity and efficiently covers the valleys and exposes the elevated areas. Methylcellulose 1%–2% is a high-viscosity fluid that may cover peaks, whereas hydroxypropylmethylcellulose 0.1% with dextran is of low viscosity and may leave valleys as well as peaks partly exposed.<sup>37</sup> It often is best to use more than one agent, depending on the particular corneal surface. Corneal dystrophies may recur after PTK. PTK may be repeated for recurrences even with previous grafts (Fig. 4.27.23). The success rate for recurrent granular corneal dystrophy type 1 or lattice dystrophy is extremely high and comparable with the high success rate for primary Reis–Bückler dystrophy, in which the deposits occur at Bowman's layer.<sup>28</sup> Macular corneal dystrophy and granular corneal dystrophy type 2 (formerly Avellino's dystrophy) have deeper lesions. Neither is usually amenable to PTK.

Elevated corneal opacities are often amenable to manual keratectomy with the use of a blade, which is efficacious when a suitable plane is found to leave a smooth surface on the cornea. When a plane cannot be found, it is possible to “debulk” the elevation and smooth the remaining area using the excimer laser. Alternatively, the epithelium may be removed from the





**Fig. 4.27.22 Granular Dystrophy.** (A) Preoperative anterior appearance of the opacities in a patient who has granular dystrophy. (B) The same eye 3 months after phototherapeutic keratectomy. (With permission from Salz JJ, McDonnell PJ, McDonald MB, editors. Corneal laser surgery. St Louis, MO: Mosby; 1995.)

area over the elevated lesion, and then photoablation performed to the underlying pathology, the surrounding epithelium is left in place to serve as a masking agent.<sup>29,31,32</sup>

### Postoperative Care

In the immediate postoperative period, a bandage soft contact lens is applied, and the patient is instructed to use broad-spectrum topical antibiotics. Topical corticosteroid, such as prednisolone acetate 1% or fluorometholone 0.1%, four times a day, is used and tapered to once daily within 1 month. Topical nonsteroidal anti-inflammatory drops may help control pain, which may be severe, so oral analgesics are frequently used.<sup>28,31,37</sup> Patients are examined every 24–72 hours until re-epithelization is complete, which generally occurs within 1 week.<sup>38</sup>

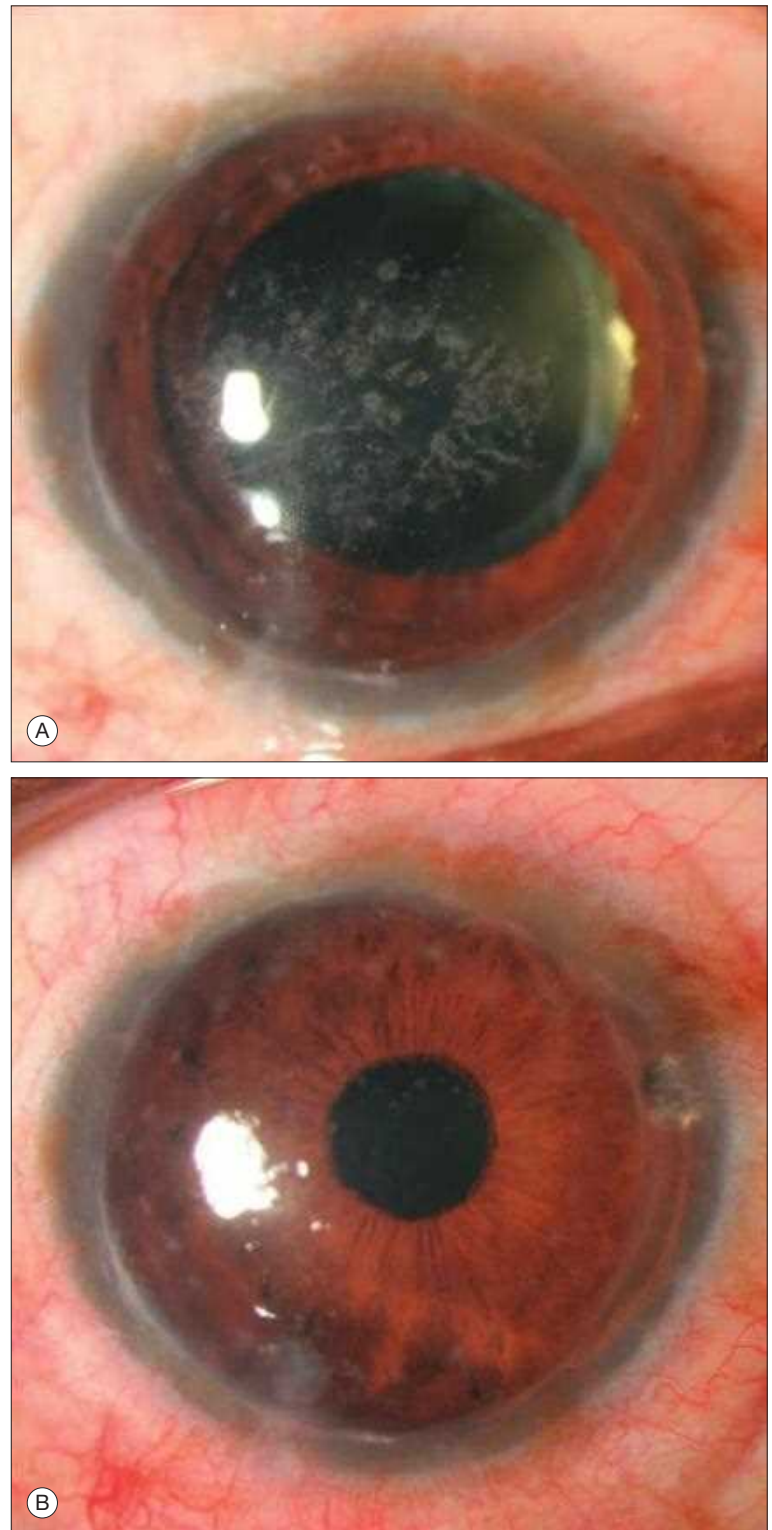
### Complications

#### Hyperopia

The most common side effect of PTK is induced hyperopia, which results from flattening of the central cornea. To avoid this problem, 1 diopter of hyperopic correction is added for every 14–20  $\mu\text{m}$  of PTK tissue ablation, performed at the time of treatment.<sup>39</sup>

#### Myopia/Myopic Astigmatism

Myopia and myopic astigmatism may be induced when the periphery or paracentral cornea undergoes a deeper ablation compared with the central cornea, and this may occur in the treatment of paracentral opacities.



**Fig. 4.27.23 Recurrent Granular Dystrophy in a Penetrating Keratoplasty.** (A) Preoperative appearance of the opacities in a patient with recurrent granular dystrophy in a penetrating keratoplasty. (B) Phototherapeutic keratectomy was performed and immediately postoperatively there was a dramatic reduction in the anterior stromal granules. (Bandage contact lens in place.) The patient ultimately developed haze and required a femtosecond-assisted lamellar keratoplasty. (Courtesy Dr. C. L. Karp.)

### Irregular Astigmatism and Decentration

Irregular astigmatism is an undesirable potential outcome that may be minimized by using masking agents to help achieve a smooth corneal contour postoperatively. Decentration may also lead to irregular astigmatism.

#### Pain

Pain may be severe after excimer laser photoablation. Judicious use of topical corticosteroids, nonsteroidal anti-inflammatory agents, chilled balanced salt solution, and oral pain medication has helped in pain control after excimer laser treatment.<sup>40</sup>

### Delayed Epithelization

Epithelial healing is usually complete within the first week. Delayed epithelial healing puts the patient at risk for infection and haze. Persistent epithelial defects or recurrent erosions may be more common in patients who have preoperative DED, herpes simplex virus infection, or diabetes. Bandage contact lenses and lubrication are helpful in the promotion of epithelial healing.<sup>28</sup> Punctal plugs often are useful in patients who have signs or symptoms of DED. The use of blood derivatives or a temporary tarsorrhaphy may be considered in recalcitrant cases.

### Bacterial Keratitis

Bacterial keratitis is a feared postoperative complication because of the presence of an epithelial defect and the placement of a contact lens on what may be an already compromised cornea. Most surgeons performing PTK believe the ability of bandage contact lenses to decrease pain and help epithelial wound healing outweighs the risk of bacterial keratitis. Prophylactic antibiotic drops are used postoperatively. Stromal infiltrates are managed similarly as in patients who have had photorefractive keratectomy. Non-steroidal anti-inflammatory agents, contact lenses, and infectious keratitis may lead to infiltrates.<sup>32,41</sup>

### Viral Keratitis

Herpes simplex virus may be reactivated after PTK. Treatment of patients who have a history of herpes is controversial. In cases that are treated, a prophylactic regimen of preoperative and postoperative oral antiviral therapy is given.

### Recurrence and Haze

Corneal dystrophies treated with PTK may recur. Retreatment may be performed, although the possibilities of increased hyperopia and anisometropia must be considered. Furthermore, haze often results after PTK and may be confluent and visually significant. Haze results from the presence of activated keratocytes and their products (newly formed collagen and proteoglycans in an irregular network).<sup>30,42,43</sup> Haze often decreases over time, and a period of 12 months is allowed to elapse before the haze is treated. The intraoperative use of mitomycin C has reduced the likelihood of haze and scarring and improved visual outcomes.<sup>44</sup>

### Graft Rejection

Corneal graft rejection in PTK-treated patients has been reported, as in Hersch et al.<sup>45</sup> for recurrent lattice dystrophy and others for postoperative

astigmatism.<sup>42</sup> Medical treatment of the rejection episodes have been reported as successful.

## Outcome

The 193 nm ArF excimer laser is an excellent tool in the treatment of anterior corneal pathology and surface irregularities. The expense and risks associated with penetrating keratoplasty, including the risks of intraocular surgery and anesthesia, may be avoided. Treatment must be individualized on the basis of the type of pathology and its ablation characteristics and depth.

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# Conjunctival Surgery

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# 4.28

**Definition:** Conjunctival procedures may be used to cover an unstable or painful corneal surface or to remove pterygia or other abnormal growths.

## Key Features

- Careful preoperative planning is critical for success.
- It is important to have a clear understanding of intraoperative and postoperative complications and management.

## Associated Feature

- Recurrences of pterygium may be more aggressive than initial pterygium.

## HISTORICAL REVIEW

Conjunctival procedures include a bridge conjunctival flap (Gundersen flap),<sup>1,2</sup> pterygium surgery, conjunctival excision for conjunctivochalasis, limbal stem cell transplantation (see Chapter 4.30), and tumor removal. In a conjunctival flap procedure, a hinged flap of conjunctiva is created to cover an unstable or painful corneal surface. Conjunctival flaps, partial or total, have remained an effective procedure over the past 100 years for the treatment of challenging ocular surface disorders in patients with poor visual prognosis.

Pterygium surgery dates back to 1855, when Desmarres<sup>3</sup> first performed a transposition of the pterygium head. In 1872, Arlt recognized the importance of covering the epibulbar defect after pterygium excision and described the first conjunctival graft.<sup>4</sup>

## ANESTHESIA

Conjunctival surgeries typically are performed under cover of local, retrobulbar, infiltrative, or (rarely) general anesthesia. To prevent squeezing during surgery, a lid block is sometimes employed. General anesthesia is reserved for pediatric patients and uncooperative adults.

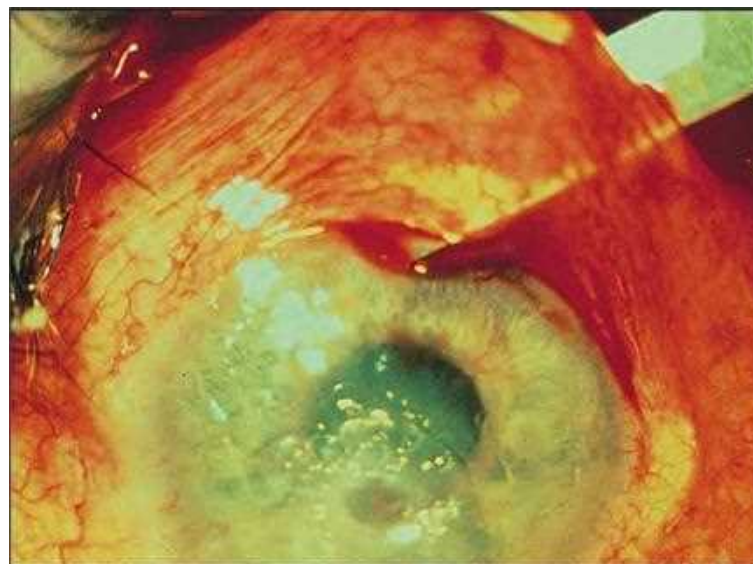
## SPECIFIC TECHNIQUES

### Conjunctival Flap

#### Preoperative Evaluation and Diagnostic Approach

Common indications for conjunctival flap include the following:

- Nonhealing sterile corneal ulcerations secondary to chemical or thermal injuries, herpetic infections, exposure keratopathies, and other neurotrophic diseases that are unresponsive to medical treatment.
- Painful bullous keratopathy or other chronically inflamed ocular surface disorders in eyes with low visual potential, in which penetrating or selective keratoplasty is not indicated; and in which simpler management techniques, such as soft contact lenses or anterior stromal puncture, have failed.
- Necrotizing scleritis resulting in severe melt that is unresponsive to systemic anti-inflammatory treatments, requiring tectonic support.
- Blind eyes in need of surface preparation for prosthetic shells or cosmetic contact lenses.



**Fig. 4.28.1 360° Peritomy.** Westcott scissors are used. The dissection is carried out toward the corneal limbus with care not to buttonhole the conjunctiva. (Courtesy Dr. R. K. Forster.)

Relative contraindications for conjunctival flap include active infectious keratitis and corneal perforation in eyes with good visual potential.

### Surgical Techniques

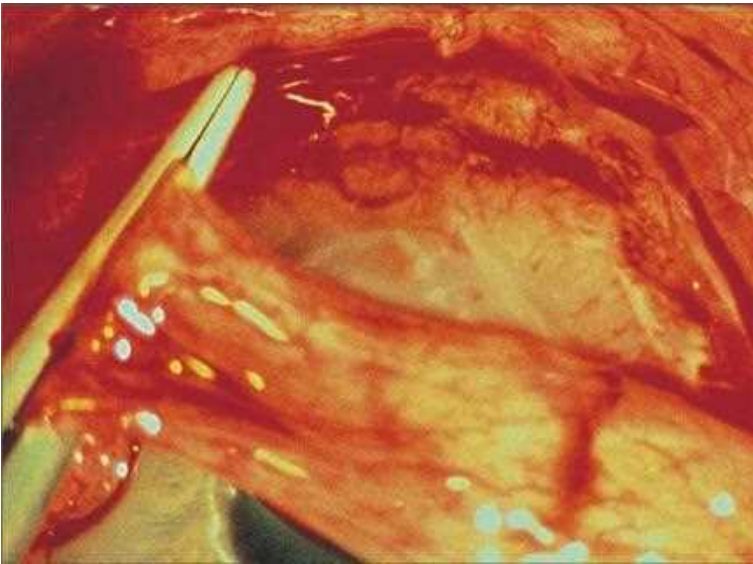
The availability of mobile conjunctiva is evaluated. Typically, the superior bulbar conjunctiva offers increased tissue availability. The corneal epithelium is mechanically debrided using a No. 64 blade or a cellulose sponge. Application of lidocaine 4% or absolute alcohol may assist in loosening the corneal epithelium. A 360° limbal peritomy is then performed (Fig. 4.28.1).

The globe is rotated inferiorly from the donor site using a traction suture placed at the limbus to increase superior exposure. A semicircular incision, parallel to the corneal limbus, is made as posteriorly as possible. The dissection of a thin conjunctival flap is carried anteriorly until the corneal limbus is reached. Adequate dissection and undermining of this flap laterally is important for the subsequent anterior mobilization of the flap over the cornea and to prevent traction. The conjunctival flap is freed completely from its underlying Tenon's capsule.

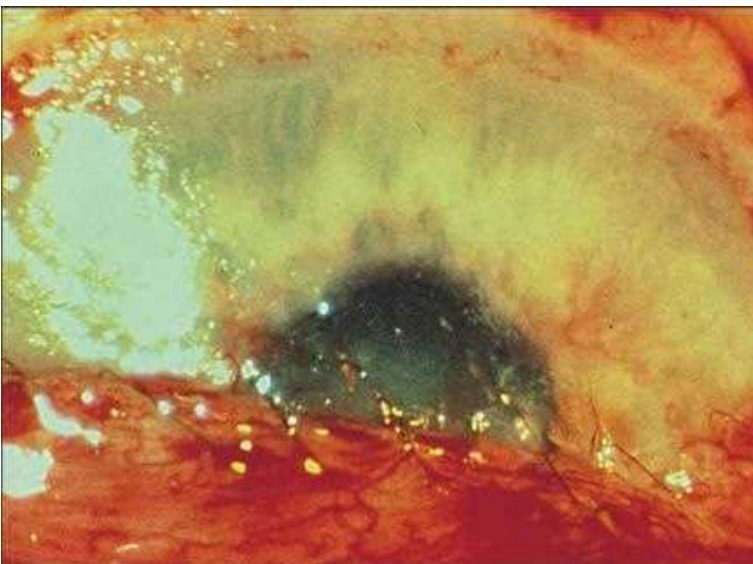
The well-mobilized conjunctival flap then is stretched to cover the desired area (Fig. 4.28.2). The superior and inferior aspects of the flap are secured on the sclera using interrupted or running 10-0 nylon sutures. The edges of the conjunctiva may be reapposed with 7-0 or 8-0 Vicryl suture in a running fashion (Fig. 4.28.3). Alternatively, fibrin glue has been shown to be a viable option for Gundersen flap surgery, with the possible advantage of reduced surgical and recovery time.<sup>5</sup>

A partial conjunctival flap is used in certain circumstances, such as for focal nonhealing corneal ulcers that do not require coverage of the entire cornea. The procedure includes scraping of the corneal epithelium, mobilization of the conjunctiva in the appropriate quadrant, and suturing of the conjunctival flap over the localized corneal defect (see Fig. 4.28.3).

A total Tenon-conjunctival flap (TCF) has been used to increase corneal thickness in mildly phthisical eyes in preparation for prosthetic scleral shells.<sup>6</sup> A modified Gundersen flap with the use of amniotic membrane transplantation has been reported in a small series of patients as a promising technique.<sup>7</sup>



**Fig. 4.28.2** Mobilization of the conjunctival flap to the desired area of the cornea. (Courtesy Dr. R. K. Forster.)



**Fig. 4.28.3** Conjunctival Flap Over a Sterile Ulcer. The flap is sutured into position with 10-0 nylon sutures superiorly and 7-0 Vicryl sutures through the inferior limbal episclera. (Courtesy Dr. R. K. Forster.)

### Complications and Postoperative Management

The most common perioperative complication is the creation of a conjunctival buttonhole during dissection. Buttonholes should be closed by using running or interrupted sutures. Postoperative complications include retraction of the conjunctival flap, hemorrhagic and epithelial mucous cysts, flap loss from epithelial ingrowth, ptosis, and progression or recurrence of inflammation or infection, such as that caused by herpes simplex virus.<sup>8,9</sup>

After healing, a cosmetic contact lens may be fitted. In some cases, penetrating keratoplasty is indicated for visual rehabilitation. Because a conjunctival flap may have destroyed corneal limbal stem cells, a limbal allograft may be considered prior to penetrating keratoplasty.

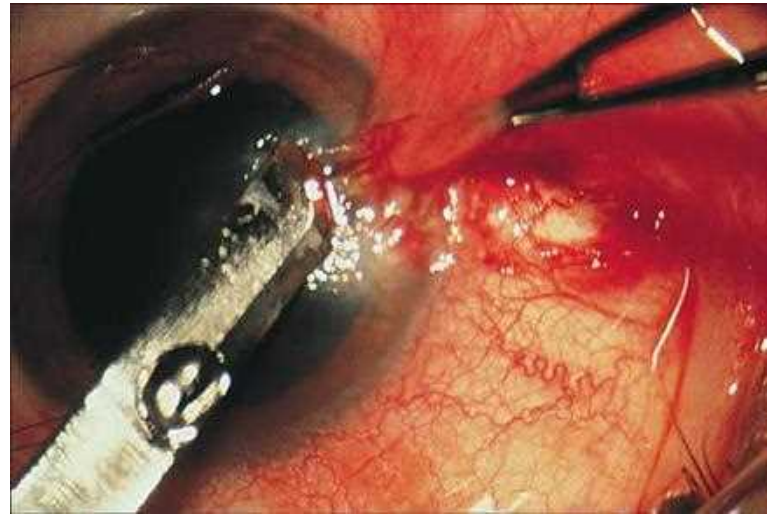
### Pterygium Surgery

Pterygium, most commonly seen at the nasal limbus, is a conjunctival fibrovascular growth over the sclera and onto the cornea (see Chapter 4.9 for more information).

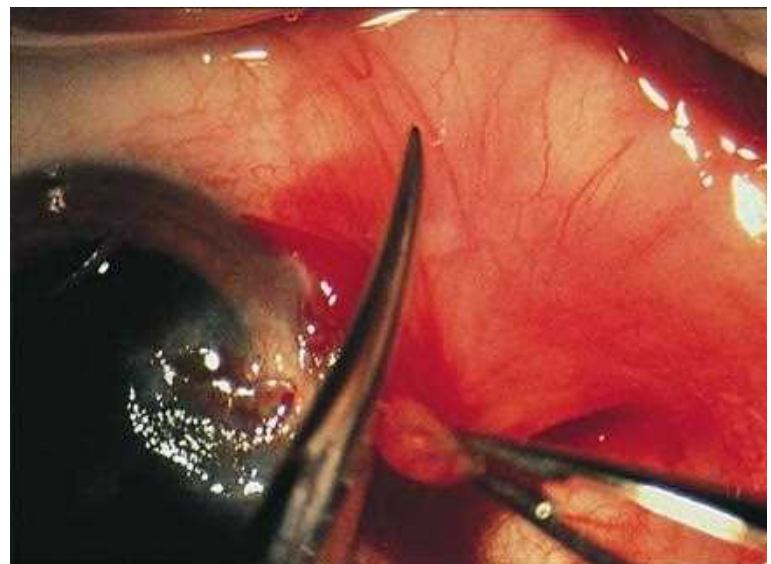
### Preoperative Evaluation and Diagnostic Approach

Surgical indications for excision of the pterygium include the following:

- Growth of pterygium such that it has impinged on or is imminently threatening the visual axis.
- Reduced vision as a result of induced astigmatism.



**Fig. 4.28.4** Dissection of the Head of the Pterygium From the Cornea. A blade is used.



**Fig. 4.28.5** Removal of the Body of the Pterygium. Westcott scissors are used with care to avoid damage to the underlying rectus muscle.

- Severe irritation not relieved by medical therapy.
- Surgery for unacceptable cosmetic appearance.
- Reduced motility secondary to pterygium.
- Recurrence, with more aggressive growth than in primary lesions.

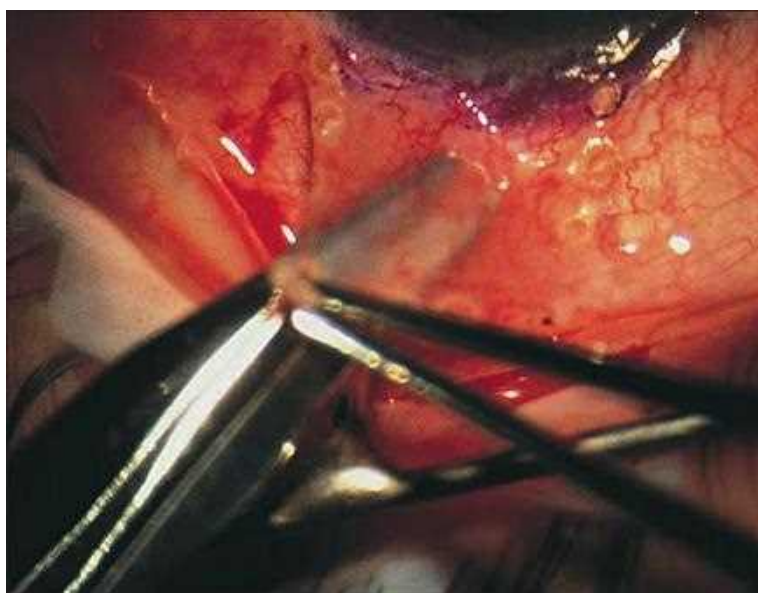
### Surgical Techniques

Several techniques have been described including bare sclera technique, conjunctival autograft placement, amniotic membrane transplantation, antimetabolites, radiation, and, in cases of severe recurrence, mucous membrane grafts.

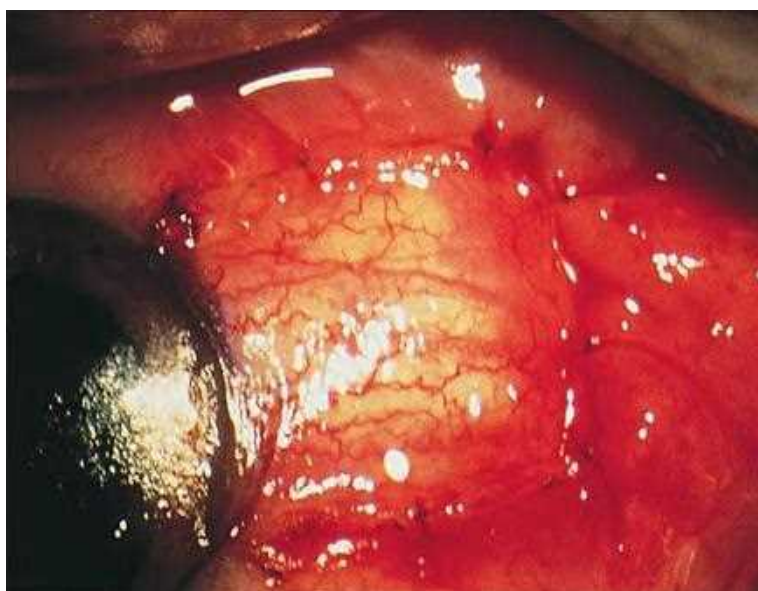
### Bare Sclera Technique/Simple Closure

Although technically simple, this technique can be associated with recurrence rates as high as 40%.<sup>9</sup> Surgically, the lesion may be outlined using spot cautery or a sterile marker. To facilitate dissection, the eye may be rotated laterally using traction sutures (6-0 Vicryl or silk) placed at the superior and inferior corneal limbus. The dissection may be initiated at the corneal side of the pterygium. Using forceps, the head of the pterygium is lifted and dissected off the cornea in a lamellar fashion using sharp dissection with a blade (Fig. 4.28.4). Alternatively, the scleral portion may be removed first, followed by blunt dissection or avulsion of the corneal portion. The scleral part of the pterygium is excised by using scissors (Fig. 4.28.5). Care is taken to identify the underlying rectus muscle, especially in surgery for recurrent pterygium. The corneal defect may be polished by using a diamond burr. Antimetabolite agents, such as mitomycin-C (MMC) 0.02%, have been used to prevent recurrence in conjunction with this technique. Care should be taken to avoid excessive contact of MMC with the sclera. Instead of leaving the sclera bare, the conjunctiva can be closed





**Fig. 4.28.6 Dissection of the Conjunctival Graft.** The limbus is marked and the healthy conjunctiva is harvested. The conjunctiva is dissected gently with care not to buttonhole the donor tissue.



**Fig. 4.28.7 Conjunctival Autograft in Position Over the Previously Excised Pterygium.** Two 10-0 nylon sutures are placed at the limbus and 8-0 Vicryl sutures are used along the conjunctiva in an interrupted fashion. Care is taken to maintain the limbus-to-limbus position of the graft.

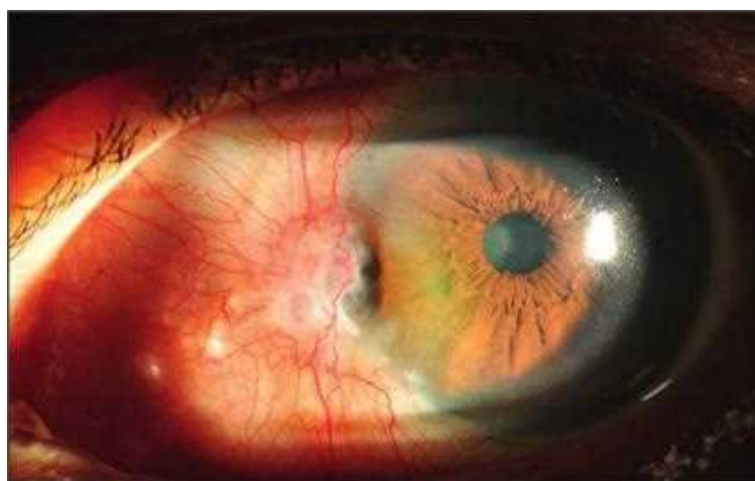
with 7-0 or 8-0 Vicryl suture, although the recurrence rates have not been shown to be significantly reduced with primary closure.<sup>10,11</sup>

### Autograft

Conjunctival autografting is considered the “gold standard” for pterygium surgery because of its low rate of recurrence (rates reported as low as 5% in primary cases) and excellent cosmesis.<sup>9</sup> After pterygium excision, the size of the defect is measured. Commonly, in a nasal pterygium, the superotemporal bulbar conjunctiva is used as the donor site. Tractional sutures may be used to rotate the eye downward. The donor conjunctiva is outlined using spot cautery or a sterile marker and a thin Tenon’s free conjunctival flap is dissected with forceps and scissors (Fig. 4.28.6). It is important to avoid buttonholes and to maintain limbus-to-limbus orientation of the conjunctival flap when transferring the flap to the recipient bed to ensure proper positioning of limbal stem cells. Alternatively, the conjunctival flap may be rotated on a pedicle. The graft is then secured using Vicryl or 10-0 nylon sutures (Fig. 4.28.7), or fibrin glue.

### Amniotic Membrane

Amniotic membrane transplantation (AMT) has been implemented as an alternative to conjunctival autografting despite its higher cost. Amniotic



**Fig. 4.28.8 Corneoscleral melt** after pterygium excision associated with the use of radiation.

membranes are secured using similar techniques as conjunctival autografts and are especially amenable to the use of fibrin glue. The amniotic membrane is placed stromal side adjacent to the scleral bed. Benefits include shortened operative time and untouched conjunctiva for future use, such as in glaucoma surgery. However, in a prospective study (mean follow-up, 11 months) comparing AMT to conjunctival autografts, AMT had higher recurrence rates for primary (10.9% versus 2.6%), recurrent (37.5% versus 9.1%), and all pterygia (14.8% versus 4.9%) compared with conjunctival autografts, respectively.<sup>10</sup> These results establish the use of conjunctival autografting as the procedure of choice for pterygium surgery unless a conjunctival preserving technique is indicated.

**Other Techniques.** Several, more recent techniques have been described to have success in preventing pterygium recurrence after excision. Limbal conjunctival autograft (LCAU), in which a free conjunctival graft is harvested to include the superficial limbus, has been demonstrated to have a low recurrence rate (6.9%) after 10 years of follow-up.<sup>12</sup> Minor ipsilateral simple limbal epithelial transplantation (mini-SLET), which utilizes amniotic membrane and the placement of limbal epithelial pieces, has been described in the treatment of 10 eyes without recurrence after 8 months of follow-up.<sup>13</sup>

**Recurrent Pterygium Excision.** Excision of recurrent pterygia can be especially tedious even for the experienced surgeon because of extensive fibrosis of the pterygium to the sclera and cornea, distortion of tissue planes and normal anatomy, and symblepharon formation. The rectus muscle should be isolated in cases of scarring of the muscle sheath prior to dissection, and all symblepharon must be released to alleviate any motility restriction.

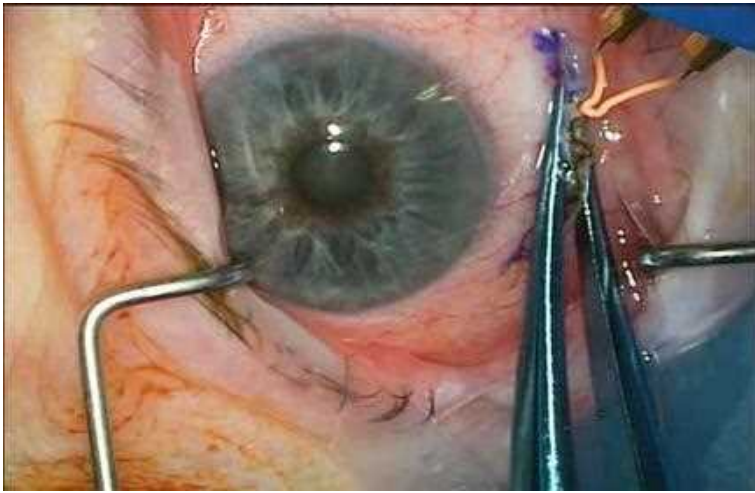
### Antimetabolites and Radiation

MMC has been used preoperatively, intraoperatively, and postoperatively in pterygium surgery and appears to reduce the recurrence rates (particularly if amniotic membrane is used). Antimetabolites, however, have been associated with serious complications, including corneal or scleral melts. Thus, MMC should be used judiciously in cases with a high likelihood of recurrence. In addition, beta radiation using strontium-90 has been employed and shown to reduce recurrence; however, it may cause significant complications such as scleral necrosis, cataract, and persistent epithelial defects (Fig. 4.28.8). Beta radiation after pterygium surgery has been supplanted largely by conjunctival or amniotic membrane transplantation.

### Fibrin Glue

Fibrin glue is a two-component tissue adhesive that is used in many surgical procedures. One component consists of a protein fibrinogen solution, and the other consists of a thrombin solution. When mixed together, a fibrin clot is formed. Several studies have shown that the use of fibrin glue decreases postoperative pain and foreign body sensation and leads to reduced operative time and blood loss during surgery.<sup>14,15</sup> It is being used with increasing frequency with both conjunctival autografts and amniotic membranes. Additionally, fibrin glue eliminates or reduces the number of sutures required. In a recent study, comparing Vicryl sutures to two of the most commonly used fibrin glues worldwide, Tisseel (Baxter Corp., Deerfield, IL) and Evicel glue (Omrix Biopharmaceuticals Ltd., Ramat-Gan, Israel), Tisseel glue was found to be superior with regard to pterygium





**Fig. 4.28.9 Thermocautery of Inferior Conjunctivochalasis.** Excess conjunctiva is grasped with smooth forceps approximately 5 mm from the limbus and then cauterized with a handheld cautery.

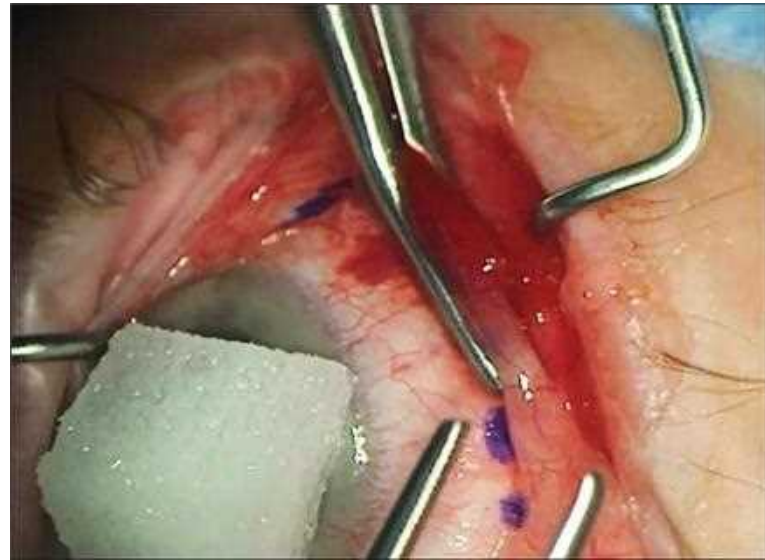
recurrence, patient comfort, and surgical time.<sup>16</sup> Patients must understand that this is an off-label use for fibrin glue. Patients also need to give their consent for blood product use because fibrin glue is derived from pooled human blood. However, it has been used for many years in thousands of surgeries with no documented cases of transmission of hepatitis B or C, human immunodeficiency virus (HIV) infection, or prion-mediated disease. Furthermore, donated plasma undergoes viral polymerase chain reaction screening prior to use.

### Complications and Postoperative Management

Complications of pterygium surgery include recurrence of the pterygium, conjunctival granuloma, subconjunctival hemorrhage, corneoscleral dellen, epithelial inclusion cysts, graft retraction or necrosis, corneal or scleral melt with the use of antimetabolites or beta radiation, and conjunctival fibrosis. Topical antibiotics and corticosteroids are prescribed after surgery. Topical corticosteroids generally are used for 1–2 months postoperatively to minimize resultant inflammation.

## Conjunctivochalasis Management

Conjunctivochalasis is a loosely adherent, redundant conjunctiva more commonly found overlying the inferior bulbar surface, typically in older individuals or those with a history of chronic inflammation. Although often asymptomatic, it may interfere with normal tear flow, lubrication of the ocular surface, and cause local exposure and associated irritation or pain. Additionally, if prominent nasally, the redundant conjunctiva may occlude the lower punctum, resulting in epiphora. In patients with significant symptoms uncontrolled with topical medications, such as artificial tears and topical corticosteroids, conjunctival cautery and surgical excision have been proposed as treatment modalities. These options must be approached judiciously, as the condition is likely to recur. Simple cauterization of the conjunctiva is usually performed in the office after topical gel anesthetic is applied using smooth forceps to grasp the excess inferior conjunctiva several millimeters from the limbus, which is then cauterized (Fig. 4.28.9). Additional options include conjunctival resection (Fig. 4.28.10) and scleral fixation of the conjunctiva. Surgical consideration should be given only when conservative treatment modalities are insufficient in providing adequate relief.



**Fig. 4.28.10 Conjunctival Resection for Symptomatic Inferior Conjunctivochalasis.** Wescott scissors and smooth forceps are used to excise the marked crescent of excess conjunctival tissue.

### Surgical Techniques

After topical anesthesia is instilled, smooth forceps are used to grasp the excess inferior conjunctiva approximately 5 mm from the limbus, which is then marked with a marking pen. Using Wescott scissors and smooth forceps, the marked crescent of conjunctival tissue is then excised (see Fig. 4.28.10). Vicryl sutures are then used for simple closure of the conjunctiva, or an amniotic membrane transplant can be sutured or glued over the defect.

### Complications

Recurrence of conjunctivochalasis after simple cautery or even excision should be discussed with the patient prior to the procedure. Other complications that may arise after conjunctival excision include conjunctival fibrosis, subconjunctival hemorrhage, granuloma formation, and cicatricial entropion.

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# Endothelial Keratoplasty: Targeted Treatment for Corneal Endothelial Dysfunction

Marianne O. Price, Francis W. Price, Jr.

# 4.29



IN THIS CHAPTER  
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**Definition:** Endothelial keratoplasty has significant advantages over penetrating keratoplasty as a targeted method to replace endothelial cells in the treatment of endothelial dysfunction.

## Key Feature

- Targeted replacement of corneal endothelium through a small 2–5 mm incision.

## Associated Features

- Rapid visual recovery.
- Few activity restrictions.
- No significant increase in astigmatism.
- Minimal disruption of corneal innervation.
- Lower risk of immunological rejection than with penetrating keratoplasty.
- Rapid sequential surgery.

## INTRODUCTION

Penetrating keratoplasty (PKP) was long considered the gold standard for the treatment of endothelial dysfunction. Advances in endothelial keratoplasty (EKP) techniques, coupled with the many advantages it offers to patients, have made it the preferred treatment for endothelial dysfunction (Fig. 4.29.1).

After PKP, it generally takes 6 months to several years for the refraction to stabilize<sup>1–3</sup>; 10%–15% of the patients typically require a hard contact lens for best vision<sup>4,5</sup>; and a final mean refractive cylinder of 4–5 D is common.<sup>3,5</sup> Furthermore, PKP incision severs all corneal nerves, so the inclination to blink and produce tears is reduced postoperatively. This, together with the prolonged presence of corneal sutures to hold the graft in place, increases the risk that ocular surface complications will interfere with recovery.<sup>6,7</sup> Moreover, because of the PKP wound, the cornea never regains the full strength of a virgin cornea, so an eye that has undergone PKP is forever at increased risk of loss from a traumatic injury.<sup>8</sup>

In contrast, EKP involves selective removal of dysfunctional recipient corneal endothelium and replacement with donor tissue consisting of healthy endothelium, with or without posterior stroma.<sup>9</sup> EKP is performed through a small incision and spares the majority of the host cornea, so corneal strength and surface topography are minimally altered, and the technique is essentially refractive-neutral.<sup>10–13</sup> Furthermore, corneal innervation is retained, and corneal sutures are not required, so ocular surface complications are minimal.<sup>14</sup> Finally, the small incision allows rapid healing and visual recovery, and patients can resume normal activities within weeks of surgery.

## EVOLUTION OF EKP TECHNIQUES

Originally described by Tillett in 1956,<sup>15</sup> EKP has evolved rapidly, particularly since 1998, when Melles reported successful replacement of dysfunctional endothelium through a scleral–limbal approach, using an air bubble

rather than sutures to secure the donor tissue, in a technique he called *posterior lamellar keratoplasty* (PLK).<sup>16</sup> Later renamed *deep lamellar endothelial keratoplasty* (DLEK), this technique required lamellar dissection of the recipient and donor corneal tissue. Both dissections were originally done manually by using a series of curved blades of increasing length.

Melles subsequently eliminated the challenging recipient stromal dissection and excision steps by peeling the Descemet's membrane (DM) and dysfunctional endothelium from the recipient cornea before implanting the donor tissue.<sup>17</sup> This EKP modification became known as Descemet's stripping with endothelial keratoplasty (DSEK).<sup>10,13</sup> Use of a microkeratome was introduced to facilitate the donor lamellar dissection,<sup>12,18</sup> and this technique variation was referred to as either DSEK or Descemet's stripping automated endothelial keratoplasty (DSAEK). In 2005, eye banks began performing the donor lamellar dissection with a microkeratome and providing “precut” tissue to surgeons.<sup>19</sup>

Even though DSEK provides 20/40 or better vision more reliably compared with PKP, fewer patients than expected achieve 20/20 vision, and variations in the donor stromal thickness increase the higher order aberrations of the posterior corneal surface.<sup>20</sup> Over time, surgeons have gravitated toward use of thinner DSEK tissue, which seems to provide better vision with less risk of rejection than thicker tissue,<sup>21</sup> although the rate of tissue loss is greater with ultra-thin DSEK.

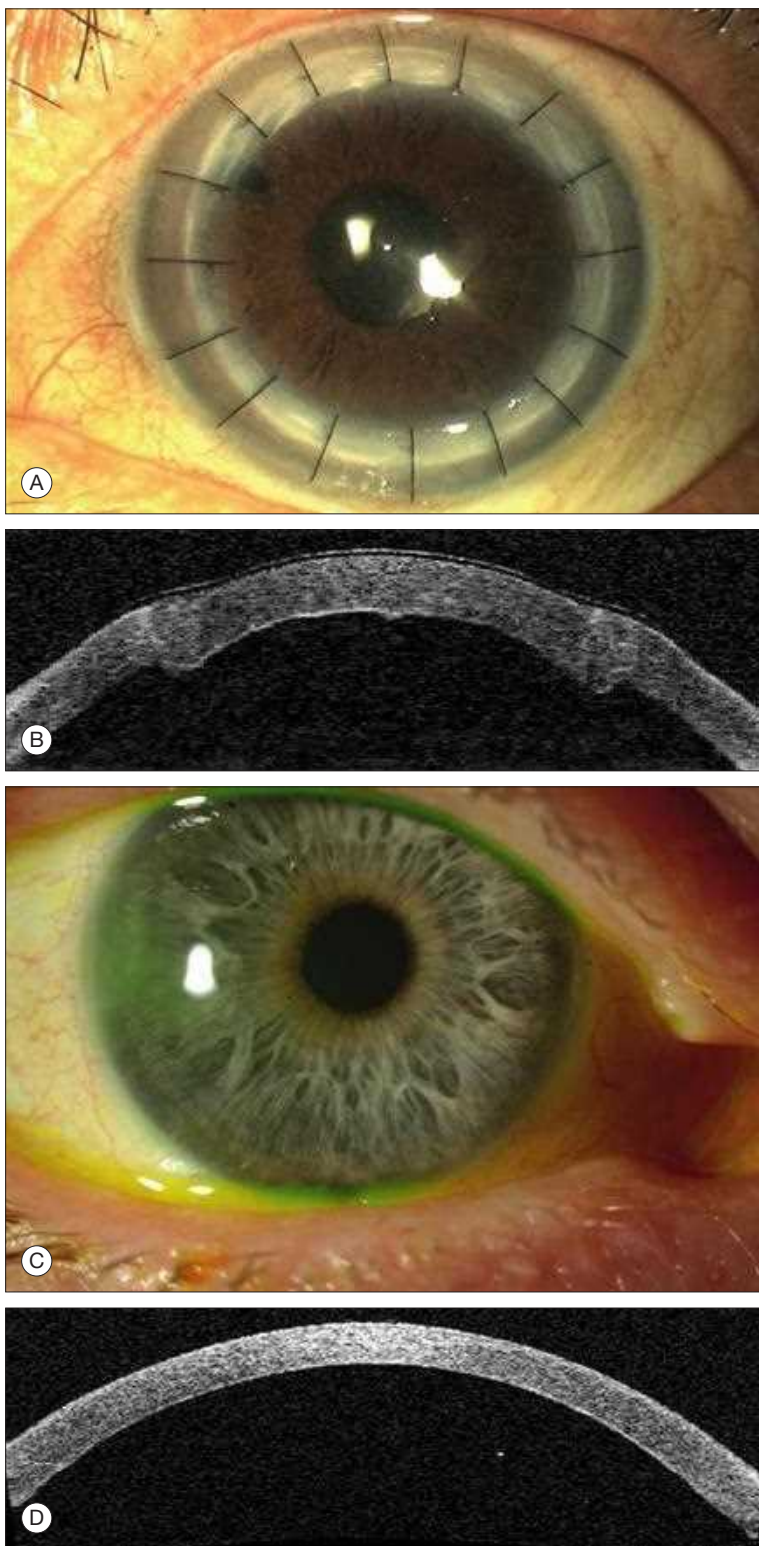
Aiming for exact anatomical replacement with the thinnest possible tissue, Melles developed a technique for peeling DM and healthy endothelium from a donor cornea and implanting it into a recipient eye in a method he called DM endothelial keratoplasty (DMEK).<sup>22</sup> The extremely thin DMEK graft is more challenging to handle compared with a thicker DSEK graft (Fig. 4.29.2), leading to the development of hybrid techniques with a narrow rim of donor stromal tissue ringing a central area of bare endothelium without stroma. The hybrid techniques, known as DMEK-S and DMAEK, were not widely adopted because the risk of tissue loss was greater than with DMEK.<sup>23,24</sup>

A variation of DMEK, called pre-Descemet's endothelial keratoplasty (PDEK), utilizes a big bubble to separate the donor Descemet's membrane and endothelium from the donor stroma.<sup>25</sup> With a type 1 big bubble, a pre-Descemet's layer remains attached to Descemet's membrane, thereby providing slightly thicker tissue than in standard DMEK. This results in easier unfolding and the ability to utilize tissue from younger donors who have a thinner Descemet's membrane. The disadvantages of PDEK are that the graft diameter is limited by the big bubble diameter to about 7–75 mm and the donor tissue must be cut from the underlying stroma with scissors. Time will tell which of these technique variations become dominant for standard noncomplicated cases, such as Fuchs' dystrophy.

## INDICATIONS

EKP is an excellent option for any type of endothelial dysfunction (Box 4.29.1).<sup>9,13,24–26</sup> With appropriate modifications, EKP can be performed in eyes with peripheral anterior synechiae, glaucoma filtration surgery, and iris abnormalities, including aniridia.<sup>26–28</sup> If anterior stromal scarring from long-standing corneal edema is significant, replacement of the full corneal thickness with a PKP may provide better visual acuity. However, in many cases, patients who have tolerated long-standing corneal edema also have other visual limitations (e.g., retinal problems). In such cases, EKP is an attractive alternative because it quickly resolves the corneal edema and





**Fig. 4.29.1** Slit-lamp images of penetrating keratoplasty (A) and Descemet's membrane endothelial keratoplasty (C), with corresponding anterior segment optical coherence tomography images (B,D). (A,B from Anshu A, Price MO, Tan DTH, et al. Endothelial keratoplasty: a revolution in evolution. *Surv Ophthalmol* 2012;57:236–52, Fig. 1.)

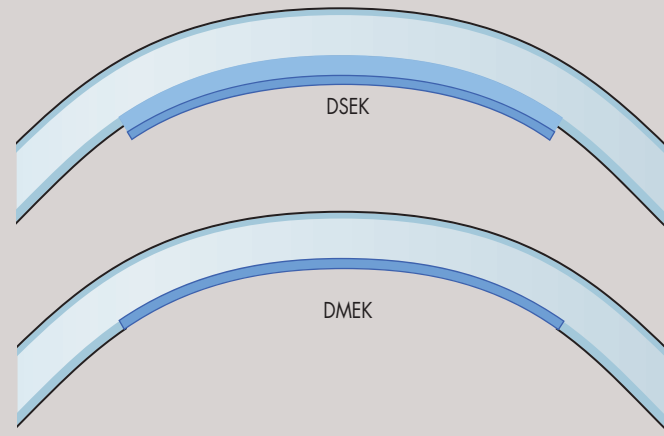
bullae while maintaining much of the structural integrity of the eye. In eyes with significant iris defects, aniridia, and/or aphakia, DSEK is preferable to DMEK, which can more easily escape into the posterior chamber or be damaged by contact with an intraocular lens (IOL) or artificial iris during unfolding.

## SURGICAL TECHNIQUE

### Anesthesia and Recipient Preparation

EKP is readily performed with topical or local anesthesia. With local anesthesia (using a retrobulbar or peribulbar block), it is important to ensure

#### PRINCIPAL EK TECHNIQUES



**Fig. 4.29.2** Diagram illustrating the differences between Descemet's stripping endothelial keratoplasty (DSEK) and Descemet's membrane endothelial keratoplasty (DMEK). The host cornea epithelial and endothelial layers are depicted in sky blue, the host stroma in pale blue, the donor endothelium in dark blue, and the donor stroma in medium blue.

#### BOX 4.29.1 Endothelial Keratoplasty: Indications and Contraindications

##### Indications

- Essentially all forms of endothelial dysfunction
- Fuchs' endothelial dystrophy
- Pseudo-phakic or aphakic bullous keratopathy
- Previous failed penetrating keratoplasty
- Posterior polymorphous dystrophy
- Congenital hereditary endothelial dystrophy
- Iridocorneal endothelial (ICE) syndrome
- Endothelial failure from trauma, previous surgery, angle closure or glaucoma drainage devices

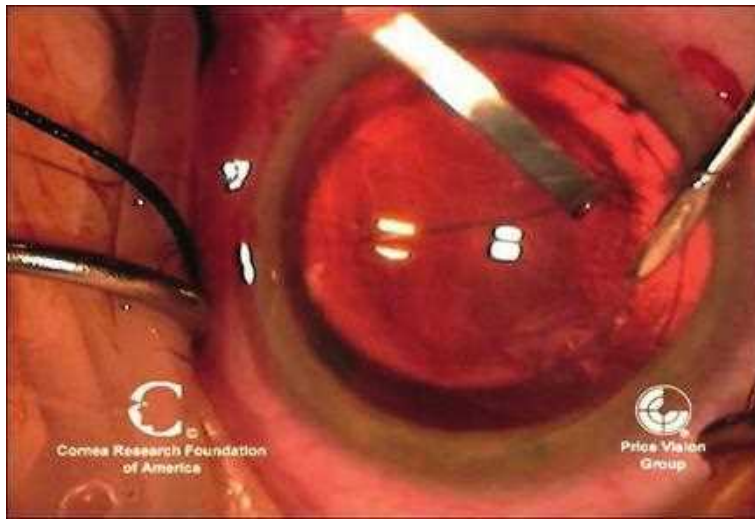
##### Contraindications

- Advanced keratoconus and anterior stromal dystrophies
- Hypotony
- Stromal opacities that would preclude acceptable postoperative vision

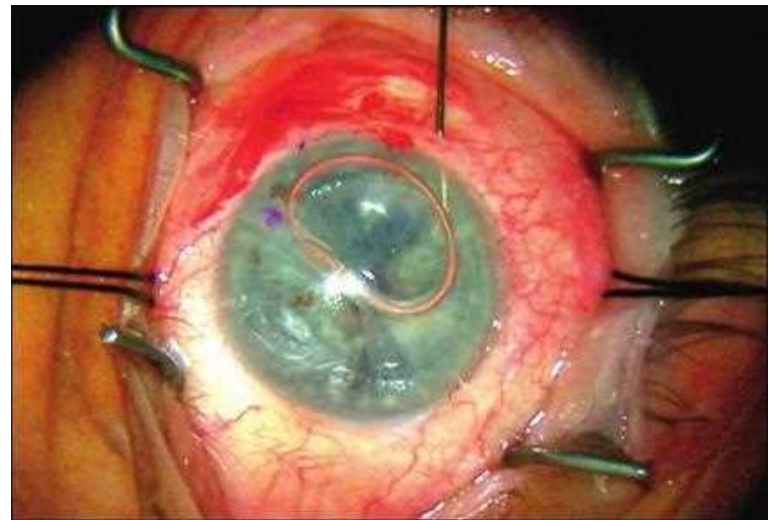
that there is no back pressure from periorbital swelling because back pressure can cause the anterior chamber to forcefully shallow while the donor tissue is being inserted and may even push the donor tissue back out of the eye.

A 2–5 mm clear corneal or scleral tunnel incision is made in the recipient eye. Temporal placement of the incision has several advantages compared with superior placement: Donor button insertion is facilitated because the corneal diameter is longer horizontally; the superior conjunctiva is preserved for future glaucoma surgery, if needed; and orbital anatomy, such as large brows or sunken globes, is not as important.<sup>10</sup> If the recipient epithelium is hazy or scarred, it can be removed, generally improving the view into the eye.

If the host Descemet's membrane has any guttae or other abnormalities, then it should be removed before implanting the donor tissue for optimal visual results. The anterior chamber is filled with air or viscoelastic to facilitate visualization of DM during its removal. A blunt Sinskey hook is used to score DM in a circular pattern to outline the area of planned membrane removal.<sup>10</sup> The far edge of DM is grasped with a stripping instrument or infusion/aspiration tip and carefully is peeled off and removed from the eye (Fig. 4.29.3).<sup>17</sup> Trypan blue can be injected into the anterior chamber immediately after stripping DM to facilitate visualization of loose pieces of Descemet's membrane or stroma.<sup>14</sup> After the membrane is removed, it can be spread on the surface of the cornea to determine whether removal was complete or whether some fragment might remain in the eye. If viscoelastic material was used, care should be taken to completely remove it from the anterior chamber and back surface of the cornea because retained viscoelastic material on the stromal surface can impede attachment of the donor tissue and impair vision.<sup>29</sup>



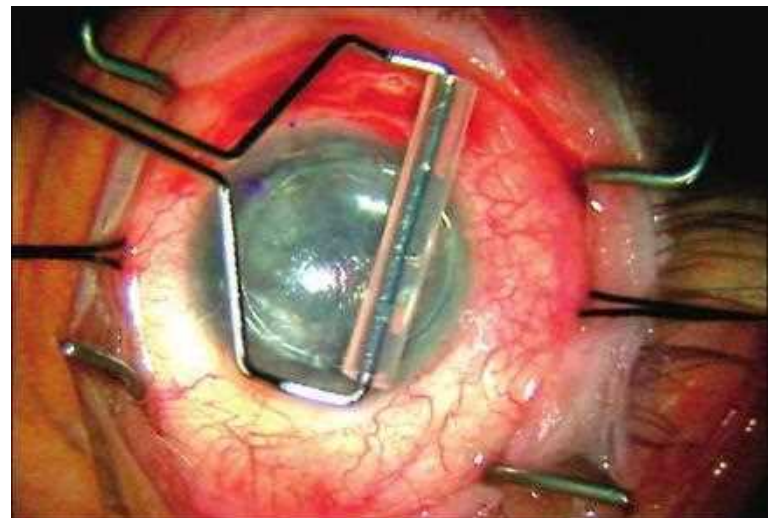
**Fig. 4.29.3** Stripping of host Descemet's membrane using a 90° angled stripper.



**Fig. 4.29.5** Air injection to lift and press the donor tissue up against the host cornea.



**Fig. 4.29.4** Lamellar dissection of the donor tissue with a microkeratome in Descemet's stripping endothelial keratoplasty (DSEK).



**Fig. 4.29.6** Massaging the surface of the recipient cornea to center the Descemet's stripping endothelial keratoplasty (DSEK) donor tissue and remove fluid from the donor/recipient interface, while the anterior chamber is completely filled with air.

## Donor Tissue Preparation and Insertion

Donor tissue preparation involves three steps: dissection; sizing to the appropriate diameter with a trephine (usually 8–9 mm); and insertion. Preparing the donor tissue before opening the patient's eye allows the surgeon to ensure that the tissue will be suitable for transplantation.

### *Descemet's Stripping With Endothelial Keratoplasty*

The lamellar dissection usually is done with a microkeratome either at the eye bank or at the time of surgery (Fig. 4.29.4).<sup>19</sup> A donor corneal/scleral shell is mounted on an artificial anterior chamber designed to accompany the microkeratome being used. The artificial anterior chamber can be filled with viscoelastic material, balanced salt solution, or tissue storage solution. The donor thickness is measured, and a microkeratome head of appropriate depth is selected to provide a posterior donor button of approximately 0.08–0.15 mm thickness, according to the surgeon's preference.

The donor tissue is carefully transferred from the artificial anterior chamber and placed endothelial side up on a standard punch trephine block, where it is punched to an appropriate diameter, taking into consideration the horizontal white-to-white dimensions of the recipient cornea and the anterior chamber depth. The donor tissue is covered with tissue storage solution while the recipient eye is prepared.

A variety of insertion techniques are available, including forceps, glides, and inserters.<sup>10,11,30–33</sup> When using forceps, the posterior donor button is folded over on itself like a “taco” with approximately 60% anterior and 40% posterior, and the folded tissue is gently grasped at the leading edge with forceps that only compress at the tip as the tissue is guided into the eye. A disadvantage of this method is that it can be difficult to unfold the donor correctly in the eye, especially for surgeons early in the learning curve. Another method is to fixate the edge of the donor with a suture, thread the

suture across the anterior chamber and out through a stab incision nasally, and pull the tissue into the eye.<sup>30</sup>

A third method is to place the tissue on a glide or insertion cartridge, insert retina/vitreous intraocular forceps through a nasal stab incision, reach across the eye and grasp the tip of the donor through the 5-mm temporal incision, and pull the tissue into the eye (Video 4.29.1).<sup>31–33</sup> The tissue also can be inserted with a single-use inserter. Use of a funnel glide or inserter helps the donor tissue curl with the endothelium inward for protection as it is inserted.<sup>32,33</sup>

Once the donor tissue is in the eye and unfolded stromal side up, the anterior chamber is filled with air to press the donor button up against the recipient cornea (Fig. 4.29.5). While the anterior chamber is completely filled with air, a LASIK (laser-assisted in situ keratomileusis) roller can be used to help center the donor tissue and massage fluid out of the donor/recipient interface (Fig. 4.29.6).<sup>14</sup> Several small incisions can be made in the peripheral recipient cornea down to the graft interface to help drain any fluid trapped between the donor and recipient tissue.<sup>14</sup> Intraoperative optical coherence tomography (OCT) can help identify fluid in the interface. After 8–10 minutes, many surgeons remove most of the air to prevent pupillary block, and leave the anterior chamber approximately one third full. Some surgeons then have the patients lay face up with a partial air bubble for 30–60 minutes. Other surgeons leave the anterior chamber completely filled for 1–2 hours. At the completion of surgery, antibiotics, corticosteroids, dilating drops, and nonsteroidal anti-inflammatory drugs (NSAIDs) are applied to the treated eye.

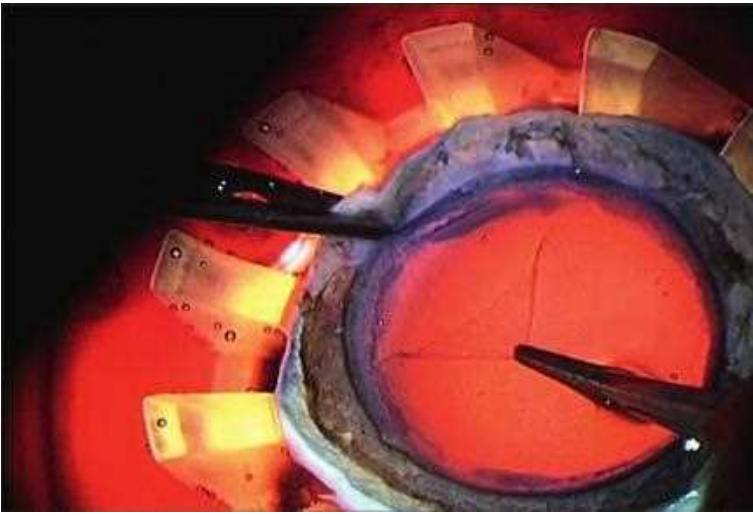
### *Descemet's Membrane Endothelial Keratoplasty*

The most common donor tissue dissection technique consists of gently peeling off DM and endothelium (Video 4.29.2).<sup>34–37</sup> First, the DM periphery

See clip:  
4.29.1

See clip:  
4.29.2





**Fig. 4.29.7 Descemet's Membrane Endothelial Keratoplasty (DMEK) Donor Tissue Preparation.** A nontoothed forceps is being used to peel Descemet's membrane and endothelium from a donor corneal/scleral rim that is submerged in corneal storage solution in a cornea viewing chamber. The corneal/scleral rim was stained with trypan blue to enhance visualization of the scored edge of the membrane.

is scored all the way around. The tissue is stained with trypan blue to enhance visualization. The peripheral edge is lifted all the way around by using a microfinger or hockey stick-shaped instrument. With the tissue submerged in tissue storage solution, an edge of the membrane is grasped with forceps and peeled about halfway to the center, quadrant by quadrant, with replacement of each section on the stromal base (Fig. 4.29.7). The tissue is partially trephined, cutting through DM but not completely through the stroma. An edge is grasped with nontoothed forceps, and the central DM is gently peeled from the underlying stroma and replaced in tissue storage solution. Donor DM and endothelium also can be isolated using air, fluid, or viscoelastic.<sup>23–25</sup> However, using a type 1 big bubble to detach DM limits the graft diameter to about 7–7.5 mm, and the graft must be cut from the stroma with scissors.



See clip:  
4.29.3

Immediately before insertion into the recipient eye (Video 4.29.3), the donor tissue is stained again with trypan blue to improve visualization. The donor tissue naturally curls up endothelium-outward and can be placed in a glass pipette or inserter, such as an IOL injector, for placement in the recipient eye. The donor DM is gently unfolded in the correct orientation with a combination of balanced salt solution and air injections. Then air or a long-acting gas (20% sulfur hexafluoride) is injected beneath the donor tissue to completely fill the anterior chamber and press the graft up against the host cornea.

Instead of allowing the donor tissue to naturally curl with the endothelium facing outward, opposite sides can be folded over the middle (trifold technique), with the endothelium facing inward.<sup>38</sup> The folded tissue is pulled into an IOL cartridge and injected into the eye or pulled in with forceps. Both the PDEK donor preparation method and the trifold DMEK insertion technique facilitate unfolding the donor tissue inside the recipient eye. Thus both allow use of younger donor tissue, which otherwise can be more challenging to unfold.

## COMBINED PROCEDURES

EKP can be combined with other intraocular surgeries, such as phacoemulsification, IOL implantation, IOL exchange, secondary lens implant, pars plana vitrectomy, or anterior vitrectomy.<sup>13,14</sup> Combining EKP with surgeries that require a larger incision can complicate wound closure and maintenance of an air-tight incision, which is important for ensuring donor attachment. A modest mean hyperopic shift typically is reported after EKP (in the range of 0.25–0.5 D after DMEK and 0.5–1.5 D after DSEK).<sup>9,13,35</sup> Therefore, when cataract extraction and IOL implantation is performed before EKP, whether as a staged or combined procedure, the expected refractive shift should be factored into the IOL calculation.

## OUTCOMES

### Visual Acuity

EKP provides more rapid and predictable visual recovery than PKP, allowing patients to return to work and daily activities sooner. In large PKP series, the rate of 20/40 or better vision has ranged from 47%–65% in Fuchs' dystrophy patients and from 20%–40% in patients with pseudo-phakic or aphakic bullous keratopathy.<sup>3–5,39</sup> Unfortunately, PKP can result in significant corneal distortion, so 10%–15% of PKP eyes generally require use of a hard contact lens for best vision, and in some cases, vision can be limited to counting fingers or worse.

DSEK is performed through a small incision and causes little to no corneal distortion. A mean corrected distance visual acuity (CDVA) of 20/40 is generally achieved within 3–6 months of DSEK, and over 90% of patients without ocular comorbidities achieve 20/40 or better vision.<sup>9,13</sup> A small percentage of patients who have undergone DSEK reach less than 20/40 vision because of irregularities resulting from the lamellar dissection or from folds that form in the donor tissue as it conforms to the back of the recipient cornea.<sup>40</sup> Thinner DSEK tissue provides better vision than thicker tissue.<sup>21</sup>

With DMEK, the visual recovery is impressive. In patients without ocular comorbidities, greater than 70% of those who have undergone DMEK achieve 20/25 or better vision within 3 months.<sup>35,41</sup> Overall the visual acuity achieved with DMEK is comparable with that in normal eyes, and DMEK achieves a more normal posterior corneal surface with fewer higher-order aberrations than DSEK or PKP.<sup>41</sup> Visual recovery is so rapid after DMEK that fellow eyes can be treated within 1–2 weeks of each other, with or without combined cataract extraction.<sup>42</sup>

### Refractive Changes

In contrast to PKP, EKP causes little to no change in corneal topography, resulting in far less change in spherical equivalent or cylinder. PKP induces +4.00–+5.00 diopters (D) of refractive cylinder on average and may exceed +8.00 D.<sup>3,5</sup> DSEK and DMEK cause no significant increase in mean refractive cylinder.<sup>9,13,35</sup> DSEK generally induces +0.50–+2.00 D of hyperopia,<sup>9,13</sup> whereas DMEK causes a smaller mean hyperopic shift of about +0.25–+0.50 D.<sup>35</sup>

### Graft Survival

It is not unusual for surgeons who are learning to perform EKP to initially have a higher rate of primary graft failure caused by surgical trauma. However, with experience, the primary graft failure rate should drop to the low levels seen with PKP.

In an initial consecutive DSEK series, the 5-year graft survival rate was similar to that reported for PKP in the large multicenter Cornea Donor Study (95% versus 93% for Fuchs' dystrophy and 76% versus 73% for pseudo-phakic or aphakic corneal edema).<sup>43,44</sup> PKP regrafts generally have a poor 5-year survival rate of 53% or less,<sup>6,39</sup> whereas the 4-year survival rate for DSEK under failed PKP was 74% in an initial consecutive series.<sup>28</sup>

Previous glaucoma surgery is a major risk factor for graft failure. Five-year DSEK graft survival was 95% in a series of eyes without previous glaucoma surgery versus 48% in eyes with one or more previous trabeculectomy or glaucoma tube shunt surgeries.<sup>45</sup>

## Complications

### Graft Detachment

Lack of complete adherence between the donor tissue and host cornea is the most frequent early complication with EKP. Reported rates have ranged from 0%–82%.<sup>9,13</sup> Detachment is addressed by reinjecting air into the eye. Keys to minimizing the risk of graft detachment are meticulous wound construction to preclude postoperative wound leaks, complete removal of fluid from the donor/host interface, achieving a firm air tamponade, and cautioning the patient not to rub the eye in the early postoperative period.

For partially detached DSEK grafts, observation is sufficient because they frequently will seal down spontaneously over time. With DMEK, partial detachments are more common and less likely to seal down spontaneously.

### Immunological Rejection

Immunological rejection is a leading cause of PKP failure. Allan et al. found that the incidence of an initial rejection episode within 2 years of



surgery was significantly lower with EKP than with PKP, and this difference was thought to be related to the frequently shorter duration of topical corticosteroid use after PKP to facilitate healing of the large incision.<sup>46</sup>

DMEK has an extremely low rate of initial rejection episodes. The 2-year probability of a rejection episode was less than 1% with DMEK, compared with 12% for DSEK and 18% for PKP, in a single-center study that utilized the same corticosteroid dosing regimen and rejection evaluation criteria for all three types of grafts and statistical methods that took length of follow-up into account.<sup>47</sup> These findings are consistent with reports from other centers that have had less than 1% cumulative rate of rejection with DMEK through 2 years compared with 3%–14% rates with DSEK.<sup>48–50</sup>

### Postkeratoplasty Intraocular Pressure Elevation

Intraocular pressure (IOP) elevation is fairly common after both EKP and PKP and primarily is associated with the prolonged use of topical corticosteroids to prevent graft rejection.<sup>51</sup> Previous history of glaucoma or ocular hypertension is a key risk factor. DMEK has such a low risk of graft rejection that it is safe to reduce the corticosteroid strength after about 1 month, and this dramatically reduces the risk of IOP elevation.<sup>52,53</sup>

EKP does not distort the corneal surface so it is easier to obtain accurate IOP measurements after EKP than it is after PKP. The addition of donor stromal tissue in DSEK does not alter IOP as measured with Goldmann applanation tonometry.<sup>54</sup>

### Infrequent Complications

Since EKP is performed with a small incision and the graft is held in place with an air bubble rather than by sutures, it avoids the suture-related complications seen after PKP, such as infiltrates/abscess, astigmatism, and suture erosions.<sup>9,13</sup> Moreover, being a closed-eye procedure, EKP provides greater tectonic stability and avoids the risk of suprachoroidal hemorrhage that can result in the loss of the eye with an open-sky procedure, such as PKP. However, interface irregularities can occur with lamellar procedures, such as EKP. Interface contaminants, such as retained viscoelastic or retained host DM with guttae, can distort vision. Epithelial down-growth or in-growth is also a rare but potentially serious complication with EKP, but it can be avoided with proper technique.

## OUTLOOK

Endothelial keratoplasty techniques continue to evolve. More work is needed to further facilitate EKP techniques, minimize endothelial cell loss, and more accurately predict the final refractive outcome following resolution of edema. Randomized prospective studies are needed to compare different techniques and determine the best methods.

Donor tissue remains scarce in developing nations. Ex vivo generation of donor corneal endothelium could allow more patients to benefit from

EKP despite a chronic worldwide shortage of donor corneas.<sup>55</sup> Studies suggest that in patients with Fuchs' dystrophy, it may be possible to stimulate host endothelial regeneration if the peripheral endothelium is relatively healthy despite central endothelial dysfunction. Further work is needed to accomplish this quickly and reliably.<sup>56</sup>

In conclusion, current EKP techniques have significantly increased the benefits and reduced the risks of grafting for patients with endothelial dysfunction. Future developments of EKP are expected to continue this beneficial trend.

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## Surgical Ocular Surface Reconstruction

4.30

Neda Nikpoor, Victor L. Perez

**Definition:** Limbal stem cell deficiency is a devastating condition that can occur as the end result of a diverse set of etiologies. There are multiple surgical options to treat this disorder that may lead to corneal blindness.

**Key Features**

- Tissue harvested from the limbal region contains both corneal epithelium stem cells and immunogenic cells.
- Surgical approach depends on degree of ocular pathology and whether ocular damage is unilateral or bilateral.
- Autologous tissue transplantation always should be assessed first, and if allogeneic tissue is used, long-term systemic immunosuppression is necessary for graft survival.

**Associated Features**

- Concurrent ocular pathologies need to be addressed as much as possible prior to undertaking ocular surface reconstruction to improve the success of the procedure.
- Restoring normal eyelid anatomy and achieving a wet ocular surface prior to surgery are essential for good outcomes.
- Amniotic membrane has been shown to have a variety of desirable effects on the ocular surface.
- Laboratory ex vivo tissue expansion plays an important role in rehabilitating the ocular surface.

**INTRODUCTION**

The maintenance of the ocular surface is the result of a delicate balance between cell death and regeneration by two rapidly renewing tissues, the corneal and conjunctival epithelia. This capacity is dependent on a reservoir of stem cells at the limbus, with the ability to provide young epithelial cells to replace the dying or damaged cells. Corneal stem cells are located mainly in the palisades of Vogt of the limbal cornea rim, with the highest concentration in the superior and inferior limbus.<sup>1</sup>

Damage to the corneal stem cells can occur as a result of a variety of insults, including mechanical, hereditary, chronic inflammatory, and chemical.<sup>2-4</sup> Stem cell deficiency is characterized by conjunctivalization of the cornea associated with persistent epithelial defects, fibrovascular pannus, and stromal scarring and can lead to a variety of ocular surface diseases, ranging from mild ocular discomfort to corneal blindness. (Fig. 4.30.1).

**HISTORICAL PERSPECTIVES**

The first modern limbal stem cell transplantation was reported by Kenyon and Tseng in 1989.<sup>5</sup> More recently, in 1997, Pellegrini et al. suggested the possibility of expanding stem cells ex vivo for later transplantation.<sup>6</sup> Since then, multiple groups have published reports utilizing different methods of ocular surface reconstruction for a variety of surface pathologies.<sup>4,5,7-10</sup> With the ever-growing number of procedures around the world, the Cornea Society issued a standardized nomenclature in 2011.<sup>11</sup>

**General Concepts**

Some of the main principles of ocular surface reconstruction are as follows:

- The environment and the extracellular matrix on the surface of the eye on which corneal stem cells are transplanted have a profound effect on



**Fig. 4.30.1** A total stem cell failure as a result of severe alkali burn.

the success of the procedure. A moist, well-lubricated environment and proper lid anatomy are crucial for increasing the survival rate of these transplants.

- Tissue harvested from the corneal-scleral area includes corneal stem cells, fibroblasts, and Langerhans' cells. The limbus is a highly vascular part of the ocular surface allowing the immune cells to have access to this area. Therefore, proper immune suppression is an essential aspect of ocular surface reconstruction when an immune-compatible source of tissue is not available and an allogeneic graft is used.
- Corneal and conjunctival stem cells may be harvested from either the patient's contralateral eye (autografting) or from a cadaveric or living-related donor (allografting). Tissue from any of these sources then can be directly transplanted or expanded ex vivo in a laboratory. The selection of certain stem cell markers, such as p63 expressed in ex vivo expanded cells, can significantly improve long-term graft survival.<sup>12</sup> More recently, nonocular stem cells have demonstrated usefulness as a source for tissue.<sup>13</sup>

**PREOPERATIVE CONSIDERATIONS**

Some of the important aspects of preoperative evaluation are listed in [Table 4.30.1](#). Preoperative evaluation can guide the surgeon to the most appropriate modality of treatment and is vital to the success of the ocular surface rehabilitation. Foremost to this preoperative planning is distinguishing between primary and secondary ocular surface failures. Primary failure is the result of the direct causal agent, which can be chemical injury, inflammatory conditions, or infections. In contrast, secondary failure derives from factors that result in a decompensated ocular surface; these include elevated intraocular pressure as well as eyelid and tear abnormalities. Before attempting surgical reconstruction, both primary and secondary causes of ocular surface failure must be addressed and corrected. If appropriate, lid repair, mucous membrane grafting, tarsorrhaphy, and PROSE (prosthetic replacement of the ocular surface ecosystem) lenses can be utilized. In addition, a systemic evaluation must be performed to ensure that the patient is a good candidate for systemic immune suppression, if needed.

In general, patients with ocular surface disorders can be divided into two main groups: (1) those with total stem cell deficiency and (2) those with partial stem cell deficiency. Each group can then be further divided



**TABLE 4.30.1** Preoperative Considerations for Ocular Surface Reconstructive Surgery

Examination Element	Clinical Finding or Significance
Establishment of the diagnosis	Loss of palisades of Vogt, persistent epithelial defects, corneal pannus, etc.
Determination of the etiology of ocular surface disease	Primary (aniridia, ectodermal dysplasia, etc.); secondary (chemical injury, OCP, Stevens–Johnson syndrome, etc.)
Extent and severity of the disease	Cornea only or conjunctival involvement
Extent of ocular inflammation	Conjunctival inflammation, intraocular inflammation, etc.
Status of the fellow eye	If normal, may be a source of tissue for autografting
Coexistent ocular pathology	Glaucoma, adnexal pathology (e.g., trichiasis, etc.)
Ocular surface lubrication	Assessment of tear film insufficiency, and dryness are vital to success and may require additional surgical considerations
General health of the patient	Renal, cardiac, hepatic status if systemic immunosuppression is required

OCP, ocular cicatricial pemphigoid.

based on unilateral or bilateral disease, which can each be subdivided into partial versus total limbal stem cell deficiency (LSCD).

## OPERATIVE PROCEDURES

### Unilateral Disease

The prototypical example is unilateral chemical injury. Many of the treatment modalities discussed above for relative stem cell deficiency may be applicable to eyes with total stem cell deficiency with some modifications. For example, application of amniotic membrane may be helpful in terms of decreasing ocular surface inflammation as an adjunct to more definitive treatments.

The main advantage in cases of unilateral stem cell deficiency is that the contralateral, unaffected eye can be a source of immunologically compatible conjunctival and corneal cells, which may allow for a safer reconstitution of the ocular surface.

### Partial Stem Cell Deficiency

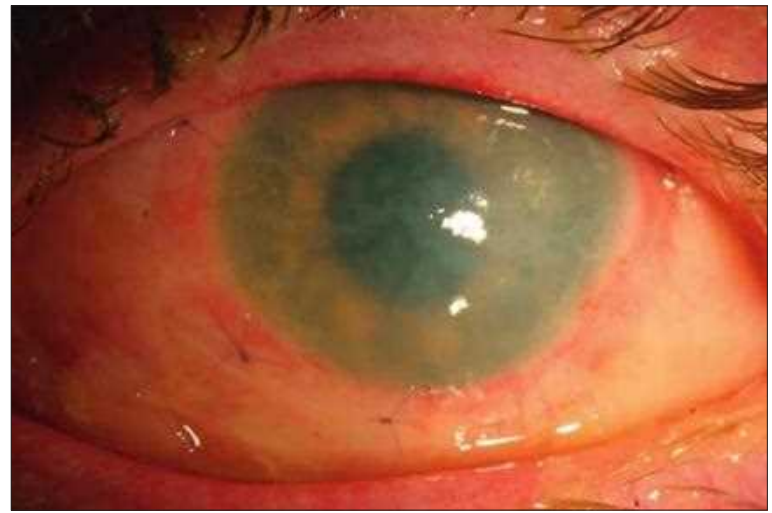
Surgical treatments are more successful in this group of patients because there are some reserves of stem cells present. Causes include entities, such as mild chemical burn, pterygia, and chronic ocular inflammation.

If the patient is asymptomatic or minimally symptomatic with a clear central visual axis, some partial peripheral conjunctivalization of the cornea can be well tolerated for long periods.<sup>7,8</sup> In these cases, simple lubrication with preservative-free artificial tears, topical anti-inflammatory drops, and close follow-up may be sufficient. In the case of acute trauma, some partial LSCD may be transient and can be observed for resolution with medical management.

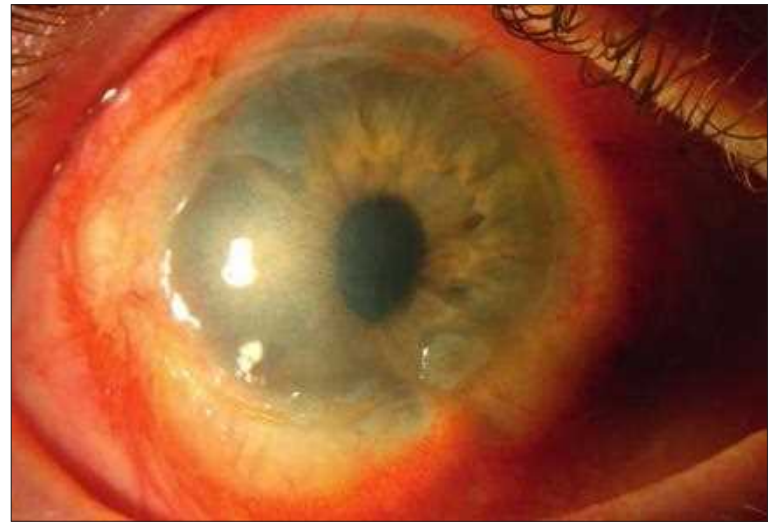
For symptomatic patients there are three main surgical procedures that can be efficacious either individually or in combination. These include mechanical debridement, application of amniotic membrane, and autologous limbal stem cell transplantation.

#### Mechanical Debridement

If the visual axis or a larger portion of the peripheral cornea is covered by conjunctival tissue, simple mechanical debridement of this tissue may allow the remaining corneal stem cells to repopulate the central cornea with normal or near-normal epithelium. The procedure can be done with topical anesthesia and consists of debriding abnormal epithelium with a crescent blade or Weck–Cel sponge followed by the application of a bandage contact lens. The goal of this procedure is to provide the patient with a fairly clear visual axis and not to make the entire corneal surface normal. Some investigators have reported success with as little as two clock hours of normal limbal cells.<sup>6,7</sup> In a variant known as sequential sector conjunctival epitheliectomy (SSCE),<sup>14</sup> conjunctival sheets are debrided every 24–48 hours until the patient has completely re-epithelized. Regardless of the number or extent of debridement, patients should be placed on postoperative topical antibiotics and artificial tears. This procedure can be done in combination with an amniotic membrane graft as described below.



**Fig. 4.30.2** An amniotic membrane application shortly after severe chemical burn.



**Fig. 4.30.3** The same patient as in Fig. 4.30.2, 2 years after the placement of amniotic membrane tissue.

#### Amniotic Membrane Grafting

The most important properties of amniotic membrane harvested from the innermost layer of the placenta include the anti-inflammatory effect through downregulation of fibroblasts and providing a substrate for proliferation of the corneal and conjunctival epithelial cells.<sup>15,16</sup> These properties are only useful when some reserve of stem cells is present because the amniotic membrane itself is not a source of stem cells.

Work by Tseng and others has shown that the application of amniotic membrane to eyes with partial stem cell deficiency can improve ocular surface health and, in some cases, even restore a near-normal corneal epithelium.<sup>17–21</sup> Examples include acute and chronic chemical injuries, acute Stevens–Johnson syndrome, and iatrogenic stem cell deficiency. In these cases, application of the amniotic membrane, with or without mechanical debridement, can result in decreased ocular inflammation and allow the remaining corneal stem cells to repopulate the ocular surface.<sup>22</sup>

Amniotic membrane is commercially available in several forms, including a preserved wet amniotic membrane, a dehydrated form, and a contact lens–mounted membrane.<sup>23,24</sup> The amniotic membrane is placed on the eye with the epithelial side up to cover the area of interest. The membrane then can be secured to the cornea or episclera with 10-0 nylon sutures or fibrin glue (Figs. 4.30.2 and 4.30.3).

#### Autologous Limbal Stem Cell Transplantation

When there is relative or sectoral stem cell deficiency and the condition is unilateral, the unaffected part of the eye or the contralateral eye can serve as a donor for stem cells. Stem cells can be harvested from either the contralateral eye or from normal areas of the affected eye and transplanted to the area of stem cell deficiency. The first option is preferred. The surgical technique used is identical to that for an autologous graft for total stem cell deficiency and is described below.

## Total Stem Cell Deficiency

In general, if there is isolated LSCD in one eye, the treatment is autologous stem cell transplantation, or simple limbal epithelial transplantation (SLET). If LSCD and a conjunctival defect exist, the treatment involves conjunctival autograft. Presence of symblepharon, conjunctival defect, and LSCD may require mucous membrane grafting as well, depending on the size of the defect and extent of symblepharon.

### Autologous Limbal Stem Cell Transplantation

The traditional surgical approach involves careful dissection of the conjunctival tissue from the limbal area of the affected eye.<sup>25–28</sup> A rim of keratolimbal tissue from the contralateral eye, including a conjunctival rim and anterior cornea, can be harvested. Several tissue grafts can be harvested from the fellow eye. The superior and the inferior 4–5 clock hours of limbus offer the highest concentration of corneal stem cells. This tissue then can be carefully transported to the prepared bed with the maintenance of correct orientation. The tissue can be sewn into place by using nonabsorbable sutures, taking care not to pass the sutures through the harvested stem cell area. However, now that fibrin glue is widely available, it can be used to attach this tissue, thus avoiding the inflammatory reaction associated with sutures.<sup>29</sup> A bandage contact lens is then applied to the eye.

More recently, Sangwan et al. described SLET, a novel technique.<sup>30,31</sup> In this procedure a 2 × 2 mm or 1 clock hour section of autologous limbal tissue was excised from the uninvolved eye. The harvested graft was then divided into eight segments. After the host cornea was scraped of any fibrovascular epithelium, and an amniotic membrane secured with fibrin glue and the segments were placed epithelial side up on the optimized ocular surface and secured with fibrin glue, a bandage contact lens was then fitted to protect the tissue.

Postoperatively, patients are treated with antibiotics, corticosteroids, and preservative-free artificial tears. The bandage contact lens can be removed when the ocular surface is stable. Long-term systemic immune suppression is not necessary in these patients.

Prior to undertaking the harvesting of limbal tissue for stem cell transplantation, it should be clearly established that the fellow eye is not affected, and that there is an ample reservoir of stem cells present. A risk of inducing relative stem cell deficiency to the donor eye does exist if too much tissue is harvested. Most clinicians avoid taking more than 4 clock hours of tissue from the donor eye. When concern exists about the health of the fellow eye, allografts may be considered (see below). This method is highly successful, with graft survival rates reported up to 100% over a 47-month period.<sup>32,33</sup>

Basu et al. recently reported long-term follow up of 125 cases and found that with this approach, patients had notable improvement in the clinical appearance of their ocular surface as well as an increase in their visual acuity during the 1.5-year follow-up. The clinical factors associated with failure were identified as acid injury, severe symblepharon, and SLET combined with keratoplasty. In addition, the chapter authors' group has observed poorer outcomes in SLET patients who had autoimmune cicatrizing conjunctivitis as the cause of their LSCD.<sup>34</sup> Another indication for SLET is LSCD after treatment of ocular surface neoplasia. It should be noted that in this scenario, it would be prudent to defer ocular surface reconstruction of the affected eye until it has been established that there is no recurrence of the neoplasia.

## Bilateral Disease

Entities that can result in total stem cell failure in both eyes include severe chemical injuries, Stevens–Johnson disease, ocular cicatricial pemphigoid (OCP), and aniridia. Of note, many known bilateral disorders can be highly asymmetrical. In cases where a patient's history would suggest a bilateral process in the setting of a clinically unilateral process, the patient should be treated as having a bilateral LSCD to avoid possible donor site complications. The conditions in this group are the most difficult to address because the surgical options to rehabilitate the ocular surface are hindered by the lack of an immunologically compatible source of stem cells. This necessitates the use of either living-related donor tissue or cells harvested from cadaver eyes and aggressive systemic and topical immunosuppression.

### Keratolimbal Allograft and Allogeneic SLET

Keratolimbal tissue can be harvested from either a living-related donor's healthy cornea or from the whole globe or from corneal tissue of a cadaveric donor. The harvested allograft can then be transplanted directly onto

the injured eye. Neither living-related donors nor cadavers are perfect sources for grafts, and thus both advantages and disadvantages must be weighed.

Living-related donor transplants are advantageous in that harvested cells are typically more immunologically compatible than from a random source, especially if human lymphocyte antigen (HLA) matching is performed. Reinhard et al. demonstrated that this allows for longer survival time of the transplanted cells.<sup>35</sup> Specifically, they showed that over 5 years the grafts with only 0–1 HLA mismatches had a 65% success rate compared with 14% of unmatched tissue. Living-related donor tissue also has the benefit of stem cells that are fresh. One recent modification is the use of allogeneic SLET, which is surgically identical to SLET described above except that the donor eye is a living-related donor or cadaver rather than the patient's fellow eye. The disadvantage of all allogeneic limbal stem cell techniques is that even with HLA matching, postoperative systemic immunosuppression is required. Furthermore, the amount of tissue that can be harvested from the donor eye is limited, and there is a risk of inducing an ocular surface disorder in the healthy eye of a donor.

For keratolimbal allograft (KLAL), the tissue can be harvested under peribulbar anesthesia, similar to what has been described above for conjunctival limbal autograft. A total of 4 clock hours of tissue may be harvested, equally divided from the upper and lower limbus. This donor tissue then is placed onto the recipient eye after peritomy and superficial keratectomy have been performed to prepare the limbus. The donor tissue is secured to the cornea anteriorly and posteriorly to the episclera using either fibrin glue or 10-0 nylon sutures. Amniotic membrane may be transplanted at the same time, as needed.

In contrast, using cadaveric donor tissue allows the surgeon to harvest greater quantities of tissue than can be removed from living eyes. This theoretically improves the success of the ocular surface reconstruction, especially in eyes with severe stem cell deficiency. However, cadaveric tissue must be screened for communicable diseases. The time necessary for these tests along with tissue damage that occurs during standard tissue processing can result in stem cells of lower quality. The Minnesota Lions Eye Bank suggested certain criteria for tissue harvested for KLAL. These criteria include obtaining tissue from the youngest donor possible (including pediatric sources), taking care to avoid damage to limbal stem cells, including a 3–4 mm skirt of conjunctiva and a large corneoscleral rim, as well as obtaining both donor eyes to ensure adequate tissue.<sup>36,37</sup>

Some investigators advocate the use of more than one donor eye to allow complete coverage of the limbus.<sup>28</sup> Penetrating keratoplasty (PKP) or anterior lamellar keratoplasty (ALK) can be performed at the same time, or at a later setting when the ocular surface is more stable.<sup>26,28</sup> In 2010, Choi et al. reported a modified technique for both graft harvesting and host bed preparation by using a femtosecond laser, which showed good short-term results.<sup>38</sup>

Postoperatively, patients are treated with topical antibiotics, corticosteroids, and systemic immunosuppression. Because of the relative abundance of Langerhans' cells and HLA-DR antigens in the limbus, a high rate of immunological reaction can be expected, which may lead to recurrence of stem cell failure, necessitating aggressive and long-term immunosuppression. Although experts agree that postoperative long-term immunosuppressive therapy is necessary for the success of nonautologous grafts, the exact regimen and timeframe for treatment are highly variable. One commonly used method for postoperative immunosuppression is the Cincinnati protocol. This technique employs 1 year of corticosteroid coverage along with systemic tacrolimus, sirolimus, and mycophenolate.<sup>39</sup> It is not yet clear to what extent and for how long patients require immunosuppression after living-related and cadaveric allogeneic SLET.

The reported outcomes of KLAL vary, depending on the underlying disease entities and the duration of follow-up. A recent study reported successful improvement in ocular surface in up to 89% of living-related donors over a 32-month follow-up.<sup>17,32,40–42</sup> In contrast, the same study reported only a 33% success rate for cadaveric donor grafts over the same period. However, the long-term follow-up has shown a trend toward progressive decline of stem cell population and destabilization of the ocular surface despite systemic immunosuppression.<sup>43,44</sup>

### Ex Vivo Expanded Limbal Stem Cells and Nonocular Tissue

The majority of recent advancements in the area of stem cell transplants have focused on the harvesting and subsequent ex vivo expansion of limbal cells. Expansion of stem cells by culturing them in vitro theoretically provides a large supply of stem cells that can be used for surface reconstruction. This allows the surgeon to not only selectively remove fibroblast and Langerhans' cells, which may affect the long-term survival of allografted



cells, but also allows for minimal tissue to be excised from a donor source, decreased the potential risks associated with tissue harvesting.

In this approach, a minimal amount of limbal tissue (1–2 mm) is harvested either from an eye with relative stem cell deficiency, or the normal contralateral eye of a patient with unilateral total stem cell deficiency. In cases where severe and total bilateral stem cell deficiency exists, cells can be harvested from either a living-related donor or cadaver eyes. Studies have demonstrated the ability to use conjunctival tissue as well.<sup>45</sup> These cells then are amplified in culture media on a carrier, which will be utilized for transport and transplant of the cells onto the diseased eye. The exact method of ex vivo expansion varies widely, with success demonstrated under many conditions, including both explants and cell suspensions with or without 3T3 mouse fibroblasts and serum. However, regardless of the method for culturing the cells, obtaining a high percentage of p63-bright cells (>3% of all clonogenic cells) is of vital importance to the success of the graft.<sup>12</sup>

The amplified cells then may be mounted on a substrate. Current substrates include petrolatum gauze, denuded human amniotic membranes, fibrin, 3T3 cells, and bandage soft contact lenses. The recipient eye is then prepared in a similar manner to the method described for keratolimbal grafting. The cultured stem cells and their carrier are transferred onto the recipient bed, anchored to the limbus with 10-0 nylon sutures and to the surrounding conjunctiva with 8-0 Vicryl sutures. A bandage contact lens often is placed on the eye and kept in place until the ocular surface stabilizes.<sup>6,46–48</sup>

Although postoperative treatment for allogeneic tissue is similar to that for patients with keratolimbal grafts as described above, autologous tissue should be used when possible to avoid the need for immunosuppression.

Schwab et al. found improvement in the ocular surface of 60% of patients with autologous cells, and in all of the patients (total 4) with allogeneic cells combined with immunosuppression, with a mean follow-up period of 13 months.<sup>46</sup> Shimazaki et al., on the other hand, found only a 46.2% success rate in achieving a stable and healthy ocular surface in allografted patients.<sup>49</sup> Furthermore, in this report, the authors did not find a difference in success rate between this technique and cadaveric limbal transplantation combined with amniotic membrane. Baylis et al. recently reviewed 28 case reports and series regarding cultured limbal stem cells published over a 13-year period and compiled outcome data.<sup>50</sup> Despite wide variation in technique, they noted an overall success rate of 77% for autografts and 73% for allografts (76% overall). They also demonstrated that failures typically occurred in the first 2 years before stabilizing. In a 10-year study of 113 eyes reported in 2010, Rama et al.<sup>12</sup> showed a 76% success rate, with most failures occurring in the first year. They noted that, as mentioned earlier, grafts with more than 3% p63-bright cells had a 78% chance of success versus only 11% in those grafts with fewer than 3%.<sup>12</sup>

## SPECIAL CONSIDERATIONS IN OCULAR SURFACE RECONSTRUCTION

Other concurrent pathologies need to be addressed fully prior to undertaking ocular surface reconstruction to improve the success of the procedure. These may include the involvement of other subspecialties, such as oculoplastic surgery to address eyelid abnormalities and glaucoma to maximize pressure control.

### Ocular Surface Optimization

The ocular surface needs to be lubricated using treatments, such as preservative-free artificial tears, punctal occlusion, or PROSE lenses. A wet ocular surface is a requirement prior to proceeding with any surface reconstruction or limbal stem cell surgery. The use of autologous serum tears may be beneficial pre- and postoperatively. In fact, Gomes et al. established that preoperative dry eye was the single most important prognostic factor for graft survival. To this end, this team recently described the successful use of preoperative transplantation of labial mucous membranes and minor salivary gland transplantation to improve the ocular surface status.<sup>51</sup> Depending on the size of the defect and the extent of the symblepharon, conjunctival autograft (for unilateral LSCD with conjunctival defect) or mucous membrane grafting (for symblepharon or bilateral disease) may be necessary. One important point to consider in reconstructing the eyelid margin and palpebral conjunctiva is that the mucous membrane graft should be smooth and not so bulky as to cause trauma to the cornea. Furthermore, the ocular inflammation needs to be maximally and aggressively

treated with the use of topical and possibly systemic immune-modulating agents.

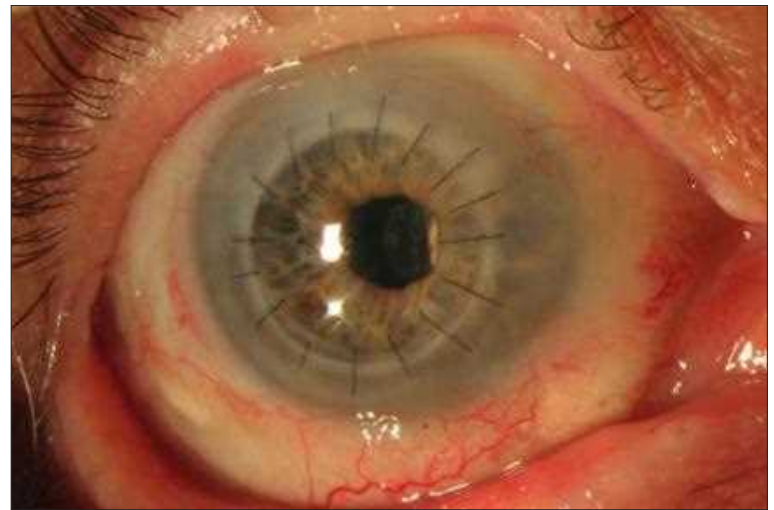
## Corneal Transplantation

Patients with stem cell failure often have corneal pathology, which may necessitate ALK or PKP. Performing keratoplasty in eyes with stem cell failure carries a very poor prognosis for graft survival because of chronic inflammation, vascularization of the ocular surface, and poor epithelial healing after surgery.

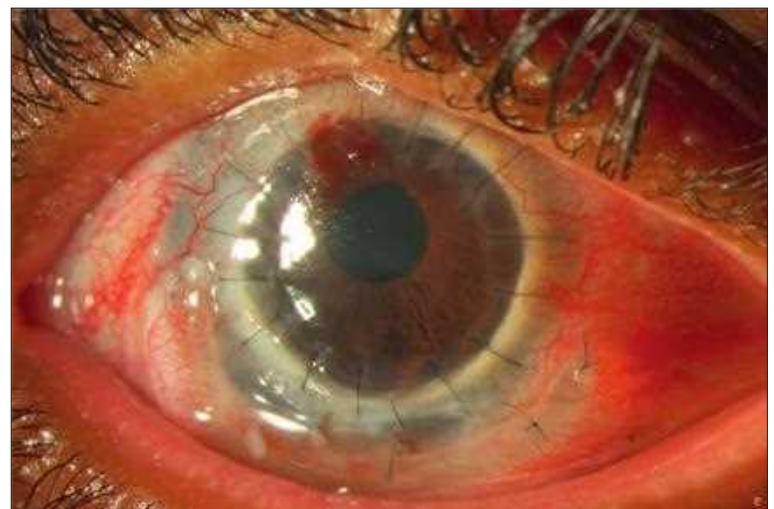
Corneal transplantation, however, may be more successful when the ocular surface has been reconstituted by using some of the approaches outlined above. The optimal timing for cornea transplantation is not well known. Some authors indicate that a stepwise approach, starting with stem cell transplantation followed by keratoplasty when the ocular surface is stable, may improve the graft survival.<sup>36,52</sup> The largest study of penetrating keratoplasty after cultivated limbal epithelial transplantation was reported by Sangwan et al., who reported a 93% success rate in terms of graft clarity, with a mean follow-up time of 8.3 months.<sup>52</sup> Currently, the literature supports a two-staged procedure for ocular surface rehabilitation. An article by Basu et al. compared an autologous cultivated limbal stem cell transplantation with either a simultaneous penetrating keratoplasty or a second procedure performed 6 weeks later.<sup>53</sup> Over a long-term follow-up, they noted an 80% graft survival for the staged procedure versus a 25% survival rate for the simultaneous technique (Figs. 4.30.4 and 4.30.5).

## CONCLUSIONS

In summary, the management of limbal stem cell deficiency requires careful preoperative case selection and control of comorbid factors, such



**Fig. 4.30.4** A cadaveric keratolimbal allograft with a subsequent penetrating keratoplasty.



**Fig. 4.30.5** The ocular surface of an eye in a patient with a total limbal stem cell deficiency following a chemical burn after a simultaneous cadaveric keratolimbal allograft, penetrating keratoplasty, and amniotic membrane tissue placement.



as eyelid anatomy, immune disease, and a wet ocular surface without exposure. Some techniques, such as minor salivary gland transplantation and mucous membrane grafts, may be useful in preparing the ocular surface for limbal stem cell transplants. In unilateral LSCD, the best results to date are with autologous stem cell transplantations, most recently with a trend toward SLET for most cases. A role still exists for ex vivo expansion of cells to avoid harm to the healthy donor eye. Bilateral cases can be treated with living-related donor or cadaver transplants and topical and systemic immunosuppression. Again, ex vivo expansion may play a role here. Finally, in refractory cases or for patients who are not candidates for the above-mentioned techniques, keratoprosthesis is an option.

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# Management of Corneal Thinning, Melting, and Perforation

4.31

Nicoletta Fynn-Thompson, Michael H. Goldstein

**Definition:** Management of full-thickness or partial-thickness loss of corneal tissue.

## Key Features

- Concurrent, aggressive treatment of the underlying infectious or inflammatory condition.
- Multiple treatment options, depending on the clinical situation.
- The primary goal is to re-establish the tectonic integrity of the globe.

## Associated Features

- Typically a true ophthalmic emergency.
- Surgical management often warranted.

## INTRODUCTION

The integrity of the cornea can be compromised by both inflammatory and noninflammatory conditions, which may lead to stromal thinning, melting, and perforation. Progression may be slow over months to years, or may be rapid over hours to days. Rapid, proper recognition and management of these conditions is crucial to restore vision and to re-establish the integrity of the eye.

## CORNEAL THINNING FROM NONINFLAMMATORY DISORDERS

Noninflammatory corneal thinning disorders cause progressive ectasia caused by thinning of the stroma. The most common of these disorders include keratoconus, pellucid marginal degeneration, keratoglobus, and posterior keratoconus. Progressive corneal thinning (ectasia) is a rare but serious complication after laser refractive surgery. These conditions generally are slowly progressive. The primary goal, therefore, is to maintain functional vision (see Chapter 4.18 for more information).

## CORNEAL THINNING AND MELTING FROM INFLAMMATORY DISORDERS

Inflammatory corneal disorders can cause thinning with stromal melting. These conditions are often associated with pain, epithelial defects, corneal neovascularization, and other inflammatory changes. Progression is fast and emergent treatment is warranted upon diagnosis.

Noninfectious inflammatory causes include peripheral ulcerative keratitis (PUK), Mooren's ulcer, Terrien's marginal degeneration, and collagen vascular disorders. Infectious inflammatory causes include viral herpetic keratitis, bacterial keratitis, and fungal keratitis.

PUK suggests an autoimmune-mediated process and often is associated with rheumatoid arthritis. PUK (see Chapter 4.16) is seen with Wegener's granulomatosis, systemic lupus erythematosus, polyarteritis nodosa, ulcerative colitis, and relapsing polychondritis.

Medical treatment is directed both locally at the cornea and systemically to address the underlying systemic inflammatory process. The goals

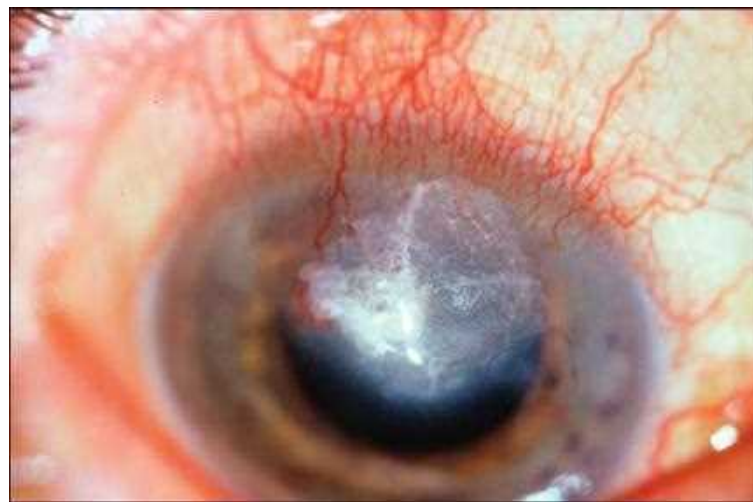
of local (ocular) treatment are to (1) provide local supportive therapy to decrease corneal melting; and (2) promote re-epithelization of the corneal surface. These goals are accomplished using the following modalities: aggressive lubrication with preservative-free eyedrops and ointments, punctal occlusion, placement of a bandage contact lens, patching, oral doxycycline (or equivalent), and tarsorrhaphy. Topical collagenase inhibitors and corticosteroids are of some value, but may delay healing and cause perforation by initiating stromal melting. The goal of systemic therapy is to suppress the underlying systemic disorder with immunosuppressive or immunomodulatory therapy. If the underlying autoimmune disease is not treated, the corneal pathology will not improve.<sup>1-3</sup>

Inflammatory corneal disorders caused by infectious organisms (viral, bacterial, or fungal) also cause thinning and melting of the corneal stroma. Treating the pathogen aggressively with both topical and oral medications is most important to reduce further destruction of stromal tissue. Some advocate the use of concomitant corticosteroid drops once the infection is controlled, but this is controversial. If, despite aggressive therapy, stromal keratolysis progresses with development of descemetocoele, impending perforation, or frank perforation, the goal becomes maintaining the eye's integrity.

## SURGICAL TREATMENT OF CORNEAL PERFORATIONS

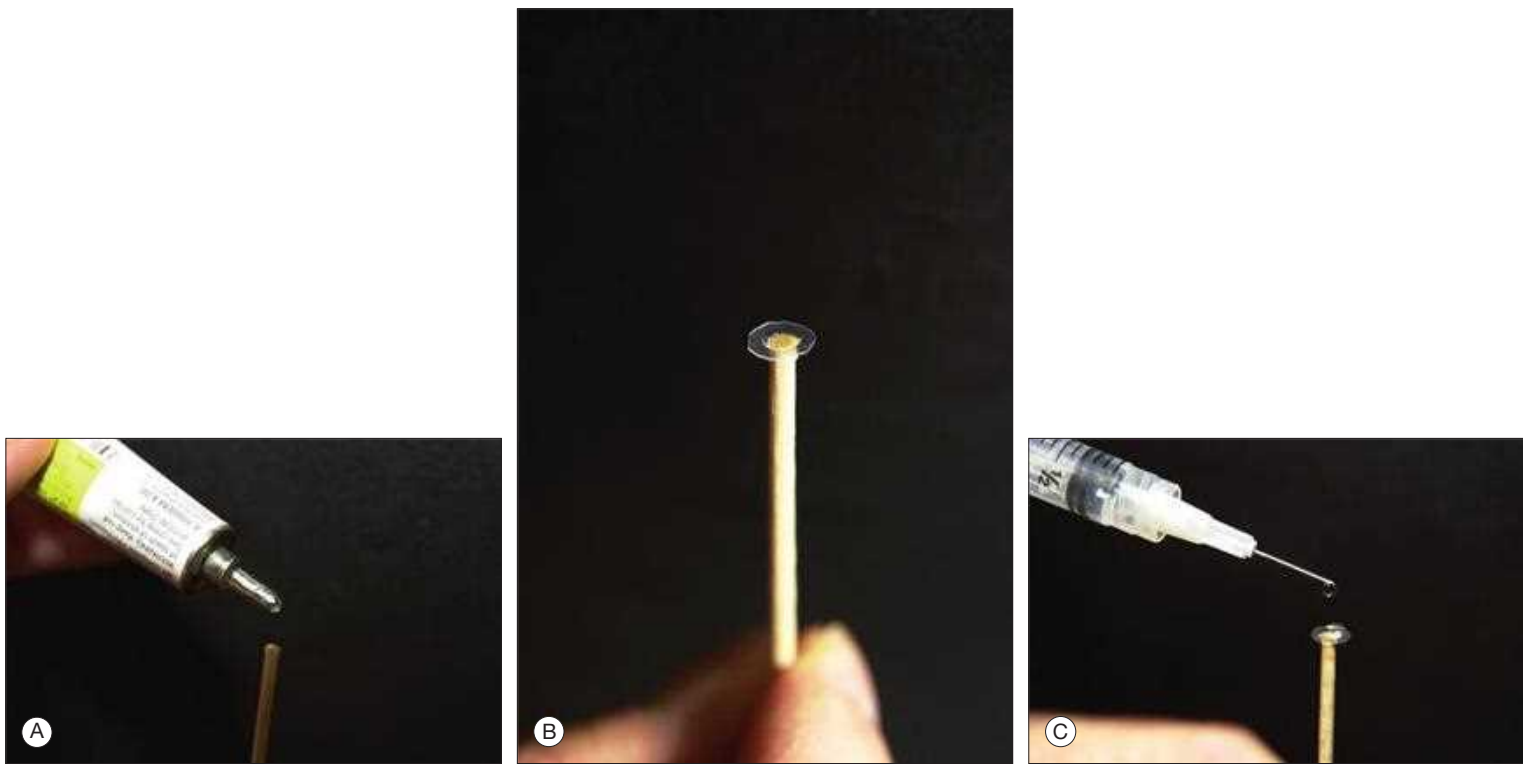
### Tissue Adhesives

Descemetocoeles or impending perforations can be stabilized or temporized by application of tissue adhesive and placement of a bandage contact lens with close follow-up. Studies have shown this procedure arrests the process of ulceration in noninfectious eyes. Application of tissue adhesive is much easier to perform in impending perforations than in frank perforations.<sup>4</sup> Frank corneal perforations, however, can be treated successfully with application of tissue adhesives. Although perforations measuring 1–2 mm are most successfully treated, those measuring up to 3 mm have been closed. Cyanoacrylate tissue adhesive traditionally has been used (Fig. 4.31.1).<sup>5</sup> Its



**Fig. 4.31.1** Corneal perforation sealed with cyanoacrylate glue. (Courtesy Michael H. Goldstein, MD.)





**Fig. 4.31.2** Technique for application of cyanoacrylate glue for treatment of larger corneal perforation. (A) Apply ointment to end of Q-tip. (B) Place small circular disc from cut drape onto Q-tip and adhere with ointment. (C) Place corneal glue onto disc and then place onto eye. (Courtesy Michael H. Goldstein, MD.)

use to seal corneal perforations was first reported in 1968.<sup>6</sup> Cyanoacrylate adhesive prevents re-epithelization into the zone of damaged stroma and prevents collagenase production, which leads to stromal melting.<sup>7</sup>

A common technique is described below, although several other excellent techniques exist. A thorough examination of the eye prior to application of the glue must be performed, with attention to the extent of perforation, possible lenticular damage, and possible uveal prolapse at the perforation site. Placing the patient in the supine position under an operating microscope is easier than examining the patient at the slit lamp. A topical anesthetic and lid speculum should be placed in the eye. Debridement of necrotic tissue from the ulcer crater is performed. This removed material is plated onto culture media to identify a possible infectious cause. The tissue adhesive adheres best to basement membrane so debridement of 1–2 mm of normal epithelium surrounding the ulcer allows for proper adhesion of the glue. A methylcellulose spear is used to dry the site. The tissue adhesive is then placed in microaliquots on the site of perforation with an applicator. The applicator can be a needle from a tuberculin syringe,<sup>8</sup> a 23-gauge Angiocath catheter (with the needle removed),<sup>9</sup> or a micropipette.<sup>10</sup> Alternatively, a polyethylene disc can be made and attached to a sterile wooden stick with ophthalmic ointment, and glue placed on the disc. Both are applied directly to the site of perforation (Fig. 4.31.2). The disc can then be removed or left in place.<sup>11,12</sup> The goal is to create a controlled method of placement of the smallest amount of glue to seal the perforation. The glue will solidify via polymerization over the next few minutes. A large, heaped mound over the crater is not necessary and can cause irritation and discomfort for the patient after the procedure.

The eye should be checked for evidence of leakage. If secure, then a bandage contact lens is applied, and the patient is checked at the slit lamp to confirm that the anterior chamber is forming and the glue is in place.

Application of tissue adhesive in frank corneal perforations is more challenging, as preparation of the site is more difficult secondary to the constant flow of aqueous from the perforation. Unless contraindicated, an air bubble can be placed into the anterior chamber to temporarily occlude the perforation by surface tension. Larger air bubbles risk pupillary block and increased intraocular pressure (IOP), so caution must be exercised.<sup>13</sup> In eyes with flat anterior chambers, to avoid incarceration of uveal tissue or the lens, viscoelastic material may be injected into the anterior chamber.<sup>14</sup>

Postoperatively, the patient may be placed on an aqueous suppressant, if medically tolerated. Patients with noninfectious perforations should receive a prophylactic broad-spectrum antibiotic four times daily. A protective shield should be kept in place at all times. Preservative-free artificial tears applied frequently will aid in lubrication with a bandage lens in place.

Patients also benefit from oral doxycycline because of its ability to inhibit collagenase. Depending on the cause, infected perforations are treated with frequent fortified antibacterial, antiviral, or antifungal therapy. Initially, patients should be examined daily, and any complaints of decreased vision, pain, tearing, or photophobia should be attended to immediately. If the bandage lens falls out, it must be replaced. If the glue becomes dislodged, reapplication is often necessary.

Corneal glue remains in place for weeks to months. It is recommended to leave it in place until it loosens and dislodges on its own, leaving behind a more healthy-appearing stromal tissue.

The reported potential complications for corneal tissue adhesive application include cataract formation,<sup>15</sup> corneal infiltrates, increased IOP,<sup>16</sup> giant papillary conjunctivitis,<sup>17</sup> retinal toxicity,<sup>18</sup> keratitis,<sup>19</sup> and iridocorneal and iridolenticular adhesions.<sup>20</sup>

Studies have shown that fibrin glue causes less neovascularization; however, a longer time is required for the adhesive plug to form. Application of fibrin glue has been shown to be successful with the additional placement of amniotic membrane grafts for structural support of a perforated cornea.<sup>21–25</sup>

## Penetrating Keratoplasty

If the corneal perforation is not amenable to treatment with corneal glue, then tectonic grafting is indicated (either a full-thickness or lamellar graft).<sup>8</sup> The smallest trephination capable of incorporating the site of perforation is chosen. Trephination of a soft eye is very difficult but is aided by the judicious use of viscoelastic materials. Alternatively, the temporary application of cyanoacrylate adhesive and sodium hyaluronate to create a normotensive eye has been described.<sup>26</sup> A customized hard contact lens applied with tissue adhesive to the corneal perforation has been reported to stabilize the eye and allow for trephination.<sup>27</sup> In some cases, handheld trephination may be needed. Care must be taken to avoid protrusion of ocular contents or damaging the iris or lens. The donor cornea should be secured with interrupted 10-0 nylon sutures.

Several case reports and case series have demonstrated the promising use of tectonic Descemet's stripping automated endothelial (DSAEK) in managing both impending and sterile corneal perforations.<sup>28,29</sup>

Postoperative care is challenging. A balance between reducing inflammation and the possibility of graft rejection, without significantly reducing the host's immunity, must be reached. Topical corticosteroids four times daily usually are required. Aggressive antibiotic, antiviral, or antifungal treatment is continued as indicated for infectious cases. For noninfectious cases, a broad-spectrum antibiotic is used four times daily.



**Fig. 4.31.3** Corneal perforation secondary to acute hydrops treated with patch graft. (Courtesy Michael H. Goldstein, MD.)

### Patch Graft

If the perforation is too large for a tissue adhesive, but too small for a full-sized penetrating keratoplasty (PKP) procedure, then a corneal patch graft can be helpful (Fig. 4.31.3). These procedures can temporarily stabilize a perforation or descemetocoele or may be a permanent treatment. It is ideal for peripheral pathology. Care should be taken when used for central pathology because it can interfere with visual outcome.

Gamma-irradiated sterile cornea now is available and very helpful in emergency situations. This tissue has a long shelf life, increasing the number of corneas suitable for transplantation. This tissue eliminates the risk of infection because of its preparation. It can be used only when viable endothelium is not necessary. Preliminary studies show it is useful in corneal patch graft surgery.<sup>30</sup>

### Miscellaneous Treatments

Multilayered amniotic membrane grafts alone may be successful in treating nontraumatic corneal perforations. More favorable outcomes are limited to perforations measuring less than 1.5 mm in diameter.<sup>13,31</sup> As

mentioned previously, amniotic membrane in conjunction with fibrin glue has been used to successfully close corneal perforations and restore globe integrity. Conjunctival flaps are useful for thinning due to ulcerations or descemetocoele formation but are contraindicated in corneal perforations. Conjunctival resection may be a useful adjuvant therapy in appropriate cases of corneal melting secondary to PUK.

### CONCLUSIONS

Corneal thinning, melting, and perforation can be caused by both inflammatory and noninflammatory conditions. Identification and treatment of these conditions is critical in the successful management of these patients. If impending or actual perforation occurs, immediate action must be taken to restore the integrity of the eye. This can be done with tissue adhesives, patch grafts, PKP, or amniotic membrane grafts.

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# Basic Science of the Lens

Michael E. Boulton

## 5.1



IN THIS CHAPTER  
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**Definition:** A normally transparent intraocular structure whose function is to alter the pathway of light that has entered the eye to focus the image on the retina.

### Key Features

- Normally transparent at birth.
- Increasing opacity with age, infection, surgery, trauma, various metabolic states.
- Can alter shape and refractive power to allow for accommodation.

### Associated Features

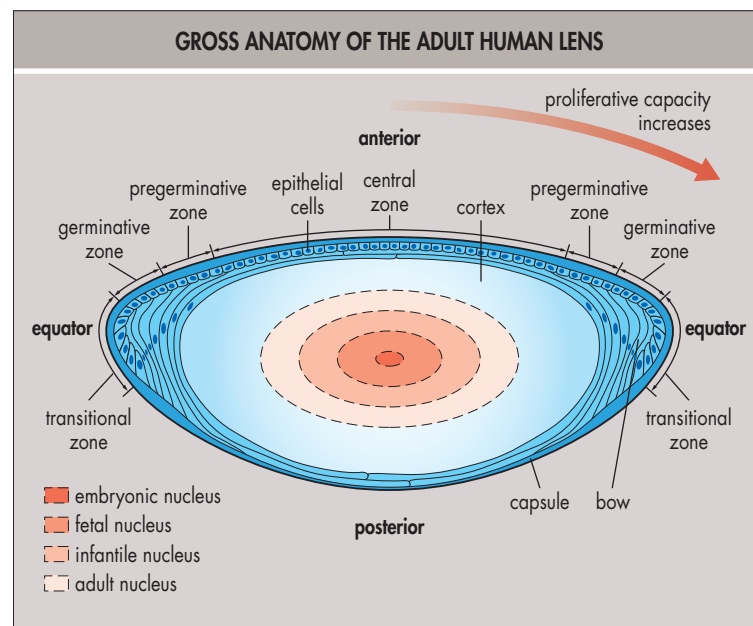
- Asymmetric oblate spheroid shape.
- Avascular.
- Located posterior to the iris and anterior to the vitreous body.
- Spectral filter.
- Suspended by the zonules.

The lens is a transparent structure that has evolved to alter the pathway of the light entering the eye. In 2002, the World Health Organization estimated that lens pathology (cataract) was the most common cause of blindness worldwide, affecting more than 17 million people across the globe.<sup>1</sup> Cataract surgery is the most common surgical procedure performed in the developed world.<sup>2</sup>

The lens is an asymmetric oblate spheroid that is avascular and lacks nerves and connective tissue.<sup>3</sup> It is located posterior to the iris with its anterior surface in contact with the aqueous and the posterior surface with the vitreous. The lens is suspended by the zonular fibers that arise from the ciliary epithelium and insert 1–2  $\mu\text{m}$  into the outer part of the capsule.<sup>4</sup> Histologically the lens consists of three major components: capsule, epithelium, and lens substance (Fig. 5.1.1).

The lens capsule is an acellular envelope that is continuously synthesized by the lens epithelium anteriorly and fiber cells posteriorly. It is composed of a number of stacked lamellae, which contain major structural proteins and fibronectin.<sup>5</sup> The lens epithelium is a single layer of cuboidal cells approximately 10  $\mu\text{m}$  high and 15  $\mu\text{m}$  wide, located beneath the anterior capsule that extends to the equatorial lens bow. Their basal surface adheres to the capsule, whereas their anterior surface abuts the newly formed elongating lens fibers. The proliferative capacity of epithelial cells is greatest at the equator, and cells in the germinative zone are dividing constantly. Here, newly formed cells are forced into the transitional zone where they elongate and differentiate to form the fiber mass of the lens.<sup>3</sup> The bulk of the lens is composed of the nucleus and cortex, which comprise densely packed lens cytoplasm (“fiber cells”) with very little extracellular space.

The lens grows throughout life but at a slower rate with increasing age. The rate of increase in lens weight and equatorial diameter is greater than that of lens thickness.<sup>6</sup> Newly formed fibers are internalized as more are added at the transitional zone of the lens, and thus the newest fibers are in the outer cortex, and the oldest fibers are found in the center of the nucleus. Each growth shell, therefore, represents a layer of fibers that are younger than those in the shell immediately preceding it.<sup>7</sup>



**Fig. 5.1.1 Gross Anatomy of the Adult Human Lens.** Note the different regions are not drawn to scale.

The metabolic needs of the lens are met by the aqueous and the vitreous humor, with the majority of glucose and amino acids coming from the aqueous. The capsule is freely permeable to water, ions, other small molecules, and proteins with a molecular weight up to 70 kDa. In addition, epithelial cells and fibers possess a number of channels, pumps, and transporters that enable transcellular movement.

The lens acts as spectral filter and readily absorbs the energetic ultraviolet (UV) component of the electromagnetic spectrum that, if transmitted, has the potential to damage the retina. The overall transmission of visible light decreases with increasing age, a feature that arises largely from age-related changes and brunescence.<sup>8</sup> The refractive index of the lens increases from 1.386 in the peripheral cortex to 1.41 in the central nucleus. In addition, the curvature of the lens increases in a similar manner. Thus each successive layer of fibers has more refractive power and can bend light rays to a greater extent. When visible light passes through the lens, it is split into all the colors of the spectrum. The different wavelengths of these colors result in differences in refraction (chromatic aberration). As a consequence, yellow light (570–595 nm) normally is focused on the retina, blue (440–500 nm) anteriorly, and red (620–770 nm) posteriorly.<sup>9</sup> The lens is designed to minimize spherical aberration (defocus caused by greater refraction of light striking the peripheral lens compared to the center) in these ways:

- The refractive index increases from the periphery to the center of the lens.
- The curvature of both the anterior and the posterior capsule increases toward the poles.
- The curvature of the anterior capsule is greater than that of its posterior counterpart.

- Modulation of pupillary size prevents light from striking the periphery of the lens under nonmydriatic conditions.<sup>9,10</sup>

Accommodation is the process by which the lens changes its optical power by altering its shape and thus its focusing ability. At rest, the ciliary muscle is relaxed and the zonules pull on the lens keeping the capsule under tension and the lens flattened. Accommodation occurs when the ciliary muscle contracts, relaxing the zonules, thus increasing the curvature of the anterior surface and decreasing the radius of curvature from 10 mm to 6 mm. The increase in curvature of the anterior surface increases the refractive power. Accommodation is accompanied by a decrease in pupil size (miosis) and convergence of the two eyes.<sup>11</sup>

Adenosine triphosphate (ATP) is the principal source of energy of the lens, the majority of which comes from the anaerobic metabolism of glucose. Approximately 90%–95% of the glucose that enters the normal lens is phosphorylated to glucose-6-phosphate (G6P) in a reaction catalyzed by hexokinase. G6P is used either in the glycolytic pathway (80% of total glucose) or in the pentose phosphate pathway. The 5%–10% of glucose that is not converted to G6P either enters the sorbitol pathway or is converted into gluconic acid.<sup>12</sup>

The protein concentration within the lens is the highest in the body. The majority of ongoing synthesis generates crystallins and major intrinsic protein 26 (MIP26). The water-soluble crystallins constitute approximately 90% of the total protein content of the lens. The three groups of crystallins can be divided into the  $\alpha$ -crystallin family and the  $\beta/\gamma$ -crystallin superfamily.<sup>13</sup>

The continuous entry of optical radiation into the lens, especially UV (295–400 nm), makes the lens particularly susceptible to photochemical reactions leading to generation of reactive oxygen species (ROS). Protection against damage induced by ROS is achieved by a complex antioxidant system that relies heavily on superoxide dismutase, ascorbate, catalase, and glutathione peroxidase.<sup>14</sup>

Numerous morphological, biochemical, and biophysical changes occur to the lens with age.<sup>15</sup> Most notable are the age-related changes in color (more yellow), light transmission (decreased), consistency (increased hardness), loss of accommodative ability (manifested clinically as presbyopia), and protein aggregation. The resultant lens opacification, referred to as cataract, results in loss of light transmission.

While cataract surgery is safe and commonly performed, a major complication is development of a secondary cataract (posterior capsular opacification or Soemmerring's ring). Posterior capsular opacification (PCO) is the most common and can be further divided into fibrosis type and pearl type (Elschnig's pearls). Vision can be affected by blockage of the visual axis (both) or by progressive decentration of the intraocular lens (IOL) due to remnant lens epithelial cell proliferation and migration, epithelial-mesenchymal transition, collagen deposition, and generation of aberrant

lens fiber cells. Soemmerring's ring is often less visually significant, as the trapped and proliferating residual lens epithelial cells are located in the periphery, behind the iris.<sup>16</sup> While currently no definitive prevention exists, newer surgical techniques and IOLs may help to decrease the incidence of new cases. The current standard treatment involves the use of a neodymium:yttrium–aluminum–garnet (Nd:YAG) laser to perform a capsulectomy in the clinical setting.

In conclusion, the lens is a deceptively complex structure that allows for the transmission and refraction of light. An orderly structure, stable metabolic state, and intact antioxidant system are mandatory to maintain clarity. A full understanding of the basic science related to the lens allows for appreciation of the numerous pathologies that affect it and thus their medical and surgical treatment.

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# Basic Science of the Lens

Michael E. Boulton

## 5.1

**Definition:** A normally transparent intraocular structure whose function is to alter the pathway of light that has entered the eye to focus the image on the retina.

### Key Features

- The lens comprises three parts: (1) the capsule, (2) the lens epithelium, and (3) the lens fibers.
- $\alpha$ -,  $\beta$ - and  $\gamma$ -crystallins constitute 90% of the total protein content of the lens.
- Lens function is dependent on the metabolism of glucose to produce energy, protein synthesis, and a complex antioxidant system.
- Lens transparency is dependent on the highly organized structure of the lens, the dense packing of crystallin, and the supply of appropriate nutrients.
- The lens can change its focusing power through a process called accommodation.
- The lens exhibits age-related changes in structure, light transmission, metabolic capacity, and enzyme activity.
- Secondary cataract occurs when residual lens cells after cataract extraction cause opacification of the visual axis.

### INTRODUCTION

The lens is a vital refractive element of the human eye. The World Health Organization estimates that lens pathology (cataract) is the most common cause of blindness worldwide, affecting over 17 million people.<sup>1</sup> Not surprisingly, cataract surgery is the most common procedure performed in the developed world.<sup>2</sup> An understanding of the basic science of the lens provides valuable insight into the various pathologies involving the lens and their treatment.

### ANATOMY OF THE LENS

The adult human lens is an asymmetric oblate spheroid that does not possess nerves, blood vessels, or connective tissue.<sup>3</sup> The lens is located behind the iris and pupil in the anterior compartment of the eye. The anterior surface is in contact with the aqueous; the posterior surface is in contact with the vitreous. The anterior pole of the lens and the front of the cornea are separated by approximately 3.5 mm.<sup>4</sup> The lens is held in place by the zonular fibers (suspensory ligaments), which run between the lens and the ciliary body. These fibers, which originate in the region of the ciliary epithelium, are fibrillin rich and converge in a circular zone on the lens. Both an anterior and a posterior sheet meet the capsule 1–2 mm from the equator and are embedded into the outer part of the capsule (1–2  $\mu$ m deep). It also is thought that a series of fibers meets the capsule at the equator.<sup>5,6</sup>

Histologically the lens consists of three major components—capsule, epithelium, and lens substance (Fig. 5.1.1).

### Capsule

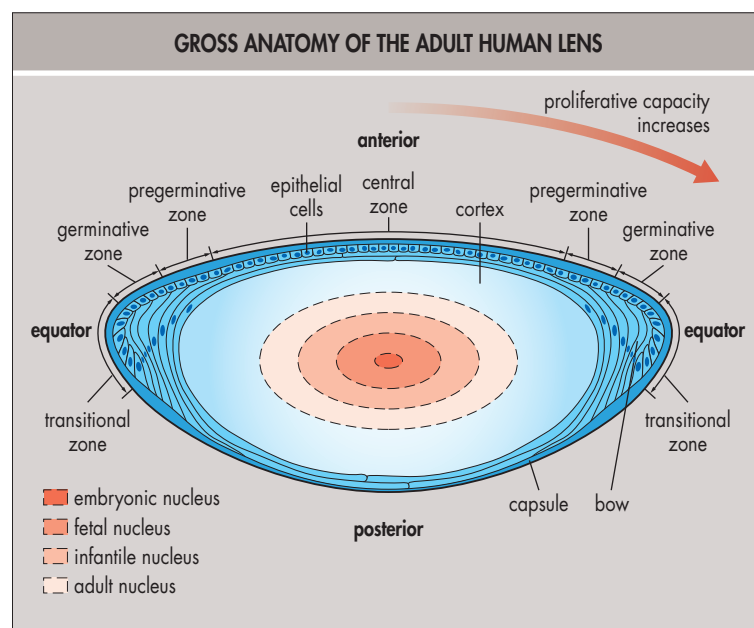
The lens is ensheathed by an elastic envelope composed of epithelial cells and fibers that allows the passage of molecules both into and out of the lens. Capsule thickness varies by location (Fig. 5.1.2) and, except for the posterior capsule, increases with age.<sup>4–6</sup> The capsule is composed of a number of lamellae stacked on top of each other that are narrowest near the outside of the capsule and widest near the cell mass.<sup>7</sup> Major structural proteins and a small amount of fibronectin are found within the lamellae.<sup>8</sup>

This structure is continuously synthesized, anteriorly by the lens epithelium and posteriorly by the fiber cells.

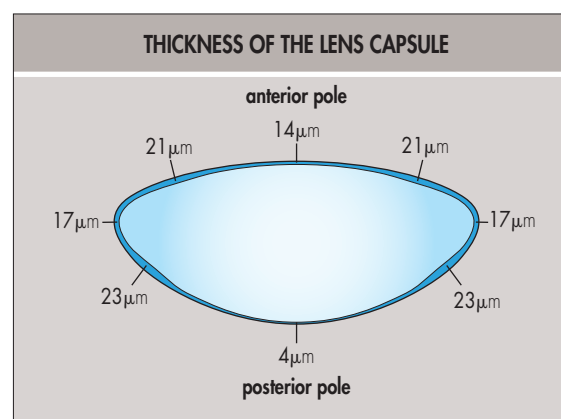
### Epithelial Cells

The lens epithelium is a single layer of cuboidal cells approximately 10  $\mu$ m high and 15  $\mu$ m wide beneath the anterior capsule that extends to the equatorial lens bow. Their basal surface adheres to the capsule, whereas their anterior surface abuts the newly formed elongating lens cytoplasm (“fibers”). Lens epithelial cells have a large array of organelles and contain dense bodies and glycogen particles. Lateral attachment to adjacent cells occurs through both desmosomes and tight junctions.<sup>3,8–10</sup>

Lens epithelial cells contain three cytoskeletal elements: microfilaments (actin), intermediate filaments (vimentin), and microtubules (tubulin). These elements form a network that provides structural support, control of cell shape and volume, intracellular compartmentalization and movement of organelles, cell movement, distribution of mechanical stress, and mediation of chromosome movement during cell division.



**Fig. 5.1.1 Gross Anatomy of the Adult Human Lens.** Note the different regions are not drawn to scale.



**Fig. 5.1.2 Changes in Thickness of the Adult Lens Capsule With Location.**

Epithelial cell density is greatest in the central zone, where cells normally do not proliferate. These cells are the largest epithelial cells found in the lens. The proliferative capacity of epithelial cells is greatest at the equator (see Fig. 5.1.1). Cells here are dividing constantly, with newly formed cells being forced into the transitional zone where they elongate and differentiate to form the fiber mass of the lens.<sup>3,11</sup>

## Lens Substance

The lens substance, the bulk of the lens, is composed of densely packed lens cells with very little extracellular space. The adult lens substance consists of the nucleus and the cortex, which are often histologically indistinct. Although the size of these two regions is age dependent, a study of lenses with an average age of 61 years indicated that the nucleus accounted for approximately 84% of the diameter and thickness of the lens and the cortex for the remaining 16%.<sup>12</sup> The nucleus is subdivided into embryonic, fetal, infantile, and adult nuclei (see Fig. 5.1.1). The embryonic nucleus contains the original primary lens fiber cells that are formed in the lens vesicle. The rest of the nuclei are composed of secondary fibers, which are added concentrically at the different stages of growth by encircling the previously formed nucleus. The cortex, which is located peripherally, is composed of all the secondary fibers formed after sexual maturation.

Fibers are formed constantly throughout life by the elongation of lens epithelial cells at the equator. Initially, transitional columnar cells are formed, but once long enough, the anterior end moves forward beneath the anterior epithelial cell layer and the posterior end is pushed backward along the posterior capsule. The ends of this U-shaped fiber run toward the poles of both capsular surfaces.<sup>3–6</sup> Once fully matured, the fiber detaches from the anterior epithelium and the posterior capsule. Each new layer of secondary fibers formed at the periphery of the lens constitutes a new growth shell. Lens fibers are bound by the interlocking of the lateral plasma membranes of adjacent fibers. Both desmosomes and tight junctions are absent from mature lens fibers, although desmosomes are found between elongating fibers.<sup>3,8,9</sup>

## Sutures

Sutures are found at both the anterior and the posterior poles. They are formed by the overlap of ends of secondary fibers in each growth shell. No sutures are found between the primary fibers in the embryonic nucleus. Each growth shell of secondary fibers formed before birth has an anterior suture shaped as an “erect Y” and a posterior suture shaped as an inverted Y. The formation of sutures enables the shape of the lens to change from spherical to a flattened biconvex sphere.<sup>3,9,13</sup>

## Growth

The lens continuously grows throughout life but at a reduced rate with increased age.<sup>7</sup> The number of both epithelial cells and fibers increases by approximately 45%–50% during the first two decades of life (Fig. 5.1.3). After this, the increase in cell numbers is reduced, with the proportional increase in fibers being very small.<sup>3</sup> During an average lifespan, the surface area of the lens capsule increases from 80 mm<sup>2</sup> at birth to 180 mm<sup>2</sup> by the seventh decade.<sup>5,7</sup>

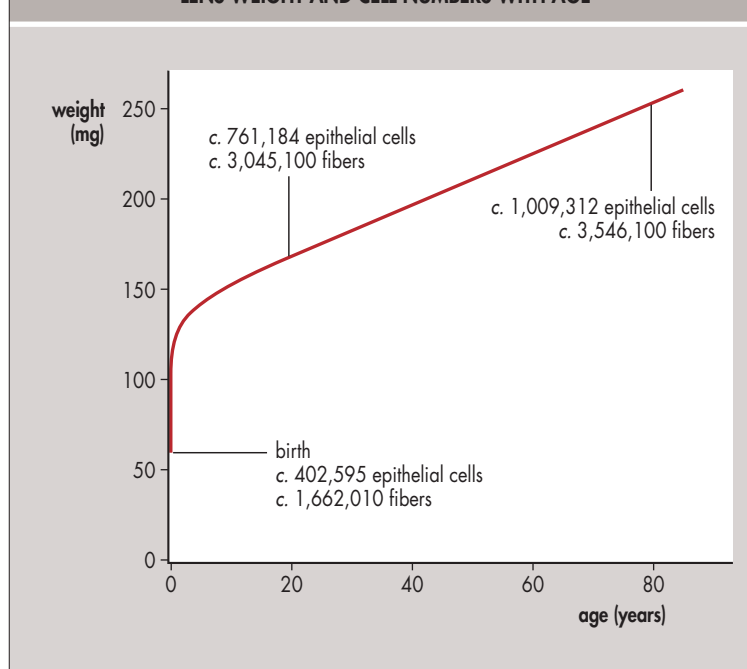
## Mass

The weight of the lens increases rapidly from 65 mg at birth to 125 mg by the end of the first year. It then increases at approximately 2.8 mg/year until the end of the first decade, reaching 150 mg. Thereafter, the rate slows to reach a weight of 260 mg by the age of 90 (see Fig. 5.1.3).<sup>14</sup> The average male lens weighs more than that of an age-matched female, with a mean difference of  $7.9 \pm 2.47$  mg.<sup>15</sup>

## Dimensions

The equatorial diameter of the human lens increases throughout life, slowing after the second decade. The diameter grows from approximately 5 mm at birth to 9–10 mm in a 20-year-old. The thickness of the lens also increases but at a much slower rate. The distance from the anterior to the posterior poles grows from 3.5–4 mm at birth, to 4.75–5 mm (unaccommodated).<sup>4,14</sup> The thickness of the nucleus decreases with age due to compaction, whereas cortical thickness increases as more fibers are added at the periphery. Because the increase in cortical thickness is greater than the decrease in size of the nucleus, the polar axis of the lens increases

### LENS WEIGHT AND CELL NUMBERS WITH AGE



**Fig. 5.1.3 Increase in Lens Weight and Cell Numbers With Age.** Note the correlation between these two parameters. (Lens weight data from Phelps Brown N, Bron AJ. Lens growth. In: Phelps Brown N, Bron AJ, Phelps Brown NA, editors. *Lens disorders. A clinical manual of cataract diagnosis*. Oxford: Butterworth-Heinemann; 1996. p. 17–31. Cell number data from Kuszak JR, Brown HG. Embryology and anatomy of the lens. In: Albert DM, Jakobiec FA, editors. *Principles and practices of ophthalmology. Basic sciences*. Philadelphia: WB Saunders; 1994. p. 82–96.)

with age.<sup>16</sup> The radius of curvature of the anterior surface decreases from 16 mm at the age of 10 years to 8 mm by the age of 80 years. There is very little change in the radius of curvature of the posterior surface, which remains at approximately 8 mm.

## PHYSIOLOGY OF THE LENS

### Permeability, Diffusion, and Transport

After involution of the hyaloid blood supply to the lens, its metabolic needs are met by the aqueous and vitreous humor. The capsule is freely permeable to water, ions, other small molecules, and proteins with a molecular weight of up to 70 kDa. Epithelial cells and fibers possess a number of channels, pumps, and transporters that enable transepithelial movement to and from the extracellular milieu.

### Transport of Ions

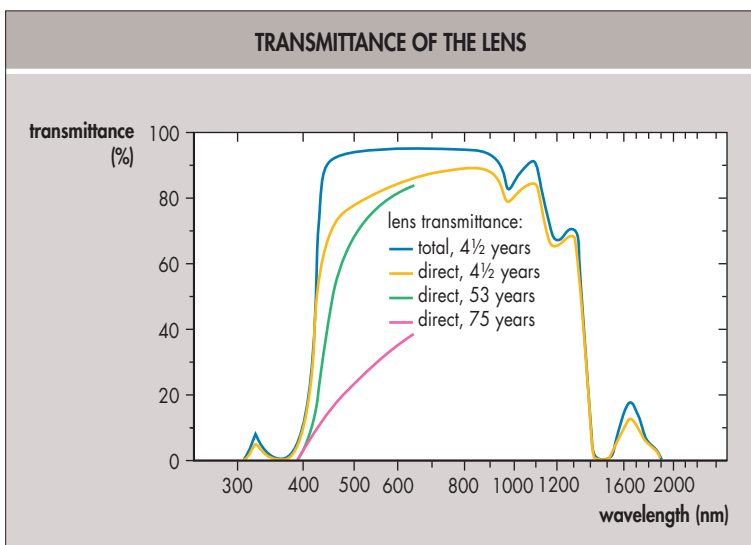
Fiber cells contain large concentrations of negatively charged crystallins. As a result, positively charged cations enter the lens cell to maintain electrical neutrality, and the osmolarity of the intracellular fluid becomes greater than that of the extracellular fluid. Fluid flow and swelling are minimized by the resting potential of the plasma membrane being set at a negative voltage through potassium (K<sup>+</sup>)-selective channels.

The Na<sup>+</sup> ions that leak into the cells are exchanged actively for K<sup>+</sup> ions, which diffuse through the lens down their concentration gradient and leave through ion channels in both the epithelial cells and surface fibers. There is a net movement of Na<sup>+</sup> ions from posterior to anterior and of K<sup>+</sup> ions from anterior to posterior.<sup>17</sup>

Although a pH gradient exists, which increases from the central nucleus to the periphery, the intracellular pH of the lens is approximately 7.0. Lens cells need to continually extrude intracellular protons, which accumulate due to inward movement of positive ions from the extracellular space and lactic acid from anaerobic glycolysis. The pH is regulated by mechanisms capable of increasing and decreasing intracellular acid levels. Molecules, especially proteins, also act as buffers.

### Amino Acid and Sugar Transport

The majority of amino acids and glucose enter the lens from the aqueous across its anterior surface. In addition, the lens can convert keto acids



**Fig. 5.1.4 Changes in Transmission (UV and Visible) of the Normal Aging Human Lens.** (From Boettner EA, Wolter JR. Transmission of the ocular media. *Invest Ophthalmol Vis Sci* 1962;1:776–83.)

into amino acids. The lens acts as a pump–leak system: Amino acids are “pumped” into the lens through the anterior capsule and passively “leak” out through the posterior capsule.

## BIOPHYSICS

### Light Transmission

The lens acts as a spectral filter absorbing long ultraviolet B (UV-B, 300–315 nm) and most of the UV-A (315–400 nm) wavelengths. While there is a transmission band centered around 320 nm of about 8% in children under 10 years, it is reduced to 0.1% by age 22. By age 60, no UV radiation transmits across the lens. The total transmittance of the young lens begins increasing rapidly at about 310 nm and reaches 90% at 450 nm, compared with the older lens, which begins transmitting at 400 nm but does not reach 90% total transmittance until 540 nm (Fig. 5.1.4). The overall transmission of visible light decreases with increasing age, a feature that arises largely from age-related changes and brunescence in the lens (see Fig. 5.1.4).<sup>18,19</sup>

### Transparency

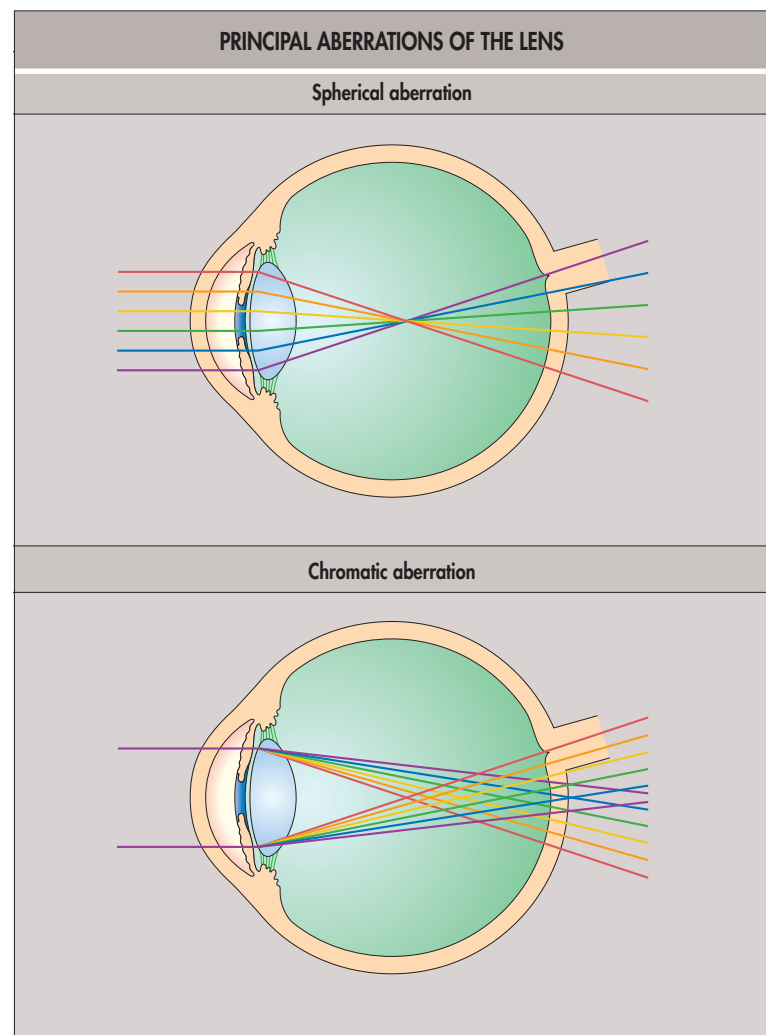
The lens is opaque during the early stages of embryonic development. As development continues and the hyaloid vascular supply is lost, the lens becomes transparent. Transparency is due to the absence of chromophores able to absorb visible light and the presence of a uniform structure that scatters light minimally (less than 5% in the normal human lens). Light scatter is minimized in fiber cells once the fibers have elongated and their organelles have degenerated. Although the epithelial cells contain large organelles that scatter light, the combined refractive index of this layer and the capsule is no different from the refractive index of the aqueous, so light scatter is very small.

### Refractive Indices

The refractive index increases from 1.386 in the peripheral cortex to 1.41 in the central nucleus of the lens. Because both the curvature and refractive index of the lens increase from the periphery toward the center, each successive layer of fibers has more refractive power and therefore can bend light rays to a greater extent.<sup>20</sup> The anterior capsular surface of the lens has a greater refractive index than the posterior capsular surface (1.364–1.381 compared with 1.338–1.357). The increase in refractive index from the surface to the center results from changes in protein concentration; the higher the concentration, the greater the refractive power. This increase must occur as a result of both packing and hydration properties, because protein synthesis in the nucleus is minimal.<sup>18,21</sup>

### Chromatic Aberration

When visible light passes through the lens, it is split into all the colors of the spectrum. The different wavelengths of these colors result in different



**Fig. 5.1.5 Principal Aberrations of the Lens.**

rates of transmission through the lens and some deviation. As a consequence, yellow light (570–595 nm) is normally focused on the retina; light of shorter wavelengths, for example blue (440–500 nm), falls in front because of its slower transmission and increased refraction compared with yellow light. Light of longer wavelengths, for example red (620–770 nm), falls behind because of the faster transmission and less refraction (Fig. 5.1.5). Because the amount of dispersion between the red and the blue images is approximately 1.50–2.00 diopters (D), very little reduction occurs in the clarity of the image that is formed. As the lens accommodates, refraction increases as a result of the increasing power of the lens and, therefore, the amount of chromatic aberration also increases.<sup>20,22–24</sup>

### Spherical Aberration

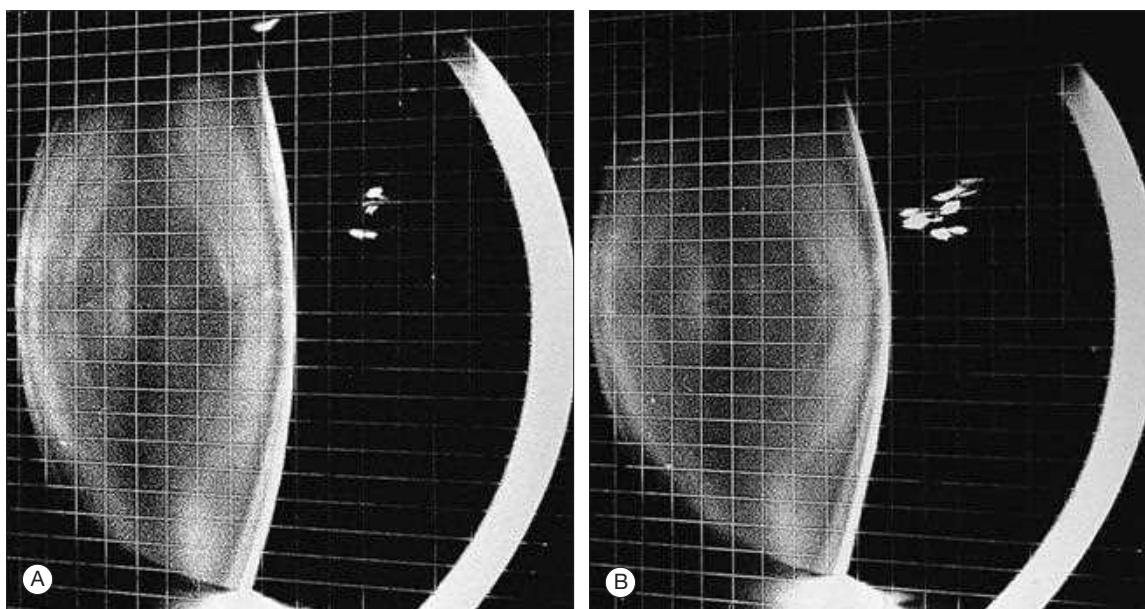
The lens of the human eye is designed to minimize spherical aberration since: (1) refractive index increases from the periphery to the center of the lens; (2) curvature of both the anterior and the posterior capsule increases towards the poles; and (3) curvature of the anterior capsule is greater than that of its posterior counterpart.

As a result of these structural features, the focal points of the peripheral and central rays are similar, which ensures that reduction in the quality of the image is minimal (see Fig. 5.1.5). The pupil diameter also affects the amount of spherical aberration, because light rays do not pass through the periphery of the lens (unless the pupil is dilated). The optimal size of the pupil needed to minimize this imperfection is 2–2.5 mm.<sup>20,22–24</sup>

### Accommodation

The lens is able to change its shape and thus the focusing power of the eye. This process is known as accommodation, and it enables both distant and close objects to be brought into focus on the retina. At rest, the ciliary muscle is relaxed and the zonules pull on the lens keeping the capsule under tension and the lens flattened. Light rays from close objects are divergent and are focused behind the retina in this configuration. The lens





**Fig. 5.1.6 Change in Form of the Lens on Accommodation in a Person of Age 29 Years.** (A) Relaxed. (B) Accommodated. (Grid squares 0.4 mm.) Note the change in curvature of the anterior surface. (From Phelps Brown N, Bron AJ. Accommodation and presbyopia. In: Phelps Brown N, Bron AJ, Phelps Brown NA, editors. Lens disorders. A clinical manual of cataract diagnosis. Oxford: Butterworth-Heinemann; 1996. p. 48–52.)

accommodates these objects by contraction of the ciliary muscles, relaxing the zonules, thus increasing the curvature of the anterior surface and decreasing the radius of curvature from 10 mm to 6 mm. The increase in curvature of the anterior surface increases the refractive power, so that the light rays from close objects are refracted toward each other to a greater extent and, therefore, converge on the fovea. Because the front of the lens has moved forward, the depth of the anterior chamber decreases from 3.5 mm to 3.2–3.3 mm. Very little change occurs in the curvature of the posterior capsule, which remains at approximately 6 mm (Fig. 5.1.6). Accommodation is accompanied by a decrease in pupil size and convergence of the two eyes.

Accommodation can be divided into both physical and physiological processes. Physical accommodation, a measure of the change in shape of the lens, is measured in terms of the amplitude of accommodation using the unit diopter. It represents a measure of the extent to which objects close to the eye can be brought into focus. Physiological accommodation, a measure of the force of ciliary muscle contraction per diopter, is measured with the unit myodioter. The myodioter increases during the act of accommodation.<sup>25,26</sup>

## BIOCHEMISTRY

The lens requires energy to drive thermodynamically unfavorable reactions. Adenosine triphosphate (ATP) is the principal source of this energy, the majority of which comes from the anaerobic metabolism of glucose. Nicotinamide adenine dinucleotide phosphate (NADPH), which is produced principally via the pentose phosphate pathway, is used as a reducing agent in the biosynthesis of many essential cellular components, such as fatty acids and glutathione.

## Sugar Metabolism

Approximately 90%–95% of the glucose that enters the normal lens is phosphorylated into glucose-6-phosphate (G6P) in a reaction catalyzed by hexokinase. Although this enzyme exists as three different isoforms, only types I and II have been found in the lens. Type I has a greater affinity for glucose and is concentrated in the nucleus, where glucose levels are low. Type II, which accounts for 70% of the hexokinase, has a lower affinity for glucose and is found predominantly in the epithelium and cortex, where glucose levels are higher. G6P is used either in the glycolytic pathway (80% of total glucose) or in the pentose phosphate pathway (hexose monophosphate shunt; 10% of total glucose) (Fig. 5.1.7). Hexokinase is saturated by physiological concentrations of glucose found in the lens and limits the rate of both glycolysis and the pentose phosphate pathway. Glycolysis also is regulated by phosphofructokinase and pyruvate kinase.<sup>27,28</sup>

The lens lacks vascularity and thus exists in a hypoxic environment, which results in at least 70% of lens ATP being derived from anaerobic glycolysis. Approximately 3% of lens glucose passes into the more efficient tricarboxylic acid cycle (see Fig. 5.1.7), generating 25% of lens ATP. Glycolysis and the tricarboxylic acid cycle generate two energy-rich molecules; the reduced form of nicotinamide adenine dinucleotide (NADH) and the

reduced form of flavin adenine dinucleotide (FADH<sub>2</sub>). These donate their electrons to oxygen, which releases large amounts of free energy that is subsequently used to generate ATP. This cycle, which is restricted to the epithelial layer, also provides carbon skeleton intermediates for biosynthesis, such as amino acids and porphyrins.<sup>27,29</sup>

The bulk of the pyruvate produced by the glycolytic pathway is reduced to lactate by lactate dehydrogenase (see Fig. 5.1.7), which is concentrated in the cortex. The formation of lactate results in the reoxidation of NADH to NAD<sup>+</sup>. Glyceraldehyde-3-phosphate dehydrogenase regulates the activity of lactate dehydrogenase by controlling the rate of conversion of glyceraldehyde-3-phosphate into 1,3-diphosphoglycerate and, therefore, the availability of NADH.<sup>27–29</sup>

The 5%–10% of glucose that is not phosphorylated into G6P either enters the sorbitol pathway or is converted into gluconic acid (see Fig. 5.1.7). Glucose is converted into sorbitol by aldose reductase, an enzyme localized to the epithelial layer. Sorbitol is converted by polyol dehydrogenase into fructose, a less optimal substrate for glycolysis. Both sorbitol and fructose have the potential to increase osmotic pressure and may help to regulate the volume of the lens.<sup>27–29</sup>

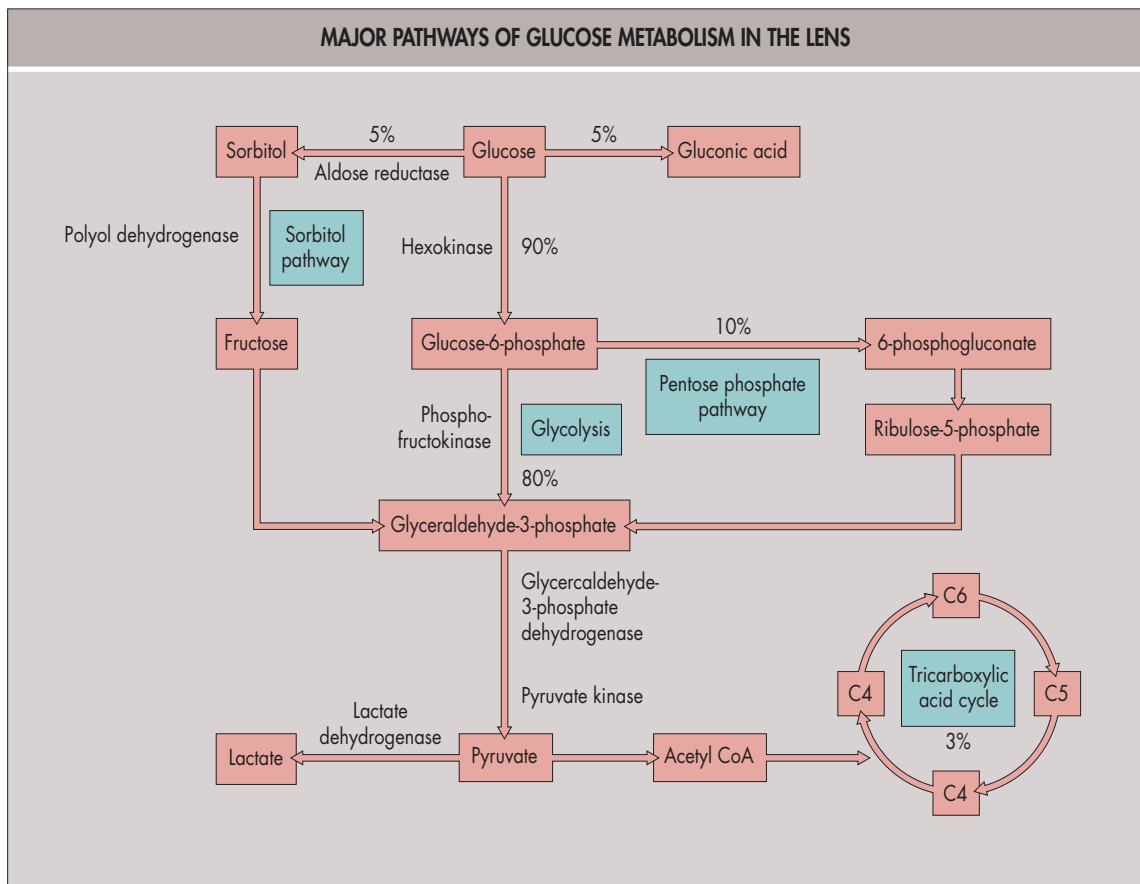
## Protein Metabolism

The protein concentration within the lens is the highest in the body. The majority of ongoing synthesis creates crystallins and major intrinsic protein 26 (MIP26). It is thought that this occurs in the epithelial cells and cortical fibers, which contain the organelles needed.<sup>30</sup>

Lens proteins remain stable for long periods because the majority of the degradative enzymes normally are inhibited. This is coordinated by marking those to be degraded with a small 8.5 kDa protein called *ubiquitin*. This system, which is ATP dependent, is most active in the epithelial layer. Lens proteins are broken down into peptides by endopeptidases and then into amino acids by exopeptidases. Neutral endopeptidase is activated by both calcium and magnesium and is optimal at pH 7.5 (the pH of the lens is approximately 7.0–7.2). The principal substrate of this enzyme is  $\alpha$ -crystallin. The calpains (I and II) are localized mainly in the epithelial cells and cortex and function to degrade crystallins and cytoskeletal proteins. They are cysteine endopeptidases, the activities of which are regulated by calcium. These enzymes are inhibited by calpastatin, a natural inhibitor found at higher concentrations than the calpains. The lens also contains a serine proteinase and a membrane-bound proteinase.<sup>28,29,31</sup> The main exopeptidase is leucine aminopeptidase, an enzyme optimal at pH 8.5–9.0, which catalyzes the removal of amino acids from the N-terminal of peptides. Aminopeptidase III has an optimal pH of 6.0 and as a result has a greater activity than leucine aminopeptidase in the normal lens.<sup>28,29,31</sup>

## Glutathione

Glutathione is found at high concentrations in the lens (3.5–5.5 mmol/g wet weight), especially in the epithelial layer. Glutathione has many important roles in the lens, including<sup>28,29,32</sup>:



**Fig. 5.1.7 Overview of the Major Pathways of Glucose Metabolism in the Lens.** Percentages represent the estimated amount of glucose used in the different pathways.

- Maintaining protein thiols in the reduced state, which helps to maintain lens transparency by preventing the formation of high molecular weight crystallin aggregates.
- Protection of thiol groups involved in cation transport and permeability; for example, oxidation of the -SH groups of the Na<sup>+</sup>,K<sup>+</sup>-ATPase pump, which results in an increased permeability to these ions.
- Protection against oxidative damage (see later in this chapter).
- Removal of xenobiotics; glutathione-S-transferase catalyzes the conjugation of glutathione to hydrophobic compounds with an electrophilic center.

### Amino Acid Transport

Glutathione has a half-life of 1–2 days and is recycled constantly by the  $\gamma$ -glutamyl cycle; its synthesis and degradation occur at approximately the same rate (Fig. 5.1.8). Glutathione is synthesized from L-glutamate, L-cysteine, and glycine in a two-step process that uses 11%–12% of lens ATP.<sup>28,29,32</sup> Reduced glutathione also can be taken into the lens from the aqueous. A reduced glutathione transporter that allows the uptake of glutathione by the lens epithelium has been characterized.<sup>33</sup> The breakdown of glutathione releases its amino acids, which are recycled.

### Antioxidant Mechanisms

The term reactive oxygen species (ROS) refers to highly reactive oxygen radicals that have the potential to damage lipids, proteins, carbohydrates, and nucleic acids. These include the superoxide anion, the hydroxyl free radical, hydroperoxyl radicals, lipid peroxyl radicals, singlet oxygen, and hydrogen peroxide (H<sub>2</sub>O<sub>2</sub>). ROS generally arise from cell metabolism or photochemical reactions. Photochemical damage occurs when light is absorbed by a photosensitizer that, upon photoexcitation, forms a transient excited triplet state that is long lived, allowing for interaction with other molecules producing free radicals or singlet oxygen. The continuous entry of optical radiation into the lens, in particular the absorption of shorter wavelengths (295–400 nm), makes lens tissue particularly susceptible to photochemical reactions. The major ultraviolet (UV) absorbers in the lens are free or bound aromatic amino acids (e.g., tryptophan), numerous pigments (e.g., 3-hydroxykynurenine), and fluorophores. Reactive oxygen species also can enter the lens from the surrounding milieu (e.g., H<sub>2</sub>O<sub>2</sub> is present at high levels in the aqueous humor, 30 mmol/L in humans).<sup>29,34</sup>

ROS have the capacity to damage the lens in many ways<sup>29,35</sup>:

- Peroxidizing membrane lipids results in the formation of aldehydes, which in turn can form cross-links between membrane lipids and proteins.
- Introducing damage into the bases of the DNA (e.g., base modifications) and reducing DNA repair efficiency.
- Polymerizing and crosslinking proteins result in crystallin aggregation and inactivation of many essential enzymes, including those with an antioxidant role (e.g., catalase and glutathione reductase).

Protection against damage induced by ROS is achieved in a number of ways. The superoxide anion undergoes dismutation by superoxide dismutase or by interaction with ascorbate (see below), which results in the formation of H<sub>2</sub>O<sub>2</sub>. This, along with the high levels of exogenous H<sub>2</sub>O<sub>2</sub>, is detoxified by the enzyme catalase or glutathione peroxidase or both (Fig. 5.1.9).<sup>36</sup> Catalase is present in epithelial cells at higher levels than in fibers. Glutathione peroxidase, however, is found in significant amounts in both epithelial cells and fibers. The glutathione system is thought to provide the most protection against H<sub>2</sub>O<sub>2</sub>, but it also protects against the lipid-free radical chain reaction by the neutralization of lipid peroxides.<sup>29,32,34,35</sup>

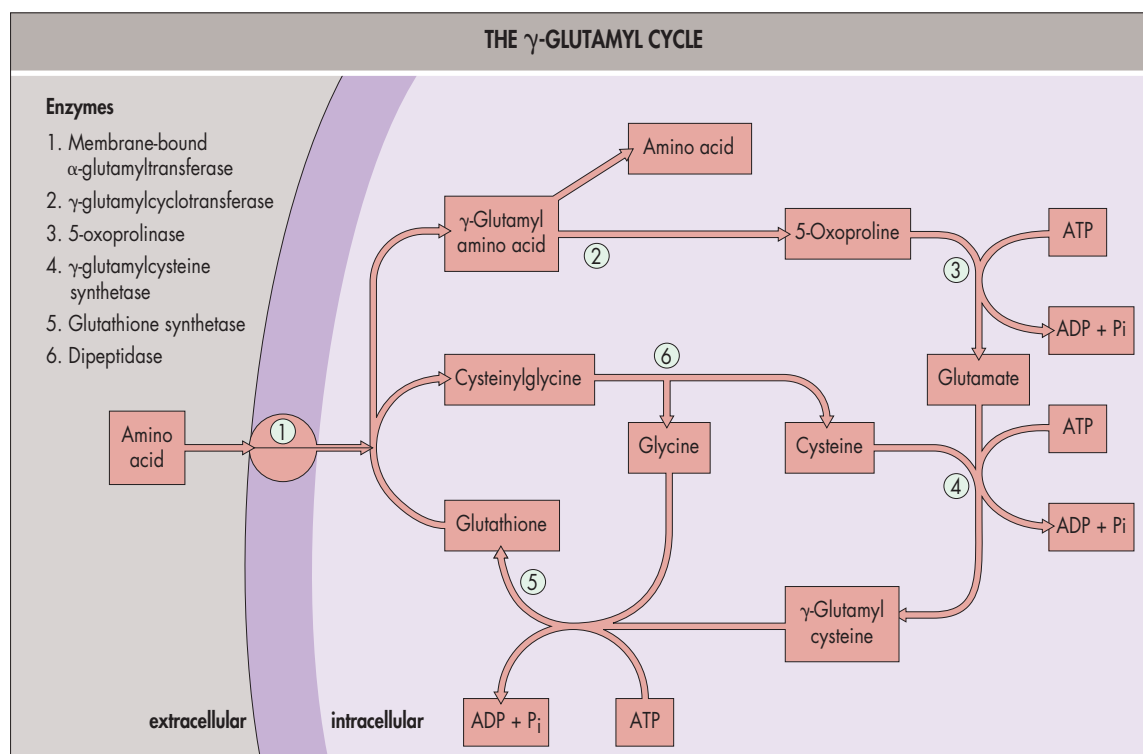
Ascorbic acid (vitamin C) plays a major role in the antioxidant system, although this may be species dependent, because the human lens is rich in ascorbate (1.9 mg/kg wet weight or 1.1 mmol/kg). Ascorbate is present at high levels in the outer layers of the lens but virtually absent from the nucleus. It reacts rapidly with superoxide anions, peroxide radicals, and hydroxyl radicals to give dehydroascorbate. It also scavenges singlet oxygen, reduces thiol radicals, and is important in the prevention of lipid peroxidation. The ascorbic acid and glutathione systems are coupled, as dehydroascorbate reacts with the reduced form of glutathione to generate ascorbate and GSSG (oxidized glutathione).<sup>31,34,37,38</sup>

This system, however, is not 100% efficient, and a low level of cumulative damage occurs throughout life.

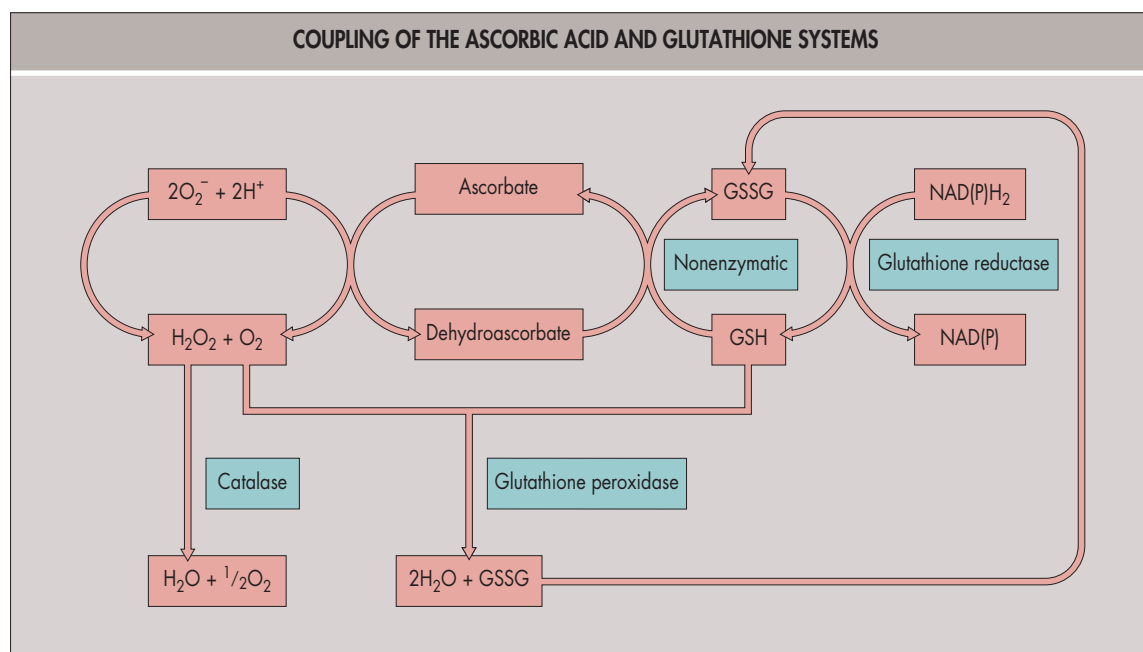
## LENS CRYSTALLINS

### Crystallin Structure

Up to 60% of the wet weight of the human lens is composed of proteins. These lens proteins can be subdivided into water-soluble (cytoplasmic proteins) and water-insoluble (cytoskeletal and plasma membrane) fractions.



**Fig. 5.1.8 The  $\gamma$ -Glutamyl Cycle.** (From Harding JJ, Crabbe MJC. The lens: development, proteins, metabolism and cataract. In: Davson H, editor. The eye. 3rd ed. London: Academic Press; 1984. p. 207–492.)



**Fig. 5.1.9 Coupling of the Ascorbic Acid and Glutathione Systems.**

The water-soluble crystallins constitute approximately 90% of the total protein content of the lens.<sup>39,40</sup>

The crystallins found in all vertebrate species can be divided into the  $\alpha$ -crystallin family and the  $\beta/\gamma$ -crystallin superfamily. The properties of these crystallins are summarized in Table 5.1.1. The  $\alpha$ -crystallins are the largest.

The  $\beta$ -crystallins are composed of light ( $\beta$ L) (c. 52 kDa) and heavy ( $\beta$ H) (150–210 kDa) fractions. The light fraction can be further subdivided into two fractions,  $\beta$ L1 and  $\beta$ L2.<sup>39–43</sup>

The smallest of the crystallins are the  $\gamma$ -crystallins. Six members of this family, known as  $\gamma$ A– $\gamma$ F, have a molecular weight of 20 kDa.

## Crystallin Gene Expression During Lens Growth

The  $\alpha$ -,  $\beta$ -, and  $\gamma$ -crystallins are synthesized in the human lens during gestation, and the absolute quantities of these crystallin families increases during development. The first crystallin to be synthesized is  $\alpha$ -crystallin, which is found in all lens cells. The  $\beta$ - and  $\gamma$ -crystallins are first detected in the elongated cells that emerge from the posterior capsule to fill the center of the lens vesicle.<sup>44</sup> Throughout life the same pattern of synthesis

is maintained, with the result that the  $\alpha$ -crystallins are found in both lens epithelial cells and fibers, whereas the  $\beta$ - and  $\gamma$ -crystallins are found only in the lens fibers.  $\alpha$ -Crystallin synthesis is far greater in the lens epithelium than in the fibers. The  $\alpha$ -crystallins are found in both dividing and nondividing lens cells, whereas the  $\beta$ - and  $\gamma$ -crystallins are found only in nondividing lens cells. Differentiation of a lens epithelial cell into a fiber, therefore, may be one of the factors that triggers a decrease in translation of the  $\alpha$ -crystallin gene and stimulates the synthesis of the  $\beta$ - and  $\gamma$ -crystallins.<sup>45</sup>

## Crystallin Function

The high concentration of crystallins and the gradient of refractive index are responsible for the refractive properties of the lens. The short-range order of these proteins ensures that the lens remains transparent.  $\alpha$ -Crystallins may be involved in the assembly and disassembly of the lens cytoskeleton. Similarities in structure between the small heat shock proteins (sHSPs) and  $\alpha\beta$ -crystallin suggest that this crystallin family may provide the lens with stress-resistant properties.<sup>40,41,46</sup>  $\alpha$ -Crystallins have chaperone-like functions that enable them to prevent the heat-denatured proteins from



TABLE 5.1.1 Properties of Different Crystallins

	$\alpha$	$\beta$	$\gamma$	$\gamma$ s
Subunits	$\alpha$ A, $\alpha$ A1, $\alpha$ B, $\alpha$ B1, up to nine minor subunits	Basic: $\beta$ B1, $\beta$ B2, $\beta$ B3 Acidic: $\beta$ A1, $\beta$ A2, $\beta$ A3, $\beta$ A4	$\gamma$ A– $\gamma$ F	$\gamma$ s
Subunit molecular weight	20 kDa	Basic: 26–32 kDa Acidic: 23–25 kDa	20 kDa	24 kDa
Native molecular weight	600–900 kDa	$\beta$ H: 150–200 kDa $\beta$ L: c. 50 kDa	20 kDa	24 kDa
Number of subunits	30–45	$\beta$ H: 0–8 $\beta$ L: 2	1	1
Thiol content	Low	High	High	High
N-Terminal amino acid	Masked	Masked	Glycine or alanine	Masked
Secondary structure	Predominantly $\beta$ -pleated sheet	$\beta$ -pleated sheet	$\beta$ -pleated sheet	$\beta$ -pleated sheet
Three-dimensional structure	Unknown	Two domains with four “Greek key” motifs	Two domains with four “Greek key” motifs	Two domains with four “Greek key” motifs
Chromosome	$\alpha$ A: 21	$\beta$ B1– $\beta$ B4: 22	2 $\alpha$ B: 11	3 $\beta$ A1/ $\beta$ A3: 17 $\beta$ A2: 2

becoming insoluble and facilitate the renaturation of proteins that have been denatured chemically.<sup>47</sup> They also act as chaperones under conditions of oxidative stress and therefore may help to maintain lens transparency.<sup>48</sup>

Although the function of the  $\beta$ -crystallins is unknown, their structural similarities with the osmotic stress proteins suggest that they also may act as stress proteins in the lens.<sup>46</sup> The  $\gamma$ -crystallins (with the exception of  $\gamma$ s-crystallin) are found in the regions of low water content and high protein concentration, such as the lens nucleus. The presence of this family of crystallins correlates with the hardness of the lens. Concentrations are higher in those lenses that do not change shape during accommodation, as in fish, than in those that do, as in the human.<sup>40</sup>

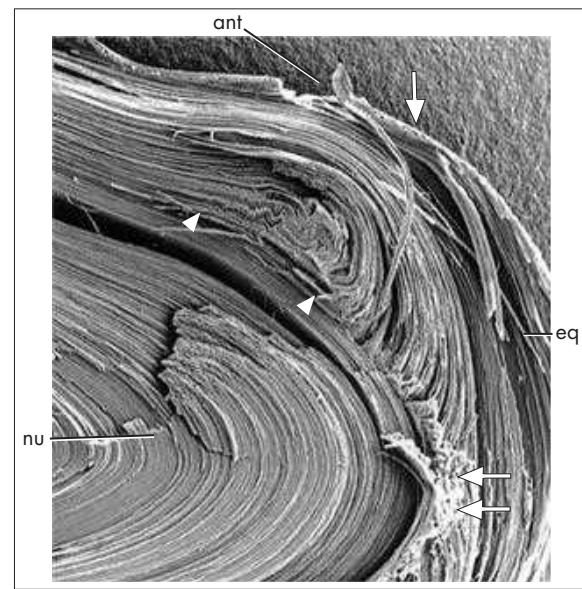
## AGE CHANGES

### Morphology

Continued increases in both the mass and dimensions of the lens are greatest during the first two decades of life. This results from the proliferation of lens epithelial cells and their differentiation into lens fibers. The oldest epithelial cells are found in the middle of the central zone under the anterior pole. Because cells are added to the periphery of this zone throughout life, the age of the cells decreases from the pole toward the outer units of this region, so that the newest cells always are found near the pregerminative zone. Because newly formed fibers are internalized as more are added at the periphery of the lens, the oldest fibers are found in the center of the nucleus and the newest fibers in the outer cortex. Each growth shell, therefore, represents a layer of fibers that are younger than those in the shell immediately preceding it.<sup>49</sup>

As the lens ages, epithelial cells become flatter, flatten their nuclei, develop end-organ failure bodies and vacuoles, and exhibit a dramatic increase in the density of their surface projections and cytoskeletal components. The basal surface area of the cell increases; thus the number of cells needed to cover a region of the growing anterior capsule is less than that needed to cover a region of the same size in a younger lens. This, in combination with the decrease in proliferative capacity, means that epithelial cell density decreases as the lens ages.<sup>49,50</sup>

Lens fibers show partial degradation or a total loss of a number of plasma membrane and cytoskeletal proteins with age. The most significant degradation is that of MIP26. Early in life spectrin, vimentin, and actin are present in both the outer cortical fibers and the epithelial layer, but they are degraded as the fibers age and are further internalized. By 80 years of age, expression of these cytoskeletal proteins is restricted to the epithelial cells. The cholesterol-to-phospholipid ratio of fiber cell plasma membranes increases throughout life, and consequently membrane fluidity decreases and structural order increases. These changes, which are known to occur from the second decade, are greatest in the nucleus and are therefore partially responsible for the increase in nuclear sclerosis (hardening).<sup>51,52</sup>



**Fig. 5.1.10 Scanning Electron Micrograph of Equatorial Region of Cortical Fiber Plasma Membranes.** Note the circular shade with the fracture of fibers in the deep equatorial cortex (eq) (arrows) and folding fibers in the anterior deep cortex (ant) (arrowheads). (nu, lens nucleus). (From Vrensen GFJM. Aging of the human eye lens – a morphological point of view. *Comp Biochem Physiol A Physiol* 1995;111:519–32.)

Furthermore, the changes in structure of the plasma membrane and the degradation of cytoskeletal components may contribute to the increase in the number of furrowed membranes and microvilli found on the fiber surface.<sup>49</sup> From the fourth decade onward, ruptures are found in the equatorial region of cortical fiber plasma membranes (Fig. 5.1.10). Reparation of these ruptures often prevents the formation of opacities. Any opacities that do develop become surrounded by deviated membranes and are therefore isolated from the remainder of the lens.

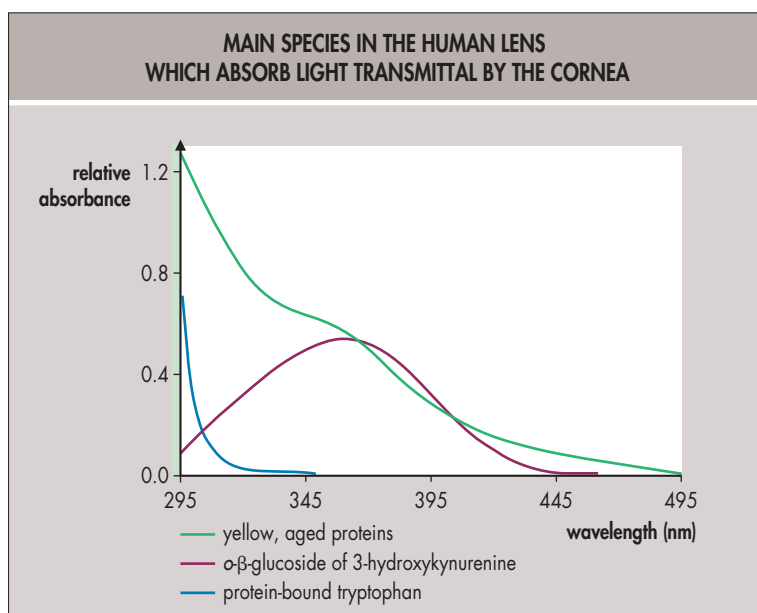
The lens capsule thickens throughout life. It also increases in surface area as a result of the growth of the lens. Ultrastructural changes include the loss of laminations and an increase in the number of linear densities. Although the young lens capsule is known to contain collagen type IV and the aged capsule collagen types I, III, and IV, the presence of types I and III collagen in the young capsule has yet to be confirmed, but their synthesis may be age related.<sup>53</sup>

### Physiological Changes

Changes to the cellular junctions and alterations in cation permeability occur with age. The major gap junction protein MIP26 loses some of its amino acids to form new variants, which include polypeptides with molecular weights of 15, 20, and 22 kDa.<sup>51,52</sup> The membrane potential of an isolated, perfused human lens may be –50 mV at the age of 20 years, but only –20 mV at the age of 80 years. Potassium ( $K^+$ ) levels remain constant at approximately 150 mmol/L, but the sodium ( $Na^+$ ) content of the lens increases from 25 mmol/L at the age of 20 years to 40 mmol/L by the age of 70 years. Thus, the  $Na^+K^+$  permeability ratio increases approximately sixfold, which results in a proportionately greater increase in the sodium content of the lens.<sup>54</sup> The change in the ratio of these two ions correlates with the increase in optical density of the lens.<sup>55</sup> The change in ion permeability with increasing fiber age is thought to occur due to a decrease in membrane fluidity as a result of the age-related increase in the cholesterol-to-phospholipid ratio. The lens, therefore, becomes more dependent on the  $Na^+K^+$ -ATPase in the epithelial cells. The decrease in membrane potential also results from changes in the free  $Ca^{2+}$  levels, which increase from 10 mmol/L at the age of 20 years to approximately 15 mmol/L by the age of 60 years. It is thought that the  $Ca^{2+}$ -ATPase may be inhibited by the decrease in membrane fluidity, which decreases the rate at which  $Ca^{2+}$  is pumped out of the cell. It also is possible that the increase in  $Na^+$  and  $Ca^{2+}$  permeability may result from the increased activity of nonspecific cation channels.<sup>54</sup>

### Biophysical Changes

The absorption of both UV and visible light by the lens increases with age. Free and bound aromatic amino acids (tryptophan, tyrosine, and phenylalanine), fluorophores, yellow pigments, and some endogenous compounds



**Fig. 5.1.11 Main Species in the Human Lens That Absorb Light Transmitted by the Cornea.** (From Dillon J. The photophysics and photobiology of the eye. J Photochem Photobiol B 1991;10:23–40.)

(such as riboflavin) are responsible for the absorption properties of the lens.<sup>51</sup> Tryptophan is cleaved in the presence of sunlight and air to form N-formylkynurenine and a series of other metabolic products, including 3-hydroxykynurenineglucoside (3-HKG). Because more than 90% of the UV radiation that reaches the lens is UV-A (315–400 nm), and 3-HKG absorbs light between 295 and 445 nm whereas tryptophan only absorbs light between 295 and 340 nm, this glucoside has a relative absorbance that is greater than that of tryptophan in the young human lens (95% compared with 5%) (Fig. 5.1.11).

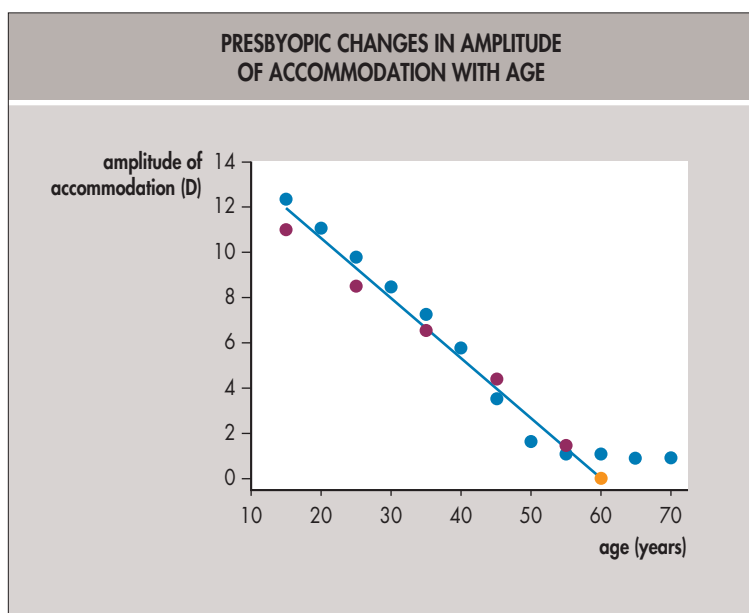
As the lens ages, it changes from colorless or pale yellow to darker yellow in adulthood, and brown or black in old age.<sup>55</sup> The autofluorescent properties of the lens also change with age. These changes in coloration, which are limited to the nucleus, are thought to result from the attachment of 3-HKG and its metabolic derivatives to proteins to produce yellow-pigmented proteins that also absorb light. As the concentration of these yellow pigments increases, they compete with 3-HKG and become the major absorbing species of the lens.<sup>56,57</sup> Because these yellow proteins are fluorescent species, the wavelength absorbed increases to approximately 500 nm (see Fig. 5.1.11). A blue fluorophore, which absorbs between 330 and 390 nm and fluoresces between 440 and 466 nm, increases as the lens ages. Oxygen-dependent photolysis of the blue fluorophore contributes to the formation of a green fluorophore, which is excited between 441 and 470 nm and emits between 512 and 528 nm.<sup>58</sup> The increased capacity of the lens to absorb visible light, in combination with the increased scattering properties of the lens (because of the aggregation of lens proteins and possibly the release of bound water), results in a decrease in transparency.<sup>50</sup> The increase in the total number of photons absorbed is accompanied by an age-related loss in antioxidant levels, increasing the amount of photo-oxidative stress.

Nonenzymatic glycation of proteins by the Maillard reaction results in the formation of advanced glycation end products, which also increase the yellowing of the lens. This reaction is initiated by the attachment of a sugar molecule (e.g., glucose) to an amino acid, normally valine or lysine. In young lenses, 1.3% of lysine residues of human crystallins are glycated, but by the age of 50 this increases to 2.7% and to approximately 4.2% in older lenses.<sup>51</sup> Yellow fluorescent photoproducts also are formed in the presence of ascorbic acid, which is present at high levels in the lens.<sup>59</sup>

## Accommodation Changes

The amplitude of accommodation decreases throughout life from 13.00–14.00 D at the age of 10 years to 6.00 D at 40 years and almost 0.00 D by the age of 60 years (Fig. 5.1.12). This manifests clinically as presbyopia. The change in accommodative power is attributable to a number of factors, including<sup>60–62</sup>:

- Young's modulus of capsular elasticity decreases from 700 N/cm<sup>2</sup> at birth to 150 N/cm<sup>2</sup> by the age of 80 years.



**Fig. 5.1.12 Presbyopic Changes in the Amplitude of Accommodation With Age.** The different colored symbols represent the data obtained from different publications. (From Fisher RF. Presbyopia and the changes with age in human crystalline lens. J Physiol 1973;223:765–79.)

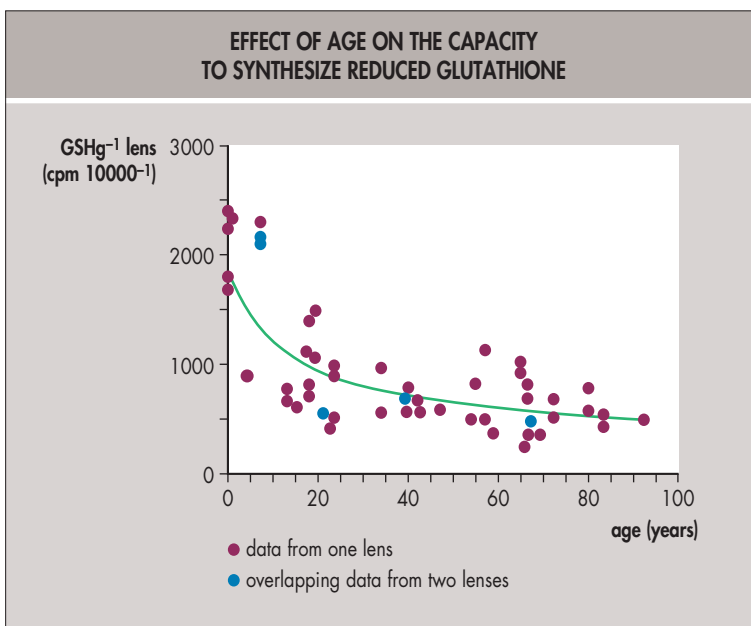
- Stiffness of the lens substance increases, which renders the lens less deformable.
- Although the cortex increases in thickness throughout life, very little change occurs in the thickness of the nucleus. The effect of the rounding of the nucleus on the change in curvature of the anterior surface during accommodation, therefore, is reduced with age.
- The radius of curvature of the anterior capsule decreases, which renders the lens rounder. Contraction of the ciliary muscle, therefore, does not greatly alter the shape of the lens.
- The distance between the anterior surface of the lens and the cornea decreases.
- The internal apical region of the ciliary body moves forward and inward with age. The zonules, therefore, no longer put the lens under as much tension in the unaccommodated state.

The increases in curvature and thickness of the lens suggest that the refractive power should increase with age, resulting in myopia. This, however, does not happen because these changes are accompanied by small alterations to the gradient of refractive index. This gradient becomes flatter near the center of the lens and steeper near the surface and, therefore, the refractive power of the eye is lowered.<sup>63</sup>

## Biochemical Changes

The overall metabolic activity of the lens decreases with increasing age, partially due to decreasing enzyme activities in the cortex and nucleus. Many of the enzymes involved in the metabolism of glucose decrease with age, including glyceraldehyde-3-phosphate dehydrogenase, G6P dehydrogenase, aldolase, enolase, phosphoglycerate kinase, and phosphoglycerate mutase. Although overall metabolic activity decreases, the lens still maintains the capacity to synthesize proteins, fatty acids, and cholesterol at substantial rates. Decreased metabolic activity, therefore, does not serve as a significant limiting factor for the production of new lens fibers.<sup>51,52</sup>

A reduction in the activity or levels or both of many antioxidants occurs with increasing age. Because this decrease is greatest in the nucleus, fibers in this region of the lens are more susceptible to oxidative damage and lipid peroxidation. As a result, they rely on the overlying cortical fibers and epithelial layer to protect them. The activity of both catalase and superoxide dismutase decreases with age, as do levels of ascorbate and glutathione.<sup>50</sup> The reduced activity of both glutathione synthetase and  $\gamma$ -glutamylcysteine synthetase, accompanied by a decrease in the uptake of L-cysteine (an amino acid needed for glutathione synthesis), decreases the rate of synthesis of reduced glutathione (Fig. 5.1.13).<sup>64</sup> This is partly due to reduced activity of glutathione reductase, which converts oxidized glutathione into reduced glutathione. Glutathione peroxidase (which is involved in the breakdown of lipid peroxides and hydrogen peroxide) levels increase from birth until approximately 15 years of age and then slowly decrease



**Fig. 5.1.13 Effect of Age on the Capacity to Synthesize Reduced Glutathione.** (From Rathbun WB, Murray DL. Age-related cysteine uptake as rate-limiting in glutathione synthesis and glutathione half-life in the cultured human lens. *Exp Eye Res* 1991;53:205–12.)

**TABLE 5.1.2 Levels of Degraded Polypeptides in Water-Soluble High-Molecular-Weight Proteins of Human Lenses**

Donor's Age (years)	HMW Protein/Lens (mg)	HMW Protein-Associated Degraded Polypeptides/Lens (mg)	HMW Protein as Degraded Polypeptides (%)
16–19	0.16	0.009	5.6
38–39	0.93	0.17	18.2
49–51	2.17	0.255	11.75
55–56	2.2	0.42	19.1
60–80	2.3	0.62	26.9

HMW, High-molecular-weight.  
Adapted from Srivastava OP, Srivastava K, Silney C. Levels of crystallin fragments and identification of their origin in water soluble high molecular weight (HMW) proteins of human lenses. *Curr Eye Res.* 1996;15:511–20.

throughout adulthood.<sup>51,52</sup> This decreased antioxidant activity coupled with increased photon absorption with increasing age promotes photo-oxidative damage in the lens.

## Crystallins

With increasing age an increase in both the complexity and the number of crystallin fractions occurs, which includes accumulation of high-molecular-weight (HMW) aggregates, partial degradation of crystallin polypeptides, increased crystallin insolubility, photooxidation of tryptophan, the production of photosensitizers, loss of sulfhydryl groups, and nonenzymatic glycation. These changes can alter the short-range spatial order of the crystallins and thus decrease transparency.<sup>50–52,56</sup>

Levels of soluble HMW aggregates (greater than  $15 \times 10^3$  kDa) increase from approximately 0.16 mg in the lenses of donors between the ages of 16 and 19 years to 2.3 mg by the age of 60 years (Table 5.1.2).<sup>65</sup> This increase occurs as the result of many factors, including reduced proteolytic enzyme activity. Most of these aggregates are localized to the lens nucleus and are, in the majority of the young, principally composed of  $\alpha$ -crystallin.<sup>50</sup> As the lens ages, these aggregates increase in complexity and become composed of a mixture of crystallins. The major subunits thought to be involved are  $\alpha$ A-,  $\alpha$ B-, and  $\gamma$ S-crystallins. Many of these polypeptides undergo posttranslational modifications, such as the formation of an intramolecular disulfide bond within  $\alpha$ A-crystallin, glycation of lysine residues, cross-linking, deamidation of  $\alpha$ A- and  $\gamma$ S-crystallins, and loss of the C-terminal end of  $\alpha$ A-crystallin. Such modifications to  $\alpha$ -crystallin result in a decrease in the capacity of this crystallin to act as a chaperone protein.<sup>50,66</sup> Below the age of 20 years, approximately 6% of the HMW protein is composed of degraded polypeptides, but by the age of 60 years this increases to 27% (see Table 5.1.2).<sup>65</sup>



**Fig. 5.1.14 Fibrosis of the Posterior Capsule.** This opacification developed in a 5-year-old child 20 days after extraction of a traumatic cataract (perforation with a knife). No intraocular lens was implanted. (From Rohrbach JM, Knorr M, Weidle EG, et al. *Nachstar: klinik, therapie, morphologic, and prophylaxe. Akt Augenheilkd* 1995;20:16–23.)

It is thought that many of the HMW aggregates act as precursors for the accumulation of insoluble proteins. Below the age of 50 years, approximately 4% of lens proteins are insoluble, but by the age of 80 years, this increases to 40%–50%.<sup>67</sup> The increase in insolubility is approximately the same in the cortex and nucleus before age 30 years, but with increasing age, insolubility increases to a greater extent in the lens nucleus. Up to 80% of the nuclear proteins of an aged lens may be insoluble, and most of the nuclear  $\alpha$ -crystallin is insoluble by the age of 45 years.<sup>51,52</sup> This contributes to the loss of lens transparency and the development of senile cataract.

Tryptophan residues in the crystallins are photooxidized to produce photosensitizers. This results in a decrease in tryptophan fluorescence and an increase in nontryptophan fluorescence throughout life. The oxidation of sulfhydryl groups results in the formation of disulfides, which may be one of the factors responsible for the age-related decrease in solubility of lens proteins. Because the  $\gamma$ -crystallins have sulfhydryl groups that are more exposed, they are more susceptible to this oxidation than are the  $\alpha$ - and  $\beta$ -crystallins.<sup>52</sup> Increases in the glycation of crystallins in the presence of glucose or ascorbic acid results in protein cross-linking and the resultant formation of HMW proteins. The  $\alpha$ - and  $\beta$ H-crystallins rapidly cross-link;  $\beta$ L-crystallins are slower, and no  $\gamma$ -crystallin cross-linking occurs. One of the modifications that occurs most frequently to aging crystallins is deamidation of asparagine residues, which results in the formation of aspartic acid residues, thus altering the structure, destabilizing the protein, and increasing its susceptibility to proteolytic degradation.

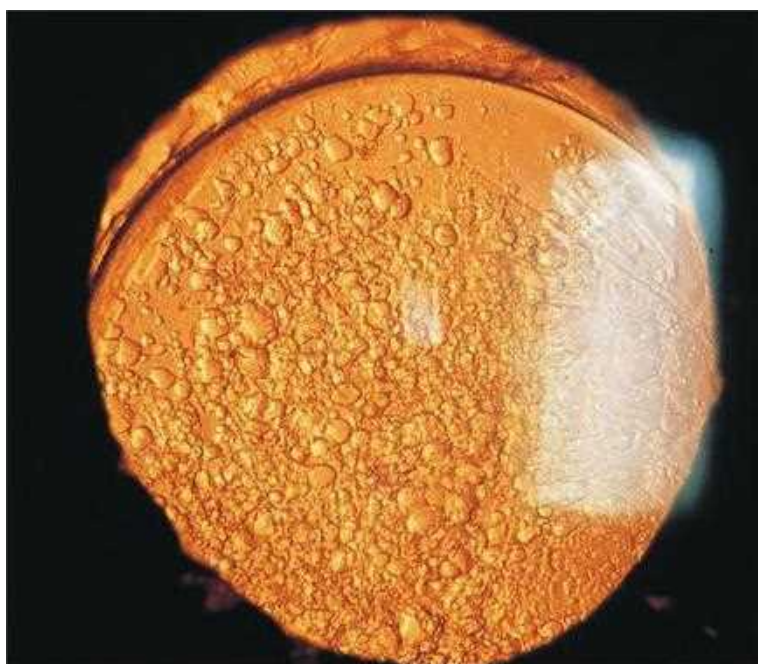
## SECONDARY CATARACT

A major complication of extracapsular cataract extraction (ECCE) is secondary cataract (also known as after cataract). Posterior capsule opacification (PCO) is the most clinically significant type of secondary cataract and develops in up to 50% of patients between 2 months and 5 years after the initial surgery. The frequency of PCO is age related; almost all children develop PCO after ECCE, but in adults the incidence is much lower. This is thought to be because of the higher proliferative capacity of lens epithelial cells in the young compared with the old.<sup>68,69</sup>

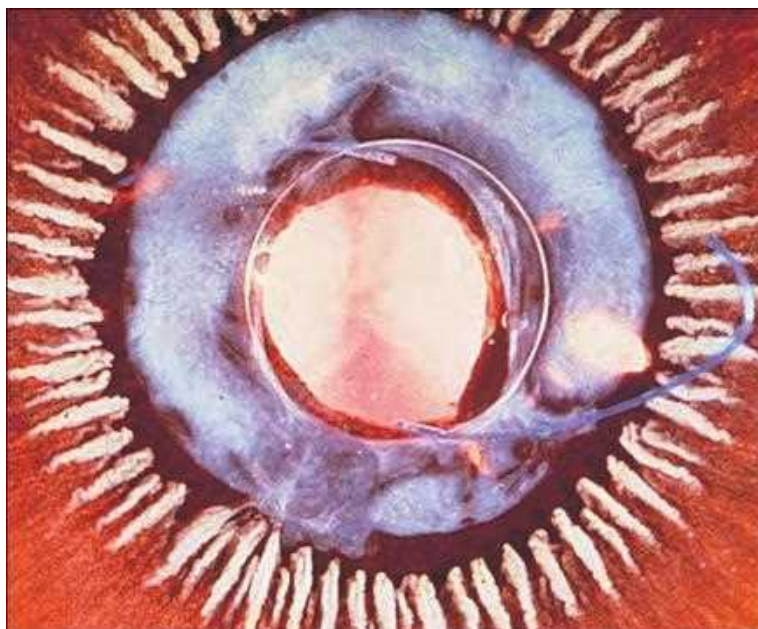
After ECCE, the lens is composed of the remaining capsule and the residual epithelial cells and cortical fibers that were not removed at the time of surgery. The lens epithelial cells still possess the capacity to proliferate, differentiate, and undergo fibrous metaplasia. Migration of these cells toward the center of the posterior capsule, together with the synthesis of matrix components, results in light scatter that reduces visual acuity. In a minority of cases, PCO results from the deposition of fibrin and other cell types onto the posterior capsule either at the time of surgery or postoperatively.<sup>69</sup>

The two morphologically distinct types of PCO are fibrosis and Elschnig's pearls, which occur concurrently. In addition, ECCE procedures may result in the formation of a Soemmerring's ring (Figs. 5.1.14–5.1.16).<sup>69,70</sup>





**Fig. 5.1.15 Elschnig's Pearls.** This opacification developed within 3 years of an extracapsular cataract extraction with implantation of a posterior chamber intraocular lens. (From Rohrbach JM, Knorr M, Weidle EG, et al. *Nachstar: klinik, therapie, morphologic, and prophylaxe. Akt Augenheilkd* 1995;20:16–23.)



**Fig. 5.1.16 Soemmerring's Ring.** Taken from behind the lens of a human eye obtained postmortem. A three-piece, modified J, polypropylene loop posterior chamber intraocular lens is present. (From Apple DJ, Solomon KD, Tetz MR, et al. *Posterior capsule opacification. Surv Ophthalmol* 1992;37:73–116.)

## Fibrosis-Type Posterior Capsule Opacification

Residual lens epithelial cells that are still attached to the anterior capsule after ECCE are thought to be the predominant cells involved in the formation of fibrous membranes that can appear within 2–6 months of ECCE.<sup>69</sup>

Remnant epithelial cells left on the anterior capsule differentiate into spindle-shaped, fibroblast-like cells (myofibroblasts), which express  $\alpha$ -smooth muscle actin and become highly contractile. These fibroblastic cells proliferate and migrate onto the posterior capsule to form a cellular layer that secretes extracellular matrix components and a basal lamina-like material. Cellular contraction results in the formation of numerous fine folds and wrinkles in the posterior capsule. At this stage the capsule is only mildly opacified. No significant visual loss occurs until the cells migrate into the visual axis.<sup>68,71</sup> More advanced stages of PCO result from further proliferation and multilayering of cells on the posterior capsule and are associated with additional extracellular matrix production and the appearance of white fibrotic opacities (see Fig. 5.1.14). The majority of the

extracellular matrix produced in the fibrosis type of PCO is composed of types I and III fibrillar collagen, collagen type IV, and a number of associated proteoglycans (dermatan sulfate, heparin sulfate, and chondroitin sulfate).<sup>72</sup>

In cases in which the cut edge of the anterior capsule rests on the intraocular lens (IOL) optic, residual anterior capsular cells may proliferate and extend from this cut edge onto the surface of the IOL, which may result in the formation of a membranous outgrowth within 1 week postoperatively.<sup>73</sup> Detailed studies using polymethylmethacrylate IOLs have shown that cells do not appear to cover the central part of the optic, and migration onto this optic decreases as the cells in the region of the anterior capsule in contact with the optic undergo fibrous metaplasia and begin to opacify. The cells on the IOL completely disappear within 3 months. It is also possible that cells may migrate around onto the posterior surface of the IOL implant and therefore contribute to the formation of PCO.

Growth factors present in both the aqueous and the vitreous have been implicated in the development of fibrosis-type PCO. These include acidic and basic fibroblast growth factors, insulin-like growth factor-I, epidermal growth factor, platelet-derived growth factor, hepatocyte growth factor, and transforming growth factor- $\beta$ .

## Pearl-Type Posterior Capsule Opacification

The pearls formed in this type of PCO are identical in appearance to Wedl (bladder) cells involved in the formation of posterior subcapsular cataracts (see Fig. 5.1.16). Because Wedl cells are known to originate from equatorial lens epithelial cells, it is believed that residual cells in this region of the capsule are the predominant cells involved in the formation of pearls. Clinically, cases of pearl formation occur somewhat later than those of fibrosis (up to 5 years postoperatively).<sup>69</sup>

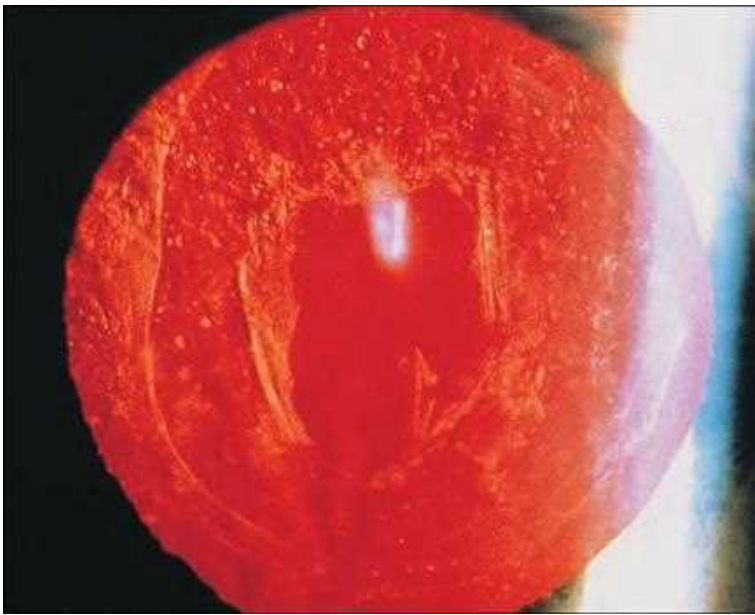
Pearls were first observed by Hirschberg<sup>74</sup> in 1901 and then by Elschnig<sup>75</sup> in 1911; they now are referred to as Elschnig's pearls. After ECCE, the fiber mass of the lens is no longer present, and as a result, no internal pressure exists. Newly formed lens fibers, therefore, are no longer forced in the anterior and posterior directions, which results in the formation of a mass of cells loosely connected and piled on top of each other. Each pearl represents the aberrant attempt of one epithelial cell to differentiate into a new lens fiber, possessing characteristics of both epithelial cells and fibers, and may be embedded in an extracellular matrix. Visual acuity is affected only if the pearls protrude into the center of the posterior capsule.<sup>76–78</sup>

## Soemmerring's Ring

Soemmerring first noticed PCO in humans in 1828.<sup>79</sup> After ECCE, the cut edge of the remaining anterior capsular flap may attach itself to the posterior capsule within approximately 4 weeks postoperatively through the production of fibrous tissue. Any residual cortical fibers and epithelial cells, therefore, are trapped within this sealed structure. The equatorial cells still retain the capacity to proliferate and differentiate into lens fibers. The increase in the volume of this lenticular material fills the space between the anterior and the posterior capsule (see Fig. 5.1.16). Proliferating epithelial cells remain attached to the anterior capsule but also are found to a lesser extent on the posterior capsule, where they form small isolated groups. In some cases the epithelial cells escape from the ring and migrate onto the anterior surface of the anterior capsule. Because the ring forms at the periphery of the lens, vision is not affected.<sup>76,80,81</sup>

## Prevention and Treatment of Posterior Capsule Opacification

Currently there is no reliable treatment to prevent PCO. Posterior capsulectomy is the treatment of choice when PCO does affect the visual field. A posterior capsulectomy removes the central part of the posterior capsule and thereby instantly improves vision. Removal is achieved using a neodymium:yttrium–aluminum–garnet (Nd:YAG) laser (Fig. 5.1.17). In some patients with posterior segment problems, proliferation of lens epithelial remnants has been observed within months of the capsulectomy. As a result, the size of the capsulectomy decreases, which may in turn reduce visual acuity. It has been postulated that this occurs because of “activation” of the cells, the release of growth factors from the vitreous, the direct stimulation of proliferation, or a combination of these factors.<sup>82</sup> Removal of the barrier between the posterior chamber and the vitreous cavity increases the risk of complications such as cystoid macular edema, retinal detachment, uveitis, and secondary glaucoma.<sup>69</sup>



**Fig. 5.1.17 Posterior Capsule Following a Nd:YAG laser posterior capsulectomy.** (From Rohrbach JM, Knorr M, Weidle EG, et al. *Nachstar: klinik, therapie, morphologic, and prophylaxe. Akt Augenheilkd* 1995;20:16–23.)

There have been numerous approaches to prevent PCO.<sup>83,84</sup> The implantation of a posterior chamber IOL into the capsular bag after ECCE is known to reduce the likelihood that a patient will develop PCO, because the IOL acts as a barrier to the migration of cells around and into the center of the posterior capsule. Posterior convex or biconvex optics sit in the capsular bag with their posterior surface firmly against the posterior capsule. Barrier-ridge optics have a rim on the posterior surface of the IOL to try to block migrating cells. Migration also has been shown to be dependent on the implant biomaterial. For example, trials have shown that the posterior capsules of patients who were given polyacrylic implants were significantly clearer 2 years after implantation than the posterior capsules of those given polymethylmethacrylate or silicone implants. Lens epithelial cells also have been shown to regress in eyes implanted with polyacrylic IOLs.<sup>84</sup>

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# Evolution of Intraocular Lens Implantation

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## 5.2



IN THIS CHAPTER  
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**Definition:** Report on the evolution of intraocular lens designs.

### Key Features

- Description of anterior and posterior chamber intraocular lens designs, including lenses now obsolete, and their interaction with intraocular tissues.
- Recent advances in intraocular lens designs/materials leading to modern, currently available intraocular lenses.

## INTRODUCTION

Cataract is the most prevalent ophthalmic disease. Although a pharmacological preventive or therapeutic treatment for this potentially blinding disease is being actively sought, the solution still appears to be many years away. Therefore, surgical treatment for cataracts, which typically includes intraocular lens (IOL) implantation, remains the only viable alternative. The implantation of IOLs is now a highly successful operation, and the safety and efficacy of the procedure are well established.<sup>1</sup>

## LENS DESIGN AND FIXATION

In 1967 Binkhorst<sup>2</sup> proposed a detailed classification of the various means of fixation for each IOL type. In a 1985 update of this classification, Binkhorst<sup>3</sup> listed four IOL types according to fixation sites: anterior chamber angle-supported lenses, iris-supported lenses, capsule-supported lenses, and posterior chamber angle (ciliary sulcus)-supported lenses. By common agreement, most surgeons today differentiate lens types as iris-supported lenses, anterior chamber lenses, and posterior chamber lenses.

From the time of Ridley's first lens implantation to the present day, the evolution of IOLs can be arbitrarily divided into six generations.

### Generation I (Original Ridley Posterior Chamber Lens)

Ridley's first IOL operation was performed November 29, 1949, on a 49-year-old woman at St Thomas' Hospital in London.<sup>4</sup> His original IOL was a biconvex polymethyl methacrylate (PMMA) disc designed to be implanted after extracapsular cataract extraction (ECCE) (Fig. 5.2.1).

### Generation II (Early Anterior Chamber Lenses)

As a consequence of the relatively high incidence of dislocations with the Ridley lens, a new implantation site was considered, with fixation of the lens in the angle recess. The anterior chamber was chosen because less likelihood existed of dislocation within its narrow confines. In addition, anterior chamber lenses could be implanted after either an intracapsular cataract extraction (ICCE) or an ECCE.

Late endothelial atrophy, corneal decompensation, and pseudophakic bullous keratopathy were observed with the original Baron anterior chamber lens and also developed with many subsequent anterior chamber



**Fig. 5.2.1 Posterior View of an Eye (Obtained Postmortem) Showing the Implantation Site of a Ridley Lens.** To the time of death, almost 30 years after implantation, the patient's visual acuity remained 20/20 (6/6) in both eyes. Note the good centration and clarity of the all-polymethyl methacrylate optic in the central visual axis. The lens was implanted by Reese and Hammdi of Philadelphia.

lens designs. The entity now termed uveitis–glaucoma–hyphema (UGH) syndrome was described first when ocular tissue damage occurred that was clearly the result of poorly manufactured early anterior chamber lenses.<sup>5</sup>

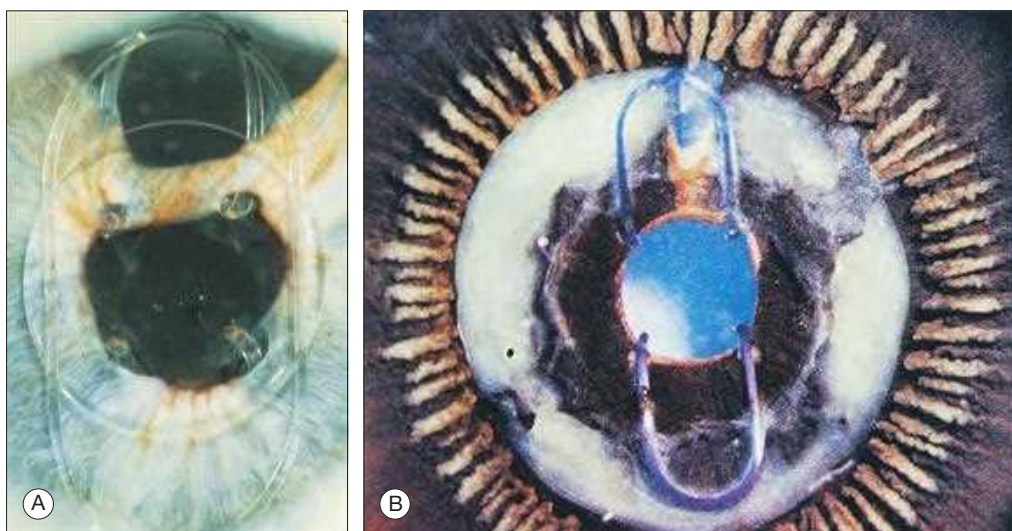
### Generation III (Iris-Supported Lenses)

Binkhorst was an early advocate of iris-supported IOLs.<sup>3,4</sup> His first lens was a four-loop, iris-clip IOL (Fig. 5.2.2A) design. Although Binkhorst initially believed that IOL contact with the iris would not cause problems, he soon noted that iris chafing, pupillary abnormalities, and dislocation developed with the early iris-clip lens. Also, in an effort to circumvent dislocation, Binkhorst made the anterior loops of his four-loop lens longer, but this led to increased corneal decompensation from peripheral touch. His initial implantations were done after ICCE, but occasionally he implanted his four-loop lens following ECCE. His positive experience with this procedure prompted him to modify his iris-clip lens design for implantation following ECCE. Binkhorst's change from ICCE to ECCE and the introduction of his two-loop iridocapsular IOL (see Fig. 5.2.2B) in 1965 were important advances in both IOL design and mode of fixation.<sup>6</sup>

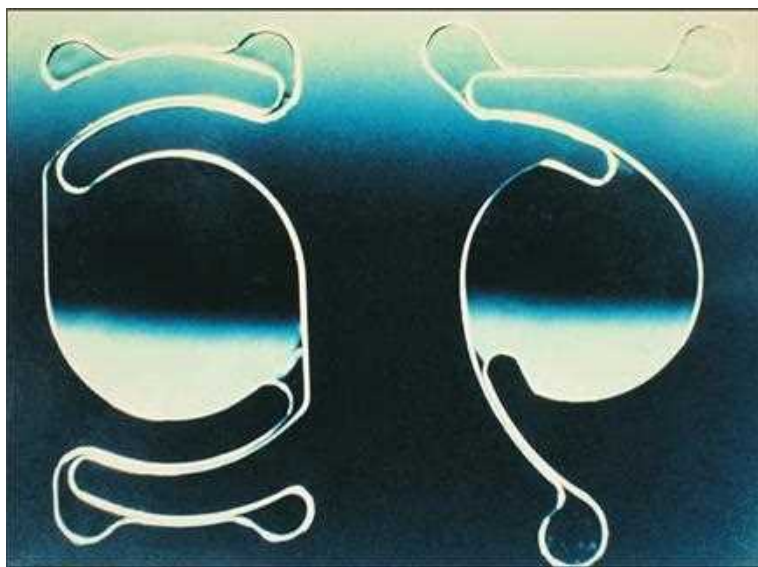
### Generation IV (Intermediate Anterior Chamber Lenses)

As iris-supported IOLs underwent major modifications from the early 1950s up to the beginning of the 1980s, several designs of anterior chamber IOLs were introduced. The problems of tissue chafing and difficulties in correct sizing associated with rigid IOLs were addressed by the development of anterior chamber lenses with more flexible loops or haptics. Unlike the ill-fated, nylon-looped lenses introduced by Dannheim in the early 1950s, the fixation elements of these anterior chamber IOLs were made from

<sup>†</sup>Deceased



**Fig. 5.2.2 Binkhorst Iris-Clip Lenses.** (A) A correctly positioned Binkhorst four-loop, iris-clip lens, well centered in an eye that had good visual acuity. Moderate pupillary distortion and sphincter erosion occur. Note the iris-fixation suture superior to the site of the large iridectomy. (B) Posterior view of an autopsy globe that contains a two-loop iridocapsular intraocular lens. Note the rod that helps to secure the lens to the iris through the iridectomy. An outer Soemmerring's ring is present, but the visual axis remains clear. The optic is well centered.



**Fig. 5.2.3 Modern One-Piece, All-Polymethyl Methacrylate, Kelman-Style Anterior Chamber Lenses of Four-Point and Three-Point Fixation Designs.** Note the excellent polishing and tissue-friendly Choyce-Kelman-style footplates. These represent modern, state-of-the-art lenses that should be distinguished clearly from the earlier, unsatisfactory, closed-loop anterior chamber lenses.

more stable polymers, usually PMMA and polypropylene. The best lenses were the various rigid<sup>7</sup> and flexible, open-loop, one-piece PMMA designs, such as the three- and four-point fixation Kelman IOLs.<sup>8</sup> Modifications of the latter have been in use since the late 1970s and are the styles most commonly implanted today (Fig. 5.2.3).

### Generation V (Improved Posterior Chamber Lenses)

The return to Ridley's original concept of IOL implantation in the posterior chamber occurred after 1975. Pearce<sup>9</sup> of England implanted the first uniplanar posterior chamber lens since Ridley. It was a rigid tripod design with the two inferior feet implanted in the capsular bag and the superior foot implanted in front of the anterior capsule and sutured to the iris. Shearing<sup>10</sup> of Las Vegas introduced a major lens design breakthrough in early 1977 with his posterior chamber lens. The design consisted of an optic with two flexible J-shaped loops. Simcoe of Tulsa introduced his C-looped posterior chamber lens shortly after Shearing's J-loop design appeared. The flexible open-loop designs (J-loop, modified J-loop, C-loop, or modified C-loop) still account for the largest number of IOL styles available today (Fig. 5.2.4).

One obvious major theoretical advantage that a posterior chamber IOL has over an anterior chamber IOL is its position behind the iris, away from the delicate structures of the anterior segment. The return to posterior chamber lenses coincided with the development of improved ECCE surgery. Shearing identified four major milestones that have marked the

evolution of ECCE surgery: microscopic surgical techniques; phaco; iridocapsular fixation; and flexible posterior chamber lenses.

### Generation VI (Modern Capsular Lenses – Rigid PMMA, Soft Foldable, and Modern Anterior Chamber)

By the end of the 1980s, surgical technique and IOL design and manufacture had advanced to a point at which the older techniques gave way to more modern ones that allowed consistent, secure, and permanent in-the-bag (capsular) fixation of the pseudophakos. A marriage between IOL design and improved surgical techniques has evolved into capsular surgery. The “capsular” IOLs are fabricated from both rigid and soft biomaterials.

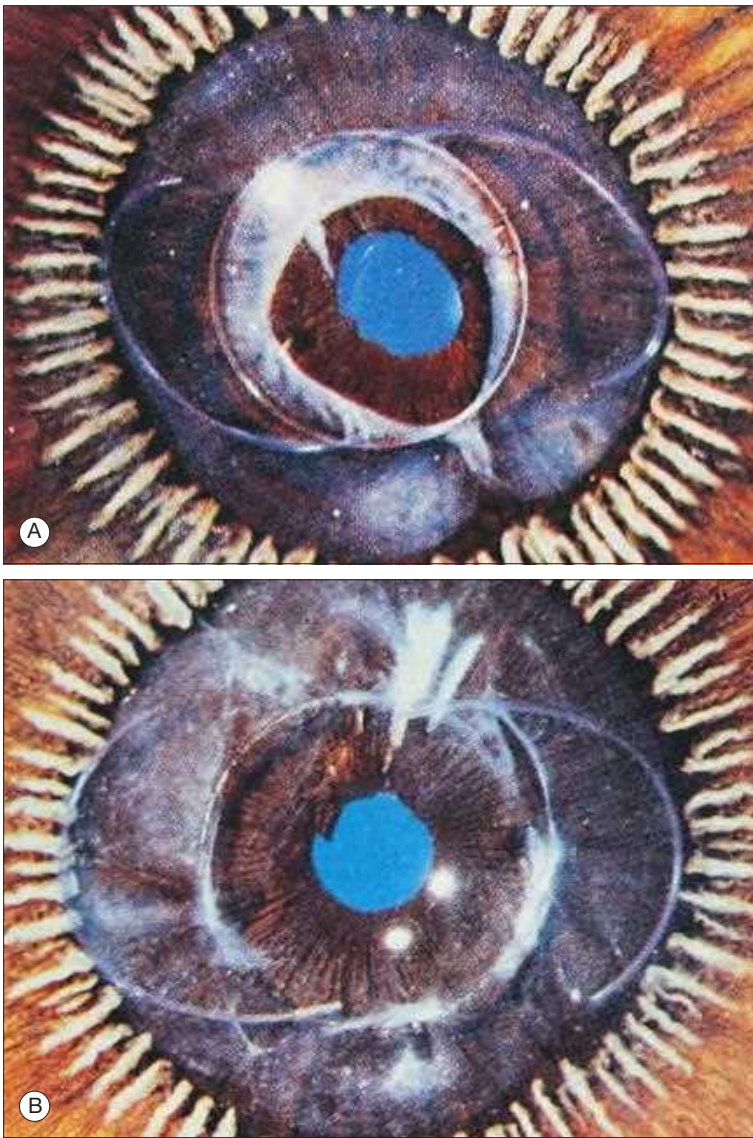
The many changes in surgical techniques that occurred after 1980 and into the 1990s include the introduction of ophthalmic viscosurgical devices (OVDs), increased awareness of the advantages of in-the-bag fixation, the introduction of continuous curvilinear capsulorhexis (CCC), hydrodissection, and the increased use of phaco. Improved small-incision surgical techniques and IOL designs have resulted in a natural evolution toward foldable lenses. Most foldable lenses today are manufactured from silicone, hydrogel, or acrylic material (Fig. 5.2.5).<sup>11,12</sup>

### RECENT ADVANCES

Some general principles and tendencies with regard to the development of new IOLs in the past decade are<sup>11,12</sup>:

- Large fixation holes or foramina incorporated in the haptic components of one-piece plate designs commonly produce fibrous adhesions between the anterior and posterior capsules following ingrowth of fibrocellular tissue through the holes, enhancing the fixation and stability of these designs within the capsular bag.
- For three-piece foldable designs, the preferred haptic materials are rigid materials with good material memory, such as PMMA, polyimide (Elastimide), or polyvinylidene fluoride (PVDF), which enhance lens centration and stability and provide better resistance to postoperative contraction forces within the capsular bag.
- One of the most important features in foldable lenses that decreases the incidence of posterior capsular opacification (PCO) is the square, truncated optic edge, which has an enhanced barrier effect against cell migration/proliferation on the posterior capsule toward the visual axis.
- Manufacturers have invested heavily and with great success in looped single-piece designs (Fig. 5.2.5B), including designs with modifications at the level of the optic-haptic junctions to obtain a nonsmooth transition between these components. This was done because some studies demonstrated that smooth optic-haptic junctions may be sites for PCO initiation.
- New injector systems to be used with the new lens designs have been developed. Manufacturers have also invested in the development of injector systems where the IOLs come preloaded and in automated injection systems.
- Special features such as multifocality, extended depth of focus, toric corrections, pseudoaccommodation, asphericity, postoperative adjustment





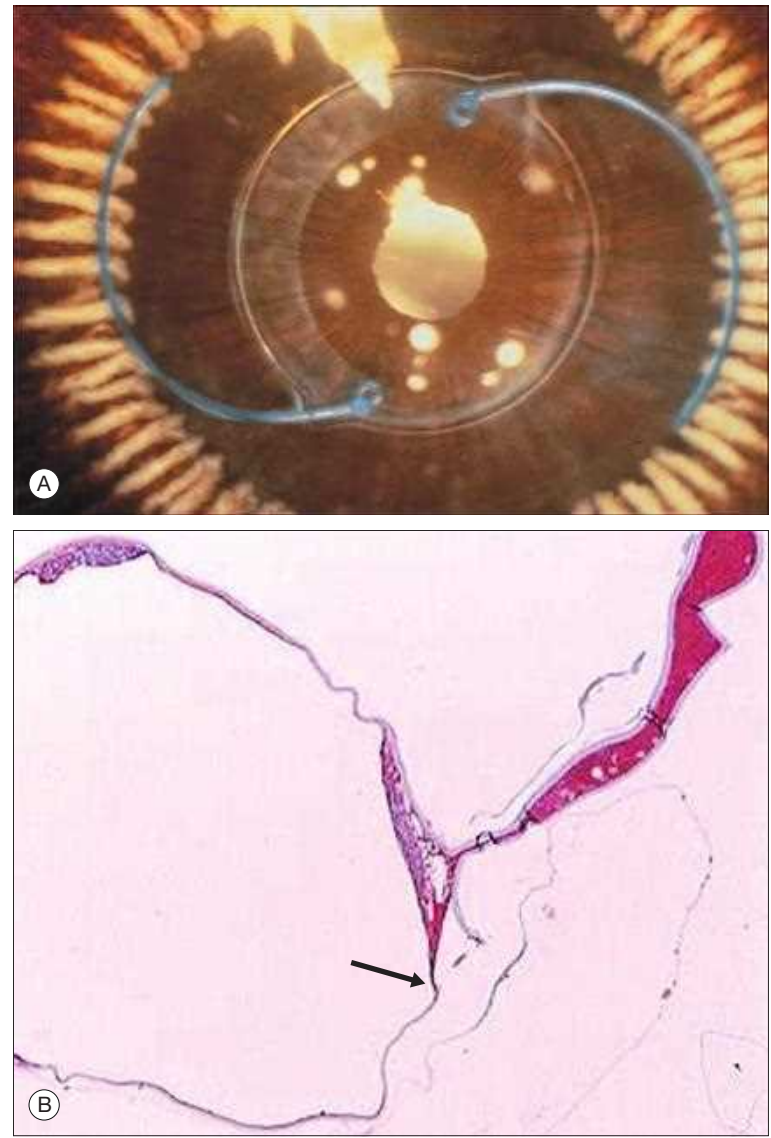
**Fig. 5.2.4 View From Behind of an Autopsy Eye.** (A) A Sinskey-style, J-loop posterior chamber intraocular lens implanted within the lens capsular bag. The optic is well centered, the visual axis is clear, and there is only minimal regeneration of cortex in scattered areas. Moderate haziness or opacity occurs at the margins of the anterior capsulotomy, which does not encroach on the visual axis. (B) The placement of the loop of this modified C-style intraocular lens in the capsular bag.

of the IOL refractive power, image magnification (telescopic lenses), and protection of the retina against blue or violet light (through incorporation of appropriate chromophores to the IOL optic material) are widely available.<sup>13</sup>

- The renewed interest in phakic IOLs, which can potentially correct any refractive error, is also progressing rapidly.<sup>14</sup> A trend exists for the use of foldable materials for these phakic lenses, designed to be inserted through small incisions and fixated to the iris or in the posterior chamber. Most of the angle-supported anterior chamber phakic IOLs have been abandoned from the market due to issues with the corneal endothelium.<sup>15</sup>
- There is a renewed interest in the piggyback IOL procedure not only for correction of residual refractive errors but also because of the potential to implant a low-power multifocal lens to provide spectacle freedom to patients who already are pseudophakic, as well as other specialized lenses such as toric and aspherical IOLs. In these cases, the “supplementary” lens is fixated in the ciliary sulcus to avoid interlenticular opacification (ILO) formation, and it is specially designed to minimize interaction with intraocular structures and provide appropriate clearance with uveal tissues and the in-the-bag IOL.<sup>16</sup>

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**Fig. 5.2.5 View From Behind an Autopsy Eye.** (A) Posterior view (Miyake technique) of a well-implanted Advanced Medical Optics three-piece silicone IOL. The lens was implanted following excellent cortical cleanup in a human eye obtained postmortem. (B) Gross photograph of the first human eye obtained postmortem with a single-piece AcrySof lens (Alcon Laboratories, Fort Worth, TX) implanted in our laboratory. The lens is well centered and the capsular bag is clear. (Reproduced from Escobar-Gomez M, Apple DJ, Vargas LG, et al. Scanning electron microscopic and histologic evaluation of the AcrySof SA30AL acrylic intraocular lens. *J Cataract Refract Surg* 2003;29:164–9.)

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# Evolution of Intraocular Lens Implantation

## 5.2

Liliana Werner, Andrea M. Izak, Suresh K. Pandey, David J. Apple<sup>†</sup>

**Definition:** Report on the evolution of intraocular lens designs.

### Key features

- Description of anterior and posterior chamber intraocular lens designs, including lenses now obsolete, and their interaction with intraocular tissues.
- Recent advances in intraocular lens designs/materials, leading to modern, currently available intraocular lenses.

## INTRODUCTION

Cataract is the most prevalent ophthalmic disease. The number of persons who became blind as a result of cataract in 1998 was estimated to be about 17 million worldwide; this number was expected to double by early in the twenty-first century.<sup>1,2</sup> Although a pharmacological preventive or therapeutic treatment for this blinding disease is being actively sought, the solution still appears to be many years away. Therefore, surgical treatment for cataracts, which increasingly includes intraocular lens (IOL) implantation, remains the only viable alternative.

Treatment of cataracts has been practiced for centuries using various surgical and nonsurgical procedures. However, avoidance of complications and attainment of high-quality postoperative visual rehabilitation were difficult in the years before the introduction of modern IOLs. Because significant dioptric power resides in the crystalline lens, its removal results in marked visual disability.

Aphakic spectacle correction has been prescribed throughout history, but spectacles are less than satisfactory because of the visual distortions inherent in such high-power lenses.

It was not until the late 1940s that the optical advantages that an IOL could provide in visual rehabilitation were understood and acted on by Ridley.<sup>3-7</sup>

The implantation of IOLs is now a highly successful operation; the safety and efficacy of this procedure are well established. The number of IOL implants in the United States in 1998 was estimated to be 1.6 million. Implantation data from other countries are scant, but the total number of implantations per year worldwide is increasing rapidly. Studies are still needed to determine which surgical technique(s) and which IOL design(s) are safest, most practical, and most economical for high-volume use in the less advantaged areas of the world. For general discussions that review the evolution and provide clinicopathological overviews of IOLs, see Apple and coworkers<sup>7-10</sup> and Binkhorst.<sup>11</sup>

Posterior chamber IOLs were reintroduced in the mid-1970s and early 1980s, following a long period of disfavor after the Ridley lens was discontinued. Jaffe and other authors compared posterior chamber lenses with iris-supported lenses and were impressed by the superior results achieved with the former type of lens using an extracapsular cataract extraction technique. The use of posterior chamber IOLs is now clearly the treatment of choice.

## LENS DESIGN AND FIXATION

In 1967, Binkhorst<sup>11</sup> proposed a detailed classification of the various means of fixation for each IOL type. In a 1985 update of this classification, Binkhorst<sup>12</sup> listed four IOL types according to fixation sites:

- Anterior chamber angle-supported lenses.
- Iris-supported lenses.
- Capsule-supported lenses.
- Posterior chamber angle (ciliary sulcus)-supported lenses.

By common agreement, most surgeons today differentiate lens types as follows:

- Iris-supported lenses.
- Anterior chamber lenses.
- Posterior chamber lenses.

From the time of Ridley's first lens implantation to the present day, the evolution of IOLs can be arbitrarily divided into six generations (Table 5.2.1).

### Generation I (Original Ridley Posterior Chamber Lens)

A practical application of the concept of IOLs began with Ridley,<sup>3-7</sup> and credit for the introduction of lens implants clearly belongs to him.

Ridley's first IOL operation was performed on a 49-year-old woman at St Thomas' Hospital in London on November 29, 1949. His original IOL was a biconvex polymethyl methacrylate (PMMA) disc designed to be implanted after extracapsular cataract extraction (ECCE) (Fig. 5.2.1).

Ridley's procedure was initially met with great hostility by several skeptical and critical ophthalmologists. However, good results were attained in enough cases to warrant further implantation of the Ridley IOL, although dislocation of the lens ultimately proved troublesome. It is gratifying to note that Ridley, who died in 2001, lived long enough to experience the acknowledgment, respect, and honor he so fully deserved for this innovation.

### Generation II (Early Anterior Chamber Lenses)

As a consequence of the relatively high incidence of dislocations with the Ridley lens, a new implantation site was considered—the anterior chamber, with fixation of the lens in the angle recess. The anterior chamber was chosen because less likelihood existed of dislocation within its narrow confines. In addition, anterior chamber lenses could be implanted after either an intracapsular cataract extraction (ICCE) or an ECCE. Also, anterior chamber placement of the pseudophakos was considered a simpler technical procedure than placement of the lens behind the iris.

TABLE 5.2.1 The Evolution of Intraocular Lenses

Generation	Date	Description
I	1949–1954	Original Ridley posterior chamber lens
II	1952–1962	Early anterior chamber lenses
III	1953–1975	Iris-supported lenses
IV	1963–1990	Intermediate anterior chamber lenses
V	1975–1990	Improved posterior chamber lenses
VI	1990 to present	Modern capsular posterior chamber lenses and modern anterior chamber lenses

<sup>†</sup>Deceased

Although many surgeons worked on the concept of this type of lens, Baron, in France, is generally credited as being the first designer and implanter of an anterior chamber lens (Fig. 5.2.2A).<sup>10</sup> He first performed this procedure on May 13, 1952.

Late endothelial atrophy, corneal decompensation, and pseudophakic bullous keratopathy were observed with the original Baron lens and developed with many subsequent anterior chamber lens designs. The entity now termed uveitis–glaucoma–hyphema (UGH) syndrome was described first when ocular tissue damage occurred that was clearly the result of

poorly manufactured anterior chamber lenses.<sup>13</sup> It took many modifications of the haptic-loop configuration and the lens-vaulting characteristics (see Fig. 5.2.2B) to develop an anterior chamber lens that allowed a reasonable prediction of long-term success. This was achieved largely because of the advances in lens design by Choyce of England and later by Kelman of New York.

### Generation III (Iris-Supported Lenses)

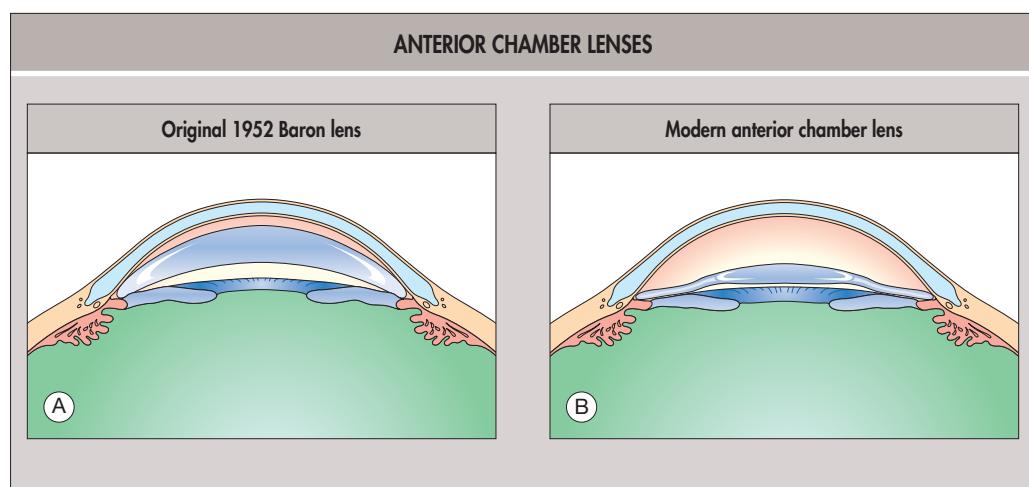
Relatively frequent dislocation of the Ridley lens and an unacceptably high rate of corneal decompensation associated with the anterior chamber lenses that were available in the early 1950s caused some surgeons to discontinue implantation of IOLs entirely.<sup>14</sup> However, iris-supported or iris-fixated IOLs were introduced subsequently in an attempt to overcome these problems.

Binkhorst in the Netherlands was an early advocate of iris-supported IOLs.<sup>11,12</sup> His first lens was a four-loop, iris-clip IOL (Fig. 5.2.3A) design. Although Binkhorst initially believed that IOL contact with the iris would not cause problems, he soon noted that iris chafing, pupillary abnormalities, and dislocation developed with the early iris-clip lens. Also, in an effort to circumvent dislocation, Binkhorst made the anterior loops of his four-loop lens longer, but this led to increased corneal decompensation from peripheral touch.

His initial implantations were done after ICCE, but occasionally he implanted his four-loop lens following ECCE. His positive experience with this procedure prompted him to modify his iris-clip lens design for implantation following ECCE. Binkhorst's change from ICCE to ECCE and the introduction of his two-loop iridocapsular IOL (see Fig. 5.2.3B) in 1965 were important advances in both IOL design and mode of fixation.<sup>15</sup> His and others' experiences with the two-loop lens style and its modifications were influential in the development of modern design concepts of IOLs, including capsular bag–fixated, posterior chamber IOLs. Binkhorst's innovative lens designs and his advocacy of ECCE came at a time when the entire future of IOL implantation was in jeopardy; they provided the major impetus that set the stage for modern posterior chamber lens implantations.



**Fig. 5.2.1 Posterior View of an Eye (Obtained Postmortem) Showing the Implantation Site of a Ridley Lens.** To the time of death, almost 30 years after implantation, the patient's visual acuity remained 20/20 (6/6) in both eyes. Note the good centration and clarity of the all-polymethyl methacrylate optic in the central visual axis. The lens was implanted by Dr. W. Reese and Dr. T. Hammdi of Philadelphia.



**Fig. 5.2.2 Sagittal Section of the Anterior Segment of the Eye.** (A) The original 1952 Baron anterior chamber lens with fixation in the angle recess. Because this one-piece lens was rigid, sizing problems were unavoidable. Note the extremely steep anterior curvature of the lens. Such excessive anterior vaulting invariably caused corneal endothelial problems. (B) Placement of a modern anterior chamber lens fixated in the angle recess. Note the more subtle anterior vaulting of the loops and lens optic.



**Fig. 5.2.3 Binkhorst Iris-Clip Lenses.** (A) A correctly positioned Binkhorst four-loop, iris-clip lens, well centered in an eye that had good visual acuity. Moderate pupillary distortion and sphincter erosion occur. Note the iris fixation suture superior to the site of the large iridectomy. (B) Posterior view of an autopsy globe that contains a two-loop iridocapsular intraocular lens. Note the rod that helps to secure the lens to the iris through the iridectomy. An outer Soemmerring's ring is present, but the visual axis remains clear. The optic is well centered.



During the early years of iris-fixated IOLs, many clinical and subclinical problems emerged, such as dislocation, pupillary deformity and erosion, iris atrophy with transillumination defects, pigment dispersion, uveitis, hemorrhage, and opacification of the media. Many of these complications were the result of chronic rubbing or chafing of the iris by IOL loops or haptics. Problems were especially severe with metal loop IOLs and occurred frequently with multiple-looped lenses because uveal contact and chafing against the mobile iris tissues were unavoidable with these designs.

An increased incidence of corneal edema occurred in association with iris-supported lens designs. Corneal decompensation and pseudophakic bullous keratopathy became major indications for penetrating keratoplasty. The well-known coexistence of pseudophakic bullous keratopathy and cystoid macular edema (CME) has been termed corneal-retinal inflammatory syndrome by Obstbaum and Galin.<sup>16</sup> Binkhorst's return to ECCE, with the introduction of his two-loop iridocapsular lens in 1965 (see Fig. 5.2.3B),<sup>17</sup> brought about an almost immediate reduction in the incidence of many of these complications.

Most iris-supported lenses were biplanar, with the optic placed in front of the pupil. In general, biplanar IOLs required a larger limbal wound opening for insertion. The change to capsular fixation after ECCE provided better stability for the pseudophakos. This important modification was a forerunner to capsular sac (in-the-bag) fixation of modern posterior chamber IOLs.

At the time when iris-supported lenses were in widespread use, and until the mid-1980s in many cases, manufacturing methods and surgical techniques were less sophisticated. It is now clear that most modern, high-quality anterior and posterior chamber IOLs provide better success than the IOLs that depend on the iris for support. At present, it is the consensus of surgeons that lens explantation and/or exchange is usually the best treatment when a patient who has an iris-supported IOL develops late complications such as inflammation or corneal decompensation that does not respond rapidly to conservative therapy.

## Generation IV (Intermediate Anterior Chamber Lenses)

As iris-supported IOLs underwent major modifications from the early 1950s up to the beginning of the 1980s, several designs of anterior chamber IOLs were introduced.

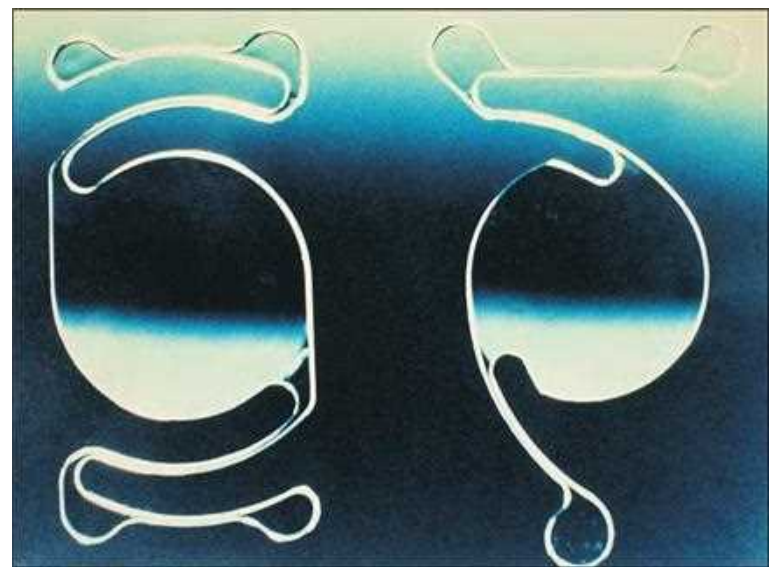
The problems of tissue chafing and difficulties in correct sizing associated with rigid IOLs were addressed by the development of anterior chamber lenses with more flexible loops or haptics (Box 5.2.1). Unlike the ill-fated, nylon-looped lenses introduced by Dannheim in the early 1950s, the fixation elements of these anterior chamber IOLs were made from more stable polymers, usually PMMA and polypropylene. The best lenses were the various rigid<sup>18</sup> and flexible, open-loop, one-piece PMMA designs, such as the three- and four-point fixation Kelman IOLs.<sup>19</sup> Modifications of the latter have been in use since the late 1970s and are the styles most commonly implanted today (Fig. 5.2.4). These lenses now are well designed, correctly vaulted, and properly sized and can provide excellent long-term results. As with the early generation of anterior chamber IOLs, new lens designs included both haptic (footplate) fixation lenses and small-diameter, round-looped IOLs.

Although in the 1950s implantations with early anterior chamber IOLs were often disappointing, some models of anterior chamber lenses provided good success, particularly when the lens was properly sized. Two important factors that led to a higher success rate with anterior chamber IOL use are improved lens designs and manufacturing techniques.

More appropriate lens flexibility has decreased the need for perfect sizing. Increased attention has been given to the anterior-posterior vaulting characteristics of IOLs, which has reduced the incidence of intermittent touch and uveal chafing problems. Design flaws in older lens styles have been identified and these lenses removed from the market in the United States. Tumble polishing of IOLs, particularly one-piece, all-PMMA lenses, produces excellent surfaces and edges. The elimination of sharp optic or haptic edges is critical in the production of anterior chamber IOLs. This is even more true than for posterior chamber IOLs, because anterior chamber IOLs are fixated in a confined space directly adjacent to delicate anterior segment tissues.

The two major disadvantages of an anterior chamber IOL, as compared with posterior chamber lens styles, are:

- The close proximity of the haptics or loops to delicate tissues such as the trabecular meshwork, corneal epithelium, angle recess, and anterior iris surface.



**Fig. 5.2.4 Modern One-Piece, All-Polymethyl Methacrylate, Kelman-Style Anterior Chamber Lenses of Four-Point and Three-Point Fixation Designs.** Note the excellent polishing and tissue-friendly Choyce-Kelman-style footplates. These represent modern, state-of-the-art lenses that should be distinguished clearly from the earlier, unsatisfactory, closed-loop anterior chamber lenses.

### BOX 5.2.1 Anterior Chamber Lenses

#### Disadvantages of Closed-Loop Anterior Chamber Lenses

- Lenses may be difficult to size
- Lenses may have inappropriate vault-compression ratios; when a lens is compressed, it may vault anteriorly or posteriorly—either type of response can cause deleterious effects
- Small-diameter loops may cause a “cheese-cutter” effect, particularly if the lens is too large; subsequent erosion and chafing can cause uveitis, including cystoid macular edema and pseudophakic bullous keratopathy
- Some lenses have a large contact zone over broad areas of the angle with the potential for secondary glaucoma
- The poorly finished, sharp edges of some lens models can cause chafing, which leads to sequelae such as uveitis or uveitis–glaucoma–hyphema syndrome
- Synechiae formation around the small-diameter loops may make the lens difficult to remove when necessary; tearing of ocular tissues, hemorrhage, and iridocyclodialysis are possible complications of intraocular lens removal if correct procedures are not used

#### Advantages of Modern, Open-Loop, One-Piece, All-PMMA Flexible Anterior Chamber Lenses

- Most modern lenses have an excellent finish with highly polished smooth surfaces and rounded edges from tumble polishing; tissue contact with any component of these intraocular lenses is much less likely to result in chafing damage
- Sizing is less critical with flexible, open-loop designs
- In contrast to a closed-loop anterior chamber intraocular lens, the vault (a well-designed, open-loop lens) is maintained even under high compression—this minimizes intraocular lens touch against the cornea anteriorly or against the iris posteriorly
- Point fixation is possible, since the haptic may subtend only small areas of the angle outflow structures
- Most open-loop intraocular lens designs are much easier to remove, when necessary, especially those with Choyce-like haptic or footplate fixation; the well-polished surfaces of these lenses usually do not become completely surrounded by goniosynechiae or cocoon membranes and thus can usually be removed if necessary without undue difficulty or excessive tissue damage

- The difficulty often encountered in IOL sizing, particularly with rigid lens designs.

The close proximity of anterior chamber lens components to the corneal endothelium is an obvious disadvantage because of the potential for corneal decompensation and/or pseudophakic bullous keratopathy as a



result of contact of the cornea with the IOL. In the past, the most common causes of pseudophakic bullous keratopathy were related to anterior chamber IOLs that were sized incorrectly, vaulted too steeply, or designed with an inappropriate amount of flexibility.<sup>20</sup>

Haptics or spatula-like footplates are one of the two types of fixation elements used for anterior chamber IOLs. Haptics or footplates, popularized by Peter Choyce, are often likened to the flattened portion of a spatula and were used originally with the more rigid IOL styles. They now are used with both rigid and flexible modern anterior chamber IOLs. When IOL removal is necessary for any reason, the footplate generally slides out of the eye much more easily than does a small-diameter loop and does so with minimal tissue damage.

Small-diameter lens loops are the second type of fixation element for anterior chamber IOLs. Loops may be of either an open or a closed design. Round, small-diameter, closed loops may cause a “cheese-cutter” effect within the eye and difficulty in removal. A 360° fibrouveal encapsulation, or “cocoon,” often forms around such small-diameter, round loops as the loops become embedded in the tissues of the angle recess. If the correct explantation procedure is not used, these adhesions may result in tissue tears, hemorrhage, and iridocyclodialysis. These anterior chamber IOLs,<sup>21–25</sup> often generically classified together as “closed-loop lenses,” do not provide the safety and efficacy achieved by other anterior chamber lens designs, such as finely polished, flexible, one-piece, all-PMMA lenses (see Fig. 5.2.4). By 1987 the U.S. Food and Drug Administration had placed IOLs of the closed-loop design on core investigational status. This had the effect of removing them from the market in the United States, although it did not prevent the export of such lenses.

The flexible, open-loop designs,<sup>24–28</sup> modifications of the original Kelman anterior chamber IOLs (with Choyce-style footplates), can be well finished using tumble polishing, which provides a rounded, “tissue-friendly” surface at points of haptic contact with delicate uveal tissues. One-piece IOLs, particularly those with a footplate design, are usually much easier to explant than IOLs with round, small-diameter loops of either closed-loop or open-loop design.

Iris- or scleral-fixated, sutured posterior chamber IOLs may be used in cases formerly reserved for anterior chamber IOLs. Results are encouraging.<sup>29,30</sup> Uncertainty still exists as to whether a retropupillary lens is superior to a modern, well-manufactured, Kelman-style anterior chamber IOL for cases such as intraoperative capsular rupture or vitreous loss or as a secondary or exchange procedure. The technique is more difficult than insertion of a single anterior chamber lens, and therefore it should be carried out only by an experienced surgeon.

## Generation V (Improved Posterior Chamber Lenses)

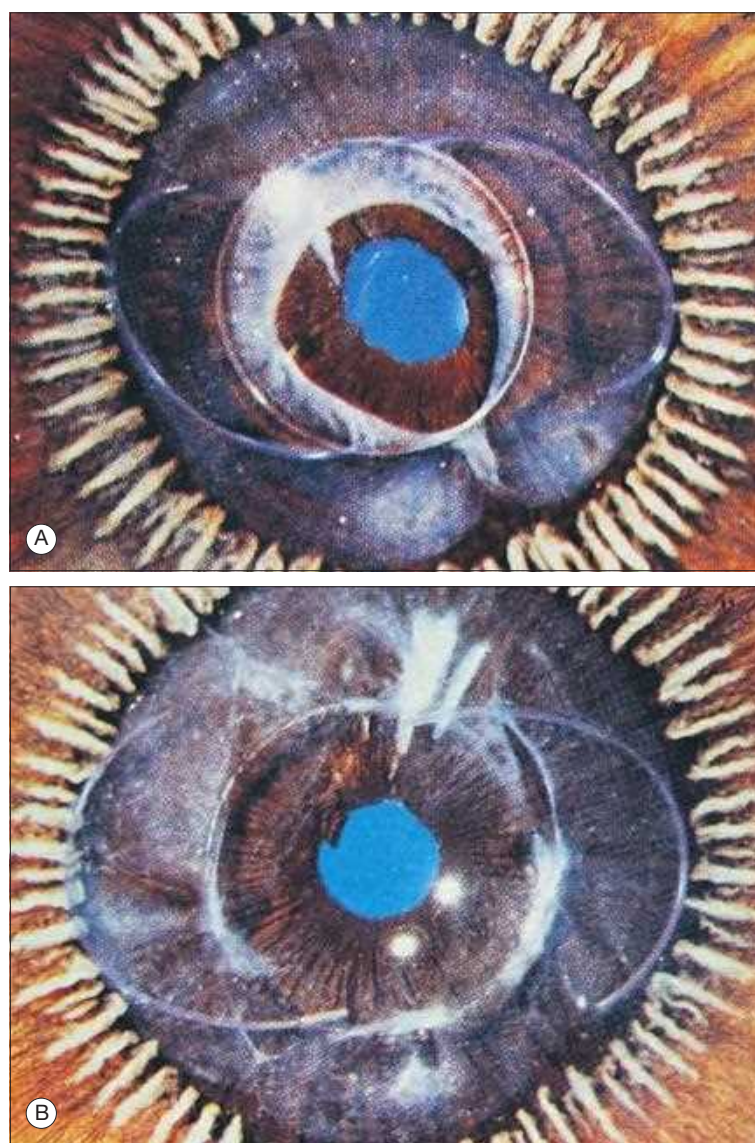
The return to Ridley's<sup>4–7</sup> original concept of IOL implantation in the posterior chamber occurred after 1975. Pearce<sup>31</sup> of England implanted the first uniplanar posterior chamber lens since Ridley.<sup>32</sup> This lens was a rigid tripod design with the two inferior feet implanted in the capsular bag and the superior foot implanted in front of the anterior capsule and sutured to the iris. Shearing<sup>33</sup> of Las Vegas introduced a major lens design breakthrough in early 1977 with his posterior chamber lens. The design consisted of an optic with two flexible, J-shaped loops. Simcoe of Tulsa publicly introduced his C-looped posterior chamber lens shortly after Shearing's J-loop design appeared. Arnott of London was an early advocate of one-piece, all-PMMA posterior chamber IOLs. The flexible open-loop designs (J-loop, modified J-loop, C-loop, or modified C-loop) still account for the largest number of IOL styles available today (Fig. 5.2.5).

One obvious major theoretical advantage that a posterior chamber IOL has over an anterior chamber IOL is its position behind the iris, away from the delicate structures of the anterior segment.

As posterior chamber lens implantation evolved, the type of fixation achieved in the early years depended largely on chance or on the surgeon's individual preference. As Fig. 5.2.6 illustrates, several loop-fixation sites are possible with modern, flexible-loop posterior chamber IOLs. In general, the loops were anchored in one of three ways:

- Both loops were placed in the ciliary region.
- Both loops were placed within the lens capsular sac.
- One loop (usually the leading or inferior loop) was placed in the capsular sac and the other loop (usually the trailing or superior loop) in a variety of locations anterior to the anterior capsular flap.

These fixation sites have been confirmed histologically by analyses of postmortem globes implanted with posterior chamber IOLs.



**Fig. 5.2.5 View From Behind an Autopsy Eye.** (A) A Sinskey-style, J-loop posterior chamber intraocular lens implanted within the lens capsular bag. The optic is well centered, the visual axis is clear, and there is only minimal regeneration of cortex in scattered areas. Moderate haziness or opacity occurs at the margins of the anterior capsulotomy, which does not encroach on the visual axis. (B) The placement of the loop of this modified C-style intraocular lens in the capsular bag.

The return to posterior chamber lenses coincided with the development of improved ECCE surgery. Shearing<sup>33</sup> identified four major milestones that have marked the evolution of ECCE surgery:

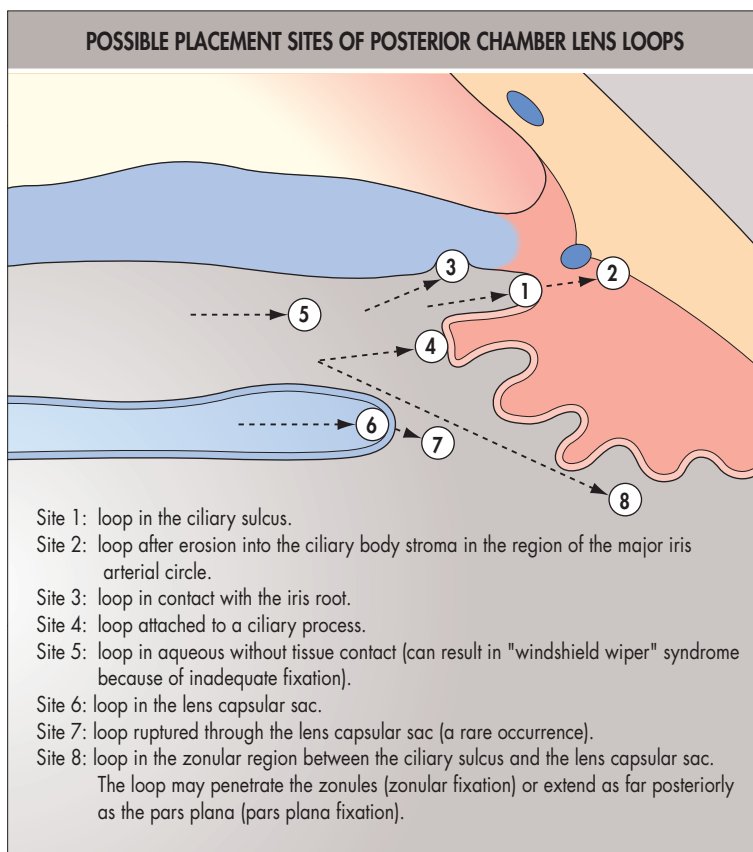
- Microscopic surgical techniques.
- Phacoemulsification (phaco).
- Iridocapsular fixation.
- Flexible posterior chamber lenses.

Without microscopic surgery, modern IOL implantation would be far more difficult. Although phaco was promoted originally because it required only a small wound, it became clear that if an IOL were to be inserted, the wound would have to be enlarged after removal of the cataract, and thus nonultrasonic surgical methods were refined. By 1974, implantation of IOLs again began to achieve significant acceptability. A natural marriage between phaco and implantation of IOLs occurred.

As noted previously, Binkhorst<sup>11,12,17</sup> was one of the pioneers in the return to the ECCE procedure. Binkhorst recognized that an intact posterior capsule enhanced stability, and he also recognized the many advantages of IOL implantation within the capsular sac. Evidence continues to accumulate that CME and retinal detachment occur less frequently with ECCE than with ICCE.

The introduction of flexible posterior chamber lenses designed to be implanted following ECCE largely resolved the debate about ECCE versus ICCE clearly in favor of the extracapsular procedure.

Securing both loops in the lens capsular sac is the only type of fixation in which IOL contact with uveal tissues is avoided.<sup>34</sup> Placement of a lens



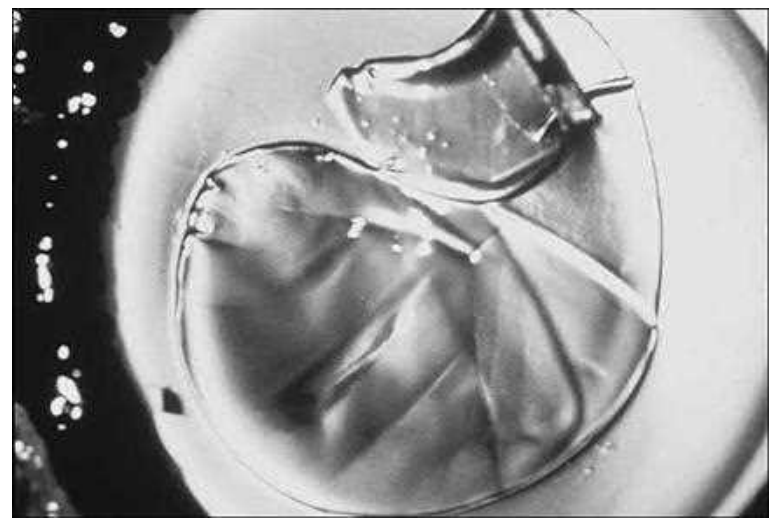
**Fig. 5.2.6 The Possible Placement Sites of Posterior Chamber Lens Loops.**

### BOX 5.2.2 Advantages of Placing Both Loops in the Lens Capsular Sac

Intraocular lens is positioned in the proper anatomical site  
 Both loops can be placed symmetrically in the capsular sac as easily as in the ciliary sulcus  
 Intraoperative stretching or tearing of zonules by loop manipulations in front of the anterior capsular leaflet is avoided  
 Low incidence of lens decentration and dislocation  
 No evidence of spontaneous loop dislocation  
 Intraocular lens is positioned a maximal distance behind the cornea  
 Intraocular lens is positioned a maximal distance from the posterior iris pigment epithelium, iris root, and ciliary processes  
 Iris chafing (caused by postoperative pigment dispersion into the anterior chamber) is reduced  
 No direct contact by, or erosion of, intraocular lens loops or haptics into ciliary body tissues  
 Chronic uveal tissue chafing is avoided, and the probability of long-term blood–aqueous barrier breakdown is reduced  
 Surface alteration of loop material is less likely  
 Intraocular lens implantation is safer for children and young individuals  
 Posterior capsular opacification may be reduced  
 Intraocular lens may be easier to explant, if necessary

with one or both loops outside the capsular bag is associated with various potential complications, including decentration and uveal erosion.<sup>34,35</sup> The consequences of uveal touch have been learned after experiences with the earlier iris-fixed IOLs. The excellent success rate now achieved with posterior chamber IOL implantation is associated with improved IOL designs and improved surgical techniques, including the meticulous placement of loops (Box 5.2.2).

Posterior capsule opacification (PCO; Elschnig pearls, secondary or after cataract) is a significant postoperative complication in IOL implantation. A well-designed posterior chamber lens in the lens capsular sac provides a gentle but taut radial stretch on the posterior capsule. Of the present open-loop flexible IOLs, the one-piece, all-PMMA posterior chamber designs with posterior convex or biconvex optics appear to be especially effective in providing a symmetrical stretch. Symmetrical stretch may help minimize PCO, as it reduces the folds in the capsular sac and holds the



**Fig. 5.2.7 Surgeon's View (Cornea and Iris Removed) of a Porcine Eye Showing the Capsulorrhexis Procedure.** Notice the smooth edges of the anterior capsular tear, which is the key feature of this procedure.

posterior capsule firmly against the posterior surface of the IOL optic. This is sometimes termed the "no space, no cells" concept.

The quality of surgery and the accuracy of loop placement are important factors that affect the outcome of the cataract operation. Two very helpful tools are available to surgeons that make precise loop or haptic placement possible:

- Ophthalmic viscosurgical devices (OVDs).
- New methods to control the size, shape, and quality of the anterior capsulotomy.
- The intercapsular (envelope) technique and its successor, circular continuous tear capsulorrhexis, greatly increase the ability to achieve accurate and permanent loop placement.

### Generation VI (Modern Capsular Lenses—Rigid PMMA, Soft Foldable, and Modern Anterior Chamber)

By the end of the 1980s, clinical laboratory studies demonstrated clearly that cataract surgical techniques and IOL design and manufacture had shown remarkable advances.<sup>36–40</sup> Surgical technique and IOL design and manufacture had advanced to a point at which the older techniques had given way to more modern ones, which allowed consistent, secure, and permanent in-the-bag (capsular) fixation of the pseudophakos. A marriage between IOL design and improved surgical techniques has evolved into capsular surgery. The "capsular" IOLs are fabricated from both rigid and soft biomaterials.

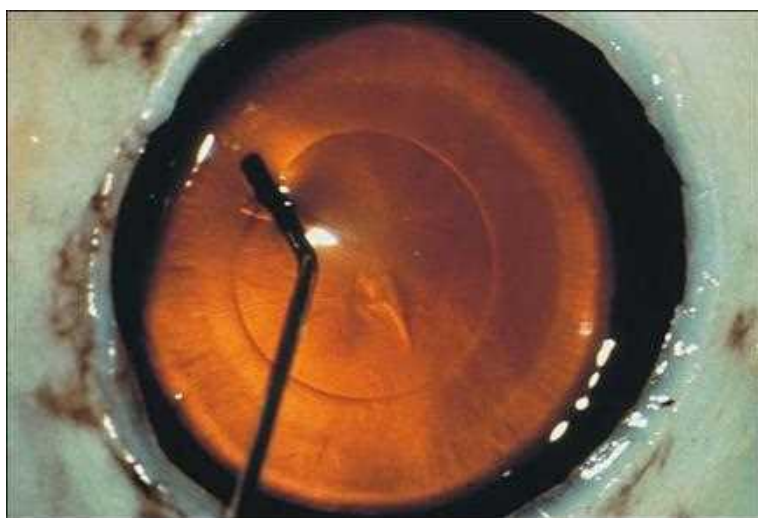
The many changes in surgical techniques that occurred after 1980 and into the 1990s include the introduction of OVDs,<sup>40–43</sup> increased awareness of the advantages of in-the-bag fixation, the introduction of continuous curvilinear capsulorrhexis (CCC)<sup>44–51</sup> (Fig. 5.2.7), hydrodissection<sup>52</sup> (Fig. 5.2.8), and the increased use of phaco. This has allowed not only much safer surgery but also implantation through a smaller incision than was possible in the early days of extracapsular extraction.

The evolution from can-opener toward capsulorrhexis (see Fig. 5.2.7) was initiated by Binkhorst, who developed a two-step (envelope) technique that eventually evolved into the single-step CCC. Two clear advantages of CCC exist over the early can-opener techniques.

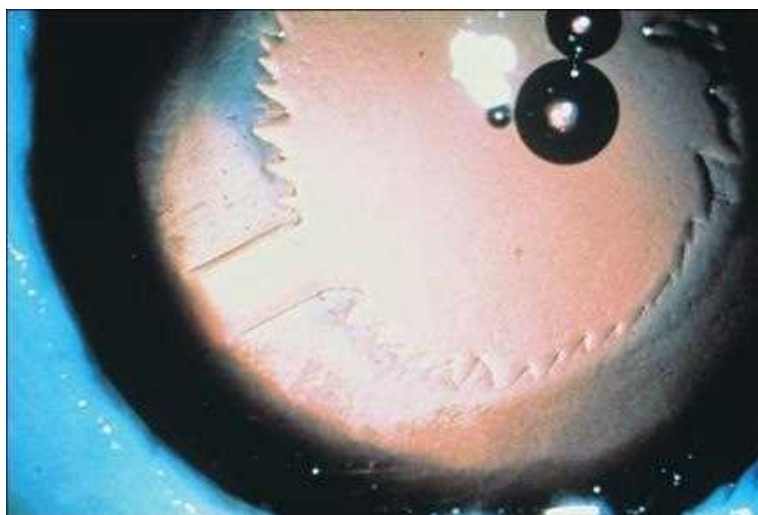
First, the formation of radial tears (Fig. 5.2.9) is reduced,<sup>47</sup> which minimizes radial tears of the anterior capsule, which in turn reduce the stability of the capsular bag and may allow prolapse of haptics out of the capsular bag through the anterior capsular tear. Second, and less commonly recognized, capsulorrhexis provides a stable capsular bag that allows copious hydrodissection, which in turn is very helpful in cortical cleanup. With a frayed, emptier capsular edge, such as seen with the can-opener technique, hydrodissection is difficult without forming unwanted radial tears.

Hydrodissection (see Fig. 5.2.8) was a term coined by Faust<sup>52</sup> in 1984. This technique, and the many variations thereof (e.g., cortical cleavage hydrodissection, hydrodelineation), makes the surgery much simpler in that mobilization and removal of cells and cortical material are rendered much easier. The long-term risk of PCO is, in turn, clearly minimized





**Fig. 5.2.8** Surgeon's View (Cornea and Iris Removed) of a Human Eye (Obtained Postmortem) Showing Experimental Hydrodissection. In this case the cannula is placed immediately under the anterior capsule (cortical cleavage hydrodissection). Hydrodissection is one of the most important maneuvers to help reduce the incidence of posterior capsular opacification.

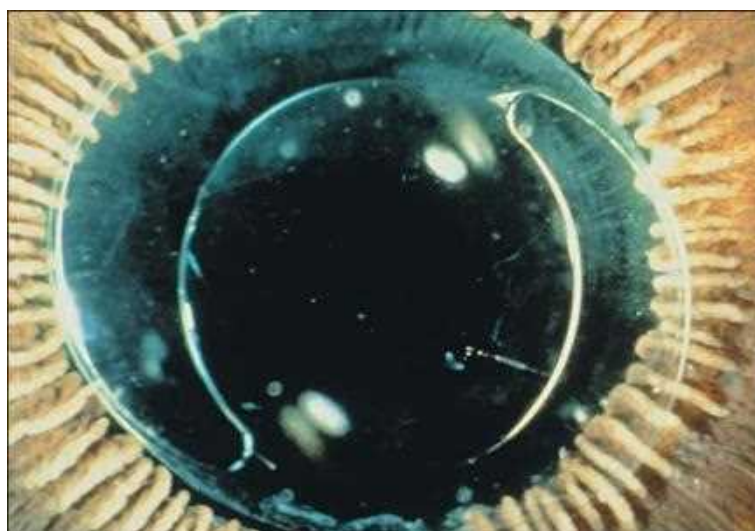


**Fig. 5.2.9** Surgeon's View of an Experimentally Performed Can-Opener Capsulectomy, With Typical Radial Tears to the Equator of the Anterior Capsule. The cornea and iris are removed from a human eye obtained postmortem. Following clinical can-opener anterior capsulectomy, one to five radial tears invariably occur. (Reproduced with permission from Assia EI, Apple DJ, Tsai JC, et al. The elastic properties of the lens capsule in capsulorrhexis. *Am J Ophthalmol* 1991;111:628–32.)

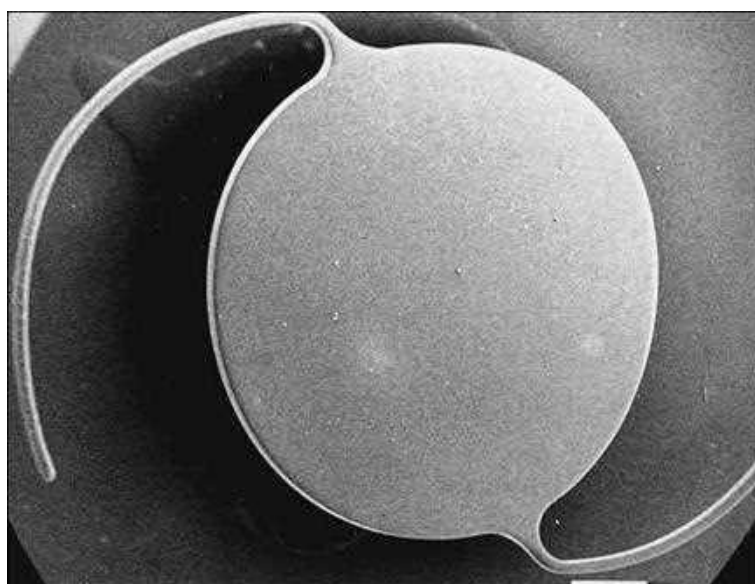
because of the more thorough removal of cells in cortical material, especially in the region of the equatorial fornix.

Modern phaco, pioneered by Kelman, has now made possible the removal of lens material through small incisions and the implantation of IOLs through incisions down to 3 mm in length, as opposed to incisions of 11 to 12 mm length in the early days of ECCE. Many real advantages of small-incision cataract surgery exist, including safer healing (with fewer risks of complications such as inflammation), more rapid healing, and rapid recovery of visual rehabilitation (with less postoperative astigmatism).

Accompanying the developments of surgical techniques that allow secure in-the-bag implantation, IOLs have evolved that work well with these techniques—both rigid PMMA designs (Figs. 5.2.10 and 5.2.11) and foldable IOLs.<sup>53</sup> Fig. 5.2.10 shows an example of a modern, state-of-the-art, one-piece, all-PMMA IOL that is designed for in-the-bag implantation. These can be inserted through incisions as small as 5.5–6 mm in length and provide an excellent alternative for the surgeon who finds the almost 50-year history of PMMA as a lens biomaterial of comfort. Long-term results with these IOLs are excellent and, indeed, these lenses provide slightly better centration than do some of the more modern foldable lenses at the present time. The ideal diameter for a one-piece IOL design such as that in Fig. 5.2.10 is 12–12.5 mm, which allows it to fit perfectly into the



**Fig. 5.2.10** A Modern, One-Piece, All-PMMA, Capsular IOL Implanted Experimentally in a Human Eye: Posterior View (Miyake Technique) of the Eye (Obtained Postmortem). Note the excellent centration and a perfect fit within the capsular bag.



**Fig. 5.2.11** Scanning Electron Micrograph of a Well-Designed, Tumble-Polished, Modified C-Loop, One-Piece, All-PMMA Posterior Chamber IOL. The total length of this capsular IOL design is 12.0 mm. Note the excellent, smooth finish of this well-polished IOL. (Original magnification  $\times 10$ .)

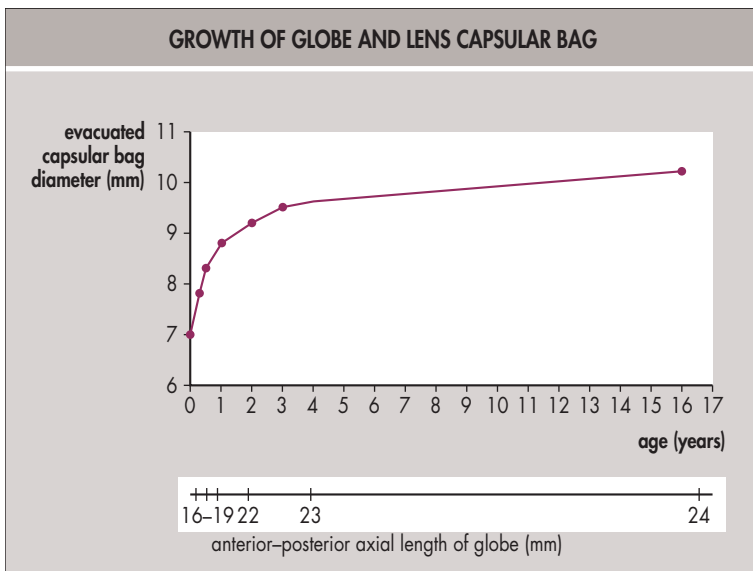
capsular bag (which measures about 10.5 mm in diameter). The diameter of the ciliary sulcus is only slightly larger (approximately 11.0 mm)<sup>53</sup> and actually decreases with age.

These rigid PMMA IOL designs have been found to be very satisfactory in pediatric IOL implantation.<sup>54,55</sup> As 90% of the growth of the infantile globe occurs during the first 18 months to 2 years (Fig. 5.2.12), it is fair to assume that “adult” 12 mm lenses can be safely implanted with the achievement of good results in children of this age and older (Figs. 5.2.12 and 5.2.13). The problem in the past with IOL implantation has been that of PCO. With present techniques, this is best prevented using primary posterior capsulectomy.

Improved small-incision surgical techniques and IOL designs have resulted in a natural evolution toward foldable lenses.<sup>56–67</sup> Most foldable lenses today are manufactured from silicone, hydrogel, or acrylic material (Figs. 5.2.14–5.2.16).

The earliest designs for which clinical usage was widespread were the plate lenses known as the “Mazzocco taco.” In early years these were manufactured poorly and often not implanted properly into the capsular bag, so many complications ensued. In recent years manufacturing quality has become much better, and these lenses are now satisfactory for clinical usage (Figs. 5.2.17 and 5.2.18). The best plate lenses are those with large positioning holes that allow in-the-bag synechia formation, which enhances fixation and stability.<sup>64</sup>

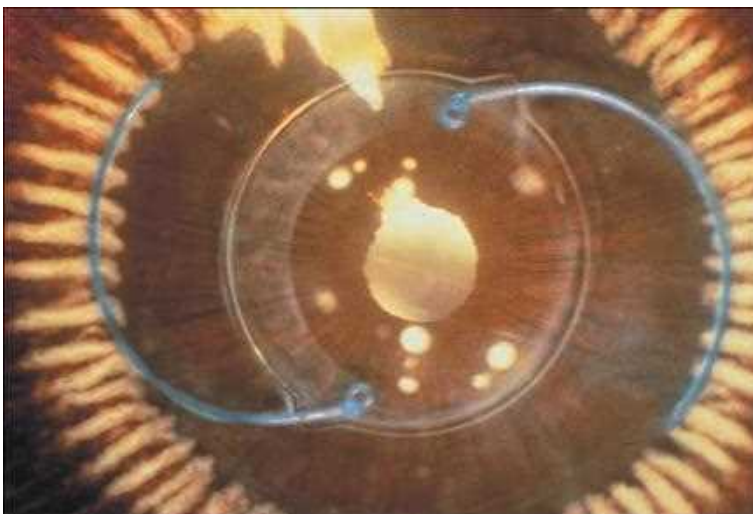




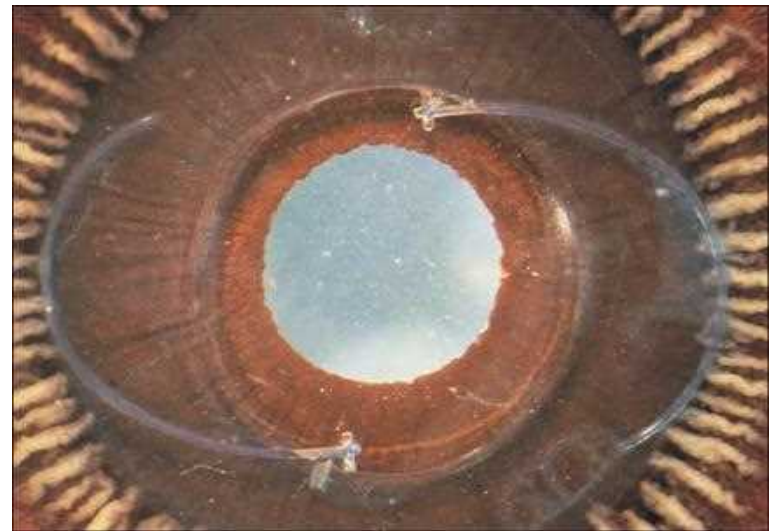
**Fig. 5.2.12 Growth of the Globe and Lens Capsular Bag.** These results are based on a study of 50 eyes obtained postmortem and demonstrate that the growth of the globe and lens capsular bag occurs relatively rapidly during the first 18 months to 2 years. (Reproduced with permission from Wilson ME, Apple DJ, Bluestein EC, et al. Intraocular lenses for pediatric implantation: biomaterials, designs, and sizing. J Cataract Refract Surg 1994;20:584-91.)



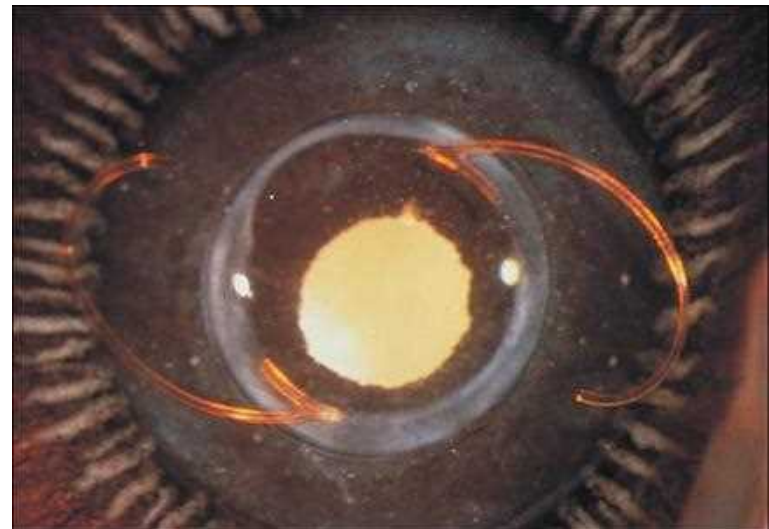
**Fig. 5.2.13 Posterior View (Miyake Technique) of an Eye of a 2-Year-Old Child (Obtained Postmortem).** This was implanted experimentally with a 12 mm, one-piece, all-PMMA IOL in the capsular bag. Note the excellent fit in the capsular bag. (Reproduced with permission from Wilson ME, Apple DJ, Bluestein EC, et al. Intraocular lenses for pediatric implantation: biomaterials, designs, and sizing. J Cataract Refract Surg 1994;20:584-91.)



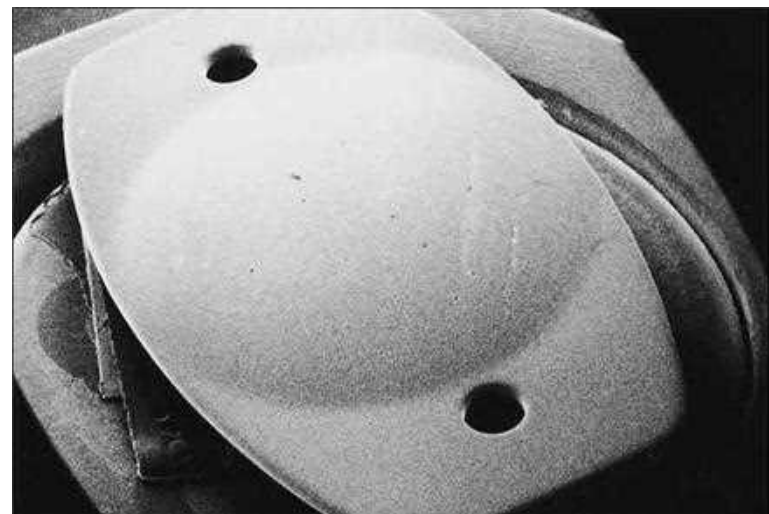
**Fig. 5.2.14 Posterior View (Miyake Technique) of a Well-Implanted Advanced Medical Optics Three-Piece, Silicone IOL.** The lens is implanted following excellent cortical cleanup in a human eye obtained postmortem.



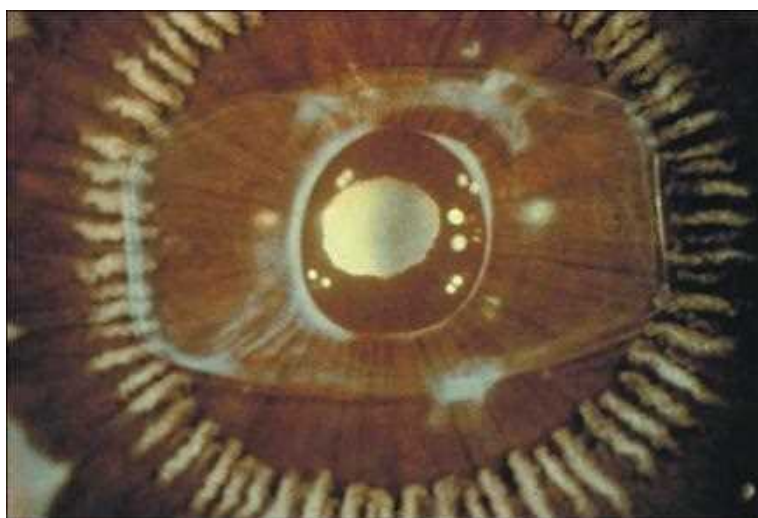
**Fig. 5.2.15 Posterior View (Miyake Technique) of a Well-Implanted Alcon Acrysof Acrylic IOL.** The lens is well centered in the capsular bag after thorough cortical removal.



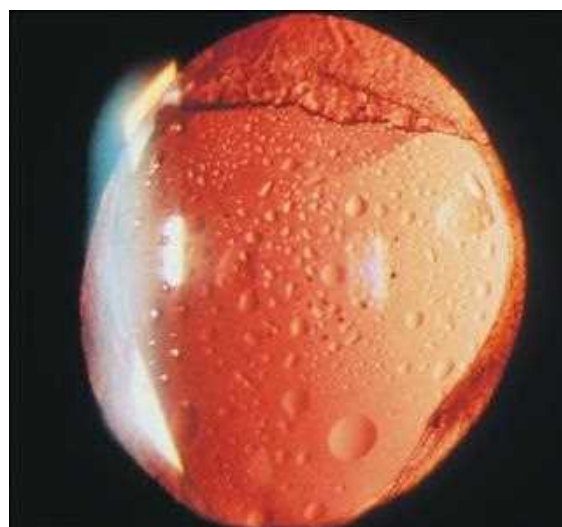
**Fig. 5.2.16 A Staar Surgical Corporation Three-Piece IOL With Polyimide Haptics: Posterior View (Miyake Technique) of an Eye (Obtained Postmortem).** The lens is well centered and positioned in a clean capsular bag.



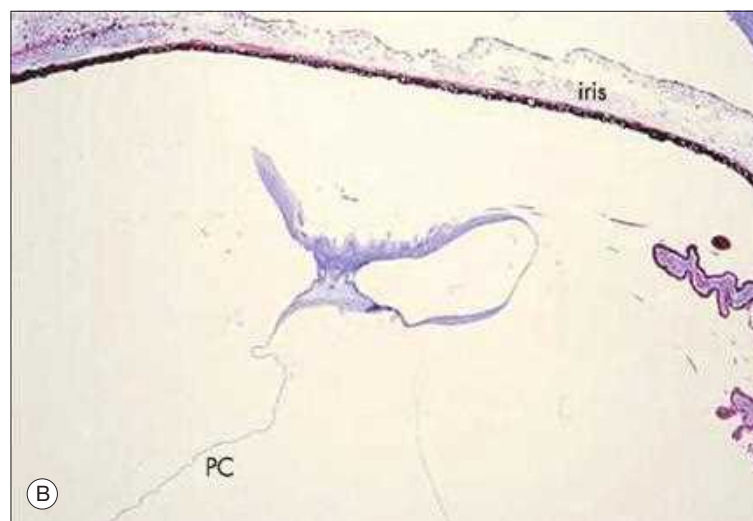
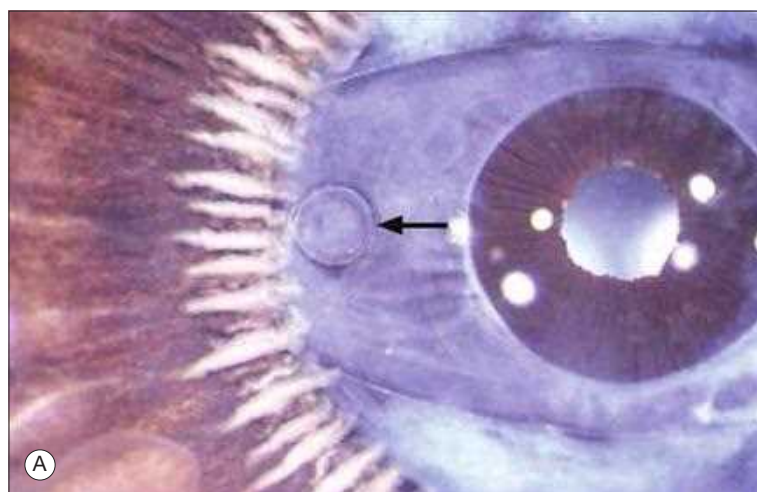
**Fig. 5.2.17 Scanning Electron Micrograph That Shows the Marked Improvement in Plate Lens Manufacture by the 1990S.** Note the excellent overall design and manufacture finish. (Original magnification  $\times 10$ .)



**Fig. 5.2.18** A Well-Implanted Staar-Chiron-Style Silicone Plate IOL, With Excellent Cortical Removal and Centration. Posterior view (Miyake technique) of the eye (obtained postmortem).



**Fig. 5.2.19** View of a Patient Who Has Silicone IOL and Who Later Required Vitreoretinal Surgery With Silicone Oil. Note the dense bubbles that cover the optic surface, impairing both vision and the surgeon's view into the eye.



**Fig. 5.2.20** Gross and Light Microscopic Photographs of a Pseudophakic Human Eye Obtained Postmortem, Implanted With a Silicone Plate Lens With Large Fenestrations. (A) Miyake–Apple posterior photographic technique. The arrow indicates the fibrotic tissue growing through one of the large fenestrations. (B) Fusion between anterior and posterior capsules promoted by the fibrocellular tissue growing through the fenestration (Masson's trichrome; original magnification  $\times 100$ ). PC, Posterior capsule. (Reproduced from Apple DJ, Auffarth GU, Peng Q, et al. Foldable intraocular lenses: evolution, clinicopathologic correlations, complications. Thorofare, NJ: Slack; 2000.)

The most commonly implanted designs at present are three-piece lenses that consist of silicone, acrylic, or hydrogel optics. Plate lenses continue to provide excellent results. These lenses can be implanted through incisions smaller than 5 mm in length. Visual rehabilitation is now incredibly fast with various further modifications, such as clear corneal incisions and topical anesthesia. Such surgery is virtually analogous to arthroscopy of the eye.

Lens design and manufacture have improved to such an extent that perhaps the most important factor in achieving a successful result is not the IOL itself, but the quality of surgery. These factors are very important now that high standards exist for results following IOL implantation, especially in this era, when IOL implantation is considered not only a means of optical rehabilitation after cataract removal but also a bona fide refractive procedure. The development of bi- and multifocal IOL designs is one example of this evolutionary process. An increased interest in clear lens extraction for myopia and the use of phakic IOLs also exemplifies the evolution toward refractive IOLs. It is of utmost importance to achieve symmetrical capsular bag fixation and good cortical cleanup to minimize the chance of complications, such as lens decentration and formation of a Soemmerring's ring.

The development of foldable lenses is one of fine-tuning. For example, much effort is now being expended to develop ever more tissue-friendly optic biomaterials. Fig. 5.2.19 reveals a complication that may occur occasionally in patients who have silicone lenses and who require subsequent

vitreoretinal surgery using silicone oil.<sup>68</sup> Work is underway to address this complication by modifications of the biomaterial to change factors such as its surface characteristics.<sup>69</sup> Work is in progress also on the attachment of different styles of haptic materials to the optic to achieve better and more stable fixation of the haptics in the capsular bag.

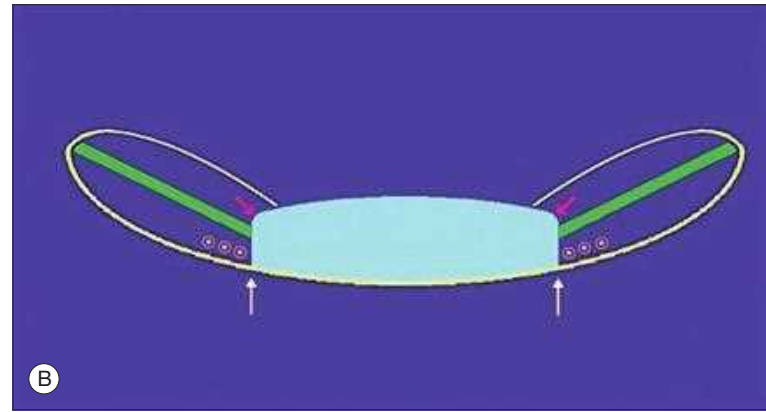
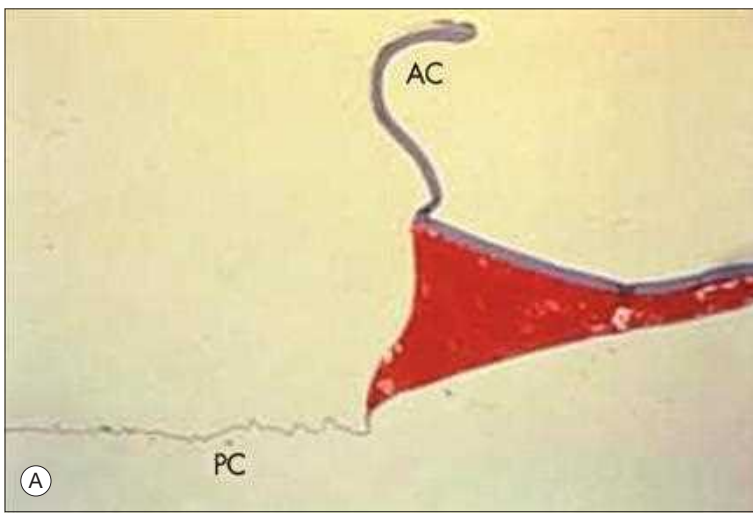
Note that the various ultramodern designs of anterior chamber lenses developed for both aphakic and phakic implantations are considered to belong to generation VI. These include the various Kelman–Choyce designs and modifications by Baikoff and Clemente (see Fig. 5.2.4). These are categorized here to separate them from the many generally inferior anterior chamber IOLs that were available in the earlier intermediate period between 1963 and 1990 (generation IV). The ultramodern designs are suitable for specific clinical indications and clearly should not be included in the generic concept that all anterior chamber IOLs are bad.

## RECENT ADVANCES

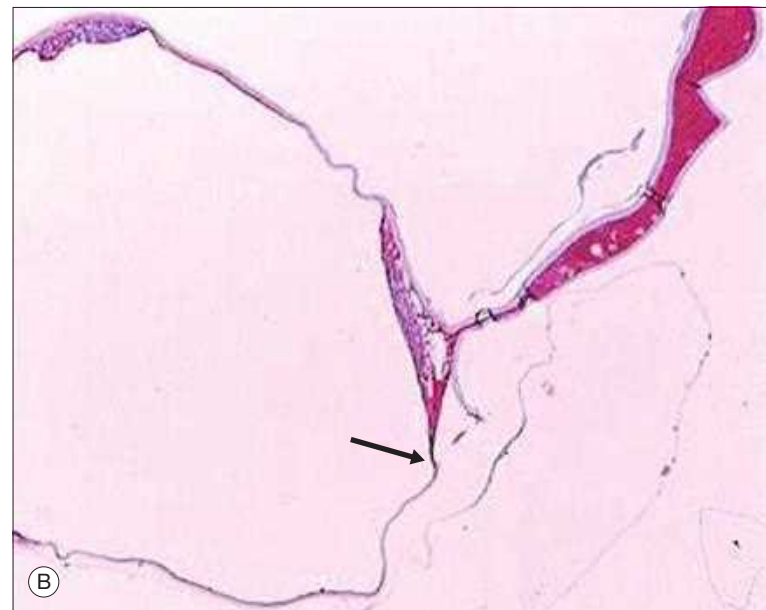
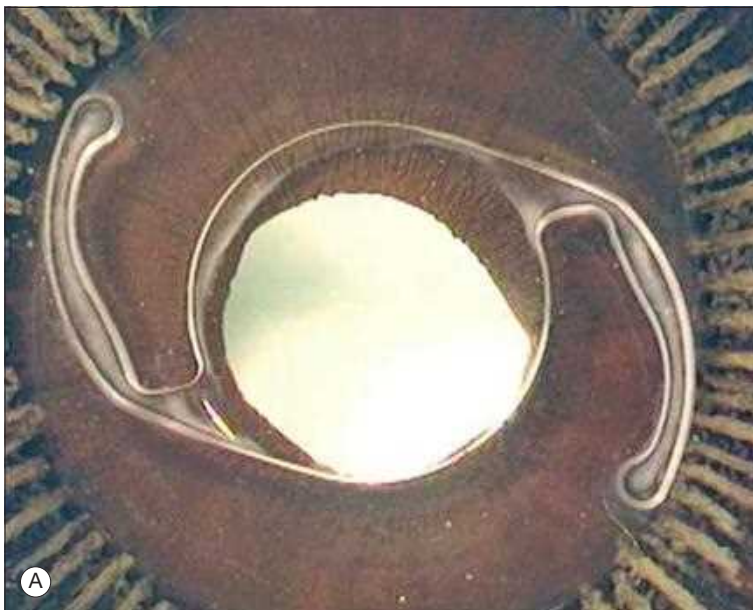
There are some general principles and tendencies with regard to the development of new IOLs.

- Large fixation holes or foramina have been incorporated in the haptic components of one-piece plate designs (Fig. 5.2.20A). Fibrous adhesions often occur between the anterior and posterior capsules following ingrowth of fibrocellular tissue through the holes (Fig. 5.2.20B). This





**Fig. 5.2.21 Light Photomicrograph and Schematic Illustration Showing the Barrier Effect of an IOL Optic With a Square Truncated Edge.** (A) Photomicrograph of a case in which the Soemmerring's ring (red) remains totally confined to the right of the square optic edge, leaving the posterior capsule (lower left) cell free (Masson's trichrome; original magnification  $\times 50$ ). (B) Square truncated optic edge seems to provide an abrupt barrier (arrows), leaving the entire optical zone free of cells. AC, Anterior capsule; PC, posterior capsule. (A, Reproduced from Werner L, Apple DJ, Pandey SK. Postoperative proliferation on anterior and equatorial lens epithelial cells. In: Buratto L, Werner L, Zanini M, et al., editors. Phacoemulsification: principles and techniques. Thorofare, NJ: Slack; 2002. p. 603–23. B, Reproduced from Peng Q, Visessook N, Apple DJ, et al. Surgical prevention of posterior capsule opacification. Part III. Intraocular lens optic barrier effect as a second line of defense. J Cataract Refract Surg 2000;26:198–213.)



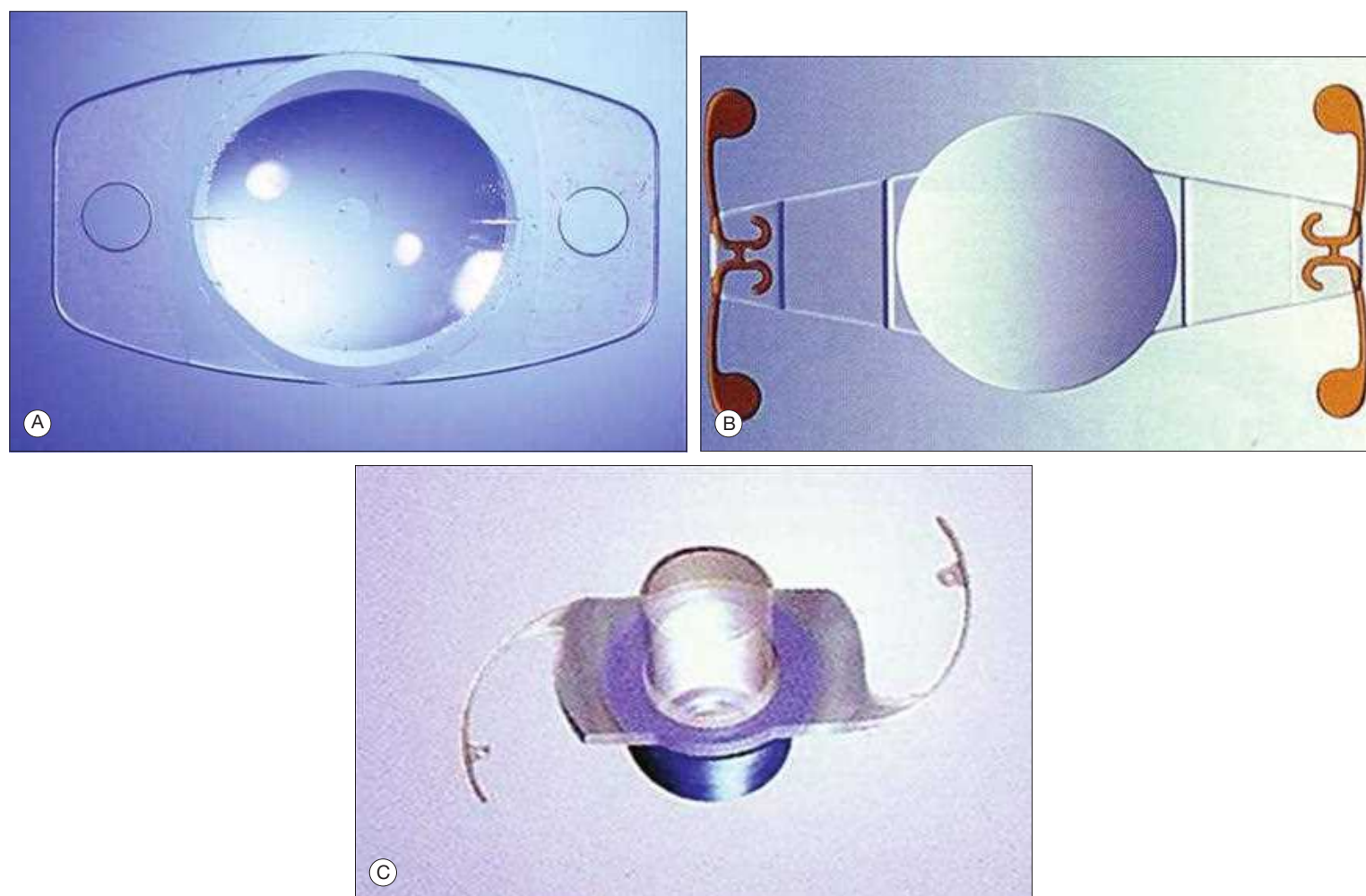
**Fig. 5.2.22 Gross and Light Microscopy Photographs of the First Human Eye Obtained Postmortem With a Single-Piece AcrySof Lens (Alcon Laboratories, Fort Worth, TX) Accessioned in Our Center.** (A) The lens is well centered and the capsular bag is clear. (B) Light photomicrograph of a histological section from the same eye. The arrow indicates the imprint of the square edge of the lens optic on the capsular bag, causing a barrier effect that prevented retained/regenerative cortical material from the Soemmerring's ring to migrate onto the posterior capsule, opacifying the visual axis (Masson's trichrome; original magnification  $\times 400$ ). (Reproduced from Escobar-Gomez M, Apple DJ, Vargas LG, et al. Scanning electron microscopic and histologic evaluation of the AcrySof SA30AL acrylic intraocular lens. J Cataract Refract Surg 2003;29:164–9.)

helps enhance the fixation and stability of these designs within the capsular bag.<sup>70</sup> It is important to note that this fibrous growth requires at least 2 weeks and often much more to establish itself and help anchor the IOL. This design feature has been incorporated into lenses manufactured from silicone (including the Staar toric IOL), hydrogel (hydrophilic acrylic IOLs), and Collamer (Staar CC4203VF) materials.

- For three-piece foldable designs, the preferred haptic materials are the relatively rigid materials with good material memory, such as PMMA, polyimide (Elastimide), or poly(vinylidene) fluoride (PVDF).<sup>71</sup> These haptics have appropriate memory characteristics that help enhance lens centration and stability and provide better resistance to postoperative contraction forces within the capsular bag.
- One of the most important features that has been incorporated in new foldable lenses in terms of decreasing the incidence of PCO is the square, truncated optic edge. Various experimental animal studies by Nishi in Japan, analyses of human autopsy globes in our laboratory, and several clinical studies with the three-piece AcrySof lens (MA30BA and MA60BM)—the first design identified with this geometric

characteristic—demonstrated an enhanced barrier effect against cell migration/proliferation on the posterior capsule toward the visual axis (Fig. 5.2.21).<sup>72,73</sup>

- Manufacturers have invested heavily and with great success in single-piece designs, all fabricated from the same material as the optic component. The Alcon (SA30AL and SA60AT) AcrySof IOL is a hydrophobic single-piece acrylic design that has provided excellent results (Fig. 5.2.22). Other looped single-piece designs are now available, with modifications at the level of the optic–haptic junctions to obtain a non-smooth transition between these components. This was done because some studies demonstrated that smooth optic–haptic junctions may be sites for PCO initiation.<sup>74</sup>
- Manufacturers also are investing in the development of injector systems to be used with the new lens designs. Other recent advances are represented by the development of injector systems where the IOLs come preloaded and by automated injection systems.
- Perhaps the most energy and funding are being spent on new and complex IOLs that not only restore the refractive power of the eye after



**Fig. 5.2.23 Special Intraocular Lenses.** (A) Gross photograph of a toric lens (AA-4203TF or AA-4203TL Staar Surgical, Inc.) This lens has basically the same design as single-piece, plate silicone posterior chamber lenses with large fenestrations but with an incorporated cylindrical correction. (B) Schematic drawing representing an accommodative lens, the Crystalens, manufactured by Bausch & Lomb (Rochester, NY). This is essentially a plate haptic lens with Elastimide haptics. It is stated that redistribution of the ciliary body mass during effort for accommodation will result in increased vitreous pressure, which will move the optic of this lens anteriorly within the visual axis, creating a more plus powered lens. (C) Schematic drawing representing the implantable miniaturized telescope (IMT) (VisionCare Ophthalmic Technologies Inc., Yehud, Israel). This is designed specifically to improve vision of patients suffering from age-related macular degeneration. The IMT is composed of two parts, an optical cylinder and a carrying device. The optic cylinder is made of pure glass. The carrying device is made of black PMMA. The latter has a general configuration of a posterior chamber intraocular lens, with two modified C-loops or haptics that hold the device in the capsular bag. Once in place, the anterior part of the optic extends anteriorly for approximately 1 mm through the pupil. It is designed to be stabilized approximately 2 mm posterior to the corneal endothelium. (A–C, Reproduced from Werner L, Apple DJ, Schmidbauer JM. Ideal IOL (PMMA and Foldable) for year 2002. In: Buratto L, Werner L, Zanini M, et al., editors. Phacoemulsification: principles and techniques. Thorofare, NJ: Slack; 2002. p. 435–52.)

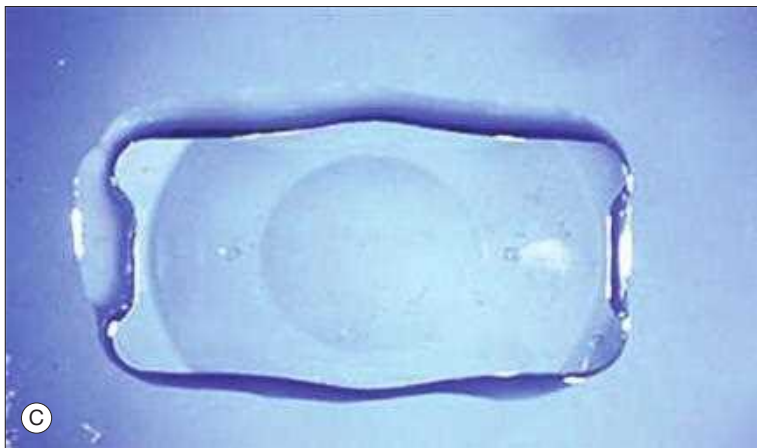
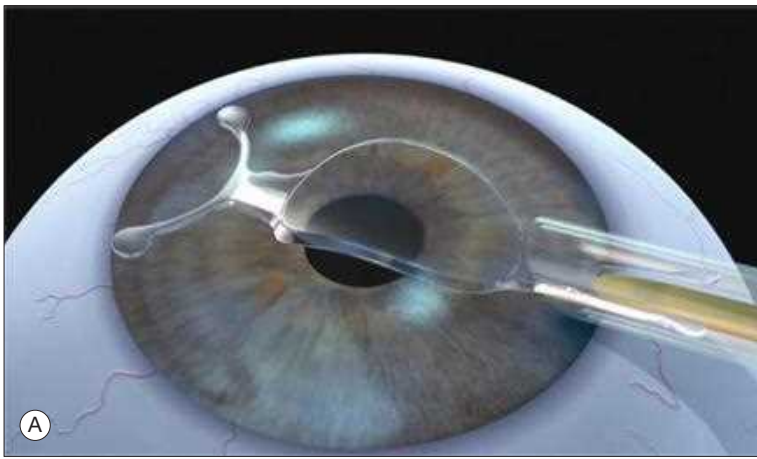
cataract surgery but also provide special features, including multifocality, extended depth of focus, toric corrections (Fig. 5.2.23A), pseudoaccommodation (Fig. 5.2.23B), asphericity, postoperative adjustment of the IOL refractive power, image magnification (telescopic lenses) (Fig. 5.2.23C), protection of the retina against blue or violet light (through incorporation of appropriate chromophores to the IOL optic material), or those that can be inserted through sub 2.0 mm incisions.<sup>75</sup>

Itemization of these IOL designs is not yet useful because proof of safety and efficacy is still in great flux. With any IOL, the issue of biocompatibility must be assessed. Not only do surgeons today seem to be seeking IOLs that are easy to insert/inject through small incisions—perhaps the main factor influencing manufacturers' IOL development—but also more attention is being paid to the interaction of each IOL design within the surrounding capsular bag. Issues such as postoperative cell proliferation within the capsular bag—including PCO, anterior capsule opacification (ACO), and interlenticular opacification (ILO) with piggyback IOLs—are used as one indication of lens biocompatibility.<sup>76,77</sup> This goes far beyond the normal postoperative inflammatory reaction observed after cataract surgery with IOL implantation. Different studies from our laboratory demonstrated that the choice of IOL design and material can largely influence the outcome of these complications, but the role of surgical techniques should not be underestimated. Last but not least, a “perfect” IOL would not be effective in preventing excess cell proliferation within the capsular bag after bad surgery.

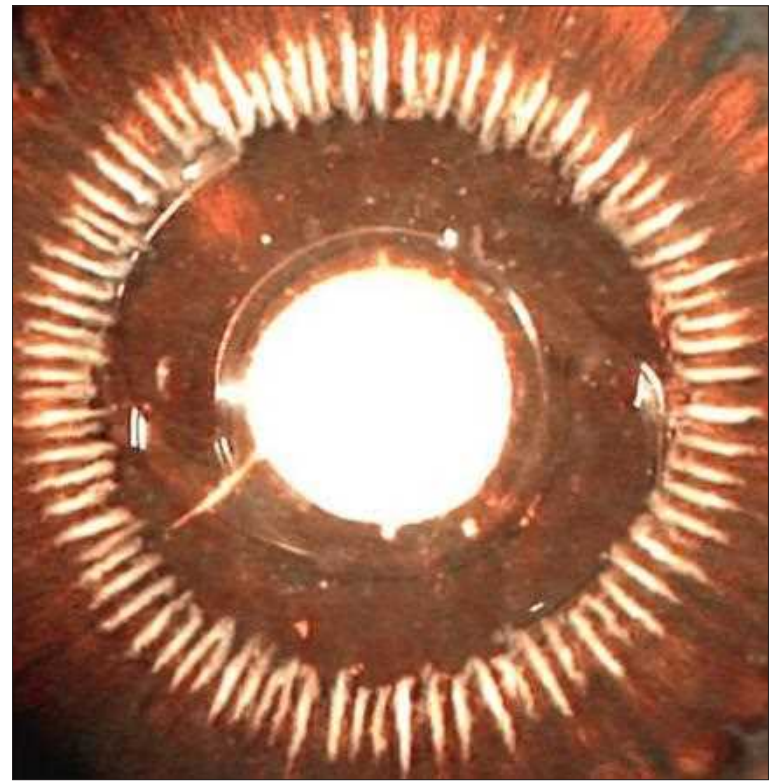
- The renewed interest in phakic IOLs, which we now realize can potentially correct any refractive error, is also progressing rapidly.<sup>78</sup> It is somewhat ironic that anterior chamber IOLs, previously relegated by many surgeons to a wastebasket of discarded devices, have been resurrected and researched as a possible lens of choice for refractive correction. Most of the angle-supported anterior chamber phakic IOLs, however, have been abandoned from the market due to issues with the corneal endothelium.<sup>79</sup> Lenses designed for iris fixation and placement in the posterior chamber are also available, with good results to date. There is a trend for the use of foldable materials for these phakic lenses, which are designed to be inserted through small incisions (Fig. 5.2.24).
- There is a renewed interest in the piggyback IOL procedure, not only for correction of residual refractive errors but also because of the potential to implant a low-power multifocal lens to provide spectacle freedom to patients who already are pseudophakic, and other specialized lenses such as toric and aspherical IOLs. In these cases, the supplementary lens is fixated in the ciliary sulcus to avoid ILO formation. A supplementary IOL for implantation in the sulcus ideally should be manufactured from a soft, biocompatible material, with a relatively large optic and overall diameters, as well as round and smooth optic and haptic edges. Also, the design configuration should provide appropriate clearance with uveal tissues and the in-the-bag IOL (Fig. 5.2.25).<sup>80</sup>

Although a large spectrum of lenses is available today, the IOL of choice still depends on a surgeon's personal preference based on multiple factors





**Fig. 5.2.24 Drawing (A) and Clinical (B) and Gross (C) Photographs Showing Different Types of Phakic Lenses.** (A) Cachet lens (Alcon Laboratories, Fort Worth, TX, USA). It has a 4-haptic, angle-supported configuration, manufactured from the same hydrophobic acrylic material as posterior chamber AcrySof lenses. (B) Artisan lens (Ophtec, Groningen, the Netherlands). This is a one-piece, iris-fixed lens manufactured from PMMA. Artisan haptics (fixation arms) attach to the midperipheral, virtually immobile iris stroma, thus allowing relatively unrestricted dilation and constriction of the pupil. Lenses with incorporated cylindrical correction and a foldable version (silicone optic) are also available. (C) Implantable contact lens (ICL) (Staar Surgical). This is a one-piece plate lens manufactured from a proprietary hydrophilic collagen polymer known as Collamer. It can be inserted or injected into the anterior chamber, then the haptics are placed behind the iris with the help of a spatula. (A, Courtesy Alcon Laboratories. B and C, Reproduced from Werner L, Apple DJ, Izak AM. Phakic intraocular lenses: current trends and complications. In: Buratto L, Werner L, Zanini M, et al., editors. Phacoemulsification: principles and techniques. Thorofare, NJ: Slack; 2002. p. 759–77.)



**Fig. 5.2.25 Pseudophakic Human Eye Obtained Postmortem, Experimentally Implanted With the Sulcoflex (Rayner Intraocular Lenses, East Sussex, UK) Supplementary IOL.** The capsular bag containing a standard posterior chamber IOL was removed for gross analysis of the positioning of the Sulcoflex haptics from the posterior or Miyake–Apple view. No disturbances/distortions to the ciliary processes were observed. This lens was designed by Amon in Austria. It is a single-piece, hydrophilic acrylic lens with an optic diameter of 6.5 mm and an overall diameter of 14.0 mm. The optic has round and smooth edges and a convex–concave configuration. The large-diameter undulating haptics are soft with round and smooth edges and a posterior angulation of 10° in relation to the optic.

personalized to each individual, largely influenced by different features unique to each patient, such as the patient's history and clinical status, but also by the occurrence of intraoperative complications.

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# Epidemiology, Pathophysiology, Causes, Morphology, and Visual Effects of Cataract

## 5.3

Mark Wevill

**Definition:** The prevalence, distribution, strategies to reduce the cataract prevalence and the disordered physiological processes, causes, and different forms of cataract are discussed.

### Key Features

- Cataracts develop earlier in developing countries, and the cataract surgical rates are lower, resulting in a higher prevalence of cataracts. But improved provision of cataract surgery in some developing nations has significantly reduced cataract prevalence.
- Factors in cataract pathogenesis include lens protein oxidation, mitochondrial function, failure of protective mechanisms, protein modification, and abnormalities of calcium metabolism, cellular proliferation, and differentiation.
- An accumulation of environmental insults (e.g., ultraviolet light, toxins, drugs, and systemic diseases) results in age-related cataracts. Minor risk factors such as ultraviolet B exposure and smoking can be modified.
- Nutritional, pharmacological, and genetic interventions are being investigated.
- Anomalies of lens growth are usually associated with other ocular or systemic disorders.

### EPIDEMIOLOGY OF CATARACTS

In 2010 the Vision Loss Expert Group funded by the Bill & Melinda Gates Foundation, Fight for Sight, and others calculated that cataracts caused blindness (visual acuity in the better eye of less than 3/60) in 10.6 million people and moderate to severe visual impairment (MSVI, visual acuity of between 6/18 and 3/60) in 34.4 million people. However, wide regional variations exist in the prevalence of cataracts. In North America, the prevalence of blindness and MSVI was 0.3% and 0.4%, respectively. In South Asia, the respective prevalence was 2% and 6.8%. Sub-Saharan Africa is similar. However, cataract blindness and MSVI have declined since 1990 due to better provision of cataract surgery. Once again the decline in prevalence shows wide regional variations, with the greatest decline in East Asia, Latin America, and Western Europe, where the prevalence fell by more than half. The region with the least decline was Sub-Saharan Africa.<sup>1</sup>

The world's population is increasing (predominantly in developing countries), and people will live to greater ages. So without accessible, efficient cataract surgery, the prevalence will increase. Developing countries bear an increasing burden for cataract blindness because cataracts occur earlier in life, and the incidence is higher. In India, visually significant cataract occurs 14 years earlier than in the United States, and the age-adjusted prevalence of cataract is three times that of the United States.<sup>2,3</sup> Cataracts are the leading cause of blindness in middle- and low-income countries, accounting for 50% of blindness but cause 5% of blindness in developed countries.<sup>4</sup>

Low-cost small-incision cataract surgery with lens implantation is a proven clinical strategy. The socioeconomic effect of cataract surgery is substantial. It allows people to increase their economic output to 1500% of the cost of the surgery in the first postoperative year, but if left untreated,

it can result in a person being removed from work and dependent on a caregiver who is also removed from work.<sup>4</sup>

The cataract prevalence is influenced by the Cataract Surgical Rate (CSR or number of cataract surgeries performed per million people per year), which varies from less than 200 to over 6000 in different regions. The CSR is determined by the effectiveness of strategies for stimulating demand from patients because of good outcomes and how well easily accessible cataract surgery is delivered.

So a high cataract prevalence rate in some developing countries is not for want of a clinical solution but partially due to ineffective implementation. For example, Sub-Saharan Africa is resource poor with low surgeon productivity (number of procedures done per year). To reduce cataract prevalence, the resource base (infrastructure, equipment, ophthalmologists, and other ophthalmic workers) must improve, as must management of the resources to build the right processes for maximal cost-effective resource utilization. Future solutions will have to address these challenges.<sup>5</sup>

### PATHOPHYSIOLOGY OF CATARACTS

The lens transmits, filters, and focuses light onto the retina. The high refractive index and transparency of the lens is due to the high concentration and orientation of intracellular structural proteins:  $\alpha$ ,  $\beta$ , and  $\gamma$  crystallins. The anterior subcapsular layer of cuboidal lens epithelial cells are nucleated, actively divide, and account for almost all the metabolic activity of the lens. Cuboidal cells in the equatorial zone of the lens undergo oxidation and other biochemical, physiological, and structural changes. The cells elongate into lens fiber cells, lose their intracellular organelles and ability to perform metabolic functions, and form mature lens fibers. Lens fibers migrate toward the nucleus of the lens and are compacted as more fibers are formed around them, resulting in nucleosclerosis and later in opacity.<sup>6,7</sup>

The transparency of the lens is dependent on the regular organization of the lens cells and intracellular lens proteins. The precise mechanisms by which lens proteins both prevent aggregation and maintain lens transparency are largely unknown. Genetic, metabolic, nutritional, and environmental insults and ocular and systemic diseases disrupt cellular organization and intracellular homeostasis, eventually causing light scattering and absorption, which compromise vision. Once damaged, the lens has limited means of repair and regeneration and may lose its transparency by the formation of opaque lens fibers, fibrous metaplasia, epithelial opacification, accumulation of pigment, or formation of extracellular materials. Several interlinked mechanisms for cataract formation have been proposed, and no single theory completely explains age-related cataract (the commonest form).<sup>7</sup> Much is still unknown about cataractogenesis, but many of the important components are becoming clearer.

### Genetics

Many inherited genetic syndromes and metabolic disorders are associated with cataracts, and at least 42 genes and loci have been found to underlie Mendelian inherited forms of isolated or primary cataract. Increasing evidence exists that several genes underlying rare forms of inherited cataract also can influence susceptibility to the much more prevalent forms of age-related cataract. These observations raise the possibility of molecular genetic links between lens development and aging.<sup>8</sup> Age-related cataracts are inherited as a multifactorial or complex trait. Determining the genetics

of age-related cataracts is difficult because only a small proportion of the genes involved have been identified, similar gene mutations result in different cataract phenotypes, and cataract epigenetics is complex.

Epigenetics are heritable changes in the gene expression without changes in the DNA sequence. Most genes involved in cataract formation show decreased expression. DNA methylation and other histone modifications inhibit RNA transcription, effectively silencing gene expression. For example, in age-related cataracts, the gene DNA for the alpha A-crystallin protein is hypermethylated.<sup>9</sup> Therapy targeted at reversing methylation and upregulating RNA transcription may prevent or reduce lens opacities. Genes that preserve lens clarity function in diverse processes including protein synthesis (e.g., structural proteins, chaperones, and cell-cycle-control proteins) and reducing oxidative stress (e.g., glutathione peroxidases). Decreased expression reduces lens epithelial cell stress tolerance and protein synthesis. Increased gene expression also can cause lens opacities, for example, by increasing lens epithelial cell ionic transport (e.g., calcium-ATPase, which controls calcium channels) and extracellular matrix protein production.<sup>10</sup> Identifying more genetic and epigenetic determinants of inherited and age-related cataracts may result in nonsurgical treatments for cataract or lifestyle interventions (e.g., diet) and may prevent or reverse cataract formation.<sup>11,12</sup>

## Cell Proliferation and Differentiation

Aqueous growth factors including fibroblast growth factor (FGF), epidermal growth factor (EGF), insulin-like growth factor (IGF), platelet-derived growth factor (PDGF), and transforming growth factor (TGF- $\beta$ ) promote proliferation, differentiation into lens fibers, and maturation of the lens fibers. These processes will not occur if growth factor or cytokine concentrations are incorrect. Then undifferentiated cells migrate to the posterior pole, causing posterior subcapsular cataracts.<sup>6</sup>

## Metabolic Disturbance and Osmotic Regulation Failure

Altered gene expression changes enzyme growth factor, membrane protein, and other protein levels, which reduces energy production; changes ion transport, calcium metabolism, and antioxidant pathways; and breaks down protective mechanisms.<sup>6</sup> For example, the lens maintains high intracellular potassium and low sodium levels with the opposite extracellular concentrations via the action of the sodium-potassium ATPase pump. Pump inactivation causes increased intracellular osmolality, which results in water accumulation and light scatter.<sup>6</sup>

The aqueous humor is a source of nutrients and mineral ions including calcium ( $\text{Ca}^{2+}$ ).  $\text{Ca}^{2+}$  is an intracellular signal that regulates many functions including the permeability of the cell membranes. The extracellular  $\text{Ca}^{2+}$  concentration is 10 times the intracellular  $\text{Ca}^{2+}$  concentration, which drives  $\text{Ca}^{2+}$  into the epithelial cell. Low intracellular  $\text{Ca}^{2+}$  levels also are maintained by intracellular organelle membrane pumps (on the endoplasmic reticulum, Golgi apparatus, and mitochondria) and by binding to

complex proteins (e.g., crystallins). Extracellular  $\text{Ca}^{2+}$  can be bound to the outer layer of the cell membrane. Reduced binding of  $\text{Ca}^{2+}$  by membrane proteins increases cell membrane permeability and causes a rise in intracellular  $\text{Ca}^{2+}$  levels, the formation of calcium oxalate crystals, binding of  $\text{Ca}^{2+}$  to insoluble lens proteins, increased light scattering, and nuclear cataract formation. Increased intracellular  $\text{Ca}^{2+}$  levels also affect lens epithelial cell differentiation, causing posterior subcapsular cataracts. Corticosteroids have been shown to mobilize intracellular  $\text{Ca}^{2+}$  in other tissues, which can increase  $\text{Ca}^{2+}$  levels. In the future,  $\text{Ca}^{2+}$ -regulating drugs may be developed to prevent cataracts.<sup>13</sup>

## Calpains

The roles of calpains in the lens are poorly understood, but they may degrade accumulated damaged lens proteins. A lack of calpains can lead to elevated levels of damaged proteins, reduce optical performance, and cause cataract. Also, excessive stimulation of calpain activity by raised  $\text{Ca}^{2+}$  levels can increase proteolysis and cause cataracts. Calpain inhibitors, therefore, could be useful in the nonsurgical treatment of cataract. However, calpain inhibitors of high molecular weight are unable to cross membranes, so have been of no therapeutic use, whereas others are poorly water soluble or are toxic to lenses.<sup>14</sup>

## Protein Modification

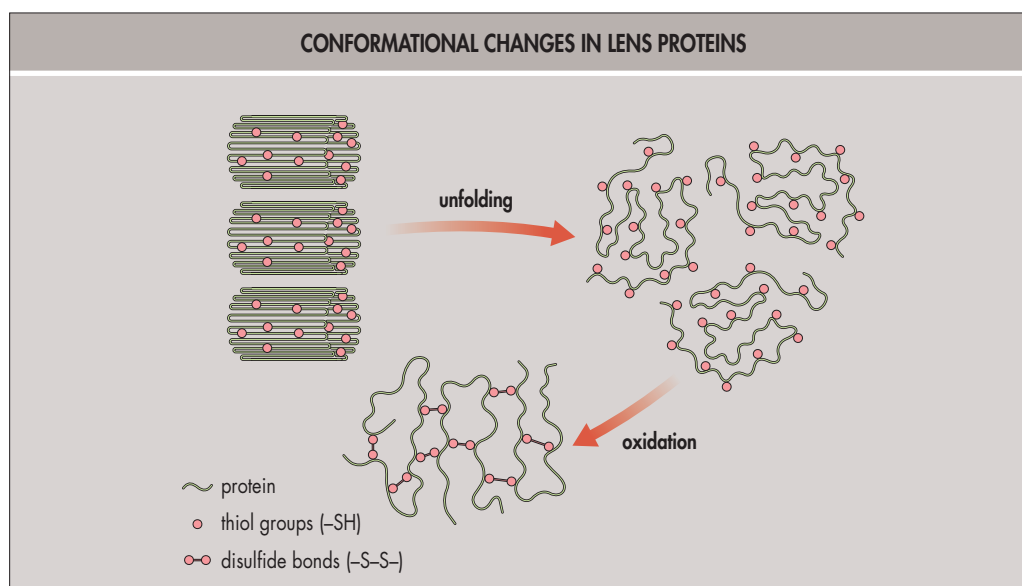
Additive modifications of lens proteins (e.g., crystallins) include methylation, acetylation, carbamylation, glycation in diabetics, and binding of ascorbate, which may be the cause of lens discoloration. These additions occur especially in disease and can alter the function or properties of a protein. Diabetes (reducing sugars), renal failure (cyanate generated from urea), aging (photooxidation products), and corticosteroid use (ketoamines) have been linked to cataracts. Additive modifications can make proteins more susceptible to photooxidation by ultraviolet (UV) light.<sup>6,15</sup>

Subtractive modifications include cleavage by enzymes (such as calpains) of crystallin that causes precipitation of lens proteins. Cleavage of channel proteins can affect intercellular communication. Neutral modifications such as isomerization can denature proteins, affecting their function. Deamidation changes the charge and affects protein-protein interactions.

Proteins in the center of the lens are as old as the individual and are very stable, but over time they can undergo conformational changes (unfolding) that expose thiol groups, which are usually “hidden” in the folds of the protein (Fig. 5.3.1). The exposed glutathione groups can be oxidized to form disulfide bonds (GSSG), causing aggregation of proteins. The conformation changes and aggregation result in scattering and absorption of light.<sup>15</sup>

## Oxidation

Oxidation is a key feature in the pathogenesis of most cataracts. Low oxygen levels ( $\text{O}_2$ ) are important for maintaining a clear lens. Free radicals and other oxidants, including reactive oxygen species (ROS) and reactive



**Fig. 5.3.1** Conformational changes in lens proteins (unfolding) exposes thiol groups ( $-\text{SH}$ ). Oxidation to disulfides ( $-\text{S}-\text{S}-$ ) causes protein aggregation and scatters light.



nitrogen species (RNS), are derived from both endogenous sources (mitochondria, peroxisomes, endoplasmic reticulum, phagocytic cells, etc.) and exogenous sources (pollution, alcohol, tobacco smoke, heavy metals, transition metals, industrial solvents, pesticides, and certain drugs like halothane, paracetamol, and radiation). Free radicals can adversely affect nucleic acids, lipids, and proteins, altering the normal redox status and leading to increased oxidative stress and cataracts.<sup>15</sup>

A steep oxygen gradient occurs from the outer part of the lens to the center. Mitochondria in the lens cortex remove most of the oxygen, thus keeping nuclear  $O_2$  levels low. However, in older people, mitochondrial function diminishes and superoxide production by the mitochondria increases, resulting in increased nuclear oxygen and superoxide levels. As the lens ages, a lens barrier develops at approximately the cortex–nuclear interface, which impedes the flow of molecules such as antioxidants (including glutathione) into the nucleus. Unstable nuclear molecules such as peroxide ( $H_2O_2$ ), which are generated in the nucleus or which penetrate the barrier, therefore, cause protein oxidation. Also, a lower concentration of antioxidants exists. Decomposition of UV filters in the nucleus also produces unstable reactive molecules that bind to proteins, especially if antioxidant glutathione (GSH) levels are low. Ascorbate becomes reactive with proteins in the absence of GSH. These oxidative changes can be detected even in the earliest cataracts and are progressive. Elevated levels of superoxide  $H_2O_2$  in the aqueous may cause cortical cataracts, since the cortex is closest to the aqueous. Copper and iron are present in higher concentrations in cataract lenses and are involved in redox reactions, which produce hydroxyl radicals.<sup>16</sup>

## Defensive Mechanisms

Antioxidant enzymes and antioxidants such as ascorbate, glutathione, tocopherols, and carotenoids maintain lens proteins in the reduced state and are the primary defense mechanisms. In advanced age-related nuclear cataracts, more than 90% of protein sulfhydryl groups and almost half of all methionine residues in the nuclear proteins become oxidized. Secondary defenses include proteolytic and repair processes, which degrade and eliminate damaged proteins, UV filters, and other molecules such as glutathione reductase and free radical scavenging systems. Failure of these protective mechanisms, a shortage of antioxidants, and increased free radicals result in cell membrane and protein damage.<sup>6,16</sup>

## Other Factors

Crystallins may have a number of functions. For example  $\alpha$ -crystallin may be a chaperone that binds to other lens proteins to prevent precipitation. Decreased crystallin levels cause proteins to precipitate, which leads to cataract formation. Phase separation of proteins refers to the hydrophobic aggregation of lens proteins causing protein rich and poor regions in the lens fibers, which results in light scatter. The lipid composition of the cell membranes also changes with age, which may have functional consequences.

## CATARACT CAUSES, ASSOCIATIONS, AND PREVENTION

### Age

The cumulative effect of many environmental factors (UV light, x-irradiation, toxins, metals, corticosteroids, drugs, and diseases, including diabetes) causes age-related cataracts. Gene expression changes result in altered enzyme, growth factor, and other protein levels. Protein modification, oxidation, conformational changes, aggregation, formation of the nuclear barrier, increased proteolysis, defective calcium metabolism, and defense mechanisms occur with increasing age. Compromised ion transport leads to osmotic imbalances and intercellular vacuolation. Age-related abnormal cellular proliferation and differentiation also produce opacities (Fig. 5.3.2). There is also an increased incidence of diseases such as diabetes that causes cataracts.

### Sunlight and Irradiation

UV-B light causes oxidative damage, which is cataractogenic. The level of free UV filters in the lens decreases with age, and breakdown products of the filters act as photosensitizers that promote the production of reactive oxygen species and oxidation of proteins in the aging lens. The risk of



**Fig. 5.3.2 Age-Related Cataract.** Nuclear sclerosis and cortical lens opacities are present.

cortical and nuclear cataract is highest in those with high sun exposure at a younger age. Exposure later in life was more weakly associated with these cataracts. Wearing sunglasses, especially when younger, has some protective effect.<sup>17</sup> Unfortunately, the risk attributable to sunlight exposure is small,<sup>18</sup> and cortical cataracts are less debilitating than nuclear or posterior subcapsular cataracts. Therefore, reducing sunlight exposure may have a limited benefit in delaying the onset of cataracts. Exposure to high levels of X-rays and whole-body irradiation also causes cataracts.

### Smoking and Alcohol

Smoking causes a threefold increase in the risk of developing nuclear cataracts, and cessation of smoking reduces this risk. Smoking also may be associated with posterior subcapsular cataracts. Smokers are more likely to have a poor diet and high alcohol consumption, which also are risk factors for cataract. Smoking causes a reduction in endogenous antioxidants. Tobacco smoke contains heavy metals such as cadmium, lead, and copper, which accumulate in the lens and cause toxicity. No association between passive smoking and cataract has been demonstrated.<sup>19,20</sup> Alcohol use has little, if any, association with cataract risk, and study reports are mixed.

### Body Mass Index

A number of health-related factors—diabetes, hypertension, and body mass index (BMI)—are associated with various forms of lens opacity, and they may be interrelated. A high BMI increases the risk of developing posterior subcapsular and cortical cataracts.<sup>20</sup> A high BMI also is associated with diabetes and hypertension, which are associated with cataracts. Severe protein-calorie malnutrition is a risk factor for cataracts. Therefore, a moderate calorie intake may be optimal to reduce the risk of developing cataracts.

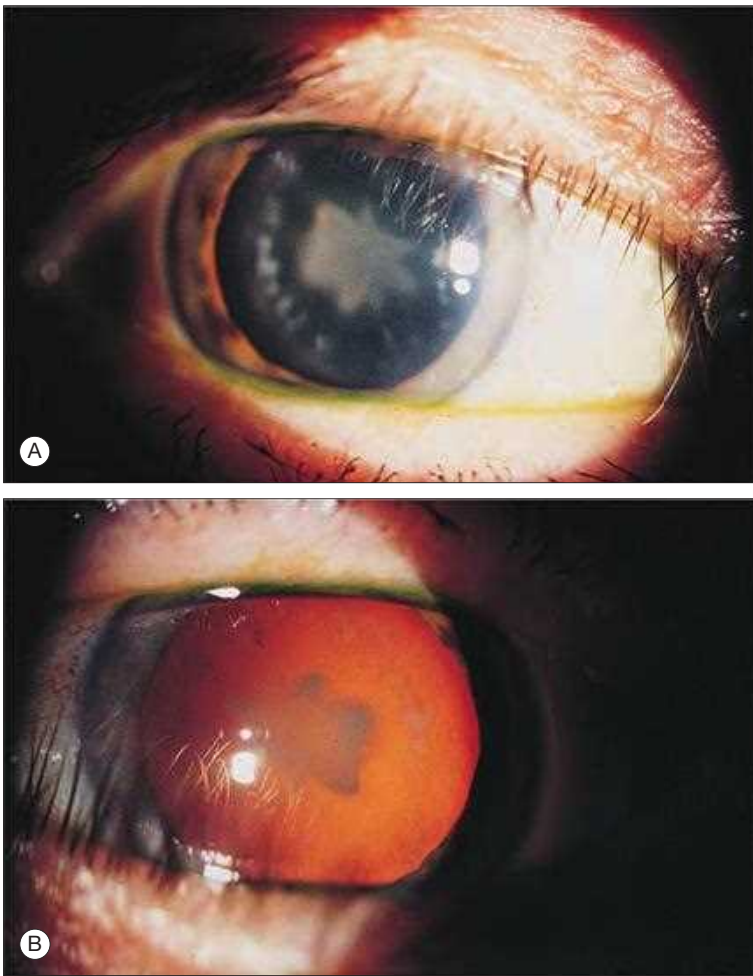
### Myopia

After controlling for age, gender, and other cataract risk factors (diabetes, smoking, and education), posterior subcapsular cataracts are associated with myopia, deeper anterior chambers, and longer vitreous chambers.<sup>21</sup>

### Trauma

Blunt trauma that does not result in rupture of the capsule may allow fluid influx and swelling of the lens fibers. The anterior subcapsular region whitens and may develop a characteristic flower-shaped pattern (Fig. 5.3.3) or a punctate opacity. A small capsular penetrating injury results in rapid fiber hydration and a localized lens opacity, and a larger rupture results in complete lens opacification. Penetrating injuries can be caused by accidental or surgical trauma such as a peripheral iridectomy or during a vitrectomy.

Electric shocks as a result of lightning or an industrial accident cause coagulation of proteins, osmotic changes, and fernlike, grayish white anterior and posterior subcapsular opacities.<sup>22</sup> Ionizing radiation, such as from X-rays, damages the capsular epithelial cell DNA, affecting protein and



**Fig. 5.3.3 Traumatic Cataract.** (A) Typical flower-shaped pattern with coronary lens opacities. (B) Seen in retroillumination in anterior subcapsular region.

enzyme transcription and cell mitosis. An enlarging posterior pole plaque develops. Nonionizing radiation, such as infrared, is the cause of cataract in glassblowers and furnace workers working without protective lenses. A localized rise in the temperature of the iris pigment epithelium causes a characteristic posterior subcapsular cataract, which may be associated with exfoliation of the anterior capsule.

## Systemic Disorders

In uncontrolled type 1 diabetes mellitus in young people, hyperglycemia causes glucose to diffuse into the lens fiber, where aldose reductase converts it to sorbitol. The cell membrane is impermeable to sorbitol, and therefore it accumulates. The osmotic effect draws water into the lens fibers, which swell and then rupture. The cataract progresses rapidly with the development of white anterior and posterior subcapsular and cortical opacities.

In type 2 diabetic adults, an early onset age-related type of cataract occurs and is more prevalent with longer duration of the diabetes. Many mechanisms are involved and include sorbitol accumulation, protein glycosylation, increased superoxide production in the mitochondria, and phase separation. During hyperglycemia, glucose is reduced to sorbitol, depleting antioxidant reserves, and less glutathione is maintained in the reduced form, which causes other oxidative damage. Levels of lens  $\text{Ca}^{2+}$  also are elevated, which activates calpains, causing unregulated proteolysis of crystallins. The cataracts are usually cortical or posterior subcapsular or, less frequently, nuclear and progress more rapidly than age-related cataract.<sup>23,24</sup>

Galactosemia is an autosomal recessive disorder in which a lack of one of the three enzymes involved in the conversion of galactose into glucose causes a rise in serum galactose levels. Galactitol accumulates in the lens fibers, drawing water into them. Infantile anterior and posterior subcapsular opacities progress to become nuclear. Galactose 1-phosphate uridylyltransferase galactosemia is associated with failure to thrive, mental retardation,

and hepatosplenomegaly. Dietary restriction of galactose prevents cataract progression. Galactokinase deficiency is associated with galactosemia and cataract but without the systemic manifestations.<sup>25</sup>

Fabry's disease is an X-linked lysosomal storage disorder that results in accumulation of the glycolipid ceramide trihexoside. The patient suffers from episodic fever, pains, hypertension, renal disease, and a characteristic rash. In the affected man and the carrier woman, a typical mild, spokelike, visually insignificant cataract develops.

Lowe's or oculocerebrorenal syndrome is a severe X-linked disorder that results in mental retardation, renal tubular acidosis, metabolic acidosis, and renal rickets. Congenital glaucoma, cataracts, and corneal keloids can cause blindness. The lens is small and discoid with a total cataract. Female carriers may show focal dot opacities in the cortex.

Alport's syndrome is a dominant, recessive, or X-linked trait disease causing hemorrhagic nephropathy and sensorineural deafness. Congenital or postnatal cortical cataract, anterior or posterior lenticonus, and microspherophakia occur.

Dystrophia myotonica is a dominantly inherited disorder and results in muscle wasting and tonic relaxation of skeletal muscles. Other features include premature baldness, gonadal atrophy, cardiac defects, and mental retardation. Cataract is a key diagnostic criterion and may develop early, but usually occurs after 20 years of age and progresses slowly, eventually becoming opaque. Early cataract consists of polychromatic dots and flakes in the superficial cortex. As the opacities mature, a characteristic stellate opacity appears at the posterior pole. Other ocular features include hypotony, blepharitis, abnormal pupil responses, and pigmentary retinopathy.

Rothmund-Thomson syndrome is an autosomal recessive disorder characterized by poikiloderma, hypogonadism, saddle-shaped nose, abnormal hair growth, and cataracts, which develop between the second and fourth decades of life and progress rapidly.

Werner's syndrome or adult progeria is an autosomal recessive disorder with features that include premature senility, diabetes, hypogonadism, and arrested growth. Juvenile cataracts are common. The condition usually leads to death at about 40 years of age.

Cockayne's syndrome causes dwarfism but with disproportionately long limbs with large hands and feet, deafness, and visual loss from retinal degeneration, optic atrophy, and cataracts.

## Dermatological Disorders

The skin and the lens are of ectodermal origin embryologically. Therefore, skin disorders may be associated with cataract formation.

Atopic dermatitis and eczema may affect any part of the body, especially the limb flexures. Localized proliferation of lens epithelium occurs in some atopic adults, usually as a bilateral, rapidly progressive "shield" cataract (a dense, anterior subcapsular plaque with radiating cortical opacities, and wrinkling of the anterior capsule). Posterior subcapsular opacities also may occur.

Ichthyosis is an autosomal recessive disorder that features hypertrophic nails, atrophic sweat glands, cuneiform cataracts, and nuclear lens opacities.

Incontinentia pigmenti is an X-linked dominant disorder that affects skin, eyes, teeth, hair, nails, and the skeletal, cardiac, and central nervous systems. Blistering skin lesions occur soon after birth, followed by warty outgrowths. Ocular pathology includes cataract, chorioretinal changes, and optic atrophy.

## Central Nervous System Disorders

Neurofibromatosis (types I and II) is an autosomal dominant disorder causing numerous intracranial and intraspinal tumors and acoustic neuromata. Ocular features include combined hamartoma of the retina and retinal pigment epithelium, epiretinal membranes, Lisch nodules (a diagnostic sign), and posterior subcapsular or cortical cataracts that develop in the second or third decade of life.

Zellweger syndrome, also known as hepatocerebrorenal syndrome, is an autosomal recessive disorder characterized by renal cysts, hepatosplenomegaly, and neurological abnormalities. Ocular features include corneal clouding, retinal degeneration, and cataracts.

Norrie's disease is an X-linked recessive disorder that causes leukokoria and congenital infantile blindness and is associated with mental retardation and cochlear deafness. In the eye, vitreoretinal dysplasia, retinal detachment, vitreous hemorrhage, and formation of a white retrolental mass occur. Eventually, a cataract forms.

## Ocular Disease and Cataracts

Inflammatory uveitis (e.g., Fuchs' heterochromic cyclitis and juvenile idiopathic arthritis) usually results in posterior subcapsular or posterior cortical lens opacities. Infective uveitis (e.g., ocular herpes zoster, toxoplasmosis, syphilis, and tuberculosis) can cause cataracts, but the organism does not penetrate the lens. In maternal rubella infection, after 6 weeks of gestation, the virus can penetrate the lens capsule, causing unilateral or bilateral, dense, nuclear opacities at birth, or they may develop several weeks or months later. Corticosteroid treatment can cause cataracts. Retinal pigment degenerations such as retinitis pigmentosa, Usher's syndrome, and gyrate atrophy are associated with cataracts, which are usually posterior subcapsular opacities. Retinal detachment and retinal surgery may cause a posterior subcapsular cataract particularly in association with vitrectomy, silicone oil injection, and tamponade, or an anterior subcapsular form may develop because of metaplasia of the lens epithelium after vitreoretinal surgery. High myopia is associated with posterior cortical, subcapsular, and nuclear cataracts. Ciliary body tumors may be associated with cortical or lamellar cataract in the affected quadrant. Anterior segment ischemia may cause a subcapsular or nuclear cataract, which progresses rapidly.

### Toxic Causes

Topical, inhaled, and systemically administered corticosteroids can cause posterior subcapsular cataracts. Direct mechanisms included interaction of corticosteroids with enzymes that affects their function, e.g., corticosteroid modulation of  $\text{Na}^+, \text{K}^+$ -ATPase may cause sodium-potassium pump inhibition affecting osmotic regulation. Corticosteroids also induce crystallin conformational changes, causing aggregation and affect intracellular  $\text{Ca}^{2+}$  homeostasis, causing protein bonding. Indirectly, corticosteroids affect DNA/RNA synthesis of proteins and enzymes, causing metabolic changes, and also may affect ciliary body growth hormone levels responsible for lens cellular differentiation, causing posterior subcapsular opacities.<sup>26</sup>

Chronic use of long-acting anticholinesterases previously used in the treatment of chronic open-angle glaucoma may cause anterior subcapsular vacuoles and posterior subcapsular and nuclear cataracts. Pilocarpine, a shorter acting agent, causes less marked changes. The mechanism of action is unknown. Phenothiazines, such as chlorpromazine, may cause deposition of fine, yellow-brown granules under the anterior capsule in the pupillary zone and may develop into large stellate opacities but are not usually visually significant. The development of the opacities may be related to the cumulative dose of the medication, and photosensitization of the lens may play a role. Allopurinol used in the treatment of gout is associated with cataracts. Psoralen-UV-A therapy for psoriasis and vitiligo has been shown to cause cataracts in very high doses in animal studies but is rare in humans; concomitant UV exposure may be a risk factor. Antimitotic drugs used in the treatment of chronic myeloid leukemia, such as busulfan, may cause posterior subcapsular cataract. The antimalarial chloroquine (but not hydroxychloroquine), which is also used in the treatment of arthritis, may cause white, flake-like posterior subcapsular lens opacities. Amiodarone is used to treat cardiac arrhythmias and causes insignificant anterior subcapsular opacities and corneal deposits. The relationship between statins and cataracts is still controversial.

Siderosis, from a ferrous intraocular foreign body, causes iron deposits in the lens epithelium and iris and results in a brown discoloration of the iris and a flower-shaped cataract. Wilson's disease, an autosomal recessive disorder of copper metabolism, causes a brown ring of copper deposition in Descemet's membrane and the lens capsule, resulting in a sunflower cataract—an anterior and posterior capsular disc-shaped polychromatic opacity in the pupillary zone with petal-like spokes that is not usually visually significant. Hypocalcemia in hypoparathyroidism is associated with cataracts. In children, the cataract is lamellar; in adults it produces an anterior or posterior punctate subcapsular opacity.

### Congenital and Juvenile Cataracts

Congenital cataracts are noted at birth, infantile cataracts occur in the first year, and juvenile cataracts develop during the first 12 years of life. Hereditary cataracts may be associated with other systemic syndromes, such as dystrophia myotonica. About one-third of all congenital cataracts are hereditary and unassociated with any other metabolic or systemic disorders.

Trisomy 21, or Down syndrome, is the most common autosomal trisomy, with an incidence of 1 per 800 births. Systemic features include mental retardation, stunted growth, mongoloid facies, and congenital heart defects. Ocular features include visually disabling lens opacities in 15% of

cases, narrow and slanted palpebral fissures, blepharitis, strabismus, nystagmus, light-colored and spotted irides (Brushfield spots), keratoconus, and myopia. Cataract also is associated with trisomy 13 (Patau's syndrome), trisomy 18 (Edwards' syndrome), Cri du chat syndrome (deletion of short arm of chromosome 5), and Turner's syndrome (X chromosome deletion).

A total cataract is a complete opacity present at birth. It may be hereditary (autosomal dominant or recessive) or associated with systemic disorders such as galactosemia, rubella, and Lowe's syndrome. Infantile cataracts cause amblyopia if unilateral and may cause strabismus and nystagmus if bilateral. The incidence is about 0.4% of newborns, but the majority of cases are not associated with poor vision. Amblyopia depends on the size, location, and density of the cataract. The causes of infantile cataracts are many and include maternal infections (such as rubella), systemic diseases, hereditary disorders, and ocular disease.

## PREVENTION OF CATARACTS

The roles and mechanisms of action of dietary antioxidant vitamins and minerals in the biochemistry and metabolism of the lens are not clear. Ascorbate is a water-soluble antioxidant. Vitamin E is a lipid-soluble antioxidant that inhibits lipid peroxidation, stabilizes cell membranes, and enhances glutathione recycling. Beta-carotene, the best-known carotenoid, is a lipid-soluble antioxidant and a vitamin A precursor and is one of 400 naturally occurring carotenoids. There are mixed reports in the literature with some studies showing no benefit and others showing some benefit with vitamin A, carotenoids, and combinations of vitamins C and E and beta-carotene supplements.<sup>27,28</sup>

Potential anticataract compounds include aldose reductase inhibitors, pantethine, and aspirin-like drugs such as ibuprofen. However, none of these agents has been shown to prevent cataracts in a trial setting. No convincing evidence exists that N-acetylcarnosine reverses cataract or prevents progression of cataract. A decreased risk of developing cataracts occurs with estrogen replacement therapy.<sup>29-34</sup> New drugs are under investigation, including lanosterol, which decreased protein aggregates in vitro, reduced cataract severity, and increase transparency in rabbit cataractous lenses in vitro and cataract severity in vivo in dogs.<sup>35</sup> Anticataract agents would need to be safe for long-term use and sufficiently inexpensive to compete with increasingly cost-effective cataract surgery.

Understanding the causes of age-related cataract will be helpful in preventing or delaying cataract formation, but our knowledge is incomplete. Minor risk factors such as UV-B exposure and smoking can be modified but are not likely to result in large reductions in visual disability. The most important risk factor, aging, cannot be modified. Other strategies such as nutritional, pharmacological, and specific medical and genetic interventions may be helpful in the future but are of unproved benefit at present. Integrated and innovative approaches to the provision of surgery, resource management, training, start-up capital equipment and consumables, and cost-recovery mechanisms are required.

## MORPHOLOGY AND VISUAL EFFECTS OF CATARACT

### MORPHOLOGY

Nuclear opacities are caused by a gradual increase in the optical density of the central nucleus, progressing slowly to involve more superficial layers (see Fig. 5.3.1). The nucleus may change color from clear to yellow to dark brown.

Cortical opacities are spokelike peripheral opacities that reduce the visual acuity as they extend toward the visual axis (see Fig. 5.3.2).

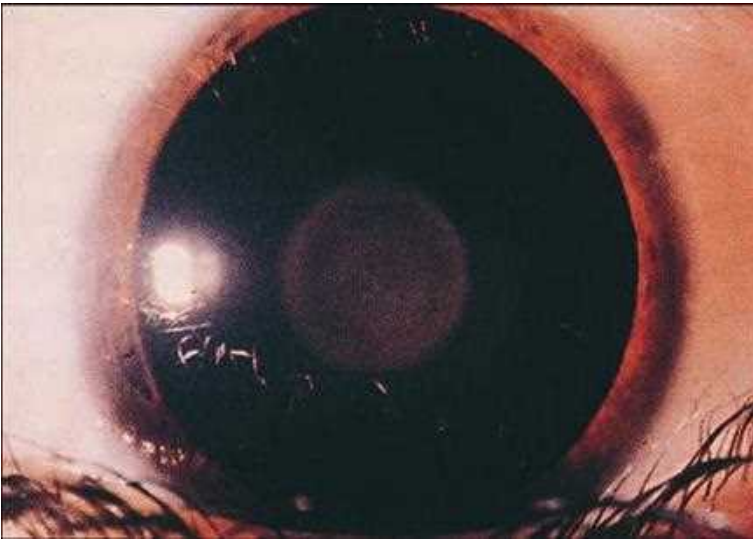
Posterior subcapsular opacities begin at the posterior polar region then spread toward the periphery. Patients have significant glare disability because of light scattering at the nodal point of the eye.

Complete opacification of the lens eventually occurs, usually with combinations of the different forms. The crystalline lens may swell to form an intumescent cataract. The cortical material may then liquefy and be absorbed causing the solid nucleus to "sink" to the bottom of the capsular bag.

## ASSESSMENT AND GRADING OF CATARACTS

Grading and classifications of cataracts (Box 5.3.1) are useful in research, to explore causation, and in trials of anticataract drugs. Slit-lamp direct and





**Fig. 5.3.4 Cataracta Centralis Pulverulenta.** Opacification of fetal nucleus.

### BOX 5.3.1 Infantile Cataracts

#### Anterior Polar Cataract

Dominantly inherited, well-defined opacities of the anterior capsule may affect the vision.

Caused by imperfect separation of lens from surface ectoderm, by epithelial damage, or by incomplete reabsorption of the vascular tunic of the lens.

May have anterior or posterior conical projections; if it extends into the cortex in a rod shape, it is called a “fusiform” cataract.

#### Spearg Cataract

Dominantly inherited, polymorphic cataract with needle-like clusters of opacities in the axial region, which may not affect vision.

#### Coralliform Cataract

Dominantly inherited cataract that consists of round and oblong opacities grouped toward the center of the lens; they resemble coral.

#### Floriform Cataract

A rare, ring-shaped, bluish white, flower-shaped cataract in the axial region.

#### Lamellar Cataract

A common, bilateral, and symmetrical round, gray shell of opacity that surrounds a clear nucleus; usually dominantly inherited cataract, which may have a metabolic or inflammatory cause.

Fibers become opacified in response to a specific insult during their most active metabolic stage and are pushed deeper into the cortex as normal lens fibers are laid down around it.

#### Cataracta Centralis Pulverulenta

Dominantly inherited, nonprogressive cataract consisting of fine, white, powdery dots within the embryonic or fetal nucleus (Fig. 5.3.4).

#### Congenital Punctate Cerulean Cataract

Bilateral, nonprogressive, small, bluish dots scattered throughout the lens with little effect on vision.

#### Congenital Suture (Stellate) Cataract

Dominantly inherited bluish dots or a dense, chalky band around the sutures affecting one or both fetal sutures, especially posteriorly; may interfere with vision.

#### Mittendorf's Dot

A small (about 1 mm diameter), nonprogressive, white condensation occurs on the posterior pole of the lens capsule; it may be decentered slightly inferonasally and may be attached to a free-floating thread in the vitreous gel, which represents the anterior part of the hyaloid artery remnant.

#### Congenital Disciform Cataract

Central thinning creates a doughnut shape, which may arise from failure of development of the embryonic nucleus.

retroillumination of nuclear, cortical, and posterior subcapsular cataracts is used in the Lens Opacification Classification System II (LOCS-II). LOCS-II is reproducible and has been validated.<sup>36</sup> A number of Scheimpflug camera and optical coherence tomography devices have been developed for objectively quantifying lens opacification.

## VISUAL EFFECTS OF CATARACTS

The effect of cataract on vision varies according to the degree of the cataract and the cataract morphology.

### Visual Acuity

Reduction in visual acuity has been the standard measure of the visual effect of cataracts. However, visual acuity can remain good despite other cataract-related effects on vision that compromise the patient's ability to function.

### Contrast Sensitivity, Glare, and Wavefront Aberrometry

Cataracts cause reduced contrast sensitivity and increased wavefront aberrations, reducing visual acuity especially at low ambient light levels.<sup>37</sup> Glare, which occurs as a result of forward scatter of light, may be produced by opacities that do not lie within the pupil diameter and, therefore, affect visual function.<sup>38</sup>

### Other Effects

The natural aging of the human lens produces a progressive hyperopic shift. Nuclear changes induce a modification of the refractive index of the lens and produce a myopic shift. Cortical opacities may cause localized changes in the refractive index of the lens, which may result in monocular diplopia. Color perception is affected by the yellowing of the lens nucleus. The morphology, density, and location of lens opacities may cause changes in the visual field.

## ANOMALIES OF LENS GROWTH

The lens is ectodermal and the vascular capsule is mesodermal in origin. A number of exogenous or endogenous influences can affect ectodermal or mesodermal development and can have multiple manifestations in the eye.

### Aphakia

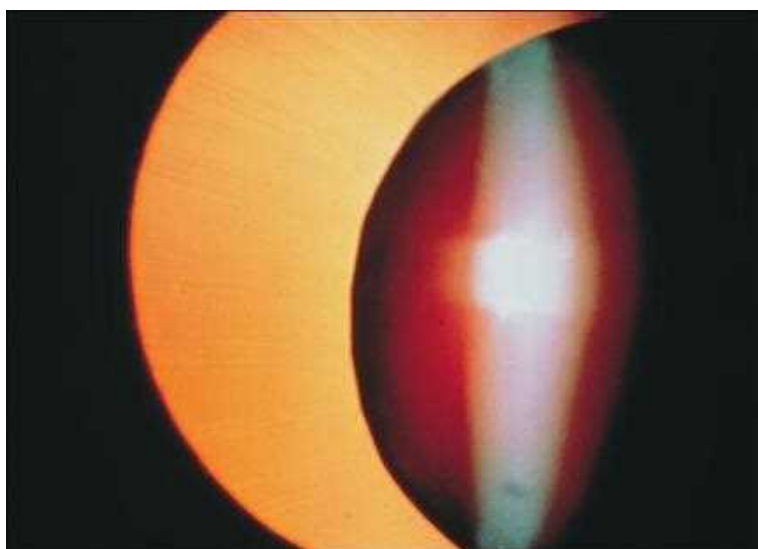
Aphakia is the absence of the lens. Primary aphakia is a rare absence of the lens. Secondary aphakia is more common, and there are lens remnants. Both occur in isolation or with other abnormalities of the anterior segment such as microphthalmos, microcornea, and nystagmus.<sup>39</sup>

### Microspherophakia

Microspherophakia is the presence of a small, spherical crystalline lens with an increased antero-posterior thickness and steeper than normal anterior and posterior lens curvatures. It is bilateral and may be familial, may occur as an isolated defect, or may be associated with other mesodermal defects, such as the Weill–Marchesani and Marfan's syndromes. The condition causes lenticular myopia and may be associated with lens dislocation (usually downward) and pupil block.<sup>40,41</sup>

### Lenticonus and Lentiglobus

Abnormalities of the central lens curvature include lenticonus (conical) and lentiglobus (spherical) and may be anterior or posterior. They may be associated with abnormalities of the lens epithelium, by traction from hyaloid remnants, or by localized areas of capsule weakness, which causes bulging. They may be inherited as an autosomal recessive trait or associated with other abnormalities, such as Alport's syndrome (familial hemorrhagic nephritis) or Lowe's oculocerebral syndrome (associated with posterior lenticonus). They can cause lenticular myopia with irregular astigmatism.<sup>39,41</sup>



**Fig. 5.3.5 Marfan's Syndrome.** A retroillumination slit-lamp photograph of ectopia lentis associated with Marfan's syndrome.

## Lens Coloboma

Lens coloboma is a unilateral, congenital indentation of the lens periphery that occurs as a result of a localized absence of zonules. It may be associated with coloboma of the iris, ciliary body, or choroid, or with ectopia lentis, spherophakia, or localized lens opacities. It may occur because persistence of mesodermal vascular capsules remnants prevents the development of zonules in that area.

## Ectopia Lentis

Ectopia lentis, or displaced lens, is usually a bilateral condition caused by extensive zonular malformation. The lens is subluxated in the opposite direction to the weak zonules (usually superomedially) and usually

presents in childhood or young adulthood. The lens may dislocate completely into the anterior chamber or vitreous or become cataractous. It may be an autosomal dominant or recessive trait or may be associated with other developmental abnormalities of the eyes such as iris coloboma, microspherophakia, aniridia, and ectopia pupillae congenita. It may be associated with systemic disorders such as Marfan's syndrome (Fig. 5.3.5), Weill–Marchesani syndrome, homocystinuria, sulfite oxidase deficiency, and hyperlysinemia. The clinical features of a subluxed lens include iridodonesis (tremulous iris), fluctuating anterior chamber depth and vision, and phacodonesis (a visibly mobile lens). Vitreous may herniate into the anterior chamber. Pupil block may occur with iris apposition to the vitreous face or an anterior dislocated lens (into the anterior chamber).

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# Patient Workup for Cataract Surgery

Frank W. Howes

## 5.4

**Definition:** Preoperative preparation prior to planned lens extraction.

### Key Features

Ophthalmic and medical considerations in the preoperative evaluation of lens surgery include:

- The morphology of lens opacities and the effects and diagnosis thereof.
- The optics of the eye, including refractive correction modalities.
- The biometric measurements in standard and nonstandard eyes.
- The optimal medical assessment of the patient for surgery.
- The social and legal considerations in final aspects of the workup are discussed.

### INTRODUCTION

Any patient undergoing cataract surgery requires an accurate ophthalmological workup and careful anamnesis. Although most cataract procedures are uneventful with regard to the patient's medical condition, any problem or crisis is potentially ruinous, especially if surgery becomes complicated or prolonged. Therefore it is incumbent on the surgical, anesthetic, nursing, and family doctor teams to be fully aware of their patient's surgical and medical status.

### MEDICAL HISTORY AND CURRENT THERAPEUTIC REGIMEN

A history of cardiac, bronchopulmonary, or cerebrovascular incidents influences the timing and management of surgery, especially if it is recent. Diabetes mellitus and systemic hypertension are common in the population predisposed to operable cataract formation, and these conditions may adversely influence both the surgery and the postoperative course of events.<sup>1</sup> Ram and coworkers<sup>2</sup> carried out a study of more than 6000 patients who underwent cataract surgery and discovered multiple morbidities that arose from a variety of conditions. The major causes included pulmonary disease, cardiovascular and hypertensive disorders, diabetes mellitus, and significant orodental problems that required intervention.

Ram et al.<sup>2</sup> also noted significant postoperative problems in 1.27% of their patients, nearly half of whom required hospitalization. Fisher and Cunningham<sup>3</sup> and Hamed et al.<sup>4</sup> noted an even higher morbidity in their cohort of patients who had cataract surgery (Table 5.4.1).

There are many factors that may affect cooperation and difficulty during surgery, varying from ventilation difficulties to substance abuse (including examination of identified cataract morphological findings), that may influence both the surgeon's and the anesthesiologist's decision about the form

of anesthetic to use and the sedation required and potentially both the pre- and postoperative management (Table 5.4.1 and 5.4.2).

### GENERAL OPHTHALMIC HISTORY AND EXAMINATION

Both eyes are assessed fully by routine ophthalmological workup, which includes tonometry, slit-lamp biomicroscope examination, and posterior segment observations under mydriasis to estimate the visual outcome and risk category of surgery for the patient. Intercurrent ophthalmic disorders may prejudice the visual outcome. For example, uveitis may be exacerbated,<sup>5</sup> herpes zoster may have left an anesthetic cornea,<sup>6</sup> atopic disease may predispose the eye to infection,<sup>7</sup> and Fuchs' endothelial dystrophy may predispose the eye to corneal edema. Diabetes mellitus increases the prospects of postoperative macular edema.<sup>1</sup>

The presence of open-angle glaucoma warrants further comment. The aforementioned disease processes need pickup and assessment to avoid deleterious effect on the eye after cataract surgery. The action of successful cataract surgery on glaucoma and ocular hypertension, however, has been demonstrated to have a positive effect on intraocular pressure (IOP) control.<sup>8</sup>

With the advent of the new minimally invasive glaucoma surgery (MIGS) procedures, the surgeon should now consider using one of these devices at the end (or beginning) of a cataract procedure to further facilitate improved aqueous outflow, lower IOP,<sup>9-11</sup> and improve glaucoma control, potentially reducing or eliminating the use of topical glaucoma drugs, which themselves can have an adverse influence on the ocular surface and visual quality both before and after cataract surgery. There are a number of MIGS devices available; see a commonly used example at Fig. 5.4.1.

Patient counseling on the procedure and explanation of postoperative expectation are vital elements of the preoperative workup. A written explanation of the background and process of cataract surgery is invaluable.

### ASSESSMENT OF LENS OPACITIES<sup>12,13</sup>

#### INTRODUCTION

The progressive insolubilization of lens protein with age is believed to cause refractive index and density fluctuations, which scatter light and impair vision.

TABLE 5.4.2 Systemic Disorders and Lens Opacities

Systemic Disorder	Appearance in the Eye
Myotonic dystrophy	Blue dot cortical cataract and posterior subcapsular cataract
Wilson's disease	Green sunflower cataract (copper) anterior or posterior subcapsular
Atopic dermatitis	Blue dot cortical cataract and posterior subcapsular cataract
Hypocalcemia	Discrete white cortical opacities
Diabetes mellitus	Snowflake opacities located in anterior and posterior subcapsular cortex
Acute onset diabetes	Cortical wedges caused by lens fiber swelling
Down syndrome	Snowflake opacities located in anterior and posterior subcapsular cortex
Systemic conditions requiring corticosteroids (any form of administration)	Posterior subcapsular lens opacities

TABLE 5.4.1 Morbidity in Cataract Surgery Patients

Condition	Percentage
Significant medical history	84
Diabetes mellitus	16
Systemic hypertension	47
Ischemic heart disease	38
Hypothyroidism	18
Undiagnosed tumors	3



**Fig. 5.4.1** Glaukos version 1 iStent (G1) (A) and version 2 iStent inject (G2) (B) Trabecular microbypass system (MIGS). (Image used with permission from Glaukos Inc.)

The impact of a patient's cataract on the retinal image may be appreciated on funduscopic examination, which can show interference with the red reflex and show the blur of fine retinal vessels.

## DIAGNOSIS OF LENS OPACITIES

Slit-lamp biomicroscopy is the major method used to observe and assess cataracts. However, the image seen often fails to correlate with the patient's visual acuity or function. The relationship between alterations in the structural proteins, the increase in light scatter associated with conventional biomicroscopy, and the capacity of visual function is not a simple one. For all lens examinations, the pupil is dilated maximally.

## CLASSIFICATION OF LENS OPACITIES

### Nuclear Opacities

Initially, an increase in optical density of the nucleus occurs (nuclear sclerosis). The fetal nucleus is first involved and then the whole adult nucleus. The increase in density is followed by an opacification, which implies a change in color, namely from an initial clear to yellow to a subsequent brown (brunescient cataract).

In certain instances, crystals appear in the adult nucleus (or in the cortex, usually posteriorly) that, on slit-lamp examination, appear to be of different colors (polychromatic luster).

### Cortical Opacities

The changes in transparency involve most of the cortex of the lens. The changes evolve as follows:

- Hydration of the cortex with development of subcapsular vacuoles.
- Formation of ray-like spaces filled with liquid (morgagnian globules), which is at first transparent and later becomes opaque.
- Lamellar separation of the cortex with development of parallel linear opacities.
- Formation of cuneiform opacities that originate at the periphery of the lens and spread toward the center.

## Posterior Subcapsular Opacities

Posterior subcapsular opacities may develop as isolated entities or may be associated with other lens opacities. The opacity begins at the posterior polar region and then spreads toward the periphery. Often, granules and vacuoles are detectable in front of the posterior capsule.

## Advanced Cataracts

The crystalline lens may swell and increase in volume because of cortical processes (intumescent cataract). Complete white opacification of the lens is called a mature or morgagnian cataract.

If the liquefied cortical material is not—or is only partially—reabsorbed, the solid nucleus may “sink” to the bottom. Reabsorption of the milky cortex causes a reduction in the lens volume, resulting in capsular folding (hypermaturation cataract).

## GRADING OF LENS OPACITIES

Gradations and classifications of cataracts are useful in determining the potential difficulty of cataract surgery, in cataract research, in studies to explore causation, and in trials of putative anticataract drugs. Devices designed to quantify lens opacification have been developed<sup>14</sup>; these instruments (such as the Kowa Early Cataract Detector and the Scheimpflug photo slit lamp) appear to be more accurate when used to assess the formation of nuclear cataracts than that of cortical cataracts.

A rapid method for the gradation of cataract in epidemiological studies has been reported by Mehra and Minassian<sup>15</sup>; the area of lenticular opacity is assessed by direct ophthalmoscopy and graded on a scale from 0 to 5. Highly reproducible, validated systems (Lens Opacities Classification System III; see next section) for cataract classification have been developed by Chylack and coworkers<sup>16</sup> to define the effects of specific cataract type and extent very accurately; these enable the effects of specific cataract types on specific visual functions to be quantified.

## Lens Opacities Classification System III

(Fig. 5.4.2)

For nuclear opalescence (NO) or nuclear color (NC), a slit beam is focused on the lens nucleus and the density of the lens is compared with a set of standard photographs. If the density is less than that corresponding to the first photograph, NO or NC is zero or “no nuclear cataract”; if NO or NC is 1, the density is equal to or less than that for the second photograph, and so on. The photographs represent lens nuclei of increasing density, and the patient's cataract is graded accordingly.

For cortical cataracts (category “C”), a retroillumination (red reflex) view through the dilated pupil is used to view the lens, focused first at the anterior capsule and then at the posterior capsule. The photographs are compared with standard photographs—each succeeding photograph shows the pupillary area covered by more cortical cataract.

For posterior subcapsular cataract (category “P”), a retroillumination (also red reflex) view of the lens is used, focused at the posterior capsule. Again, the patient's cataract is graded according to standard photographs (see Fig. 5.4.2).

## EFFECTS OF OPACITIES ON VISION

### Visual Acuity Reduction

Measurement of visual acuity can remain high despite age-related lens opacities.<sup>17–18</sup> The severity of the visual disability measured using high-contrast Snellen acuity charts is not sensitive to visual disability characterized by loss of contrast sensitivity.

Usually, visual acuity testing is conducted under ideal circumstances that are not normally met in the real world. Although not a definitive measurement of visual dysfunction, simple Snellen acuity is the most used index to determine whether cataract surgery should be performed. The Preferred Practice Pattern of the American Academy of Ophthalmology recommends Snellen acuity as the best general guide to the appropriateness of surgery but recognizes the need for flexibility with due regard to a patient's particular functional and visual needs, environment, and risks, which may vary widely.<sup>19</sup>

When the cataract is very dense and opaque, visual acuity may be reduced to light perception only (cataract is still the major cause of blindness throughout the world).



**Fig. 5.4.2** Lens Opacities Classification System III Simulation Chart.

## Contrast Sensitivity Reduction

Patients with cataracts commonly complain of loss of the ability to see objects outdoors in bright sunlight and of being blinded easily by approaching headlamps in nighttime driving.<sup>20</sup>

Typically, loss of contrast sensitivity in patients who have cataracts has been reported to be greater at higher spatial frequencies. All cataracts lower contrast sensitivity—the posterior subcapsular opacities have been reported to be the most destructive.

## Myopic Shift

The natural aging of the human lens produces a progressive hyperopic shift. Nuclear changes induce a modification of the refractive index of the lens and produce a myopic shift that may be of several diopters or greater. It is possible to predict that an aging person who had emmetropia previously but who can now read with no correction (“second sight”) is developing nuclear cataract. Together with this aging effect goes the loss of the negative asphericity of the lens in youth, balancing the positive asphericity of the natural cornea.<sup>21</sup> The shift to more positive asphericity of the lens with progressive nuclear cataract also reduces visual quality.

If the lens structure becomes heterogeneous, with cortical spoke cataract for example, the change in refractive index may be uneven and may produce some degree of internal irregular astigmatism and disturbance of the higher-order aberrations of Zernike (third order).

## Monocular Diplopia

Monocular diplopia is common in patients who have lens opacities, particularly cortical spoke cataract, and in conjunction with water clefts that form radial wedge shapes and contain a fluid of lower refractive index than the surrounding lens. In some cases, patients may complain of polyopia.

## Glare

Even minor degrees of lens opacity cause glare because of the forward scatter of light.<sup>22</sup> Such patients often see more poorly in daylight conditions than in the context of night driving. Unlike contrast sensitivity reduction, some glare may be produced by opacities that do not lie within the pupil diameter. The differences between measured visual acuity in a darkened room and acuity in ambient light that produces glare are useful as subjective criteria for the justification of surgery.

## Color Shift

The cataractous lens becomes more absorbent at the blue end of the spectrum, especially with nuclear opacities. Usually patients are not aware of this color visual defect until after cataract surgery and visual rehabilitation.

## Visual Field Loss

According to the morphology, the density, and the location of the opacities, the field of vision may be affected.

## INVESTIGATIONS FOR FURTHER SURGICAL REFINEMENT

### CORNEAL TOPOGRAPHY<sup>23</sup>

The use of corneal topography<sup>24</sup> is facilitatory in the fulfillment of current expectations of outcomes of surgery of within 0.5 diopters (D) of emmetropia, with minimal astigmatism.

### PREOPERATIVE TOPOGRAPHY

The preoperative assessment of corneal topography has a number of roles in cataract surgery. First, as an alternative to keratometry, it can provide a representative measure of the corneal curvature or power necessary to calculate intraocular lens (IOL) power. Second, knowledge of the magnitude and location of pre-existing astigmatism is important if it is to be reversed by appropriate placement and construction of incisions during surgery. Furthermore, with the advent of toric IOLs, the decision whether to use this technology is based on the topographic or keratometric measurement of corneal astigmatism. Variations in the measurement of corneal astigmatism are often seen from instrument to instrument with the inherent danger of mal-powering or mal-placing the toric IOL, hence the need to perform more than one form of keratometric assessment.

Modern topographic devices are now capable of measuring higher-order aberrations (Zernike), which can further help with optimizing surgical outcomes. The second and third order aberrations of Zernike may be reduced by removal of the cataract and by accurate biometric measurements. The fourth order aberration, in particular spherical aberration, which changes with age,<sup>21</sup> can be modified by IOL choice (differing spherical aberration values) to provide better acuity or greater depth of focus.<sup>25</sup>

### DETERMINATION OF IOL TYPE AND POWER

Prior to cataract surgery, the power of the IOL that is required to give the desired postoperative refraction is determined. The final refractive result is dependent on the accuracy of the biometric data and its appropriate use in relevant calculations.

Achieving emmetropia (or the desired refractive outcome) by optimal biometric assessment is the most important aspect of the workup for cataract surgery. With the advent of the new extended range of focus IOLs now available on the market, the default position of the standard monofocal



IOL is being challenged. The surgeon is now potentially in the position where he or she should discuss in detail with his patient why he or she should not have one of these new lenses. The scope of the art of surgery has widened since the introduction of these lenses.

The factors under consideration for the surgeon are therefore:

- Is the patient ready for surgery (risk–benefit analysis)?
- If so, what is the scope of the workup required as calculated against the patient's medical and ophthalmological status?
- What are the patient's optical needs and what technologies are required to fulfill expectations?
- What workup is required to enhance the accuracy of outcome for those needs?
- What is the surgeons' expectation in terms of his or her capability of providing the match for the patient's expectation?
- And finally, have all the above been conveyed in an understandable manner to the patient?

## PLANNING THE INCISION

The final part of the patient workup for cataract surgery is planning the incision. This involves making the decision on the optimal corneal position of the operative incision in relation to the surgical accessibility (nose, operating table, side, etc.) for efficient execution of the surgery and whether the operative incision should be the same as the therapeutic incision for the management of the corneal astigmatism. The effect of the incision on astigmatism is modifiable by the axis location of the incision, the length of the incision, and the proximity to the visual axis (scleral, limbal, or corneal).

The incision-making process also is modified by the decision about whether to use the toric IOL technology. The factors used in this decision-making process relate to the degree of astigmatic refractive error, IOL availability, outcome target, and keratometric and topographic measurements. Technology improvements have permitted the importation of keratometric data from the workup room to the operating theater. Manufacturers have created imaging systems within microscopes that recognize and track the eyes being operated on and provide overlay information through the microscope oculars to demonstrate exactly where corneal incisions should be placed and on what axis a toric IOL should be positioned. Capabilities even extend to overlays for particular capsulorrhexis size and IOL centration.

## GOOD CLINICAL PRACTICE (SOCIAL AND LEGAL ASPECTS)

The indications for surgery vary from patient to patient, especially with the current minimally invasive nature of cataract and lens implant surgery (compared with such surgery performed only a few years ago). The visual needs of patients vary according to their ages, occupations, and leisure interests. A cataract may not be symptomatic. Visual symptoms and outcome expectation affect the risk–benefit ratio.

Although the risks of technically well-performed small incision surgery are few in a healthy eye, patients require enough information on which to base their decision to proceed. Most patients are inclined to accept the professional judgment of the ophthalmic surgeon, but it is implicit that an adult of sound mind has the right to determine whether surgery should proceed. Therefore, in the context of cataract surgery, how much information is it necessary for an ophthalmologist to disclose to a patient? To what extent should an ophthalmologist shield a patient from the anxieties that can accompany a full explanation of diagnosis and treatment?

An ophthalmologist must strike a balance between providing enough information to enable the patient to give informed consent with respect to treatment and engendering the confidence and trust that encompasses a joint decision to proceed. The surgeon shoulders the major responsibility for this, which should be accepted as a consequence of medical and specialist training.

In the application of professional judgment, the consideration of alternative management strategies, risks, and benefits allows a patient to make some sort of informed evaluation of the options. Statistical information based on published data may be confusing: Where does the patient fit into the statistics? What are the personal outcome statistics for the surgeon who offers advice? What guarantees are there that a particular surgeon will perform the surgery?

A problem arises if potential material risks and dangers are not disclosed to a patient before surgery and a complication occurs. The patient may claim that, with prior knowledge of such a risk, he or she would not have consented to the surgery. A risk is material when a rational patient considers the risk of undergoing a certain type of treatment to be significant.

Problems that arise from consent to perform surgical procedures can be minimized but not completely avoided, because every contingency cannot be reviewed completely. Taking the following steps will ensure that a thorough approach has been used.

Appropriate patient education is required—the procedure is described in a manner that allows the patient to appreciate what will be done to treat the eye. Although the decision to proceed has to be the patient's, the surgeon must not pass all the responsibility on to the patient; instead the surgeon should communicate the appropriate degree of confidence in the procedure's outcome.

The surgeon has to assume much of the responsibility for treatment advice, because the patient cannot appreciate the intricacies of every surgical situation. Ultimately, the patient has to have faith in the ability of the surgeon not only to carry out the procedure but also to make the judgment that the benefits far outweigh the risks. An analogous situation might be that of a passenger contemplating a journey on a commercial airliner. If the passenger inquires of the pilot what the potential risks are, common sense suggests that the answer would be that they are high in number but low in expectation. A passenger who decides to make the trip has confidence in the airline and the crew to complete a successful journey. So it is with surgery: The patient must have confidence in the ability of the surgeon and the surgical team to carry out a successful procedure without knowing each and every pitfall that exists.

Alternative approaches to the management of an ophthalmic condition are explained to the patient to enable patient participation in the final direction of treatment.

When uncertainties exist, the patient is advised of the predictability of the planned procedure, its stability, and its safety. Statistical information on outcome is of limited value when given in a general sense. Few surgeons are in a position to give specific statistical information about the outcome of their own practices or of certain procedures.

The patient must be given adequate time to decide. At the end of the consultation, a patient must have an opportunity to consider the treatment that has been advised or to reverse a decision to proceed. It is inappropriate to obtain a patient's signed consent for a procedure and then proceed at very short notice (the same day) with that treatment. The delay between consent and treatment must be sufficient to allow the patient to consider the matter fully.

To ensure that a patient is fully informed with regard to consent for a surgical procedure, the issues listed in [Box 5.4.1](#) should be covered.

The patient should sign a consent form that states that the procedure has been explained fully in language that is comprehensible and that there has been sufficient opportunity to ask questions and reconsider consent prior to surgery. A written guide helps patients comprehend the nature of the planned surgery.

Any surgical intervention is essentially a matter of trust and confidence—the trust of the patient in the surgeon's ability and integrity and the trust of the surgeon in the patient's ability to comprehend and follow the process and to comply with prescriptions for managing the condition before, during, and after surgery.

### BOX 5.4.1 Issues to Discuss With a Patient Prior to Cataract Surgery

- The purpose of the surgery
- The surgical procedure
- The anesthetic requirements
- Commonly experienced visual conditions after the surgery, even if temporary
- That temporary postsurgical visual conditions may become permanent under certain conditions
- The serious complications that may follow surgery
- Potential pain or ocular discomfort
- The refractive requirements after the surgery (the need to wear and the provision of spectacles and/or contact lenses)
- The potential need for additional procedures (planned staged procedures)
- Alternative management of the condition

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# Intraocular Lens Power Calculations

Li Wang, Kourtney Houser, Douglas D. Koch

# 5.5

**Definition:** Intraocular lens (IOL) power calculation is a process to determine the optimal IOL power to achieve the desired refraction following cataract surgery.

### Key Features

- Accurate IOL power calculation depends on the precision of the preoperative biometric data and the accuracy of the IOL formulas.
- New biometers using interferometry and swept-source OCT have improved accuracy and expanded the number of biometric parameters that can be measured.
- IOL power calculation is less accurate in special eyes, including short eyes, eyes with ectatic corneas, or eyes that have undergone corneal refractive surgery or keratoplasty. The American Society of Cataract and Refractive Surgery (ASCRS) postrefractive IOL calculator is a useful tool.
- When selecting the toricity of the toric IOL, several factors must be taken into account. Imaging and guidance systems for toric IOL alignment have been developed.

### INTRODUCTION

Accurate intraocular lens (IOL) power calculation is a crucial element for meeting the ever-increasing expectations of patients undergoing cataract surgery. Despite advances in technology and IOL calculation formulas, much is yet to be done. The accuracy of IOL power calculations depends on the precision of the preoperative biometric data, the accuracy of the IOL formulas, and the IOL quality control by the manufacturer.

In this chapter, we will discuss (1) ocular biometry; (2) IOL power formulas; (3) IOL power calculations in special eyes, including short eyes, long eyes, and eyes with previous corneal refractive surgery; (4) toric IOL selection; (5) intraoperative wavefront aberrometry; and (6) postoperative IOL adjustment.

### OCULAR BIOMETRY

Accurate biometry is of vital importance in achieving a predictable postoperative refraction following cataract surgery. Norrby<sup>1</sup> analyzed the sources of error in IOL power calculation by analyzing the precision of the biometric and clinical measurements. He concluded that the three greatest sources of error were axial length (AL), effective lens position (ELP), and postoperative refraction, contributing 79% of the total error.

### Ultrasound Biometry

AL has traditionally been measured using ultrasound biometry. With the applanation technique, the ultrasound probe is placed in direct contact with the cornea, and corneal compression typically causes the AL to be falsely shortened. Applanation biometry has given way to noncontact methods. Although the immersion technique has been shown to be more reproducible than the applanation technique, both require mindfulness of the properties of ultrasound. In eyes with high to extreme axial myopia, the presence of a posterior staphyloma should be considered. Erroneously long AL readings may occur in eyes with staphylomata. An immersion A/B-scan approach for AL measurement has been described in the setting of posterior staphyloma.<sup>2</sup>

With A-scan biometry, errors in AL measurement account for 54% of IOL power error when two-variable formulas are used.<sup>3</sup>

### Optical Biometry

Optical biometry has been shown to be significantly more accurate and reproducible and is rapidly becoming the most prevalent methodology for the measurement of AL. The most commonly used optical biometers are IOLMaster (Carl Zeiss Meditec, Jena, Germany) and Lenstar (Haag-Streit, Koeniz, Switzerland).

- **IOLMaster:** The IOLMaster 500 was introduced in 2000 as the first optical biometer. Based on partial coherence interferometry technology, it uses a 780-nm laser diode to measure AL. The device also provides measurements of keratometry, anterior chamber depth (ACD), and white-to-white (WTW) distance.

The newer version of this device (IOLMaster 700) uses an optical configuration that allows telecentric and thus distance-independent keratometry measurement. It uses swept-source optical coherence tomography (OCT) to measure axial length, central corneal thickness (CCT), and lens thickness (LT). It displays a full-length OCT image, showing anatomical details of a longitudinal cuts through the entire eye (Fig. 5.5.1).

- **Lenstar:** Based on optical low-coherence reflectometry technology, the Lenstar uses an 820-nm laser diode to measure AL, ACD, CCT, and LT. It calculates keratometry from an array of 32 light reflections projected off the anterior corneal surface.
- **Argos (Movu Inc, Komaki, Japan) and OA-2000 (Tomey, Nagoya, Japan):** These are two other new swept-source biometers that recently been introduced.

Studies<sup>4-6</sup> have shown that the repeatability of the IOLMaster and Lenstar for all biometric parameter measurements is excellent and that agreement between these devices is good. The differences in AL, ACD, and LT between these devices were not shown to produce a statistically significant difference in IOL power calculation.

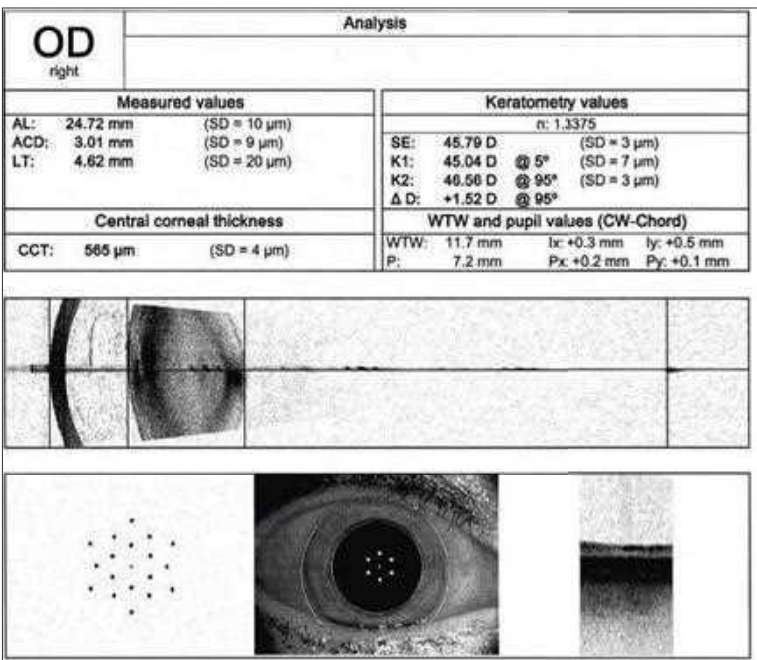
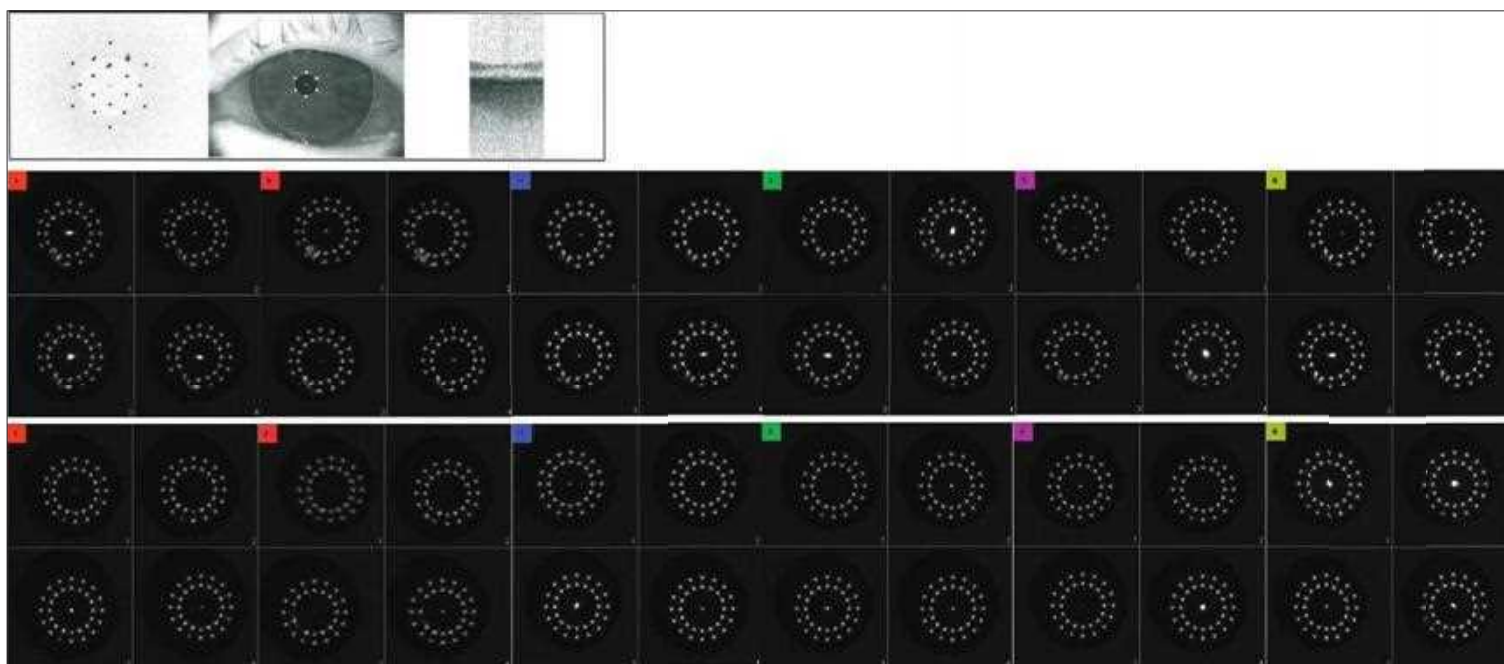


Fig. 5.5.1 Display From the Swept-Source Optical Coherence Tomography Biometer IOLMaster 700.



**Fig. 5.5.2** Poorly reflected LED images from the anterior corneal surface using IOLMaster 700 (top); poorly reflected LED images from the anterior corneal surface using Lenstar with average keratometry and corneal astigmatism of 43.24 D and 2.05 D@174° (middle), and repeated measurements with average keratometry and corneal astigmatism of 44.36 D and 0.25 D@167° (bottom).

Although measurements with optical biometry are mostly operator independent, careful alignment during the scan and inspection of the measurement quality are still necessary for optimal refractive outcomes (Fig. 5.5.2).

The primary limitation of optical biometry is its inability to measure through dense cataracts and other media opacities that obscure the macula. It was reported that with use of an earlier generation of IOLMaster, approximately 10% of eyes could not be accurately measured due to such opacities or fixation difficulties.<sup>6</sup> The IOLMaster 700 showed better penetration in dense posterior subcapsular cataracts, measuring AL successfully in 96% of cases.<sup>5</sup>

## IOL POWER FORMULAS

The first IOL power formula was published by Fyodorov in 1967. Subsequent formulas were developed and traditionally were classified as the second, third, fourth, and newer generations of IOL formulas. Due to the development of more advanced IOL formulas, a new classification based on how they work is more appropriate.

### Vergence Formulas

The majority of IOL formulas are vergence-based formulas. Based on the number of variables they use to calculate ELP, these formulas can be categorized into the following groups:

- **Two-variable formulas:** These include the Holladay 1, Hoffer Q, and SRK/T, and they use AL and keratometry to calculate the distance from the principal plane of the cornea to the thin lens equivalent of the IOL (i.e., ELP). Thus, a short eye or an eye with a flatter cornea will have a shallower anterior chamber. However, Holladay has shown that exceptions to these assumptions exist.<sup>7</sup>
- **Three-variable formula:** The Haigis formula uses AL, keratometry, and ACD.
- **Five-variable formula:** The Barrett Universal II formula uses AL, keratometry, ACD, LT, and WTW.
- **Seven-variable formula:** The Holladay 2 formula uses preoperative refraction, age, AL, keratometry, ACD, LT, and WTW.

### Ray Tracing Formulas

- **PhacoOptics:** With PhacoOptics, IOL power is calculated based on exact ray tracing (Snell's law of refraction). It incorporates the latest generation ACD prediction algorithms based on the complex relationship between the preoperative ocular dimensions (ACD and LT) and the postoperative position of the IOL (postoperative ACD).<sup>8</sup> Measurements

of the anterior and posterior corneal curvatures as along with conic coefficients (Q-values) obtained by modern anterior segment imaging systems can be used directly by the program.

- **Okulix:** Okulix<sup>9</sup> is a program package that calculates single rays using Snell's law. AL can be entered either manually or by a computer link to the measuring device. As an alternative to entering corneal radii by hand, they also can be taken from a two-dimensional corneal topographic map.

## Artificial Intelligence Formulas

- **Radial basis function (RBF):** The Hill-RBF calculator<sup>10</sup> is an advanced, self-validating method for IOL power selection employing pattern recognition and a sophisticated form of data interpolation. Based on artificial intelligence, this methodology is entirely data driven. Pattern recognition for selecting an IOL power is achieved through the process of adaptive learning, the ability to learn tasks based solely on data. Unlike static theoretical formulas, this approach will be an ongoing project and continuously updated as a "big data" exercise. The greater the number of surgical outcomes that are fit to the RBF model, the greater the overall depth of accuracy.
- **Neural network:** Clarke<sup>11</sup> developed a computational method based on neural network in which the software is trained to predict IOL powers using large amount of clinical data from one surgeon with one IOL. Clinical data include preoperative AL, keratometry, ACD, and LT.

## Combination Formulas

- **Super formula:** The Ladas super formula<sup>12</sup> amalgamates outcomes from the above-mentioned two-variable and three-variable vergence formulas and has a small component of artificial intelligence.

All of these formulas have some element of regression, as they include constants that are derived from prior patient outcomes. Note that two critical data points are not measured: posterior corneal curvature (although this is slowly being integrated) and ELP. Better predictive formulas for estimating ELP will likely require more sophisticated measurements, possibly to include lens diameter, lens volume, and certain angle and iris features.

## IOL CALCULATIONS IN SPECIAL EYES

### IOL Power Calculation in Short Eyes

In short eyes, the importance of accurate ELP prediction is magnified due to the high power of the IOL and the relatively short distance from the IOL to the retina. Olsen<sup>13</sup> showed that 0.25 mm error in postoperative ACD

corresponds to a 0.1 diopter (D) error in long eyes with 30 mm AL and a 0.5 D error in short eyes with 20 mm AL.

In IOL calculation formulas that do not use ACD in the ELP calculation, it is assumed that short eyes have a proportionally shallower anterior chamber. However, this assumption breaks down in the many short eyes that in fact have normal anterior chamber anatomy with normal ACD.

Several studies in the literature have compared different IOL power formulas and their accuracy in short eyes. Although it is believed that newer IOL power prediction formulas perform best in short eyes, uncertainty still exists in the literature on whether any of the available formulas perform better than the others.<sup>14–16</sup>

In general, our approach for short eyes is to use the Holladay 1, Holladay 2, Hill-RBF, Olsen, and Barrett, favoring the Olsen when there is disagreement. We also try to operate on the nondominant eye first so that we can use its refractive outcome to adjust the IOL power for the second eye, generally changing the calculated IOL power by one-half of the prediction error in the first eye.

## IOL Power Calculation in Long Eyes

In long eyes, IOL power formulas tend to select IOLs of insufficient power, leaving patients with postoperative hyperopia. Inaccurate measurement of preoperative AL has been reported to be the main reason for postoperative refractive error in axial high myopia.<sup>17</sup> The incidence of posterior staphyloma increases with increasing AL. Ultrasonic biometric methods can produce errors in the presence of a posterior staphyloma by giving falsely long AL.

Theoretically, optical biometry permits more accurate measurements when a posterior staphyloma is present. However, in a study investigating the accuracy of SRK/T formula in eyes with negative or zero-powered IOLs, MacLaren and colleagues<sup>18</sup> reported consistent hyperopic errors across all three methods of biometry (A-scan, B-scan, and optical). This indicates that eliminating or minimizing the adverse impact of posterior staphylomata on IOL calculations does not prevent hyperopic surprises in long eyes.

We proposed a method for optimizing AL in long eyes (Wang–Koch adjustment).<sup>19</sup> Our results showed that this method significantly improved the accuracy of IOL power calculation in eyes with IOL powers  $\leq 5.00$  D and significantly reduced the percentage of eyes that would be left hyperopic. We recommend using the optimized AL in eyes with AL  $> 25.2$  mm. Based on the formula, the optimized AL is calculated from the measured optical or ultrasonic AL using the following equation:

$$\text{Holladay 1 Optimized AL} = 0.8289 \times \text{Measured AL} + 4.2663$$

$$\text{Haigis Optimized AL} = 0.9286 \times \text{Measured AL} + 1.562$$

$$\text{SRK/T Optimized AL} = 0.8544 \times \text{Measured AL} + 3.7222$$

$$\text{Hoffer Q Optimized AL} = 0.853 \times \text{Measured AL} + 3.5794$$

Then the optimized AL is entered into the IOLMaster or Lenstar and the calculation is performed again. We recommend selecting the IOL power that predicts a minus prediction error close to zero ( $-0.1$  to  $-0.2$  D), since slight myopic results may occur with this approach of optimizing AL.

A recent advance has been the development of the Barrett Universal II formula, which has been refined to improve outcomes in long eyes. In a study of eyes with AL  $\geq 26.0$  mm, Abulafia et al.<sup>20</sup> reported that for IOL powers  $< 6.00$  D, best results occurred with the Holladay 1 with Wang–Koch adjustment, Haigis with Wang–Koch adjustment, and Barrett Universal II formulas.

Due to the low IOL powers required in long eyes, accuracy of ELP estimation is not as important as in normal and short eyes. By refining the AL value used in current formulas, excellent outcomes can be anticipated as shown in these studies.<sup>19,20</sup>

## IOL Power Calculation in Eyes With Previous Corneal Refractive Surgery

Cataract surgeons are facing challenges in IOL power calculation in eyes that have undergone excimer laser photorefractive keratectomy (PRK), laser in situ keratomileusis (LASIK), or radial keratotomy (RK).

## Factors Contributing to Challenges in IOL Power Calculation

There are two factors that primarily contribute to challenges in IOL power calculations in eyes with previous LASIK, PRK, or RK: difficulties in obtaining accurate corneal refractive power and problems in ELP prediction. Following LASIK/PRK/RK, the predicted ELP would be misleading if the postoperative corneal power were used in the ELP calculation. To avoid the ELP-related IOL prediction error, Aramberri proposed the double-K method.<sup>21</sup> With the double-K version of the IOL formulas, the prerefractive surgery corneal power is used to estimate the ELP and the postrefractive surgery corneal power is used to calculate the IOL power. This approach had been previously used by Holladay in his Holladay Consultant Program. Several studies have shown that the double-K method improves the accuracy of IOL power calculation after LASIK/PRK.<sup>21–23</sup>

## Methods to Improve the Accuracy of IOL Power Calculations in Postrefractive Eyes

Many approaches have been proposed to improve the accuracy of IOL power calculation in eyes following LASIK/PRK/RK. These can be categorized into three groups depending on the use of historical data acquired before refractive surgery was performed.

### Methods Relying on Prior Clinical Data

Methods in this category use completely historical data. Clinical studies have shown that they are less accurate than the formulas in other categories described in the following sections.<sup>24</sup> The concern with these methods is their sensitivity to errors in the historically obtained data. A 1.00 D error in either the keratometric or refractive values translates to nearly a 1.00 D postoperative refractive error.

### Methods Using a Combination of the Surgically Induced Refractive Change ( $\Delta$ MR) and Current Corneal Power Values

These methods modify either corneal power measurements at the time the patient presents for cataract surgery or calculated IOL power based on  $\Delta$ MR.

These methods multiply  $\Delta$ MR by a fraction of between 0.15 and 0.33, depending on the formula. This translates to an error of 0.15–0.33 D for each 1.00 D of error in  $\Delta$ MR, reducing potential errors caused by having inaccurate historical data. Studies have shown that some of these methods have consistently been among the more accurate approaches.<sup>24</sup>

### Methods Requiring No Historical Data

Several methods requiring no historical data have been proposed. Surgeons use these approaches most often. The formulas fall into two categories:

- Formulas that adjust measured corneal power from the anterior corneal surface based on either regression analysis or assumed posterior corneal power, such as the Wang–Koch–Maloney, Shammas, Haigis-L, Potvin-Hill Pentacam, and Barrett True K No History formulas.
- Formulas based on corneal power measurements from both anterior and posterior corneal surfaces. Using the RTVue (Optovue Inc, Fremont, CA), Tang and colleagues<sup>25</sup> developed an OCT-based IOL calculation formula using the anterior and posterior corneal powers and the central corneal thickness.

Methods requiring no historical data have been shown to perform as well as those using a combination of  $\Delta$ MR and current corneal power values. Promising results for the OCT-based IOL formula and Barrett True K formula have been reported.<sup>26,27</sup> However, the percentage of eyes within 0.5 D of target refraction was under 70% for all formulas, the highest value being 68.3% for the OCT formula. Obviously, more studies are needed to improve the accuracy of corneal power measurements and to develop new IOL power calculation formulas in these eyes.

### Web-Based Post-Refractive IOL Calculator

To simplify the complicated and time-consuming calculations discussed above, we developed a web-based post-refractive IOL power calculator in 2007 (Fig. 5.5.3) (<http://www.ascrs.org/>). This calculator can be used for eyes with previous myopic LASIK/PRK, hyperopic LASIK/PRK, or RK. We have performed major updates to the online calculator in the past and will continue to update it. During the past year, the number of visits to this calculator was over 120,000.

### Radial Keratotomy

IOL power calculation in RK eyes is even more difficult due to the greater irregularity of the anterior corneal curvature and the posterior corneal



**IOL Calculator for Eyes with Prior Hyperopic LASIK/PRK**  
(Your data will not be saved. Please print a copy for your record.)

**Please enter all data available and press "Calculate"**

Doctor Name: <input style="width: 90%;" type="text"/>	Patient Name: <input style="width: 90%;" type="text"/>	Patient ID: <input style="width: 90%;" type="text"/>
Eye: <input style="width: 90%;" type="text"/>	IOL Model: <input style="width: 90%;" type="text"/>	Target RefrID: <input style="width: 90%;" type="text"/>

**Pre-LASIK/PRK Data:**  

Refraction* <input style="width: 150px;" type="text"/>	Cyl(D) <input style="width: 100px;" type="text"/>	Vertex (if empty, 12.5 mm will be used) <input style="width: 150px;" type="text"/>
Keratometry <input style="width: 150px;" type="text"/>	K2(D) <input style="width: 100px;" type="text"/>	

**Post-LASIK/PRK Data:**  

Refraction* <input style="width: 150px;" type="text"/>	Cyl(D) <input style="width: 100px;" type="text"/>	Vertex (if empty, 12.5 mm will be used) <input style="width: 150px;" type="text"/>
Topography <input style="width: 150px;" type="text"/>	<b>EyeSys</b> SRMP <input style="width: 100px;" type="text"/>	
<b>OCT (RTVue or Avanti)</b> <input style="width: 150px;" type="text"/>	Net Corneal Power <input style="width: 100px;" type="text"/>	Posterior Corneal Power <input style="width: 100px;" type="text"/>
	Central Corneal Thickness <input style="width: 100px;" type="text"/>	

**Optical/Ultrasound Biometric Data:**  

Ks** <input style="width: 100px;" type="text"/>	K1(D) <input style="width: 100px;" type="text"/>	K2(D) <input style="width: 100px;" type="text"/>	Device Keratometric Index (n) <input style="width: 100px;" type="text"/>	<input type="radio"/> 1.3375 <input type="radio"/> 1.332 Other <input style="width: 100px;" type="text"/>
	AL(mm) <input style="width: 100px;" type="text"/>	ACD(mm) <input style="width: 100px;" type="text"/>	Lens Thick (mm) <input style="width: 100px;" type="text"/>	WTW (mm) <input style="width: 100px;" type="text"/>
Lens Constants*** <input style="width: 100px;" type="text"/>	A-constants (SRK/T) <input style="width: 100px;" type="text"/>	SRK(Holladay 1) <input style="width: 100px;" type="text"/>		
	Height a0 (if empty, converted value is used) <input style="width: 100px;" type="text"/>	Height a1 (if empty, 0.4 is used) <input style="width: 100px;" type="text"/>	Height a2 (if empty, 0.4 is used) <input style="width: 100px;" type="text"/>	

\*If entering "Sph(D)", you must enter a value for "Cyl(D)", even if it is zero.  
 \*\*See manual/Screen from other devices.  
 \*\*\*Enter the constant available; the other will be calculated. If Ultrasound AL is entered, be sure to use your ultrasound lens constants. It is preferable to use optimized A0, a1, and a2 Height constants.

**IOL Powers Calculated Using Double-K Holladay 1<sup>1</sup>, Shammas PL<sup>2</sup>, Hoffer 1<sup>3</sup>, OCT-based<sup>4</sup>, & Barrett True K<sup>5</sup>**

Using JMR	Using no prior data
<sup>1</sup> Calculated SRMP	--
<sup>1</sup> Average A0 0-3	--
<sup>1</sup> Maxwell Formula	--
<sup>1</sup> Modified Hoffer	--
<sup>1</sup> Barrett True K	--
<sup>2</sup> Shammas	--
<sup>3</sup> Hoffer	--
<sup>4</sup> OCT	--
<sup>5</sup> Barrett True K by Hoffer	--

**Average IOL Power:** --  
**Min:** --  
**Max:** --

**IOL Calculator for Eyes with Prior RK**  
(Your data will not be saved. Please print a copy for your record.)

**Please enter all data available and press "Calculate"**

Doctor Name: <input style="width: 90%;" type="text"/>	Patient Name: <input style="width: 90%;" type="text"/>	Patient ID: <input style="width: 90%;" type="text"/>
Eye: <input style="width: 90%;" type="text"/>	IOL Model: <input style="width: 90%;" type="text"/>	Target RefrID: <input style="width: 90%;" type="text"/>

**Pre-RK Data:**  

Refraction: <input style="width: 150px;" type="text"/>	Cyl(D) <input style="width: 100px;" type="text"/>	Vertex (if empty, 12.5 mm will be used) <input style="width: 150px;" type="text"/>
--	---	--

**Post-RK Data:**  

Refraction: <input style="width: 150px;" type="text"/>	Cyl(D) <input style="width: 100px;" type="text"/>	Vertex (mm) <input style="width: 150px;" type="text"/>
Topography <input style="width: 150px;" type="text"/>	<b>EyeSys</b> SRMP <input style="width: 100px;" type="text"/>	Average Central Power <input style="width: 100px;" type="text"/>
Atlas Ring Values <input style="width: 150px;" type="text"/>	1mm <input style="width: 100px;" type="text"/>	2mm <input style="width: 100px;" type="text"/>
Pentacam <input style="width: 150px;" type="text"/>	Posterior Corneal Power <input style="width: 100px;" type="text"/>	Central Corneal Thickness <input style="width: 100px;" type="text"/>
<b>OCT (RTVue or Avanti)</b> <input style="width: 150px;" type="text"/>	Net Corneal Power <input style="width: 100px;" type="text"/>	

**Optical/Ultrasound Biometric Data:**  

Ks** <input style="width: 100px;" type="text"/>	K1(D) <input style="width: 100px;" type="text"/>	K2(D) <input style="width: 100px;" type="text"/>	Device Keratometric Index (n) <input style="width: 100px;" type="text"/>	<input type="radio"/> 1.3375 <input type="radio"/> 1.332 Other <input style="width: 100px;" type="text"/>
	AL(mm) <input style="width: 100px;" type="text"/>	ACD(mm) <input style="width: 100px;" type="text"/>	Lens Thick (mm) <input style="width: 100px;" type="text"/>	WTW (mm) <input style="width: 100px;" type="text"/>
Lens Constants*** <input style="width: 100px;" type="text"/>	A-constants (SRK/T) <input style="width: 100px;" type="text"/>	SRK(Holladay 1) <input style="width: 100px;" type="text"/>		

\*If entering "Sph(D)", you must enter a value for "Cyl(D)", even if it is zero.  
 \*\*See manual/Screen from other devices.  
 \*\*\*Enter the constant available; the other will be calculated. If Ultrasound AL is entered, be sure to use your ultrasound lens constants.

**IOL calculation formulas used: Double-K Holladay 1<sup>1</sup>, OCT-based<sup>4</sup>, & Barrett True K<sup>5</sup>**

<sup>1</sup> EyeSys SRMP	--
<sup>1</sup> Average Central Power (other)	--
<sup>1</sup> Atlas 1-4	--
<sup>1</sup> Pentacam	--
<sup>1</sup> IOLMaster/Vermeer	--
<sup>4</sup> OCT	--
<sup>5</sup> Barrett True K	--

**Average IOL Power:** --  
**Min:** --  
**Max:** --

curvature changes. Furthermore, it has been reported that 20%–50% of RK eyes have a gradual hyperopic shift. We recommend using topographically derived average corneal power over the central 2–4 mm zone. Compensation for potential error in ELP is still required, with use of double-K version of IOL formulas if the corneal power is used for ELP prediction.

We find relatively lower accuracy in post-RK eyes compared with eyes following LASIK/PRK. In 95 post-RK eyes, we<sup>28</sup> evaluated the accuracy of newer IOL formulas (OCT and Barrett True K), and the percentage of eyes within 0.5 D of target was less than 50% for all formulas. Further

IOL calculations are more difficult in eyes with keratoconus, presumably due to the irregularity of the cornea and the change in ratio of anterior to posterior corneal curvatures. Using the Holladay 1, Barrett, and Olsen

formulas in 21 keratoconic eyes, we found that the mean refractive prediction errors were +1.25 D, +1.15 D, and +1.36 D, respectively, and the magnitude of the hyperopic prediction error with Holladay 1 formula increased with increasing corneal power. Improved corneal imaging technology for accurate anterior and posterior corneal power measurements is needed.

## IOL Power Calculation in Eyes Following Keratoplasty

Eyes following penetrating keratoplasty may have high amounts of irregular anterior corneal astigmatism and uncertain posterior corneal values. With Descemet's stripping automated endothelial keratoplasty, corneal power changes are less pronounced with minimal astigmatic change but with a hyperopic shift of around 0.70–1.5 D. Descemet membrane endothelial keratoplasty induces even more modest refractive changes, with a reported hyperopic refractive shift of 0.24–0.50 D and minimal change in refractive astigmatism. Although the complexity of IOL calculation has diminished as procedures have advanced, it remains challenging to perform IOL power calculation in these eyes.

## TORIC IOL CALCULATION

It has been estimated that 30% of cataract patients have more than 0.75 D of corneal astigmatism. Toric IOLs provide consistent and stable correction of astigmatism. Accurate measurement of total corneal astigmatism is a critical element in correcting astigmatism during cataract surgery.

## Impact of Posterior Corneal Astigmatism

Newer technologies, such as Scheimpflug devices and OCT systems, are now used in the clinical setting for measuring the posterior corneal surface. Several studies using different methodologies reported that the posterior cornea has astigmatism that ranges from 0.26 to 0.78 D.<sup>29,30</sup> There were three new findings in our study<sup>30</sup>: (1) in corneas with anterior corneal with-the-rule (WTR) astigmatism, as astigmatism increases, the posterior cornea is increasingly steep vertically; (2) posterior corneal astigmatism is relatively constant in corneas with anterior against-the-rule (ATR) astigmatism; and (3) much individual variability occurs in posterior corneal astigmatism, exceeding at extremes over 0.5 D.

## Selection of Toric IOL Toricity

Several approaches are available to guide the selection of IOL toricity:

- **Baylor Toric IOL Nomogram:** Using regression analysis,<sup>31</sup> we developed the Baylor Nomogram (Table 5.5.1). It provides a clinical method to compensate for posterior corneal astigmatism as a function of the meridian and magnitude of anterior corneal astigmatism.
- **Abulafia–Koch Formula:** Based on outcomes of patients implanted with toric IOLs, Abulafia–Koch<sup>32</sup> proposed an improved regression formula to refine the precision of incorporating the posterior corneal astigmatism into toric IOL planning. This has been incorporated in the new Hill-RBF calculator that is available on the Lenstar.

**TABLE 5.5.1 Baylor Toric IOL Nomogram<sup>a</sup> (Postoperative Target: Up to 0.40 D With-the-Rule Astigmatism)**

Effective IOL Cylinder Power at Corneal Plane (D)	WTR (D)	ATR (D)
0 <sup>b</sup>	≤1.69 (PCRI)	<0.39
1.00	1.70–2.19	0.40 <sup>a</sup> –0.79
1.50	2.20–2.69	0.80–1.29
2.00	2.70–3.19	1.30–1.79
2.50	3.20–3.69	1.80–2.29
3.00	3.70–4.19	2.30–2.79
3.50	4.20–4.69	2.80–3.29
4.00	4.70–5.19	3.30–3.79

ATR, Against-the-rule astigmatism; D, diopter; PCRI, peripheral corneal relaxing incision; WTR, with-the-rule astigmatism.

<sup>a</sup>Values in the table are the vector sum of the anterior corneal and surgically induced astigmatism.

<sup>b</sup>If an SN6AT2 is available, consider implanting it in WTR astigmatism of 1.40–1.69 D, and in ATR of 0.30–0.49 D (in this latter case, T3 would be implanted in astigmatism ranging from 0.50–0.79 D).

- **Barrett Toric Calculator:** This calculator predicts posterior corneal astigmatism based on regression analysis in patients implanted with toric IOLs.
- **Holladay Toric Calculator:** With this calculator, IOL spherical power and the predicted ELP in each eye are used to estimate the effective IOL cylinder power at the corneal plane. It has the option to use the Baylor nomogram to take into account posterior corneal astigmatism.
- **Toric calculators provided by manufacturers:** The Alcon toric calculator uses the Barrett toric calculator. The Johnson & Johnson toric calculator is based on outcomes of their clinical studies combined with the Baylor nomogram. The PhysIOL toric calculator integrates the Abulafia–Koch formula to account for posterior corneal astigmatism when standard keratometry are used.

When selecting the IOL toricity, several factors must be taken into account:

- The cylindrical power of the toric IOL should be chosen based on the total corneal astigmatism, taking into consideration anterior and posterior corneal astigmatism and surgically induced astigmatism.
- The impact of ELP and IOL power on the effective cylinder power of the IOL at the corneal plane should be considered. Effective toricity of the IOL diminishes with increasing ACD and lower IOL spherical power.
- It is desirable to leave patients with a slight WTR astigmatism due to the normal tendency for corneal astigmatism to drift ATR with advancing age.<sup>33</sup>

Abulafia et al.<sup>34</sup> reported that with the Barrett toric calculator, 75% and 100% of eyes were within  $\pm 0.50$  D and  $\pm 1.00$  D of the predicted residual astigmatism, respectively. In another study, Abulafia et al.<sup>32</sup> evaluated and compared the accuracy of two toric IOL calculators (the original Alcon toric calculator and the Holladay toric calculator) with or without the Abulafia–Koch formula. Results showed that adjustment of these commercial toric IOL calculators by the Abulafia–Koch formula significantly improved the prediction of postoperative astigmatic outcome with 76.9%–78.2% of eyes within  $\pm 0.5$  D and 97.4%–98.7% within  $\pm 1.00$  D.

## Imaging and Guidance Systems for Toric IOL Alignment

Accurate toric lens alignment at the desired meridian is crucial to achieve effective astigmatism correction. When a toric IOL is misaligned, a reduction occurs in the cylinder correction along the desired meridian and induction of cylinder at a new meridian.

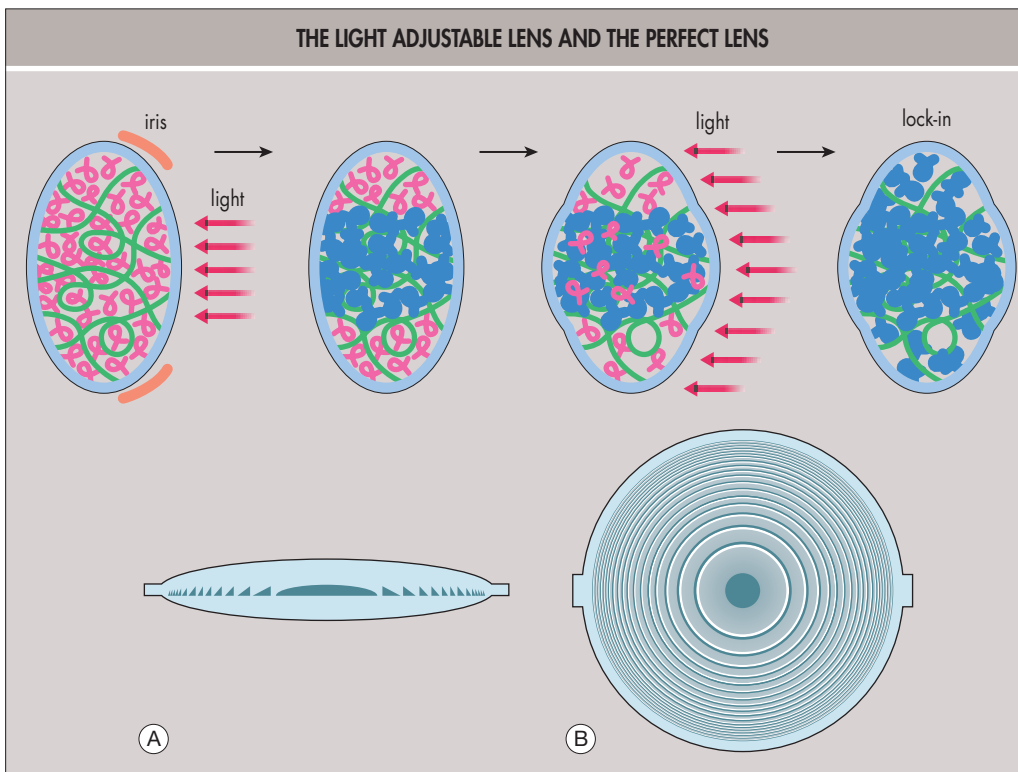
Traditionally, the eye is manually marked preoperatively. With advances in technology, several imaging and guidance systems for toric IOL alignment have been developed:

- **TrueVision 3D visualization and guidance system (TrueVision 3D Surgical, Santa Barbara, CA):** The Cassini topographer (i-Optics, The Hague, Netherlands) is used to obtain an image of the patient's eye preoperatively. This source image is then uploaded to the TrueVision system in the operating room for intraoperative registration.

In a recent study, we evaluated the accuracy of toric IOL alignment in femtosecond laser-assisted cataract surgery using the TrueVision system compared with manual marking combined with femtosecond laser marks.<sup>35</sup> No significant difference existed between these two methods.

- **Callisto eye system (Carl Zeiss Meditec, Jena, Germany):** Preoperatively, an image of the eye is taken along with keratometry measurements using the IOLMaster. Both the reference images and keratometry data are transferred to the Callisto eye computer-assisted surgery system. The toric assistant feature, Z ALIGN, uses the reference axis from the IOLMaster and the projected target axis in the microscope eyepiece to ensure toric IOL alignment.
- **VERION image guided system (Alcon Laboratories, Ft. Worth, TX):** This system is composed of the Reference Unit and the Digital Marker. The Reference Unit measures both keratometry and pupil size and captures a high-resolution reference image of the eye that is used for intraoperative tracking and registration. The Digital Marker uses the preoperative image and intraoperative registration to guide toric IOL alignment.

Elhofi and Helaly<sup>36</sup> compared clinical outcomes following toric IOL alignment with digital image guidance using the VERION and manual slit-lamp-assisted preoperative marking. The use of the VERION system resulted in less postoperative deviation from the targeted astigmatic axis.



**Fig. 5.5.4 The Light Adjustable Lens and the Perfect Lens.** **Top:** Exposure to targeted ultraviolet light in the Light Adjustable Lens resulting in a predictable shape change and subsequent locking of the treatment. **Bottom:** (A) Side view of the Perfect Lens and (B) top view of the Perfect Lens. The concentric diffractive zones are visible.

All of these automated systems using anatomic or topographic landmarks to guide toric IOL alignment seek to decrease the inherent error associated with preoperative manual marking alone. As our study showed, manual marking can achieve accuracy that matches the automated systems, but the latter clearly have the advantage of greater convenience. However, there is still a need for clinical studies assessing the efficacy of each of these systems.

## INTRAOPERATIVE WAVEFRONT ABERROMETRY

Intraoperative wavefront aberrometry is a tool designed to fine-tune cataract surgery results through aphakic refraction. It allows the surgeon to confirm or revise the IOL power, confirm or rotate the toric IOL meridian, titrate limbal relaxing incisions, and open penetrating relaxing incisions. Currently, there is only one commercially available device:

- **Optiwave Refractive Analysis (ORA) system (WaveTec Vision Systems Inc, Aliso Viejo, CA):** Using infrared light and Talbot-Moiré interferometry, the ORA system measures the aphakic refraction intraoperatively after cataract extraction. The system calculates the optimal IOL power based on the aphakic spherical equivalent, the patient's preoperatively measured AL and keratometry, and the estimated ELP using a proprietary algorithm.

In 246 myopic LASIK/PRK eyes, Ianchulev and colleagues<sup>37</sup> reported that ORA achieved the greatest predictive accuracy compared to Haigis-L and Shammas method, with 67% of eyes within 0.5 D and 94% within 1.00 D of the predicted outcome. Fram et al.<sup>38</sup> compared the accuracy of ORA, OCT-based formula, Haigis-L, and Masket formula in LASIK/PRK eyes. There was no significant difference among the methods.

The aphakic refractive data obtained with intraoperative aberrometry devices take into account a variety of factors, such as the posterior corneal astigmatism. However, these measurements have two limitations: (1) ELP cannot be measured with these devices and has to be estimated, and (2) the cornea and perhaps other factors have been modified by the drops and surgical trauma. Further studies are desirable to evaluate the performance of intraoperative wavefront aberrometry in patients undergoing cataract surgery.

## POSTOPERATIVE IOL ADJUSTMENT

The "holy grail" in this field may be an adjustable IOL. Once the postoperative refraction has stabilized, the IOL could be modified to eliminate the residual spherical and astigmatic refractive errors and residual

higher-order aberrations. Ideally, such an IOL could be modified multiple times to adapt to patient's changing visual needs and to compensate for aging changes of the cornea.

The Light Adjustable Lens (LAL; Calhoun Vision, Pasadena, CA) (Fig. 5.5.4) enables residual spherical and cylindrical errors to be corrected or adjusted after the postoperative refraction has stabilized.<sup>39–41</sup> In 34 myopic LASIK/PRK eyes, Brierley<sup>39</sup> reported that LAL produced refractive prediction errors within 0.25 D in 74% of eyes, 0.50 D in 97% of eyes, and 1.00 D in 100% of eyes. Villegas and colleagues<sup>40</sup> found that the combination of two light adjustments induced a maximum change in spherical power of the LAL of between  $-1.98$  D and  $+2.30$  D and in astigmatism of up to  $-2.68$  D with axis errors below  $9^\circ$ .

Another adjustable IOL under development is the Perfect Lens (Perfect Lens, LLC, Irvine, CA) (see Fig. 5.5.4). This technology involves using a femtosecond laser to modify the hydrophilicity and thus the refractive index and refractive characteristics of defined zones within a standard IOL. Changing the relative heights and profiles of the concentric refractive zones with the femtosecond laser enables modification of IOL spherical aberration, asphericity, toricity, and multi-focality with a repeatable, in-office procedure. In a study by Sahler et al., Perfect Lens technology altered the power of the IOL to within 0.1 D of the targeted change without decreasing the optical quality of the lens.<sup>42</sup>

## CONCLUSION

Optical biometry is the clinical standard for ocular biometry. With advanced IOL power calculation formulas, the accuracy of IOL power prediction has improved dramatically in recent years. However, refractive surprises still occur, especially in eyes with previous corneal refractive or endothelial replacement surgery.

In these challenging cases, we warn patients of IOL power calculation inaccuracy and the possible need for additional surgery, with its associated cost. The most prudent strategy for the surgeon may be to obtain IOL calculations using several different methods and select the IOL power based on the consensus of multiple methods. Future advances are needed in all areas, including methods of measuring corneal power, predicting effective lens position, and calculating the lens power.

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# Indications for Lens Surgery/Indications for Application of Different Lens Surgery Techniques

Frank W. Howes

## 5.6

**Definition:** Surgery to the crystalline lens of the eye.

### Key Features

- Lens surgery is the most common eye operation.
- Technical indications for lens surgery are divided into two main categories: medical and optical.
- All lens surgery for whatever indication should be considered refractive surgery.

## INTRODUCTION

The indications for lens surgery today may be classified into two main categories:

- Medical – surgical or pathological indication, and
- Optical – or refractive lens exchange.

Medical indications arise from pathological states of the lens of varying causes, usually related to lens clarity, lens position, or other lens-related conditions, such as inflammation, glaucoma, or the threat of glaucoma. Surgical or pathological indications have existed for centuries, if not millennia, and are generally indisputable. Refractive indications for lens surgery, in contrast, include clear lens ametropic refractive states. The current high standards of lens surgery in terms of safety, accuracy, and customization have opened a new world of refractive correction for many patients who were previously considered untreatable. Lens surgery has found an indisputable position in refractive surgery among the various competitors of laser surgery, phakic IOL (intraocular lens) surgery, and incisional corneal surgery. As customization has improved for each age group and each refractive error group, so have the various treatment modalities expanded or contracted with respect to patient safety and accuracy of outcome.

## MEDICAL INDICATIONS FOR LENS SURGERY

### Lenticular Opacification (Cataract)

The medical indications for lens surgery (Box 5.6.1) are true pathological states, some of which may threaten the integrity of the whole organ (the eye). They also interfere with a major ocular function: focused vision. Lenticular malformation and opacification obstruct the pathway of light; reduce the available quantity of light; scatter light off axis; reduce contrast sensitivity; diminish color intensity; reduce resolution acuity; may alter lens texture in such a way as to contribute to a decrease in accommodation amplitude, particularly in the case of presenile nuclear sclerosis; and, in the case of progressive nuclear sclerosis, often result in a myopic alteration of a previously stable lifelong refractive state.

It is generally agreed that surgical intervention is indicated when there is “functional” visual impairment.

The boundary between refractive surgery and cataract surgery remains somewhat blurred, especially in view of the variable nature of what patients deem loss of “functional” vision. A boundary, however, is necessary for the

### BOX 5.6.1 Medical Indications for Lens Surgery

- I. Lenticular opacification (cataract)
- II. Lenticular malposition
  - A. Subluxation
  - B. Dislocation
- III. Lenticular malformation
  - A. Coloboma
  - B. Lenticonus
  - C. Lentiglobus
  - D. Spherophakia
- IV. Lens-induced inflammation
  - A. Phacotoxic uveitis (phacoanaphylaxis)
  - B. Phacolytic glaucoma
  - C. Phacomorphic glaucoma
- V. Lenticular tumor
  - A. Epithelioma
  - B. Epitheliocarcinoma
- VI. Facilitatory (surgical access)
  - A. Vitreous base
  - B. Ciliary body
  - C. Ora serrata

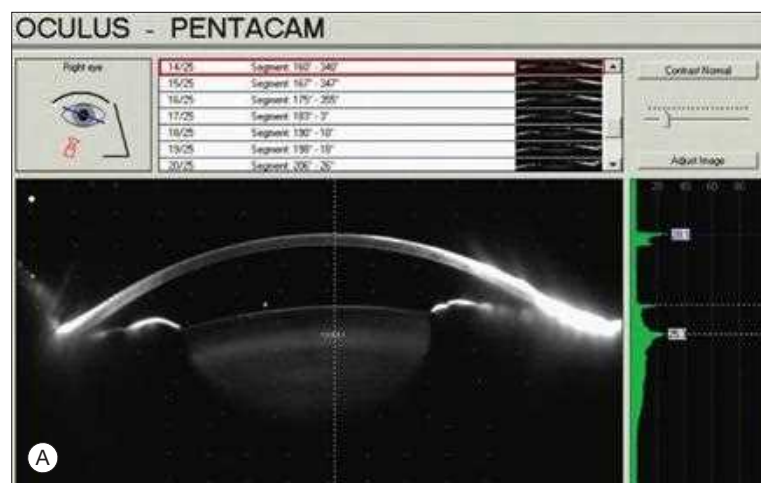
separation in terms of insured payments. The degree to which the opacification obstructs light can, additionally, be measured by laser interferometry.<sup>1</sup> Progressive changes in cataract density over time can be documented by slit-lamp estimation using the Lens Opacification Classification System (LOCS-III) devised by Chylack and coworkers,<sup>2</sup> by Scheimpflug photography of nuclear cataracts<sup>3</sup> and by Neitz-Kawara retroillumination photography of posterior sub-capsular cataracts.<sup>4</sup> A useful figure to use for cataract/noncataract separation is approximately 20% opacification on Pentacam Scheimpflug densitometry (Fig. 5.6.1).<sup>5</sup>

### Cataract in the Presence of Other Ocular Disorders

The decision regarding whether and when to remove a cataract in an otherwise healthy eye usually depends on the impact of the cataract on the visual function of the eye and the impact of that level of visual impairment on the person's life. The status of the other eye also is important. In healthy eyes whose only disorder is cataract, the presumed outcome after uncomplicated surgery is better vision than before surgery. Indeed, in high-volume cataract units, a success rate of 98% can be expected. Thus when one applies a risk-benefit ratio with such a high degree of success, surgery is usually the mutually agreed upon course.

However, such may not be the case when the cataract is associated with other disorders, especially if they are contributing factors to the loss of vision of an eye. Therefore, such conditions as amblyopia, corneal opacification, vitreous opacification, maculopathy, retinopathy, glaucoma, and optic neuropathy may alter or delay the decision to operate, based not so much on the expected risks but rather on the limited benefits. In some cases, lens surgery is indicated to preserve peripheral vision only for functional ambulation. In other cases, maintenance of a posterior segment view for treatment purposes in progressive posterior segment conditions is an indication for lens surgery, even when the expectation for visual





**Fig. 5.6.1** Pentacam Scheimpflug densitometry (A) and slit-lamp imagery of Lens Opacification Classification System III NO3 cataract (B). (Courtesy Dr Lee Lenton, Vision Eye Institute Australia.)

improvement may be minimal.<sup>11</sup> Also, if the other eye is blind, the surgery may be delayed.

Systemic conditions may play a role in deciding whether and when to remove a cataract. Is the patient's diabetes under control? Has there been a stroke with hemianopia? Is the patient on systemic anticoagulants? Is the patient terminally ill or immunologically suppressed? Does the patient have Alzheimer's disease or severe co-operation difficulty?

Thus, the decision to remove a cataract may become a collaborative endeavor, with participation by the patient, the patient's family, the patient's primary physician, the surgeon, a governmental agency, and a third-party payer. The decision, therefore, is determined not only by technological findings and expectations, but also by a "holistic" evaluation of the impact of such a decision on that person's life, as defined by that society. Various tests are available to assess degrees of disability, such as the Visual Function Index (VF-14)<sup>6-9</sup> or the Activities of Daily Vision Scale (ADVS).<sup>10,11</sup>

## Lenticular Malposition

Subluxation (the displacement of the lens within the posterior chamber) and dislocation (displacement of the lens out of the posterior chamber into the anterior chamber or vitreous) of the lens are different degrees of the same phenomenon and result from dysfunction of the zonules. The zonules may be defective as a result of congenital malformation, total or partial agenesis, or a hereditary metabolic disorder, such as Marfan's syndrome. Chronic inflammation and pseudoexfoliation have been shown to be associated with a weakness in the zonular fibers or their attachments. Ocular trauma is an obvious cause. Subluxation, in the absence of associated sequelae, may not be visually significant and may not be an indication for lensectomy. Similarly, complete dislocation of an intact lens into the inferior vitreous may be a quiescent event in the absence of inflammation and may simply produce a state of refractive aphakia, correctable nonsurgically with a spectacle or contact lens or surgically with IOL implantation. Subluxation to the extent that the equator of the lens is visible in the mid-sized pupil is usually visually significant, causing glare, fluctuating vision, and monocular diplopia. This symptom complex would qualify for lens surgery.

## Lenticular Malformation

These conditions of abnormal lens development are congenital. They may be genetic, hereditary, or the result of intrauterine infection or trauma. These conditions include lens coloboma, lenticonus, lentiglobus, and spherophakia, as well as varieties of congenital cataract, such as rubella and Lowe's syndrome. Partial iris coloboma or total aniridia, whether congenital, traumatic, or surgical, may be an indication for lens surgery to improve visual function or for cosmesis. The availability of aniridia IOLs (Fig. 5.6.2A) and opaque endocapsular rings (see Fig. 5.6.2B,C) offers great improvements for such patients.

The indications for surgery depend on the degree to which the specific malformation interferes with vision or the integrity of the involved eye. Such abnormalities may be associated with amblyopia. Early detection and surgical intervention should be incorporated with a plan for amblyopia therapy.

## Lens-Induced Ocular Inflammation

Phacoanaphylactic endophthalmitis (phacotoxic uveitis) occurs in an immunologically mature and competent host and is related to physical or chemical disruption of the lens capsule. Surgery may be the appropriate treatment for this form of ocular inflammation.

## Lens-Induced Glaucoma

### Inflammatory Glaucoma (Phacolytic Glaucoma)

Phacolytic glaucoma occurs in an eye with a mature lens in which the lens capsule is intact. Denatured, nonantigenic liquefied lens material leaks out through the intact lens capsule and elicits a macrophagic, inflammatory reaction. The macrophages, engorged with lens material, clog the open angle, leading to a secondary open-angle glaucoma. Removal of the lens and intraocular lens placement is usually curative, obviating the need for other forms of medical or surgical pressure management.

### Pupil Block and Angle Closure (Phacomorphic Glaucoma)

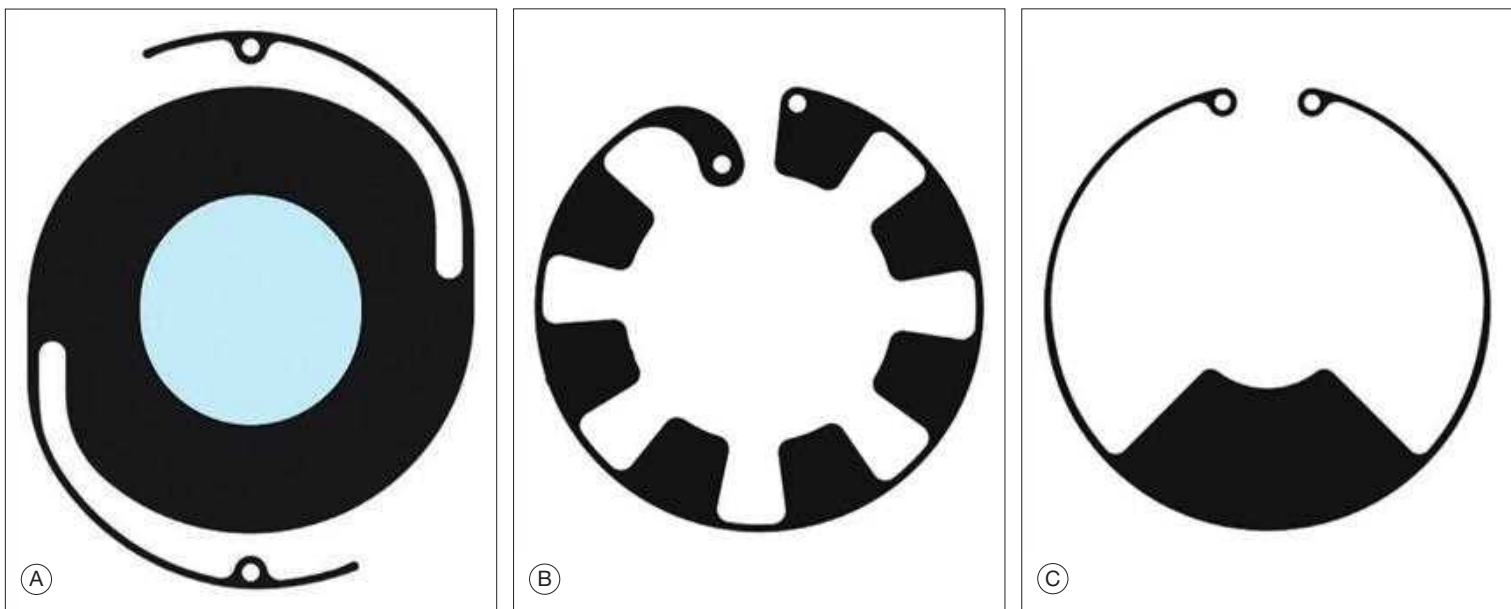
Similarly, removal of the lens in this instance is also curative. The growth of the lens with age progressively engulfs anterior segment space and may ultimately lead to acute angle-closure glaucoma through the mechanism of pupillary block. This is more likely in hyperopic eyes due to the short axial length and already crowded anterior segments. Lens removal and replacement with an intraocular lens greatly increases anterior segment space and in most instances resolves the glaucoma.

## REFRACTIVE INDICATIONS FOR LENS SURGERY

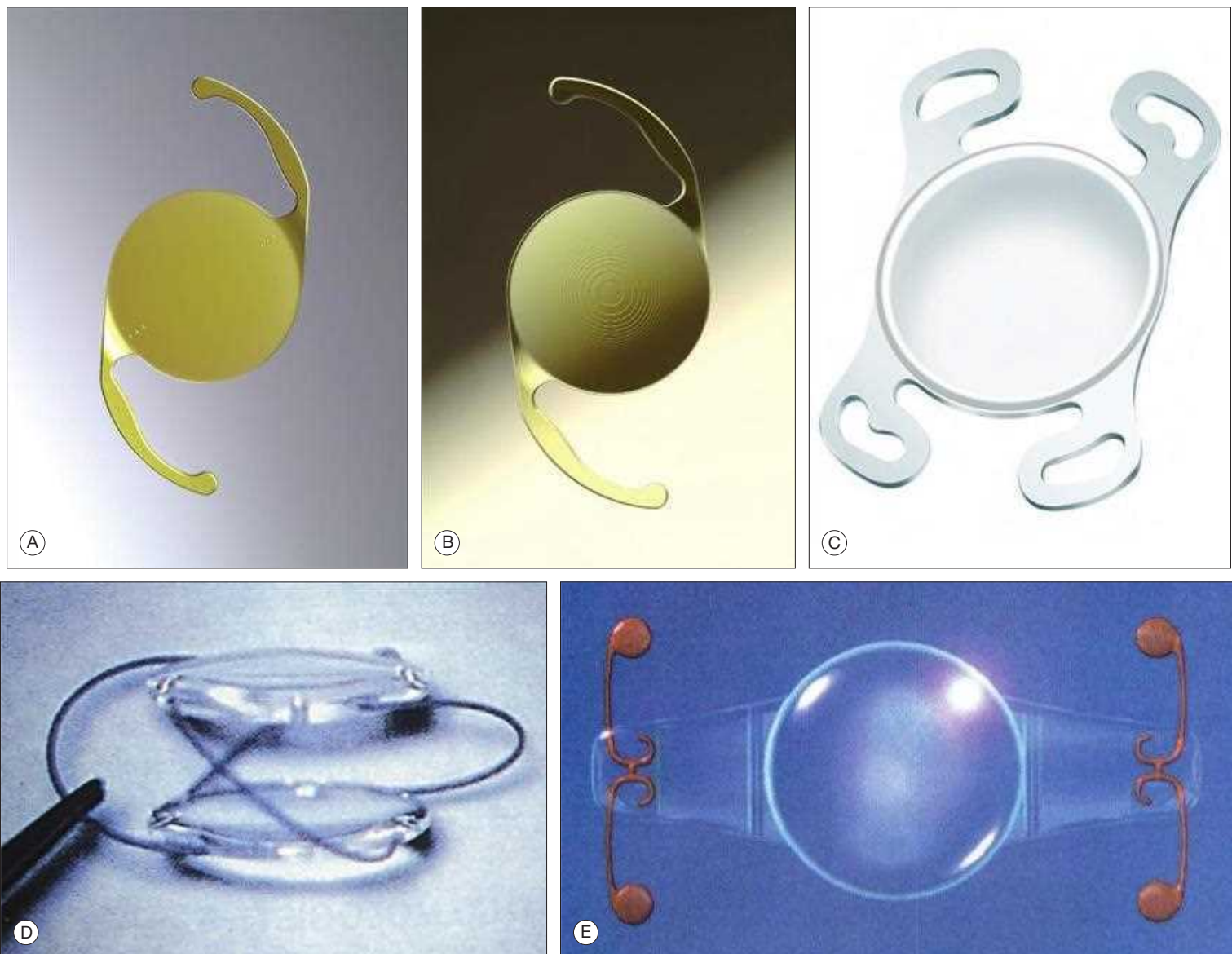
Refinements in measurement technology, ocular anesthesia, incision technology, lensectomy techniques, ophthalmic viscosurgical devices (OVD) tissue protection, and IOL technology has allowed the accurate and successful correction of refractive errors.

Almost all the operable tissues and spaces of the eye have, over decades, come under investigation as locations for refractive surgical modulation: corneal epithelial surface, corneal stroma, corneal endothelial surface, anterior chamber, iris, pupil, posterior chamber, lens, and sclera. The lens, therefore, assumes its role among the others as a popular location for surgical refractive modulation, sparing the other tissues where appropriate or necessary.

Clear lens replacement stands as a viable procedure today for both myopia and hyperopia, with the abilities now to control astigmatism (Fig. 5.6.3A),



**Fig. 5.6.2 Iris Defect Prostheses.** (A) Aniridia intraocular lens with opaque peripheral "pseudiris." (B) Aniridia endocapsular ring. (C) Iris coloboma endocapsular ring (diaphragm type 96G). (Courtesy Morcher, GmbH, Germany.)



**Fig. 5.6.3 Older and Modern Intraocular Lens Modifications Providing Functions Additional to Pure Spherical Dioptric Correction.** (A) Alcon toric IOL with blue light filter (from AcrySof IOL). (B) Alcon multifocal IOL with apodized rings also with blue light filter (from AcrySof IOL). (C) Bausch and Lomb (B&L) Akreos aspherical IOL. (Courtesy B&L Australia). (D) Older-style accommodative polymethyl methacrylate polypseudophakic intraocular lens (Courtesy T. Hara). (E) The C&C Vision CrystaLens model AT-45 silicone multipiece intraocular lens. (Courtesy C&C Inc.)

modulate higher-order aberration (see Fig. 5.6.3C), and reduce presbyopic symptoms (see Fig. 5.6.3B,E). Patient demand for these services has increased dramatically in recent times.

Multifocal IOLs (see Fig. 5.6.3B) represent some of the first attempts at the intraocular correction of presbyopia. Other attempts at the development of a truly accommodative pseudophakos have included the intracapsular injection of liquid silicone<sup>12-14</sup> and the intracapsular placement of high-water-content poly-HEMA lenses,<sup>15</sup> a liquid silicone-filled intracapsular balloon,<sup>16,17</sup> multiple IOLs (polypseudophakia)<sup>18,19</sup> (see Fig. 5.6.3D), and the flexing haptic accommodative IOLs (see Fig. 5.6.3E).

## INDICATIONS FOR DIFFERENT LENS SURGERY TECHNIQUES

Surgery affecting the human lens can be organized historically by its chronology of development (Table 5.6.1) or divided into four major categories by technique (Box 5.6.2). The indications for a particular lens surgery technique may be determined by several factors (Box 5.6.3). Different medical conditions or pathological states of the eye and the lens may favor one technique over another. In some countries, the availability of equipment and the level of training of the surgeon may be factors that dictate technique. Certain countries have governmental agencies, professional organizations, academic institutions, insurance payers, or surgical facilities that regulate and control the types of surgical techniques surgeons may perform. For the purpose of this text, however, only specific medical or pathological conditions of the eye are discussed as factors determining the choice of surgical technique.

### Intracapsular Cataract Extraction

The intracapsular cataract extraction (ICCE) method of lens removal has not been the procedure of choice in industrialized nations since the

**TABLE 5.6.1 History of Cataract Surgery Techniques**

Year	Technique	Place	Surgeon
800	Couching	India	Unknown
1015	Needle aspiration	Iraq	Unknown
1100	Needle aspiration	Syria	Unknown
1500	Couching	Europe	Unknown
1745	ECCE inferior incision	France	Daviel
1753	ICCE by thumb expression	England	Sharp
1860	ECCE superior incision	Germany	von Graefe
1880	ICCE by muscle-hook zonulysis and lens tumble	India	Smith
1900	ICCE by capsule forceps	Germany	Verhoeff Kalt
1940	ICCE capsule suction erysiphake	Europe	Stoewer I. Barraquer
1949	ECCE posterior chamber IOL and operating microscope	England	Ridley
1951	Anterior chamber IOLs	Italy Germany	Strampelli Dannheim
1957	ICCE by enzyme zonulysis	Spain	J. Barraquer
1961	ICCE by capsule cryoadhesion	Poland	Krawicz
1967	ECCE by phacoemulsification	United States	Kelman J. Shock
1975	Iris-pupil supported IOLs	Netherlands	Binkhorst Worst
1984	Foldable IOLs	United States South Africa	Mazzocco Epstein

ECCE, Extracapsular cataract extraction; ICCE, intracapsular cataract extraction; IOL, intraocular lens.

### BOX 5.6.2 Lens Surgery Techniques

- I. Lens repositioning (“couching”)
  - A. Extracapsular
  - B. Intracapsular
    1. Physical (instrumental) zonulysis
    2. Pharmacological (enzymatic) zonulysis
- II. Lens removal
  - A. Total (intracapsular)
    1. Capsule forceps
    2. Suction erysiphake
    3. Cryoextraction
  - B. Partial (extracapsular)
    1. Anterior capsulotomy/capsulectomy
      - a. Discontinuous
      - b. Continuous (capsulorrhexis)
      - c. Linear
    2. Nucleus removal
      - a. Assembled delivery (large incision)
        - (1) Expression (“push”)
        - (2) Extraction (“pull”)
      - b. Disassembled extraction
        - (1) Phacosection
        - (2) Phacoemulsification-aspiration
          - (a) Ultrasound
            - (i) linear
            - (ii) torsional
          - (b) Laser
          - (c) Water jet
          - (d) Impeller
      3. Cortex removal
        - a. Irrigation
        - b. Aspiration
  - III. Lens replacement (intraocular lens implantation)
    - A. Locations
      1. Anterior chamber
        - a. Angle fixation
        - b. Iris fixation
      2. Pupil
      3. Posterior chamber
        - a. Iris fixation (sutured or enclavated)
        - b. Ciliary sulcus (sutured or unsutured)
    4. Lens capsule
      - a. Anterior capsule
        - (1) Haptic sulcus/optic bag
        - (2) Optic posterior chamber/haptic bag
      - b. Intracapsular (“in the bag placement”)
      - c. Posterior capsule (haptic bag/optic Berger’s space)
    5. Pars plana (sutured)
  - B. Optic materials
    1. Hydrophobic
      - a. Polymethyl methacrylate (PMMA)
      - b. Silicone
      - c. Acrylic
    2. Hydrophilic
      - a. Poly hydroxyethyl methacrylate (poly-HEMA)
      - b. Acrylic
      - c. Collagen-copolymer
  - C. Optic types
    1. Monofocal
      - a. Spherical
        - (1) Plus
        - (2) Minus
      - b. Toric
      - c. Telescopic
      - d. Prismatic
    2. Multifocal
    3. Accommodative
- IV. Lens enhancement: reversal of presbyopia by scleral expansion
  - A. Ciliary cerclage
  - B. Radial anterior ciliary sclerotomy



development of modern extracapsular techniques in the late 1970s, primarily because of lower rates of postoperative posterior segment complications such as hemorrhage, vitreous loss, retinal detachment, and cystoid macular edema. Current indications for planned intracapsular cataract surgery are therefore related only to situations where zonular laxity or deficiency exists and where capsular bag instability is predicted. Under these circumstances, safe and successful extracapsular surgery with intra-ocular lens implant, is often unlikely. Conditions likely to be associated with these conditions are physical trauma to the eye, diseases processes such as Marfans Syndrome and psuedoexfoliation, and isolated congenital anomalies. Significant subluxation or dislocation of the crystalline lens necessitates removal of the entire organ, done either by intracapsular cataract surgery or by pars plana fragmentation and aspiration.

Traditionally, ICCE involved removal of the complete intact lens through a large incision measuring 12–14 mm. In earlier years these eyes were left aphakic, with aphakic spectacle correction offered where available. Bilateral surgery was invariably necessary to minimize aniseikonic problems, although contact lens correction was satisfactory. Many of these eyes have subsequently had secondary IOLs implanted, with the choice of IOL being angle based, iris fixed (anterior or posterior) (see Fig. 5.6.4A), or sutured to the ciliary sulcus.

Modern sulcus fixation IOLs now have design features that enable them to fibrose into the ciliary processes and sulcus (Fig. 5.6.4B), minimizing the chances of posterior dislocation common in previous sulcus fixation IOLs. In addition, these lenses are foldable, allowing small-incision

surgery and adherence to the principles of astigmatism avoidance and correction. In the majority of primary situations for ICCE, the wound needs to be large and hence constructed appropriately for minimization of astigmatism induction.

## Extracapsular Extraction (Large-Incision Nuclear Expression Cataract Surgery)

This technique became popular in the 1980s, as surgeons who had been performing large-incision ICCE and anterior chamber implantation desired the benefits derived from an intact posterior capsule and posterior chamber implantation. The technique persists today and is performed in large numbers, particularly in developing countries, where the more advanced small-incision techniques of phacoemulsification (phaco) and foldable lens implantation are not yet available for the masses.

The only indications for nuclear delivery now relate to (1) hard nuclei that cannot be safely emulsified by phaco and (2) capsule rupture with vitreous presentation mid procedure. Cataracts with high-risk corneas (e.g., Fuchs' endothelial dystrophy, corneal graft) were previously considered to be best dealt with by nuclear expression via continuous linear capsulotomy and intercapsular techniques.<sup>20,21</sup> With optimal use of OVDs ("soft shell")<sup>22</sup> and good technique,<sup>23</sup> however, small-incision procedures are now the procedure of choice.

## Small-Incision Nuclear Expression Cataract Surgery ("Mini-nuc" and Other Techniques)

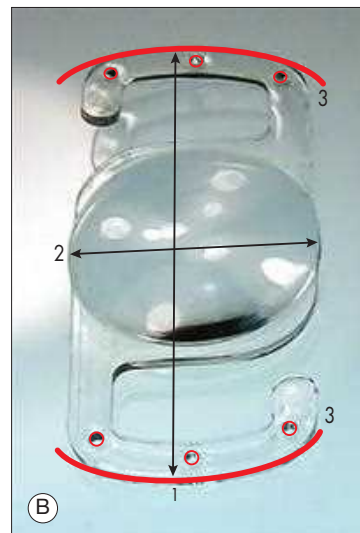
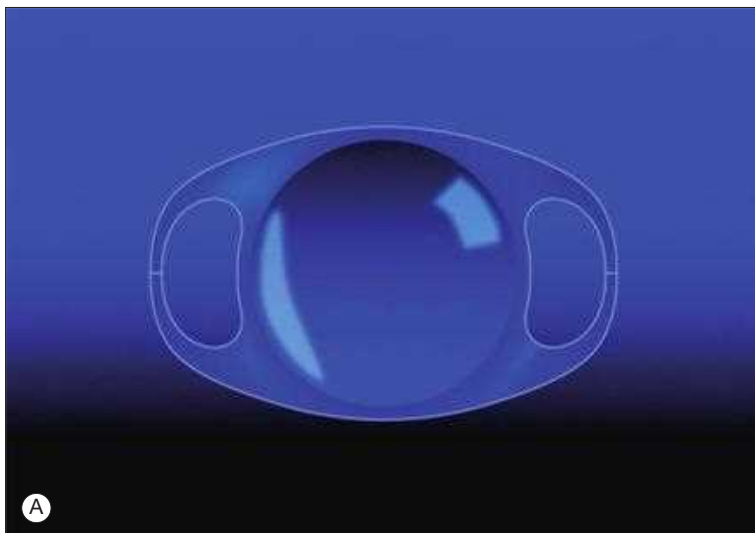
The indications for these techniques<sup>24,25</sup> relate in the majority to the benefits of smaller incision surgery. Socioeconomic factors and instrumentation availability together with surgeon experience also play a significant part in the choice of this type of surgery.

## Phacoemulsification

This technique of nucleus removal has been performed through incisions ranging from 3.2 mm down to less than 1.0 mm. Combined with foldable lens implantation, the major advantage of phaco is the small incision. Many phaco techniques have been described (Box 5.6.4), as have some nonultrasound techniques<sup>26,27</sup> (of which very few can compete with ultrasound). Current techniques use phaco through self-sealing, sutureless scleral and clear corneal incisions measuring 1.9–3.2 mm. The smaller incisions are astigmatically neutral. These corneal incisions, if made on the steep axis of astigmatism and made wider or moved centrally from the limbus, can be used to titrate the amount of astigmatic correction. These effects can be doubled by making similar incisions on the opposite side of the steep axis on the cornea as well (see Table 5.6.2). The presence therefore of corneal cylinder is an indication for phaco and foldable lens implantation just as is the absence of corneal cylinder. The newest of the cataract surgery techniques involves a combination of techniques, using femtosecond laser-assisted phaco, where the femtosecond laser can cut precise corneal incisions, an accurately sized and truly circular capsulorrhexis and partial fragmentation of the lens nucleus, permitting less

### BOX 5.6.3 Lens Removal Techniques: Ocular Indications

- I. Intracapsular extraction
  - A. Zonular absence/dialysis
  - B. Lens subluxation
  - C. Lens dislocation
- II. Nuclear delivery
  - A. Status of cornea
    1. Low endothelial cell count
    2. Guttate dystrophy
  - B. Status of cataract
    1. Brunescant nuclear sclerosis
    2. Cataracta nigra
  - C. Torn posterior capsule during phacoemulsification
  - D. Zonulodialysis
- III. Phacosection
  - A. Same corneal, cataract, and capsular indications as nuclear delivery
  - B. Astigmatism management
- IV. Phacoemulsification
  - A. Status of cornea
    1. Normal endothelial cell count
    2. No guttate dystrophy
  - B. Status of cataract
    1. Immature nuclear sclerosis
    2. Cortical or subcapsular cataract
  - C. Astigmatism management



**Fig. 5.6.4 Examples of Newer Intraocular Lens (IOL) Designs for Use in Eyes Without Capsular Support.** (A) Artisan IOL for iris fixation, either anterior or posterior. (B) FH1000 (Lenstec) hydrophilic acrylic foldable IOL for sulcus fixation by suture with long-term stability by fibrosis through peripheral haptic fibrosis holes shown. The radius of the haptics matches a 13 mm wide sulcus (3) and the optic is reinforced to counteract any torsional forces. Length of IOL: 13.25 mm (1); optic width: 6.0 mm (2).



**Fig. 5.6.5 Capsulotomy and Capsulectomy in Femtosecond Laser Assisted Cataract Surgery.** (Acknowledgments to C. Chan and G. Sutton, Vision Eye Institute, Chatswood, Sydney, Australia.)

#### BOX 5.6.4 Phacoemulsification Techniques

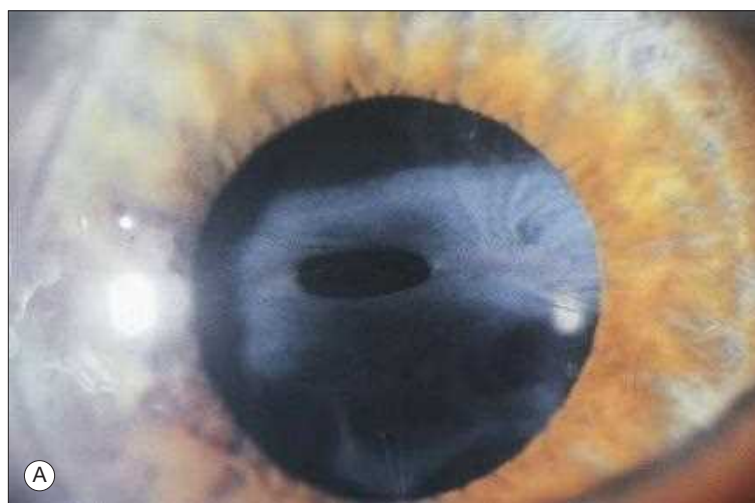
- I. Location
  - A. Anterior chamber (Kelman, Brown)
  - B. Iris plane (Kratz)
  - C. Posterior chamber (supracapsular) (Maloney)
  - D. Capsule (endolenticular, in situ)
    1. Anterior capsulectomy (Sinsky)
    2. Anterior capsulotomy (intercapsular) (Hara)
- II. Techniques
  - A. Carousel
  - B. Chip-and-flip (Fine)
  - C. Phacofracture
    1. Divide-and-conquer (Gimbel)
    2. Four-quadrant pregrooved (Shepherd)
    3. Nonstop chop (Nagahara)
    4. Stop-and-chop (Koch)
    5. Double chop (Kammann)

ultrasonic energy release.<sup>28,29</sup> Where necessary, this technique can be combined with posterior vitrectomy in a safe manner.<sup>30</sup>

### Surgery of the Lens Capsule

The femtosecond laser currently provides the state of the art for capsulectomy. This capsular opening is software guided, so it is perfectly circular and set to a diameter and position of choice (Fig. 5.6.5). The continuous curvilinear capsulorrhexis or CCC<sup>31</sup> remains the capsulectomy of choice when a femtosecond laser is not available. The size of the capsulectomy is usually approximately 4.5–5.5 mm, sufficient to cover the IOL optic edge for “in the bag” placement of an IOL. The continuous margin of the rhexis provides strength for manipulation during surgery, keeps the IOL in the bag away from the iris pigment, and holds the IOL optic and haptic in position for refractive stability and posterior capsular clarity. Where nucleus expression is required (unusual) and the opening is too small for passage of the nucleus,<sup>34</sup> slits in the rhexis margin may be necessary.

Good view with optimal red reflex is necessary to execute a CCC. When lens maturity is such that no or poor red reflex is present, capsular staining with trypan blue or indocyanine green is most helpful for visualization. Discontinuous capsulorrhexis and inadvertent anterior radial tears or posterior capsular tears can cause vitreous presentation and unwanted IOL complications.<sup>32–34</sup> Care is required where the zonule is weak. Capsulophimosis can occasionally be seen where the zonule is weak or damaged with significant CCC contracture (Fig. 5.6.6A and B). Nd:YAG laser anterior capsular widening may be necessary under these circumstances. Capsular contracture can be vigorous and cause the cessation of accommodative effect in most of the accommodating IOLs currently available. The



**Fig. 5.6.6 Anterior Capsular Fibrosis.** (A) Asymmetric and (B) symmetric anterior capsule fibrosis leading to varying degrees of capsular phimosis. (Courtesy John Shephard, MD, Las Vegas, NV.)

contracture occasionally can be asymmetrical and cause refractive shift (the Calhoun light adjustable IOL<sup>35</sup> can combat these shifts). Usually, however, the contracture onto the new-generation square-edged IOLs designed for the capsular bag maintains posterior capsular clarity.<sup>33</sup> Occasionally the lens epithelial cells (LECs) that induce these changes also migrate behind the IOL, causing posterior capsular pearls and opacity and necessitating Nd:YAG posterior capsulectomy (Fig. 5.6.7). Attempts have been made to destroy remaining LECs with various instruments and chemicals<sup>36–41</sup> but without great success in vivo up to now (Box 5.6.5). Where an IOL requires sulcus fixation in proximity to the posterior iris and pigment, a round anterior edge is necessary to prevent iris chafe, pigment dispersion, and secondary inflammation and glaucoma (Fig. 5.6.8).

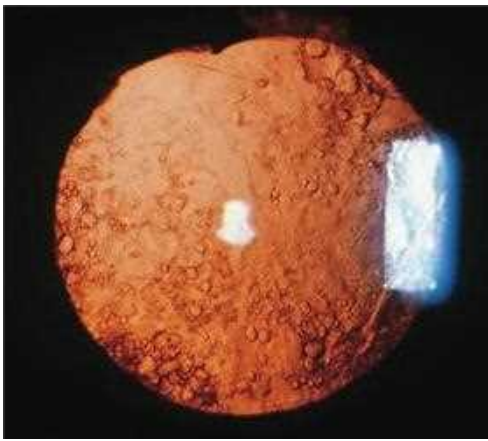
### Zonular Surgery

Maintaining adequate zonular strength as well as capsular bag integrity, as discussed earlier, is vital to the long-term stability of an intraocular lens. Occasionally the zonule is segmentally damaged, causing segmental capsular bag laxity and potential surgical difficulty and IOL decentration. A number of surgeons have devised similar devices to stabilise segmental laxity of the capsular bag. These devices called capsular tension rings are inserted into the the fornix of the capsular bag to provide sufficient tension for intra-ocular lens stability and centration. Cionni (Cincinnati, OH) designed modifications to the polymethylmethacrylate capsule tension rings (CTRs) to allow them to be sutured to the eye wall,<sup>42</sup> thus creating a synthetic “pseudozonule” attached to an intracapsular skeletal-supporting apparatus (Fig. 5.6.9A,B,C).

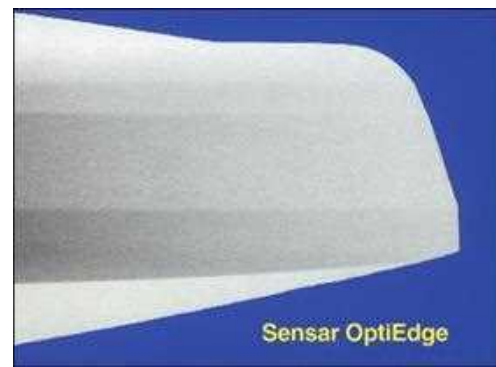
### Surgery for Presbyopia

Many attempts have been made at surgical restoration of accommodation. Many have failed or have had poor outcomes. These range from scleral implants to expand the anterior peripheral sclera in attempts to allow

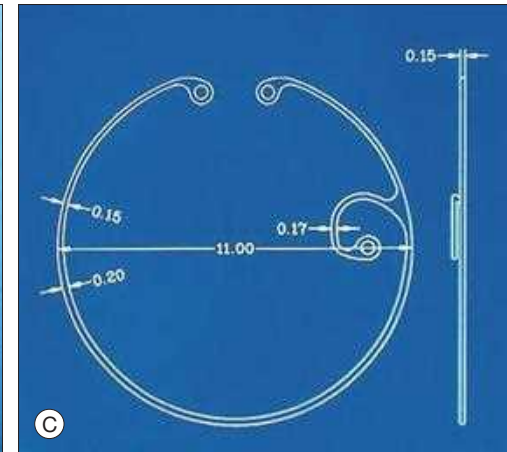
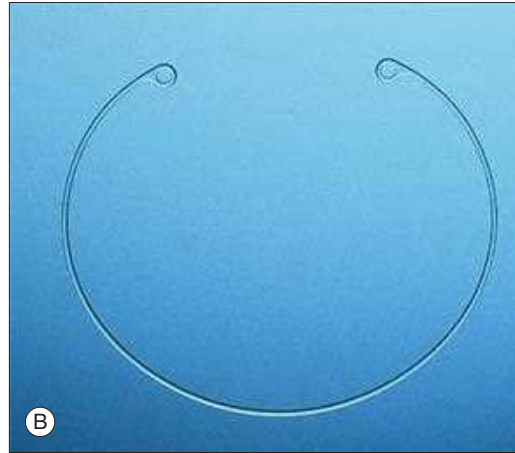
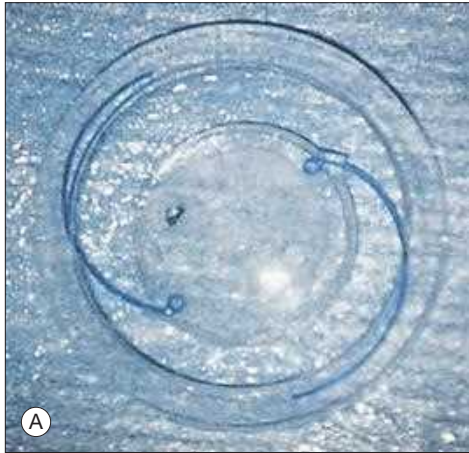




**Fig. 5.6.7** Posterior Capsular Opacification by Lens Epithelial Cell Hyperplasia.



**Fig. 5.6.8** Many Intraocular Lenses Are Now Produced With Squared Posterior Edges to Minimize Lens Epithelial Cell Migration Toward the Visual Axis. This example shows the AMO Sensor AR40e, with rounded anterior edge and squared posterior edge. (Courtesy Abbott Medical Optics Inc.)



**Fig. 5.6.9** Solutions Past and Present for Zonular Deficiency. (A) Complete closed circular, foldable silicone endocapsular ring. (Courtesy T. Hara.) (B) Open polymethyl methacrylate endocapsular ring. (Courtesy Morcher, GMBh, Germany.) (C) Cionni-modified endocapsular ring for suturing to sclera to create a pseudozonule. (Courtesy Morcher, GMBh, Germany.)

### BOX 5.6.5 Lens Epithelial Cell Surgery

- I. Primary procedures
  - A. Mechanical
    1. Capsular polishing
    2. Capsular vacuuming
    3. Capsular vacuuming with ultrasound
    4. Capsular curettage
    5. Capsular cryotherapy
  - B. Pharmacological
    1. Hypotonic hydrolavage
    2. Antimetabolites
    3. Antiprostaglandins
  - C. Immunological
    1. Monoclonal antibodies
  - D. Prophylactic posterior capsulotomy/capsulectomy (CCC)
- II. Secondary procedures
  - A. Invasive
    1. Capsulotomy/capsulectomy (CCC)
    2. Curettage
    3. Vacuuming
  - B. Noninvasive
    1. Nd:YAG laser capsulotomy/capsulectomy

further space for ciliary action, to accommodative IOL designs placed in the capsular bag. These spectacularly well-engineered devices have regrettably performed poorly in the majority. Substances injected into the capsular bag<sup>38</sup> to restore youthful accommodation have yet to reach the commercial market. Monovision and multifocality remain the mainstay of the surgery for presbyopia. These techniques continue to provide the most satisfactory results with appropriate patient selection. Attempts have been made to use pinhole technology to provide a depth of field where neither

near nor distance acuity is compromised (as incorporated into both corneal inlay and intraocular lens by Acufocus) for those who have difficulty with the compromises of multifocality or those who have difficulty with the anisometropia of monovision. These technologies have been slow to gain momentum as the multifocal technology has shown significant improvement in recent times. Some of the surgical IOL companies have modified their multifocal technologies to soften the distance optical aberrations inherent in this technology at the small expense of a near point pushed slightly further out. Because of significant improvement in the optics of these lenses, companies are using new terms for the extended depth of focus these lenses have instead of the term multifocal. Research continues in this field to maintain an extended depth of focus without penalty of aberration.

### Monovision

Monovision is the state of anisometropia geared toward emmetropia in one eye (usually the dominant eye) and near-weighted ametropia (myopia) usually in the nondominant eye. Strictly optically speaking, a myopic outcome of  $-3.00$  diopters (D) would provide a near focal point at 33 cm. This amount of anisometropia would in many instances produce asthenopic symptoms. In practice, patients need only small amounts of residual myopia to be able to read and perform near visual tasks.

The target refraction, which in the nondominant monovision reading eye provides the best reading acuity with the least distance acuity loss and with least anisometropic asthenopia, is between  $-0.75$  D and  $-1.50$  D. This amount of ametropia, particularly when blended with a small amount of aspherical defocus<sup>43</sup> provides the easiest rehabilitation for the monovision patient while maintaining a reasonable amount of near and intermediate visual acuity. In spite of these guidelines, patients should still undergo, at the very least, a loose lens (trial frame) demonstration of the monovision and, at best, a prolonged contact lens simulation of the suggested surgical treatment.

This route maximizes significantly the number of satisfied patients after the surgery.



## Astigmatism

As discussed earlier, the surgeon attending to the needs of the lensectomy patient, whether of medical or refractive indication, needs to maintain a holistic approach to the correction of their patient's problem. The following items need to be considered to optimize the outcome for the patient:

- The removal of the opacity or error in the optical system (the cataract).
- The accurate correction of the optical state of the eye (biometry techniques and formulas, astigmatism induction avoidance, and pre-existing astigmatism correction).
- The execution of the surgery in the safest possible way in the prevailing circumstances to minimize complications (sterility, incision creation and location, wound closure, perioperative antibiotics, surgical technique, etc.) while assessing and attending to these items, ensuring that the best combination of techniques provides the optimal solution for the patient, and that includes maintaining the ability to readdress non-optimal outcomes.

The management of the astigmatism in lens surgery (or any anterior segment surgery) has become an essential and integral part of the execution of the operation.

A number of techniques have been described to control astigmatism, both in minimizing induction and treating pre-existing cylindrical error. The most useful technique that covers the most common astigmatic errors is “on-axis” incision for small-incision surgery (i.e., operative incision placement on the periphery of steep axis of the astigmatism). Other schools of thought suggest that the surgery should be performed with the smallest incision possible (astigmatically neutral), then placing the on-axis incisions in the appropriate meridian, either partial thickness (limbal relaxing incision [LRI]—vertical partial-thickness corneal incisions)<sup>44,45</sup> or penetrating (penetrating astigmatic keratotomy [PAK]—self-sealing, full-thickness, perforating incisions, obliquely orientated through the cornea). PAK is the most effective means of controlling astigmatism but does implicate corneal perforating, the mechanism of the power of the procedure. Keeping the incisions single pass and thus reducing instrument passage enhances the watertight closure, minimizes wound leak, and potentially minimizes infective risk. The power of correction in PAK can be enhanced further by creation of a second keratotomy on the opposite side of the first incision (180° opposed). The effect is greatest with penetration, reaching corrections as high as 6.00–7.00 D of astigmatism with a single pair of incisions. The PAK nomogram listed in Table 5.6.2 demonstrates the titration of the astigmatic corrective effect by variation of incision width against the optical zone radius (OZR—the proximity of the incision to the pupil/astigmatic centrum).<sup>45</sup> In the execution of cylinder correction, the patients' axes must be marked prior to lying down for anesthesia (local, topical, or general) to avoid cyclotorsional error.

TABLE 5.6.2 Penetrating Astigmatic Surgery (PAK) Nomogram

Cyl to Correct	Incision Size (mm)	Distance From Visual Axis (mm)	Opposite Incision Size (mm)	Distance From Visual Axis (mm)
1.00–1.50	3.2	6.0	nil	nil
1.50–2.00	3.2	6.0	3.2	6.0
2.00–2.50	3.5	6.0	3.5	6.0
2.50–3.00	3.5	5.5	3.5	5.5
3.00–3.50	3.5	5.0	3.5	5.0

High levels of astigmatic correction by incision as above can cause secondary higher-order aberration induction (quadrafoil). Now with the availability of a number of different toric IOLs (up to 6 D and built on an aspherical base), all providing a stable astigmatic correction, the need for high-level PAK is no longer present. It should be noted that in the selection of a toric IOL, more than one keratometric/topographic method should be used to ascertain the presence of corneal cylinder for correction. Unnecessary correction or overcorrection of cylinder should be avoided.

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# The Pharmacotherapy of Cataract Surgery

5.7

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**Definition:** Medications used in cataract surgery.

## Key Features

- Pharmacotherapeutic agents are used in the preoperative, intraoperative, and postoperative periods of cataract surgery.
- Preoperative medications are used as mydriatics, prophylactic antibiotics, and anesthetics.
- Intraoperative pharmacotherapeutic agents include irrigating solutions and additives to irrigating solutions, as well as ophthalmic viscosurgical devices and intracameral drugs.
- Postoperative medications include antibiotics, corticosteroids, and nonsteroidal anti-inflammatory drugs.

## INTRODUCTION

With the current ongoing rapid evolution of cataract surgical techniques, corresponding changes in the pharmacotherapeutic management of cataract patients are inevitable. In this chapter, current pharmacotherapeutic practices in the pre-, intra-, and postoperative periods are reviewed.

## PREOPERATIVE MEDICATIONS

Table 5.71 provides a summary of commonly used preoperative pharmacotherapeutic routines for cataract surgery.

## Pupil Dilatation

Sympathomimetic mydriatic agents (phenylephrine 2.5%) and parasympatholytic cycloplegics (tropicamide or cyclopentolate 1.0%) usually are used together before extracapsular nuclear expression, phacoemulsification (phaco), or femtosecond laser-assisted cataract surgery (FLACS). Used excessively, sympathomimetics increase the possibility of a severe systemic hypertensive response with associated systemic risks in older adults.<sup>1</sup> For this reason, phenylephrine 10% is not recommended routinely. To assist adequate pupil dilatation, pilocarpine and other cholinergic miotics should be discontinued 12 to 24 hours before surgery (approximately twice the expected duration of action of the specific agent).

Topical nonsteroidal anti-inflammatory drugs (NSAIDs) are commonly used in cataract surgery to prevent pupillary miosis, reduce surgically induced inflammation, and prevent postoperative cystoid macular edema.<sup>2</sup> NSAIDs inhibit cyclooxygenase, decreasing prostaglandin synthesis from arachidonic acid.<sup>2,3</sup> Prostaglandin E2 (PGE2) enhances the constrictor action of the iris sphincter through a mechanism not dependent on cholinergic receptors.<sup>4,5</sup> Topical flurbiprofen 0.03%, the first agent used for this indication, was demonstrated to be clinically superior to topical indomethacin 1%.<sup>5</sup> Currently, diclofenac 0.1%, ketorolac 0.5%, and nepafenac 0.1% have the same indication.<sup>6</sup> Although diclofenac and flurbiprofen adequately maintain mydriasis during surgery,<sup>7</sup> ketorolac appears to inhibit miosis more effectively.<sup>8</sup>

Intracameral mydriatic solutions using cyclopentolate 0.1%, phenylephrine 1.5%, xylocaine 1% or tropicamide 0.5%, phenylephrine 5%, and diclofenac 0.1%, in preservative-free solutions are safe to the corneal endothelium and effective in producing and maintaining pupillary dilatation and are used in various combinations (Table 5.72).<sup>9–11</sup> Effective redilatation has also occurred with use of these mydriatics intracamerally during surgery on contracted pupils.<sup>12</sup>

**TABLE 5.7.1** Commonly Used Agents in the Routine Preoperative Pharmacotherapy of Cataract Surgery

	Class and Agent	Concentration	Dosage
Nonsteroidal anti-inflammatory drugs to prevent miosis	Diclofenac	0.10%	1 drop 2–4 times over 1 h preceding surgery
	Ketorolac	0.50%	
	Flurbiprofen	0.03%	
	Indomethacin	1%	
	Nepafenac	0.1%	
Cycloplegics	Tropicamide	1%	1 drop 2–4 times over 1 h preceding surgery
	Cyclopentolate	1%	
Mydriatics	Phenylephrine	2.50%	1 drop twice over 0.5 h preoperatively
Antibiotic prophylaxis	Gramicidin-neomycin-polymyxin B	0.025 mg/ml 2.5 mg/ml 10.000 IU/ml	1 drop 2–4 times over 1 h preceding surgery
	Gentamicin	0.30%	
	Tobramycin	0.30%	
	Ciprofloxacin	0.30%	
	Ofloxacin	0.30%	
	Gatifloxacin	0.30%	
	Moxifloxacin	0.50%	
	Trimethoprim-polymyxin B	1 mg/ml (10.000 IU/ml)	
Anesthetic: retrobulbar or parabulbar (use becoming increasingly rare)	Lidocaine	1–2%	3–9 mL
	Mepivacaine	1–2%	
	Bupivacaine	0.25–0.75%	
Anesthetic: intracameral (use becoming increasingly common)	Isotonic, nonpreserved lidocaine	1–2%	0.1–0.6 mL
Anesthetic: topical	Proparacaine	1–2%	1–2 drops prior to surgery, and then every 10 minutes or as needed during surgery
	Tetracaine	0.50%	
	Benoxinate (oxybuprocaine)	0.40%	
	Lidocaine	4%	
	Bupivacaine	0.75%	

**TABLE 5.7.2** Various Popular and Commercially Available Intracameral Mixtures to Achieve Dilatation and Anesthesia

Drug	Behndig IC Mixture (Also Made by Leiter's in USA)	Mydrane®	Xylo-Phe	Phenocaine®
Tropicamide	–	0.02%	–	–
Phenylephrine hydrochloride	1.5%	0.31%	0.08%	0.1%
Lidocaine	1.0%	1%	1%	1%

The above are various popular and commercially available intracameral mixtures to achieve dilatation and anesthesia by injecting as the first step in cataract surgery. The mixture manufactured by Leiter's Pharmacy in the USA is taken from articles by Behndig et al. from Sweden, Mydrane® is manufactured by Thea, in France, and Phenocaine® by Entod UK. Xylo-Phe has been proposed by one of the authors (SAA) to be formulated in the operating room, with details available from the author.

## Anti-infective Prophylaxis

No worldwide consensus exists on prophylactic topical antibiotics in cataract surgery, although their use has been an accepted practice for decades. A large randomized study of preoperative topical antibiotics for the prevention of endophthalmitis has yet to be carried out. The most important source of potential infectious organisms is the patient's own natural conjunctival and skin flora. Intraoperative cultures indicate that 5% of



intraocular surgeries result in measurable anterior chamber contamination from indigenous flora, but the vast majority of patients develop no adverse clinical sequelae.<sup>13</sup> Cultures from the conjunctiva and anterior chamber of patients who subsequently developed endophthalmitis usually yielded the same bacterial strains. Staphylococci (*Staphylococcus epidermidis* and *S. aureus*), diphtheroids (*Corynebacterium*), streptococci (*Streptococcus viridans*), and Gram-negative bacilli (pseudomonas, serratia, and enterobacteriaceae species, anaerobic *Propionibacterium acnes*, and others) are the most common infecting agents in decreasing order of occurrence.<sup>14–15</sup> Medications should adequately cover these bacteria during the operative and perioperative periods. Before cataract surgery, topical anti-infective regimens historically included gramicidin–neomycin–polymyxin B sulfate; aminoglycosides, such as gentamicin or tobramycin (which provide Gram-negative and pseudomonas coverage); and the fluoroquinolones—ciprofloxacin, norfloxacin, ofloxacin 0.3%<sup>7,16,17</sup> or levofloxacin 0.5%. Of these, levofloxacin provided superior coverage and anterior-chamber penetration, before fourth-generation fluoroquinolone (G4FQ) became available.<sup>18–21</sup> The G4FQs gatifloxacin 0.3% and moxifloxacin 0.5% are currently preferred because they offer better penetration compared with previous generations (moxifloxacin appears to be better than gatifloxacin),<sup>22,23</sup> broader-spectrum coverage, lower incidence of bacterial resistance, and equal safety.<sup>24–26</sup> Antibacterial prophylaxis for cataract surgery has become an increasingly prominent issue after the confirmation of increased incidence of postoperative endophthalmitis with clear corneal incisions.<sup>27</sup> Retrospective studies indicate that endophthalmitis rates are lower with the postoperative use of topical G4FQ compared with historical controls.<sup>28</sup> There have been no prospective studies determining ideal dosing for prophylactic use, but some authors have suggested that administration of antibiotics 3 days preoperatively may yield superior intraocular drug levels at surgery. A similar consensus of antibiotic use 1 to 3 days preoperatively occurred in the 2007 ASCRS member survey.<sup>27,29–32</sup> There appeared to be no difference in bacterial load with the use of moxifloxacin either 1 or 3 days preoperatively.<sup>33</sup> Several recent cases raised concerns that prophylactic use of potent antibiotics in healthy patients with cataract may lead to bacterial resistance, thereby theoretically increasing the risk of postoperative infection with a resistant strain in patients so treated. Ong-Tone<sup>34</sup> demonstrated that the aqueous concentration of antibiotics administered topically is maximal when the drops are given within 2 hours of surgery, rendering their administration days in advance unnecessary. Therefore, topical antibiotic administration every 15 minutes for three to four doses before surgery seems optimal, yielding the highest anterior chamber concentration, which permits insufficient time for resistant strains to take hold.<sup>34</sup> On a population scale, the authoritative Medical Letter has stated that the risk of causing resistant strains from the use of antibiotics in ophthalmology is minimal because of the low number of viable bacteria exposed to the agent; therefore, long-term preoperative administration of topical antibiotics may select out existing resistant strains but cannot induce new ones.<sup>35–37</sup>

Subconjunctival injections of antibiotics has been shown to reach adequate aqueous humor concentrations.<sup>38</sup> Retrospective studies have found that subconjunctival antibiotics are effective at lowering the incidence of postoperative endophthalmitis.<sup>39,40</sup>

Complete conjunctival sterility is not achievable with the use of preoperative antibiotics alone.<sup>7</sup> The topical nonselective antiseptic agent povidone-iodine 5%, instilled as a single drop 10 to 30 minutes before surgery, is one of the most effective measures to decrease this bacterial flora.<sup>41</sup> In fact, a recent prospective study found that topical moxifloxacin 0.5% lacked a significant additive effect on the preoperative reduction of conjunctival bacterial colonization beyond the effect of povidone-iodine 5%.<sup>42</sup> No consensus currently exists with regard to the use of 5% or 10% concentration of povidone-iodine.<sup>43</sup> In the event of a known or suspected iodine allergy, polyhexidine or chlorhexidine gluconate is a well-tolerated alternative, and chlorhexidine is used as a standard in Sweden instead of povidone-iodine.<sup>44</sup>

Novel approaches for prophylaxis may be on the horizon, including drug delivery nanoparticles and presoaked intraocular lenses (IOLs) with antibiotic.<sup>45</sup>

### ANESTHETICS

Anesthetics are covered in detail in Chapter 5.8. Local injection anesthesia, both retrobulbar and peribulbar, has fallen increasingly out of favor, and the use of intracameral isotonic nonpreserved lidocaine 1%, preceded by topical lidocaine, has become the standard in many centers. Lidocaine gel is claimed to provide increased corneal hydration and anesthesia equal to that of injections and drops<sup>46,47</sup> while minimizing patient discomfort, but

	Class and Agent	Concentration	Dosage
Agents added to irrigating solutions	Antibiotics		0.3–0.5 mL of 1:1000 nonpreserved epinephrine 500 mL irrigating solution
	Vancomycin plus	20 µg/mL	
	Gentamicin	8 µg/mL	
	Gentamicin	8–80 µg/mL	
	Sympathomimetics to prevent miosis		
Agents used at the end of the procedure	Nonpreserved epinephrine		0.1 mL intracapsularly via side port at end of procedure
	Antibiotics		
	Vancomycin	1 mg/0.1 mL	
	Cefuroxime	1 mg/0.1 mL	
	Cefazolin	1–2.5 mg/0.1 mL	
	Gatifloxacin	100 µg/0.1 mL	0.5 mL injected into anterior chamber via side port to cause miosis
	Moxifloxacin	100 µg/0.1 mL 100–500 µg/ 0.1–0.2 mL	
	Parasympathomimetics		
	Acetylcholine	1%	
	Carbachol	0.01%	

its popularity seems to be decreasing in favor of intracameral injection. Furthermore, presence of lidocaine gel prior to povidone-iodine instillation may reduce its antimicrobial efficacy.<sup>48</sup> Topical lidocaine 4% as the sole anesthetic agent in uncomplicated cataract surgery is also being used increasingly.<sup>49</sup>

## INTRAOPERATIVE MEDICATIONS

### Additives to Irrigating Solutions, Intracameral Antibiotics, and Other Intraocular Drugs Used During the Surgical Procedure

Table 5.7.3 gives a summary of commonly used intraoperative pharmacotherapeutic routines. In general, the addition of antibiotics, mydriatics, epinephrine (adrenaline), or lidocaine (lignocaine) is not recommended by the companies that produce irrigating solutions for cataract surgery because any effect on stabilizers and preservatives in the solutions could alter their pH, chemical balance, or osmolarity and influence the potential toxicities of both the irrigating solution and the additive. Caution is advised with any alteration to commercial irrigating solutions.

To prevent intraoperative miosis, nonpreserved epinephrine (1:1000) 0.5 mL/500 mL is the most frequently used additive. This concentration appears nontoxic to the corneal endothelium and allows normal endothelial function.<sup>50</sup>

A new U.S. Food and Drug Administration (FDA)–approved combination drug, phenylephrine 1.0%–ketorolac 0.3% (Omidria) has been studied for the treatment of intraoperative miosis and postoperative ocular pain.<sup>51</sup> The study found that this medication was better than placebo in maintaining mydriasis and preventing postoperative pain in the early postoperative period.

Insufficient evidence exists to support the addition of antibiotics into the irrigating solution, although smaller studies previously demonstrated a benefit.<sup>52</sup> Vancomycin (20 µg/mL (0.02 mg/mL)) combined with gentamicin (8 µg/mL (0.008 mg/mL)) in the irrigating solution, has been reported to eradicate Gram-positive, coagulase-negative micrococci,<sup>53</sup> with minimal associated complications.<sup>54</sup> Gentamicin alone has been used intraoperatively in the dosage range of 8 to 80 µg/mL in the irrigating solution, which avoids retinal toxicity and also decreases the intracameral bacterial load.<sup>55</sup> However, a recent large study showed no significant benefit of antibiotics added to the irrigating solution, whereas intracameral antibiotics were very effective.<sup>56</sup>

The postoperative capsular bag is a sequestered avascular site that harbors a foreign body (the intraocular lens) and may act as the nidus for most cases of endophthalmitis. Introduced by James Gills in the early 1990s, intracameral vancomycin (1 mg in 0.1 mL balanced salt solution [BSS]) was the first antibiotic agent injected directly into the capsular bag as the final surgical step. This mode of delivery is considered superior to antibiotics

added in the irrigating solution because the concentration achieved in the anterior chamber is much higher; furthermore, it is done at the end of the procedure, leaving a high dose in the anterior chamber for the early postoperative period.<sup>52,57</sup> Considerable discussion occurred among clinicians and researchers about the safety and efficacy of intracameral injections until the large, multicenter, prospective, randomized, controlled European Society of Cataract and Refractive Surgeons (ESCRS) study showed intracameral cefuroxime (1 mg in 0.1 cc, first proposed by Montan et al.) to be effective in producing an 80% reduction in endophthalmitis rates.<sup>58–61</sup> The global use of prophylactic intracameral antibiotics with cataract surgery has been steadily increasing since the ESCRS study. Dilution of cefuroxime remains a problem in the United States, but outside North America, prediluted cefuroxime is available from Thea (France) as Aprokam. However, cefuroxime does not cover multiresistant enterococci. A recent multicenter retrospective analysis of postoperative endophthalmitis in immediate sequential bilateral cataract surgery found intracameral vancomycin (1 mg in 0.1 mL) and moxifloxacin (100–500 µg in 0.1–0.2 mL) to be at least as effective as cefuroxime.<sup>56</sup> Routine use of vancomycin is controversial because it is reserved as the last resort for multiresistant bacteria. The recent discovery of 36 cases of vancomycin-associated hemorrhagic occlusive retinal vasculitis has reduced surgeons' enthusiasm about using prophylactic intracameral vancomycin.<sup>62</sup> Intracameral moxifloxacin has theoretical benefits because of its potent bactericidal activity, availability as a self-preserved commercial formulation (Vigamox®; Alcon Laboratories, Fort Worth, TX) requiring only very simple dilution, if any, and the fact that its mechanism of action differs from current antibiotics of choice for endophthalmitis, theoretically making any possible breakthrough endophthalmitis cases easily treatable.<sup>63–67</sup> Its use is steadily increasing globally. Mounting evidence supports the use of intracameral antibiotics at the conclusion of surgery because they achieve supra-threshold antibiotic levels for an extended period.<sup>60,68,69</sup>

Rapid miosis can be produced at the end of the surgical procedure by using intraocular parasympathomimetics acetylcholine chloride 1% or carbachol 0.01%.<sup>70</sup> Current commercial preparations show no evidence of endothelial toxicity, and the choice of agent depends on the desired clinical features. Acetylcholine 1% has an onset of less than 1 minute with a relatively brief 10-minute duration of miosis, whereas carbachol 0.01% takes 2 minutes to act and lasts 2 to 24 hours. Both agents lower postoperative intraocular pressure spikes.<sup>71</sup> Topical carbachol 0.2% is effective to induce 24-hour miosis and reduce postoperative IOP spikes but is no longer commercially available; therefore, pilocarpine 2% may be used, but its effect lasts only 8 hours, so the patient may be given the pilocarpine minim (in countries where minims are available; Bausch & Lomb) to reapply one drop at bedtime (personal observation – SAA).

Agents currently under investigation include low-molecular-weight heparin, enoxaparin (10 IU/mL added to standard irrigating solution), which produces a decreased inflammatory response immediately after cataract surgery with minimal side effects (e.g., hemorrhage).<sup>72,73</sup> A preliminary study of ozonated water (4 parts per million [ppm] concentration) in anterior chamber irrigation confirmed its bactericidal effects, and this may potentially be another tool against endophthalmitis.<sup>74</sup>

### Irrigating Solutions

In the early days of phaco, the only irrigating solutions available were normal saline, Plasma-Lyte, and lactated Ringer's solution. Their main adverse effect was endothelial cell toxicity. Irrigating solutions with calcium, glutathione, and bicarbonate form more physiologically balanced solutions (Table 5.7.4).<sup>75</sup> Several comparative studies found BSS Plus to be protective of the corneal endothelium and hence superior to BSS and other irrigating solutions. Unlike BSS, BSS Plus is physiologically similar to human aqueous and vitreous, especially with regard to calcium concentration and the addition of glucose, glutathione, and bicarbonate. BSS Plus maintains endothelial cell function over periods ranging from 15 minutes to in excess of a few hours.<sup>58</sup> The buffer in BSS Plus is bicarbonate, which is an improvement over the sodium acetate and citrate buffers in BSS. Nevertheless, BSS Plus is currently used much less frequently compared with BSS because of cost and the progressive reduction in the volume of irrigating fluid used in surgery as techniques improve over time.

Corneal surface irrigation to maintain hydration and surgical clarity has traditionally been performed throughout intraocular procedures with BSS. The development of an elastoviscous Hylan Surgical Shield 0.45% (HSS), which decreases the surgeon's dependence on manual corneal irrigation, is an improvement over BSS in maintaining corneal hydration and clarity intraoperatively.<sup>76</sup> Some surgeons use a drop of ophthalmic viscosurgical

**TABLE 5.7.4 Chemical Composition of Human Aqueous Humor, Vitreous Humor, BSS Plus, and BSS**

<b>Ingredient</b>	<b>Human Aqueous Humor</b>	<b>Human Vitreous Humor</b>	<b>BSS Plus</b>	<b>BSS</b>
Sodium	162.9	144	160	155.7
Potassium	2.2–3.9	5.5	5	10.1
Calcium	1.8	1.6	1	3.3
Magnesium	1.1	1.3	1	1.5
Chloride	131.6	177	130	128.9
Bicarbonate	20.15	15	25	–
Phosphate	0.62	0.4	3	–
Lactate	2.5	7.8	–	–
Glucose	2.7–3.7	3.4	5	–
Ascorbate	1.06	2	–	–
Glutathione	0.0019	–	0.3	–
Citrate	–	–	–	5.8
Acetate	–	–	–	28.6
pH	7.38	–	7.4	7.6
Osmolality (mOsm)	304	–	305	298

(Adapted from Edelhauser HF. Intraocular irrigating solutions. In: Lamberts DW, Potter DE, Potter DE, editors. Clinical ophthalmic pharmacology. Boston, MA: Little, Brown and Company; 1987. p. 431–44.)

device (OVD) on the cornea at the beginning of surgery to achieve prolonged wetting and reduced need for BSS irrigation with two newer topical OVDs specifically targeting this use: Visthesia (NaHa 0.3% + lidocaine 2%; Carl Zeiss Meditech) and Cornea Protect (HPMC 2%; Bausch & Lomb).

### OPHTHALMIC VISCOSURGICAL DEVICES

The introduction of Healon in 1980 for ocular surgery ushered in the era of viscosurgery. OVDs consist of solutions of long-chain biopolymers (hyaluronic acid with or without chondroitin sulfate, or only hydroxypropyl methylcellulose) in low concentration. They are all pseudoplastic in their rheological behavior. Their physical properties tend to correlate with each other (i.e., the most viscous solution is also the most elastic and the most cohesive) and are a function of the chain length distribution of the rheologically important constituent polymer and its concentration. Recently, the advent of DisCoVisc, a viscous dispersive OVD, demonstrated that the tight correlation between viscosity and cohesion in OVDs can be avoided, resulting in a new two-dimensional classification, based on zero-shear viscosity and cohesive-dispersive properties (measured as the cohesion-dispersion index [CDI]) (Table 5.7.5). OVDs cannot be correctly referred to generically, as each one has different rheological properties, and they are not generically interchangeable in that many surgical maneuvers can be achieved more easily with one type of OVD than another. Before the advent of viscoadaptive OVDs, superviscous-cohesive and viscous-cohesive OVDs were recognized as best for creating, stabilizing, and maintaining spaces (to deepen the anterior chamber in the presence of positive vitreous pressure and to stabilize the anterior chamber facilitating capsulorrhexis and foldable intraocular lens implantation). Alternatively, medium- and lower-viscosity-dispersive OVDs are excellent for the selective isolation of areas of the intraocular surgical field and for enabling fluid partition of the anterior chamber (to protect marginal corneas from the turbulence of phaco, or to keep a frayed piece of iris or bulging vitreous away from the phacoemulsifying or irrigation-aspiration tip).<sup>77</sup> Superviscous-cohesive and viscous-cohesive OVDs cannot be used to partition fluid-filled spaces. To achieve the benefits of both types of older OVDs and to avoid having to deal with their disadvantages, the “soft shell technique,” or preferably variations of the “Tri-Soft shell technique” can be utilized.<sup>78–81</sup> Healon5 and MicroVisc Phaco (iVisc Phaco, Hyvisc Phaco, BD MultiVisc) are viscoadaptive OVDs that exhibit either highly viscous-cohesive or pseudodispersive properties, depending on fluid turbulence in the anterior chamber.<sup>82</sup> The dispersive behavior of lower-viscosity OVDs and the pseudodispersive behavior of viscoadaptives are very different.<sup>82–84</sup> These characteristics allow the use of viscoadaptives for chamber partitioning and yield enhanced versatility over earlier OVDs during phaco.<sup>85–89</sup> The “ultimate soft shell technique” further enhances the scope of utility of viscoadaptive OVDs<sup>90,91</sup> and enables the benefits of the soft shell technique to be attained using a single viscoadaptive OVD. The “tri-soft shell technique” amalgamates the methodology of all preceding “soft-shell techniques” into a single systematic method,

TABLE 5.7.5 New Classifications of OVDs, 2005, Modified and Updated to 2016

		← Cohesive - Dispersive →	
V <sub>0</sub> (zero-shear viscosity) range (mPa.s)		Cohesive OVDs CDI ≥ 30 (% asp/mm Hg)	Dispersive OVDs CDI < 30 (% asp/mm Hg)
7–18 × 10 <sup>6</sup> (ten millions)	↑ Viscosity	I. Viscoadaptives *Healon 5* iVisc** (MicroVisc***, Phaco, BD MultiVisc#	
1–5 × 10 <sup>6</sup> (millions)		II. Higher viscosity cohesives A. Super viscous cohesives *Healon GV* iVisc** (MicroVisc***, HyVisc***), Plus BD Visc#, AcnHylon Plus##  B. Viscous cohesives *Healon* iVisc** (MicroVisc***, HyVisc***) Eyefill HC### Ophthalmol Plus## *Provisc† Opegan Hi†† Rayner FR Pro+++ *Amvisc* Ophthalmol## Eyefill SC###	II. Higher viscosity dispersives A. Super viscous dispersives none  B. Viscous dispersives *DisCoVisc† *Amvisc Plus†
10 <sup>5</sup> –10 <sup>8</sup> (hundred thousands)			
10 <sup>4</sup> –10 <sup>5</sup> (ten thousands)			
†Modified from: Arshinoff SA, Jafari M.  A new classification of ophthalmic viscosurgical devices (OVDs). J Cataract Refract Surg. 2005; 31:2167–71.		III. Lower viscosity cohesives A. Medium viscosity cohesives none  B. Very low viscosity cohesives none	III. Lower viscosity dispersives A. Medium viscosity dispersives *Viscoat† *Vitrax*, Healon D*, Healon Endocoat* Endogel## Rayvisc+++ Opelead® *Cellugel† Eyefill HD###  B. Very low viscosity dispersives Opegan†† *OccuCoat†† Icell**, Visilon, Ocuvis, Hymecel, Adatocel, Celoftal, ...HPMCs
10 <sup>3</sup> –10 <sup>4</sup> (thousands)			
* Abbot Medical Optics, ** iMed Pharma, *** Bohus Biotech, # Bectin Dickinson, ## Carl Zeiss Meditech, ### Croma Pharma, † Alcon laboratories, †† Seikagaku Corporation-Santen, ††† Biotechnology General, †† Bausch & Lomb, ††† Rayner, ° Shisheido Co., HPMC = hydroxypropylmethylcellulose, * Available in USA			

permitting the surgeon to achieve the benefits of all soft-shell techniques in a single systematic approach. DisCoVisc is a new, viscous, dispersive OVD with zero-shear viscosity and is similar to Healon but resembles Viscoat's dispersive properties, thus permitting the chamber maintenance properties of Healon and the dispersive endothelial protection of Viscoat using a single OVD syringe.<sup>83</sup> Ophtheis FR Pro (Free Radical Protection; Rayner, UK) is another new type of OVD that possesses rheological properties similar to those of Healon but contains sorbitol, as a free-radical scavenger, with the intention of increasing endothelial protection. The advent of FLACS may revolutionize our choices and uses of OVDs because the need to stabilize and pressurize the anterior chamber for capsulorrhexis disappears. We will have to study the remaining aspects of FLACS to see what changes to OVDs will optimize surgery.

## Intracameral Medications to Replace Postoperative Drops

In the last few years, a few ophthalmologists have begun injecting an antibiotic-corticosteroid combination, Ti-Moxi (triamcinolone-moxifloxacin) or Tri-Moxi-Vanc (triamcinolone-moxifloxacin-vancomycin; Imprimis Pharmaceuticals, San Diego, CA) transzonularly as the final step in cataract surgery to avoid using postoperative topical eyedrops. Some authors have adapted this approach, and some have been very critical.<sup>92,93</sup>

## POSTOPERATIVE MEDICATIONS

Postoperative drugs are listed in Table 5.7.6.

TABLE 5.7.6 Commonly Used Agents in the Routine Postoperative Pharmacotherapy of Cataract Surgery

	Class and Agent	Concentration	Dosage
Corticosteroids	Dexamethasone	0.10%	1 drop 4 times daily for 3–4 weeks postoperatively
	Prednisolone	1%	
	Betamethasone	0.10%	
Nonsteroidal anti-inflammatory drugs	Diclofenac	0.10%	1 drop 4 times daily for 4 weeks postoperatively 1 drop 3 times daily for 2 weeks postoperatively
	Ketorolac	0.50%	
	Nepafenac	0.10%	
Antibiotics	Gramicidin-neomycin-polymyxin B	0.025 mg/mL	1 drop 4 times daily for 3–4 weeks postoperatively
	Gentamicin	2.5 mg/mL	
	Tobramycin	10 000 IU/mL	
	Ciprofloxacin	0.30%	
	Ofloxacin	0.30%	
	Gatifloxacin	0.30%	
	Moxifloxacin	0.30%	
	Trimethoprim-polymyxin B	0.30%	
		0.50%	
		1 mg/mL (10 000 IU/mL)	



## Antibiotics

Postoperative regimens of topical antibiotics vary but generally consist of one drop to the operated eye four to six times daily for 1 to 2 weeks. Recent studies support the practice of starting topical antibiotics immediately after cataract surgery, rather than waiting until the first postoperative day.<sup>94–96</sup> The duration of treatment varies from 5 days in uncomplicated surgery to weeks if prolonged inflammation occurs. Injections and collagen shields are increasingly falling out of favor.

Subconjunctival injections of antibiotics deliver high aqueous humor levels but have a greater associated risk, notably perforation of the eye, macular infarction, and retinal toxicity. Oral or parenteral antibiotics (e.g., fluoroquinolones) reach substantial levels in the anterior chamber but, being associated with increased side effects, are not advantageous over topical routes of administration.<sup>97,98</sup>

## Corticosteroids and Nonsteroidal Anti-inflammatory Drugs

The use of topical corticosteroids and NSAIDs after cataract surgery reduces postoperative noninfectious inflammation. Both are efficacious in decreasing inflammation,<sup>6,99–101</sup> with no difference between them in terms of astigmatic decay. The development of an intraocular biodegradable drug delivery system containing dexamethasone appears to be an effective alternative to topical drops,<sup>102</sup> and because a variety of drugs may be bound to the polymer matrix, it may play a role in the long-term prevention or treatment of cystoid macular edema. Topical NSAIDs have a specific advantage over corticosteroids if there are contraindications to corticosteroid use in a particular patient, as in those with corticosteroid-responsive elevations of intraocular pressure, recurrent herpes simplex infection,<sup>103</sup> or concern about delayed wound healing.<sup>104</sup> Ketorolac 0.5% has shown similar efficacy as a single agent in antimiotic and anti-inflammatory activity to an NSAID–prednisolone 1% combination.<sup>105</sup> However, an increased risk of corneal or scleral perforation in the presence of an epithelial defect exists when NSAIDs are used without concomitant administration of topical corticosteroids, most commonly reported with diclofenac.<sup>106,107</sup>

Pretreatment for 3 days with an NSAID decreases the postoperative level of inflammation.<sup>108,109</sup> Corticosteroids and NSAIDs are used postoperatively, although not as a single solution. The addition of an NSAID to an antibiotic-corticosteroid postoperative regimen reportedly has decreased the incidence of noninfectious postoperative inflammatory conditions.<sup>110</sup> The corticosteroids dexamethasone 0.1%, prednisolone 1%, and betamethasone 0.1% are used most commonly. A new corticosteroid, rimexolone 1%, seems to be similar in efficacy, with less potential intraocular pressure increase compared with either dexamethasone or prednisolone because its lipophilic nature reduces intraocular penetration.<sup>111</sup> In a recent study, a single intraoperative sub-Tenon's injection of triamcinolone (30–40 mg)<sup>112,113</sup> or intracameral triamcinolone (1.8–2.8 mg)<sup>114</sup> seemed to reduce the inflammatory response postoperatively. The most frequently used topical NSAIDs are diclofenac 0.1%, ketorolac 0.5% and, more recently, nepafenac 0.3%, and 0.1%.<sup>115–117</sup> Corticosteroid and NSAID regimens are identical and consist of one drop to the affected eye four times daily for up to 4 weeks (only once or twice daily for nepafenac), usually in conjunction with a topical antibiotic. Combination NSAID–antibiotic drops have been formulated to minimize the number of different bottles a patient must use postoperatively, without altering either the drug's efficacy or penetration.<sup>118</sup>

## LATE POSTOPERATIVE MEDICATIONS

### Treatment of Endophthalmitis

Endophthalmitis has been treated with antibiotics systemically, intravitreally, and topically. See Chapter 79 for details.

### Treatment of Cystoid Macular Edema

Cystoid macular edema (CME) usually manifests 1 to 3 months postoperatively as either decreased visual acuity or changes on fluorescein angiography or optical coherence tomography (OCT) resulting from serous exudate leaking from incompetent intraretinal capillaries into the outer plexiform

layer of Henle.<sup>119</sup> Most patients recover spontaneously, with full restoration of visual acuity within 6 months; however, it may require 1 to 2 years to achieve complete spontaneous resolution.<sup>2</sup>

Prophylaxis and treatment have been suggested in the form of systemic and topical NSAIDs. Oral NSAIDs, with regimens of indomethacin 25 mg three times daily 1 week before surgery and 3 weeks postoperatively,<sup>2</sup> or ibuprofen 200 mg preoperatively and postoperatively, have received mixed reviews.<sup>120</sup> Literature supports the efficacy of topical NSAIDs,<sup>121–123</sup> such as flurbiprofen 0.03%, diclofenac 0.1%, ketorolac 0.5%, bromfenac 0.09%, and nepafenac 0.1% used prophylactically and after surgery to reduce inflammation.<sup>124,125</sup> Piroxicam 0.5% solution used postoperatively appears as effective as diclofenac, with less ocular irritation.<sup>126</sup> The prodrug Nepafenac 0.1% has shown significantly greater ocular bioavailability and potency compared with ketorolac 0.4% and bromfenac 0.09%.<sup>125</sup> Usually, preoperatively and postoperatively, one drop is administered two to four times daily for up to 3 weeks to prevent CME. Frequently, in the acute postoperative period, topical corticosteroids used in conjunction with NSAIDs in the treatment of CME<sup>127</sup> produce a synergistic effect.<sup>128</sup> Recent evidence also suggests that solitary topical NSAID treatment is superior to lone corticosteroid prophylaxis.<sup>129–132</sup> In chronic cases, management continues until resolution.<sup>2</sup> Indefinite NSAID treatment may be required to maintain CME regression,<sup>133</sup> which increases interest in the utility of a sustained drug delivery system, such as Ozurdex.<sup>134</sup> Once it has been established, CME is treated with oral acetazolamide, topical corticosteroids with NSAIDs, or posterior sub-Tenon's injection of long-acting corticosteroids (see Chapter 6.35). Single-dose intracameral, intraoperative, and multiple intravitreal postoperative injections of triamcinolone also have safely prompted regression of chronic CME with minimal changes in intraocular pressure.<sup>99,135–137</sup> Oral cyclooxygenase-2-inhibitors were found to successfully resolve CME unresponsive to oral or topical NSAIDs in a small number of patients, with improvement in visual acuity,<sup>138</sup> as has high-dose methylprednisolone (1000 mg for 3 days)<sup>139</sup> in the past. Recent case series investigations suggest anti-vascular endothelial growth factor (VEGF) as an alternative for recalcitrant CME, but large controlled trials are lacking.<sup>140–143</sup> Oral carbonic anhydrase inhibitors (CAIs) may be effective in treating refractory CME, but their use is guarded because of severe adverse effects.<sup>144</sup> Antiglaucomatous prostaglandin analogues may enhance disruption of the blood–aqueous barrier, increasing the incidence of CME after cataract surgery, but this appears to be a response to the drug's preservative, and not the drug itself. The concurrent application of NSAIDs decreases the incidence of CME secondary to these medications and does not adversely influence the anti-glaucoma drug's effect on intraocular pressure.<sup>145,146</sup>

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# Anesthesia for Cataract Surgery

Keith G. Allman

# 5.8



**Definition:** Procedures and medications given to allow successful completion of lens removal with minimal risk, pain, and anxiety.

## Key Features

- Consideration of patient characteristics.
- Local anesthesia: considerations, sedatives used, local anesthetics used.
- Local techniques: topical, retrobulbar—advantages, disadvantages; peribulbar and sub-Tenon's—comparison.
- General anesthesia: techniques, advantages, disadvantages, and complications.

## INTRODUCTION

The advent of small, self-sealing cataract incisions has allowed a change in the practice of anesthesia for cataract surgery. Local and topical techniques are now the norm, with less than 2% of patients requiring general anesthesia.<sup>1</sup> However, anesthesiology input remains important, as even topical techniques have been shown to require anesthesiologist intervention for 22%–28% of cases.<sup>2,3</sup>

A team approach is important because it allows the surgeon to concentrate on the operation while the anesthesiologist cares for the patient.<sup>4</sup>

## MEDICAL ASPECTS OF ANESTHESIA FOR CATARACT SURGERY

### Cataract Type and Associated Medical Conditions

Cataracts can be either congenital or acquired and may be an ocular manifestation of a systemic disease. Younger patients may have uncommon medical conditions, whereas those with acquired cataracts are usually older (average age 75 years) and have comorbidities, such as ischemic heart disease and chronic obstructive airway disease. In an audit of 1000 cases in Auckland, 43% were identified as American Society of Anesthesiologists (ASA) grades 3–4.<sup>5</sup> There is also a significant increase in overall mortality in those with concurrent hypertension (48%), ischemic heart disease (38%), and diabetes (16%).<sup>6</sup>

Routine preoperative investigations, however, are not usually indicated, with the exception of testing for clotting in some patients taking oral anticoagulants, for electrolytes in those having dialysis, and for blood sugar in those with a history of diabetes.<sup>7,8</sup> An assessment of the patient's ability to lie flat and still is important.

### Specific Conditions

#### Ischemic Heart Disease

Ischemia can be provoked by stress and anxiety at the prospect of surgery and anesthesia. If possible, surgery should be avoided for 3 months after myocardial infarction, angioplasty, or coronary revascularization. Phenylephrine drops may result in a significant rise in blood pressure and should be limited to a 2.5% solution. The oxidative damage resulting in cataract formation is linked to free radical formation and atherosclerosis, which

explains the high proportion of patients with coexisting ischemic heart disease.<sup>6</sup>

### Anticoagulants

Patients on oral anticoagulants and antiplatelet therapy, including aspirin and clopidogrel, should continue with these throughout surgery.<sup>9–12</sup> The risks of cardiovascular complications if these agents are stopped outweigh the potential risks of hemorrhage. General anesthesia, sub-Tenon's block, or topical local anesthesia is recommended.

### Diabetes Mellitus

Local anesthesia causes the least disruption to diabetic management and is preferred.<sup>13</sup> Normally, patients do not need to fast (see below).

## LOCAL ANESTHESIA

Local anesthesia can be classified into topical, retrobulbar, peribulbar, and sub-Tenon's block.

### General Considerations

The main advantage of local anesthesia is minimal disruption for the patient. Sedation may be useful, particularly in the anxious.<sup>14</sup> Patients given local anesthesia without sedation or with “minimal” sedation (as defined by the ASA) need not be starved.<sup>15,16</sup> Guidelines for standard fasting times should be followed for deeper sedation or general anesthesia.<sup>16</sup>

Minimal monitoring should include electrocardiography (ECG) and pulse oximetry. Older adults and those with systemic illnesses should be anesthetized in an appropriate environment with backup facilities if inpatient or critical care is required.<sup>17</sup> Supplemental oxygen is given to avoid hypoxia and to minimize claustrophobia. Rebreathing can occur under the drapes even at 6 L/min of oxygen.

Nonmedical personnel often perform an assessment prior to surgery. Accurate listing for local or general anesthesia can be a problem because many patients have comorbidities. A questionnaire filled in by patients has been shown to be a good initial screening tool, with supplemental medical input as required.<sup>14</sup>

Many patients have visual experiences under local anesthesia; in one survey 16% found this distressing.<sup>18</sup> Counseling preoperatively has been shown to be beneficial in reducing this distress.<sup>19,20</sup>

All operating room personnel must be trained in basic life support, and at least one member should have advanced training. The Joint Royal Colleges in the United Kingdom recommend that an anesthetist be present throughout, whether general or local anesthesia is used, and this is essential if sharp needle technique or sedation is contemplated. For patients undergoing topical anesthesia or sub-Tenon's block, an anesthetist does not need to be present, unless the site is isolated.<sup>8,17</sup>

There are few absolute contraindications to local anesthesia, but patient refusal and the possibility of noncooperation during surgery remain the commonest.

### Topical Anesthesia (see Box 5.8.1)

More than 60% of all cataract operations are performed with the patient under topical anesthesia in the United States and around 33% in the United Kingdom.<sup>21</sup> Oxybuprocaine (benoxinate) 0.4%, an ester anesthetic,

### BOX 5.8.1 Advantages and Disadvantages of Topical Anesthesia

#### Advantages

- No risk associated with needle insertion
- Reduced risk of periocular hemorrhage
- Functional vision is maintained; advantageous for unioocular patients
- Reduced postoperative diplopia and ptosis

#### Disadvantages

- An awake and talkative patient can be distracting for the surgeon
- No akinesia of the eye
- Less effective anesthesia compared with sub-Tenon's block
- Increased risk of surgical complications; if difficulties or problems occur, anesthesia may be inadequate
- May be unsuitable for less experienced surgeons

#### Adverse Effects of Topical Ocular Anesthetics

- Direct corneal effects—alteration of lacrimation and tear film stability
- Epithelial toxicity—healing has been shown to be delayed when an epithelial defect occurs (lidocaine does not appear to affect healing)
- Endothelial toxicity—this occurs when penetrating trauma is present and appears to be related to the preservative benzalkonium
- Systemic effects—lethal toxicity (this is only a problem with cocaine)
- Allergy and idiosyncratic reactions

#### Secondary Adverse Effects

- Surface keratopathy

### BOX 5.8.2 Advantages and Disadvantages of Retrobulbar Block

#### Advantages

- Reliable akinesia
- Onset of block is quicker than with peribulbar anesthesia
- Low volumes of anesthetic result in a lower intraorbital tension and less chemosis than with peribulbar blocks
- Temporary loss of visual acuity occurs more reliably than for peribulbar block

#### Disadvantages

- Risk of brainstem anesthesia—reason for the development of the peribulbar block
- Risk of myotoxicity and globe perforation

is frequently used. Proparacaine (proxymetacaine) 0.5% is less toxic to the corneal epithelium, does not sting on application, but has a shorter duration of action (20 minutes). Other agents, including tetracaine (ame-thocaine) 0.5%–1%, lidocaine 1%–4%, and bupivacaine 0.5%–0.75%, have longer durations of action but increased corneal toxicity and pain on application.

Topical anesthesia may be combined with subconjunctival or, more commonly, intracameral anesthesia to improve patient comfort. Preservative-free lidocaine 1% 0.3–0.5 mL appears to be effective and safe.<sup>21,22</sup>

As visual perception is not lost, the patient is asked to focus on a light, the intensity of which is reduced. Subconjunctival injection of antibiotics can be painful and can be avoided by intracameral administration.

Use of topical anesthesia has been increasing throughout the United States and Europe despite several studies demonstrating inferior analgesia compared with both peribulbar and sub-Tenon's blocks and a possible increase in surgical complication rate (4.3% posterior capsular tear for topical compared with 2.1% for sub-Tenon's anesthesia).<sup>4,23–25</sup>

With correct selection of patients and surgery performed by experienced surgeons, many centers have shown good results, but because there is no akinesia of the eye, it may not be suitable for inexperienced surgeons or uncooperative patients.<sup>26</sup>

### Retrobulbar Block (see Box 5.8.2)

With this technique, the aim is to block the oculomotor nerves before they enter the four rectus muscles by depositing the local anesthetic directly into the posterior intraconal space (Fig. 5.8.1). Although the resultant akinesia is usually profound, serious complications, such as brainstem anesthesia, globe perforation, and myotoxicity, have rendered the technique

#### ADVANCEMENT OF NEEDLE IN RETROBULBAR BLOCK

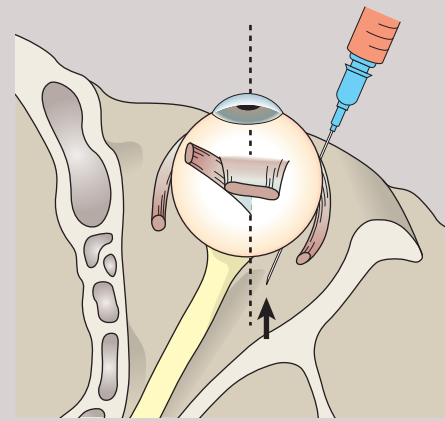


Fig. 5.8.1 Advancement of needle in retrobulbar block.

TABLE 5.8.1 Comparison of Peribulbar and Sub-Tenon's Block

Peribulbar Block	Sub-Tenon's Block
More pronounced akinesia	Less akinesia
Lower rates of chemosis and subconjunctival hemorrhage	High rates of chemosis and subconjunctival hemorrhage
Risk of globe perforation, retrobulbar hemorrhage, myotoxicity	Complications rarely serious
Small risk of brainstem anesthesia	Improved analgesia
	Lower dose and volume of anesthetic agent are used
	Less painful to perform

relatively obsolete. For sharp needle anesthesia, peribulbar block offers a safer, equally effective method.<sup>27,28</sup>

### Peribulbar Block (see also Table 5.8.1)

The principle of this technique is to instill the local anesthetic outside the posterior muscle cone and thereby avoid accidental injection into the optic nerve (which would cause brainstem anesthesia). This utilizes higher volumes (6–10 mL) of the local anesthetic compared with the traditional retrobulbar block, and the application of a pressure device is often needed.

#### Technique

With the eye in primary gaze, local anesthetic drops are applied to the cornea. At the inferotemporal lower orbital margin, a 25-gauge, 25-mm needle is advanced parallel to the plane of the orbital floor either transcutaneously or transconjunctivally. A degree of upward and inward angulation may be needed once the needle goes past the equator of the globe. Local anesthetic (4–6 mL) is injected at a depth of about 20 mm from the inferior orbital rim (in an eye of normal axial length). No resistance to injection should be felt, and prior aspiration should be performed (Fig. 5.8.2 and Fig. 5.8.3).

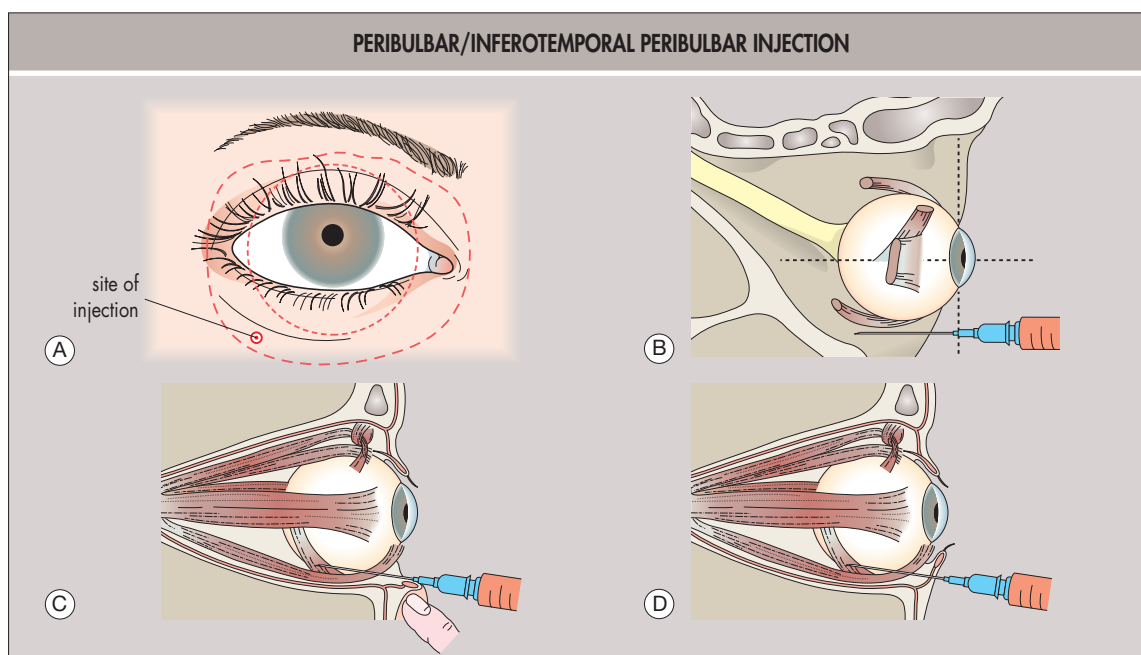
After 5 minutes, the degree of akinesia is assessed. If a second medio-canal injection is required, a 25-gauge, 25-mm needle is inserted between the medial canthus and the caruncle and directed immediately backward. The medial check ligament is often penetrated. At a depth of 15 mm, after prior aspiration, another 4–6 mL of solution is injected to produce a more complete block, with akinesia of the orbicularis oculi and levator palpebrae superioris. A Honan balloon or pressure-lowering device is often applied for 5–10 minutes.

Peribulbar block has been reported to be more painful than using topical anesthesia.<sup>29,30</sup> It is important that adequate training be given to decrease complications from the use of all of these blocks.

#### Local Anesthetic Agent

The most common agent used is lidocaine 2% plus hyaluronidase 15 IU/mL. If greater duration of anesthesia is required, the lidocaine can be mixed in a ratio of 50:50 with bupivacaine 0.5%.

Other agents used include 2-chloroprocaine 2%–3%, mepivacaine 1%–2%, bupivacaine 0.25%–0.75%, prilocaine 3%, and ropivacaine 0.75%.<sup>31</sup> Levobupivacaine is the L-isomer of bupivacaine with a higher safety index, especially in terms of cardiac toxicity. Articaine 2%–4% is an amide local



**Fig. 5.8.2** Inferotemporal peribulbar injection. (A) The needle enters the orbit at the junction of its floor with the lateral wall, very close to the bony rim. (B) The needle passes backward in a sagittal plane parallel to the orbit floor. (C) It passes the globe equator when the needle-hub junction reaches the plane of the iris. (D) After test aspiration, up to 10 mL anesthetic solution is injected. (Adapted from Hamilton RC. Techniques of orbital regional anaesthesia. *Br J Anaesth* 2001;86:473–6.)



**Fig. 5.8.3** Transconjunctival peribulbar injection technique.

anesthetic of low toxicity used predominantly in dentistry. Because of its rapid onset, short duration of action, low toxicity, and better penetration of tissues, it has been shown to produce good quality blocks.<sup>32–36</sup>

Epinephrine 5 µg/mL is sometimes added to improve onset time, quality, and duration of the block. However, it should be avoided in older patients with atherosclerosis and has been implicated in optic artery thrombosis secondary to vasoconstriction. A 50% decrease in pressure in the ophthalmic artery has also been noted.

Hyaluronidase is an enzyme derived from the testicles of rams (previously from the testicles of cattle), although a recombinant version is now available. It hydrolyzes C1–C4 bonds between glucosamine and glucuronic acid in connective tissue, thus enabling the local anesthetic to penetrate tissues more effectively. The required quantity of the local anesthetic, therefore, is reduced, and the time to onset decreased. Hyaluronidase may also help prevent damage to the extraocular muscles, especially the inferior rectus muscle, preventing diplopia.<sup>37</sup>

### Complications

Most serious complications of peribulbar anesthesia are associated with the use of sharp needles.

- **Globe perforation/penetration.** Incidence 1.4–1.9 per 10 000.<sup>38–40</sup> More common in high myopes (>26 mm axial length) and with inexperience. Usually results in marked visual loss because of permanent retinal damage.
- **Retrobulbar hemorrhage.** Incidence 0.6–4.2 per 10 000.<sup>38–40</sup> More common in those taking anticoagulants. May require surgical decompression.
- **Extraocular myotoxicity.** Incidence 25–100 per 10 000.<sup>41,42</sup> Related to inadvertent direct injection of the local anesthetic into the muscle

belly. Myocyte cell death is followed by hypertrophic regeneration and shortening.<sup>43,44</sup>

These serious complications have led some authorities to recommend abandoning sharp needle techniques altogether.<sup>42</sup> The UK Royal College of Ophthalmologists has also stated:

“Sharp needle local anaesthetic techniques have a higher risk of ocular and systemic complications than sub-Tenon’s or topical techniques and should only be used when the anaesthetist and surgeon consider it absolutely necessary.”<sup>45</sup>

In 2017 the UK National Institute for Health and Care Excellence (NICE) concluded that peribulbar anesthesia should no longer be used for routine cataract surgery where Topical or sub-Tenon’s anesthesia is possible.<sup>46</sup>

Certainly, sharp needle blocks are responsible for the majority of ophthalmic anesthesia-related problems and are the most common cause of regional anesthesia-related litigation after centroneuraxial blockade in the United Kingdom (average settlement £24 000).<sup>47,48</sup>

### Sub-Tenon’s Block (see also Table 5.8.1)

This was first described by Turnbull in 1884 when he used open dissection of Tenon’s layer followed by instillation of cocaine. Later modifications were introduced by Stevens, Greenbaum and Allman.<sup>49–53</sup>

Sub-Tenon’s block involves surface anesthesia and surgical access to sub-Tenon’s space. In the United Kingdom, this now is the most common method used in cataract surgery, comprising 47% of cases.<sup>54</sup>

### Anatomy

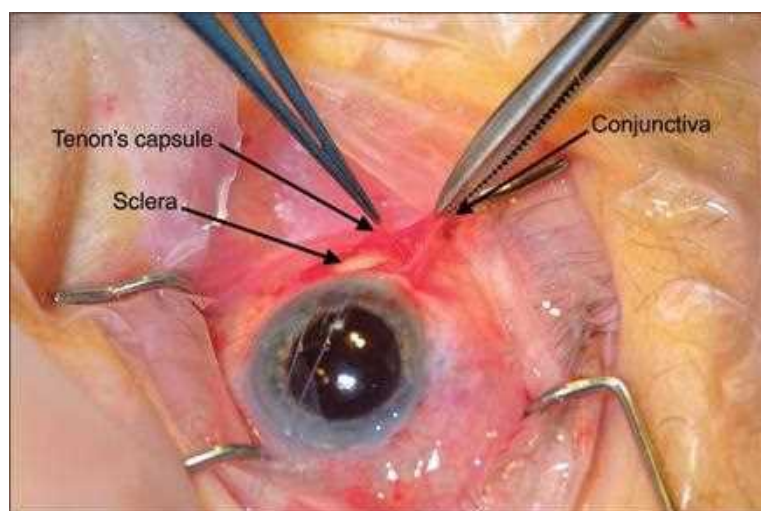
This is described in more detail elsewhere in this text. Briefly, Tenon’s capsule (after Jacques René Tenon [1724–1816], French anatomist/surgeon) is a facial sheath, a thin membrane enveloping the eyeball and separating it from orbital fat. The inner surface is smooth and shiny, separated from the outer surface of the sclera by a potential space, the episcleral or sub-Tenon’s space. Anteriorly, the capsule fuses with conjunctiva 5–10 mm from the limbus. Posteriorly, it fuses with the meninges around the optic nerve. It has been suggested that it is a lymph space and is crossed by numerous delicate bands.

### Technique

The conjunctiva is anesthetized first with a topical local anesthetic of choice. The most common approach is via the infranasal quadrant because this allows for good distribution of the anesthetic while decreasing the risk of damage to the vortex veins. The eye is cleaned with 5% iodine, and the patient is asked to look upward and outward. Aseptically, the conjunctiva and Tenon’s capsule are held 3–5 mm from the limbus using nontoothed Moorfield’s forceps (Fig. 5.8.4).<sup>52</sup> A small incision is made through these layers using blunt-tipped, sprung Westcott scissors, exposing the sclera. A cannula is then advanced into the sub-Tenon’s space and around the globe.

Sub-Tenon’s anesthesia can be broadly divided into anterior and posterior techniques. In the former, the cannula tip remains anterior to the





**Fig. 5.8.4** Incision for sub-Tenon's block. Arrows point to conjunctiva, Tenon's capsule, and shining sclera under the Tenon's capsule. (Reprinted with kind permission from Kumar CM, Williamson S, Manickham B. A review of sub-Tenon's block: current practice and recent development. *Eur J Anaesthesiol* 2005;22:567–7, Figure 2c, European Academy of Anaesthesiology, published by Cambridge University Press.)

globe equator. This reduces the risk of inadvertent misplacement but increases the rate of chemosis and can make akinesia difficult to achieve. For more profound akinesia, the cannula tip should be placed posterior to the equator but must be positioned with care, gently following the curve of the globe (Video 5.8.1).



See clip:  
5.8.1

Numerous cannulae have been described.<sup>55</sup> The plastic Greenbaum cannula (12-mm 15-gauge) is suitable for anterior blocks, whereas a metal Stevens cannula (25-mm 19-gauge) is most suitable for posterior techniques (Fig. 5.8.5).

An alternative technique that requires no prior conjunctival incision uses a pencil-point cannula (25-mm 21-gauge Triport cannula; Eagle Laboratories).<sup>55</sup> This reduces the amount of conjunctival damage and decreases reflux of the local anesthetic. The blunt cannula entry site leaves a very small, self-sealing wound, which then heals rapidly with less conjunctival scarring compared with traditional techniques (Video 5.8.2).



See clip:  
5.8.2

The sub-Tenon's (or episcleral) space also can be accessed using a “B” beveled needle, as described by Jacques Ripart.<sup>56</sup> Although a useful and reliable technique, this somewhat negates the advantages of using a blunt cannula.

The local anesthetic in a dose of 3 to 5 mL is injected; the greater the volume, the greater is the degree of akinesia. Lidocaine 2% is usually used in combination with hyaluronidase. Addition of hyaluronidase reduces the median effective volume (EV50) needed from 6.4 to 2.6 mL.<sup>57</sup> Articaine 2%–4% may be even more effective.<sup>36</sup>

A Honan's balloon can be used to increase dispersal; however, it is not usually needed.

Complications are mainly minor (chemosis and subconjunctival hemorrhage), although orbital inflammation, scleral perforation, cardiovascular collapse, and sight-threatening and life-threatening complications have all been reported.<sup>58–61</sup>

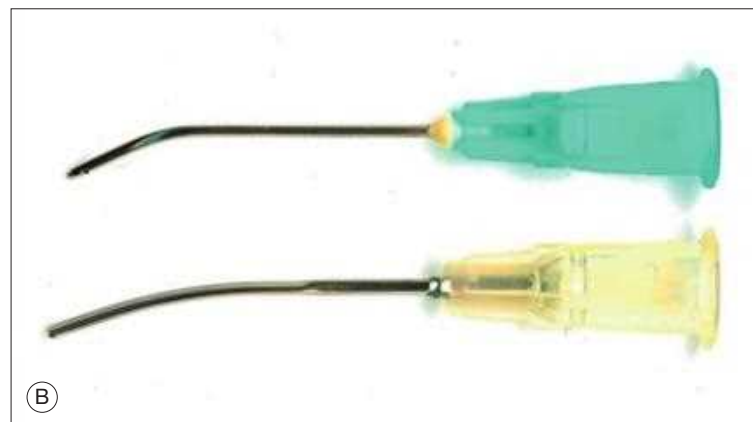
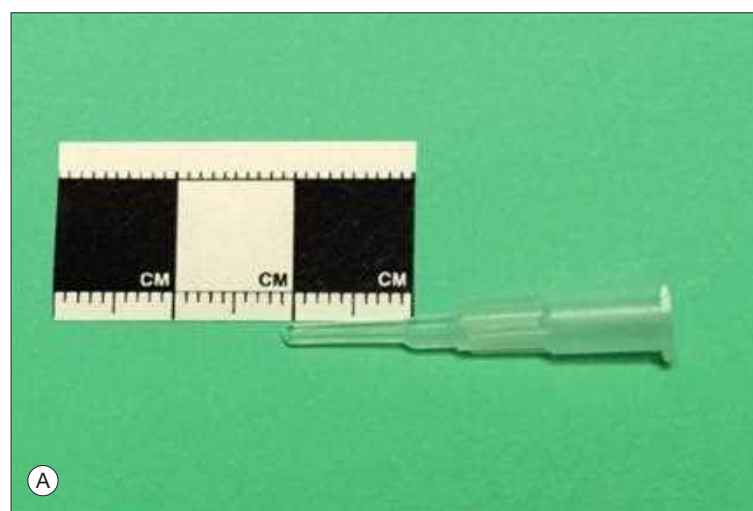
## SEDATIVE AGENTS

Sedation is a useful adjunct to local anesthesia for many patients—particularly those who are unduly anxious.

Midazolam, a short-acting, water-soluble benzodiazepine with a half-life of 2 hours, has both amnesic and anxiolytic properties, lacks venous sequelae, and allows rapid patient recovery. It is given intravenously in 0.5- to 1-mg increments. Adequate time between doses must be allowed in older adults, or oversedation could result. Overdoses can be reversed with flumazenil, a specific benzodiazepine antagonist, but its half-life is 1 hour, so resedation can occur.

Propofol, a short-acting phenol, is an intravenous induction agent suitable for infusion and sedation. It is characterized by the patient's rapid and clear-headed recovery and is associated with a low incidence of nausea and vomiting. It causes respiratory depression and a fall in blood pressure.

Propofol and midazolam have both been used for patient-controlled sedation.<sup>62</sup>



**Fig. 5.8.5** Three cannulae used for sub-Tenon's anesthesia. (A) Greenbaum cannula 15-gauge 12-mm. *Middle*, Triport cannula (Eagle Laboratories) 21-gauge 25-mm. (B) Steven's cannula (Visitec) 19-gauge 25-mm.

### BOX 5.8.3 Advantages and Disadvantages of General Anesthesia

#### Advantages

- Patient comfort
- Ideal operating conditions—a quiet, immobile patient and soft eye
- Allows for rapid alterations in intraocular pressure, if required
- No risk of complications associated with local anesthetic blocks
- No residual paralysis of the eye when the patient is awake
- Bilateral surgery can be performed
- Better conditions for teaching

#### Disadvantages

- Slower turnaround times
- More expensive
- Greater risk in frail older adults
- Greater physiological disruption for patient

Fentanyl is a potent, short-acting narcotic analgesic with a duration of action of about 30 minutes. Given in doses of 25–50 µg, it provides analgesia with minimal sedation and is a useful adjunct to midazolam or propofol. Side effects include respiratory depression, nausea, and vomiting.

Remifentanyl is a potent, ultra-short-acting alternative but can cause a marked fall in heart rate and blood pressure in older adults.

Dexmedetomidine, an  $\alpha_2$  agonist, has also been used as a sedative agent with good effect.<sup>63</sup>

## GENERAL ANESTHESIA

General anesthesia is useful in those patients unsuitable for local anesthesia; it is the method of choice for babies, children, and the uncooperative (see Box 5.8.3).<sup>64</sup>

In the past, it was necessary to intubate, paralyze, and ventilate the patient. However, with the advent of phacoemulsification (“phaco”) and

small incision surgery, plus the use of propofol with a laryngeal mask airway, it is now feasible to have the patient breathing spontaneously. Avoiding intubation allows for the use of a lighter anesthetic, decreases cardiovascular depression, and improves recovery. In patients 80 years of age or older, psychomotor testing has shown that total intravenous anesthesia with propofol and remifentanyl results in significantly faster recovery of cognitive function compared with etomidate–fentanyl–isoflurane.<sup>65</sup>

A recent study that compared balanced anesthesia with total intravenous anesthesia (TIVA) showed similar cardiovascular effects but decreased nausea and vomiting, faster recovery, better patient satisfaction, and lower costs with TIVA.<sup>66,67</sup>

## Technique

### Spontaneous Respiration

A laryngeal mask is inserted, and anesthesia is maintained with either a continuous propofol infusion or a volatile agent of choice. Target-controlled infusion regimens are commonly employed. Propofol 4.5 µg/mL bolus for induction followed by 3.26 µg/mL maintenance target infusion levels can be combined with either an alfentanil (target blood concentration 25 ng/mL) or remifentanyl (target blood concentration 1–1.5 ng/mL) infusion, although propofol plus topical anesthesia is usually sufficient. The use of a laryngeal mask enables faster turnaround times and reduces the cough associated with extubation. It provides a stable, easily controlled anesthetic, resulting in rapid recovery and a low incidence of nausea and vomiting.

### Ventilation

The traditional method involves endotracheal intubation, although controlled ventilation is possible with a laryngeal mask. This combines the benefits of avoiding intubation and causing paralysis in the patient. Suxamethonium is avoided, if possible, because a transient rise in intraocular pressure occurs with its use. Short-acting nondepolarizing blockers are preferred. Maintenance consists of using a volatile agent or a propofol infusion. Although patient throughput may be slower, this technique provides stable, well-controlled anesthesia and is the method of choice for certain patients in whom spontaneous respiration would be inappropriate (e.g., obese individuals).

### Conclusions

Both spontaneous respiration and ventilation methods are suitable for day-case anesthesia. They are both widely used in all other specialties. Both propofol and the newer volatile agents sevoflurane and desflurane provide a particularly rapid and clear-headed recovery.

Hypotension needs to be aggressively treated with vasoconstrictors, such as ephedrine or metaraminol, to minimize morbidity.

## POSTOPERATIVE CARE

Cataract extraction by phaco is relatively pain-free. In the majority of cases, simple oral analgesics are sufficient. Nonsteroidal anti-inflammatory drugs should be used with caution in older adults. Topical nonsteroidal analgesics can decrease pain and inflammation<sup>68</sup> and have been shown to be equally effective in reducing the inflammatory response compared with corticosteroids, with fewer side effects. Corticosteroids should be reserved for cases with more severe inflammation.<sup>69</sup> Topical local anesthesia can also be used as an adjunct, as it reduces systemic anesthetic requirements. This may reduce postoperative nausea and vomiting by avoiding the use of opiates. Propofol also has antiemetic properties.

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# Phacoemulsification

David Allen

## 5.9



**Definition:** A surgical technique to remove the nuclear portion of a cataractous lens using an aspirating and vibrating ultrasonic handpiece.

### Key Features

- Changing phacoemulsification (“phaco”) “power” or “amplitude” is achieved by changing the stroke length of needle vibration, not by changing the frequency.
- Evidence is accumulating that direct mechanical action is the most important factor in phaco.
- Power modulation significantly increases the efficiency of longitudinal phaco as well as improving the thermal safety. It is less important with torsional phaco.
- Modern pump systems are efficient and high vacuums can be achieved very quickly with modern flow-based (peristaltic) systems.
- In a flow-based machine, the aspiration flow rate can be adjusted completely independently of the preset vacuum limit.
- In a vacuum-based (Venturi) machine, the aspiration flow rate is generated by the pressure difference between the vacuum chamber and the eye. In most machines, the two cannot be completely dissociated, and a high vacuum results in higher flow rates compared with a lower vacuum.
- Modern machines feature a variety of strategies to minimize postocclusion surge. Postocclusion surge potential is directly related to the maximum set vacuum for any given needle/sleeve/tubing complex.

### INTRODUCTION

As surgical techniques for the removal of cataract along with drug modulation of the consequent biological responses have become more refined, the problems of postoperative infection and inflammation are less important concerns of lens surgeons. As a consequence, it has become possible to concentrate on the further refinement of the actual process of lens removal. Phacoemulsification (“phaco”) offers the surgeon the possibility to break the nucleus into smaller pieces and even into a fine emulsion of material, all of which can be removed through the probe used to achieve the breakup. As a result, it is now possible to minimize trauma to the structures of the eye and to have minimal impact on its shape as a consequence of modern cataract surgery. Achieving this, however, requires the use of very powerful tools. Unfortunately, many surgeons fail to understand the principles that underlie the machines they use. As a consequence of this relative ignorance, surgery is sometimes performed less efficiently and possibly more dangerously than necessary.

### HANDPIECES AND TIPS

The phaco handpiece houses an ultrasonic transducer—a device that converts electrical energy into mechanical vibratory energy. Standard handpieces couple the crystal to the phaco tip in such a way that the tip moves backward and forward when the crystals deform. In 2006, Alcon Surgical (Fort Worth, TX) introduced a handpiece (OZil) that can cause the tip to tort or twist when the crystals deform. It is constructed in such a way that when oscillating at 32 kHz the crystals produce torsion, and when stimulated at 44 kHz, they produce traditional linear movement. If a tip with a

bend in the shaft (Kelman tip) is attached to such a handpiece, then the twisting of the shaft is converted into a sweeping side-to-side motion at the end of the tip. Following this, Abbot Medical Optics (AMO, Santa Ana, CA) introduced a third modality whereby with their new handpiece (Ellips FX), the phaco needle is made to traverse laterally while it moves forward, taking what they call an *elliptical path*.

The frequency at which a handpiece is set to work depends on the design and materials used. Adjustment of the power setting on the machine affects the stroke length (the distance traveled by the tip during one cycle), but not the frequency. Power is expressed as a percentage of the maximum travel the crystal-tip complex can produce. It is clear that if the frequency remains constant but the distance traveled in each stroke increases, the acceleration of the tip and the maximum speed it reaches must be greater. It is important to recognize that the power settings on the machine console are indicative only. Some systems have a nonlinear relation between commanded power and stroke length. The smallest stroke (at minimum power setting) also varies among systems. In one commercially available system, 20% power produces tip travel of 50  $\mu\text{m}$ , whereas this travel is reached only at 60% power in another machine. As a consequence, any comparisons between the “efficiency” of different phaco machines based on comparisons of “power used” are spurious.

The physical mechanisms that break up nuclear material when a phaco tip is used have been difficult to elucidate, and the relative importance of the various factors is still unclear.<sup>1,2</sup> For example, a phaco tip operated at a frequency of 44 kHz has a maximum speed of 66 ft/second (20 m/second) when operated at full power, and the acceleration of the tip is >168 300 ft/second (>51 000 m/second). Under these conditions, the direct impact of the tip breaks the frictional forces within the nuclear material. This direct effect is reduced, however, by the forward-propagating acoustic waves or fluid and particle waves generated by the tip, which tend to push away any piece of nucleus in contact with the tip. However, some still postulate that the acoustic shock waves themselves tend to weaken or break some of the bonds that hold nuclear material together. The role of cavitation in breaking down lens material remains controversial, but some evidence exists that it is not required for effective phaco.<sup>3</sup>

Various tip designs are available for the surgeon, but there are three key design variations, and each of the tip designs usually is available with a “cutting tip” angle of 30° or 45°. The tip may be straight with a uniform diameter along its length. The Kelman tip has a 22° angle in the shaft 3.5 mm from the tip. This design is thought to enhance the emulsification action of the tip, as well as allowing the surgeon to use it as a manipulator. Some tips have a flared termination of the tip (i.e., the outer and inner diameter at the end of the tip is greater than that 1–2 mm behind). While the larger mouth creates more holding force, the restriction of the inner lumen behind the flare helps suppress postocclusion surge. More recently, a completely new tip design has been introduced. When torsional phaco was developed, the already available Kelman design tip was used. It seemed logical that rotating the shaft along its long axis would result in a sweeping side-to-side action at the tip end. Although this proved to be the case, it was later realized that there was not just simple rotation of the shaft with this design. This realization resulted in a completely new tip shape, specifically designed for torsional phaco (the “balanced” tip) (Fig. 5.9.1). By significantly reducing the unwanted movement in the shaft, more of the energy produced by the ultrasound crystals is translated into sweeping movement at the very end of the tip, giving a stroke length of 190  $\mu\text{m}$  at maximum amplitude compared to 130  $\mu\text{m}$  with the Kelman tip.<sup>4</sup>



**Fig. 5.9.1** The balanced tip developed specifically for torsional phaco. (Courtesy Alcon Surgical.)

## POWER MODULATION

Although some form of simple power modulation (pulsed phaco) has been available for a long time, the introduction in 2001 of the Whitestar software for the AMO Sovereign phaco machine marked a paradigm shift in the way surgeons controlled the application of phaco power. Breakup of phaco into pulses or bursts has two advantages. First, the pauses (off-period) allow the machine fluidics to pull material back into contact with the tip following repulsion caused by the jack-hammer effect in traditional longitudinal phaco. Second, the pauses prevent significant buildup of heat as a result of frictional movement within the incision, making thermal damage to the cornea less likely. Several machines now allow almost infinite variation of both duty cycle (the ratio of on-time to off-time) and the length of the on-period. It has been shown that such power modulation significantly improves the “efficiency” of phacoemulsification (i.e., quicker surgery and reduced amount of phaco energy used).<sup>5</sup> With the introduction of torsional phaco the reduced repulsion and reduced thermal effect mean that power modulation is less important, although many surgeons continue to apply modulations.

When first introduced, pulses had a fixed duty cycle of 50% (i.e., the period with power on and with power off were equal), but power was variable, whereas bursts were of fixed width, usually with fixed power also. First Bausch & Lomb (Bridgewater, NJ) and now most other manufacturers have enhanced the various possible combinations of modulation, and this distinction has become blurred and is probably no longer helpful to try to distinguish between them in advanced machines.

## PUMPS AND FLUIDICS

The function of the phaco pump is twofold—to hold the nucleus onto the tip and to remove debris created by the tip. With modern techniques the pump also is used increasingly to aspirate directly the softer parts of the nucleus. There are two pump principles in general use—flow-driven and vacuum-driven. Some machines now have the ability to switch between the two modes during surgery.

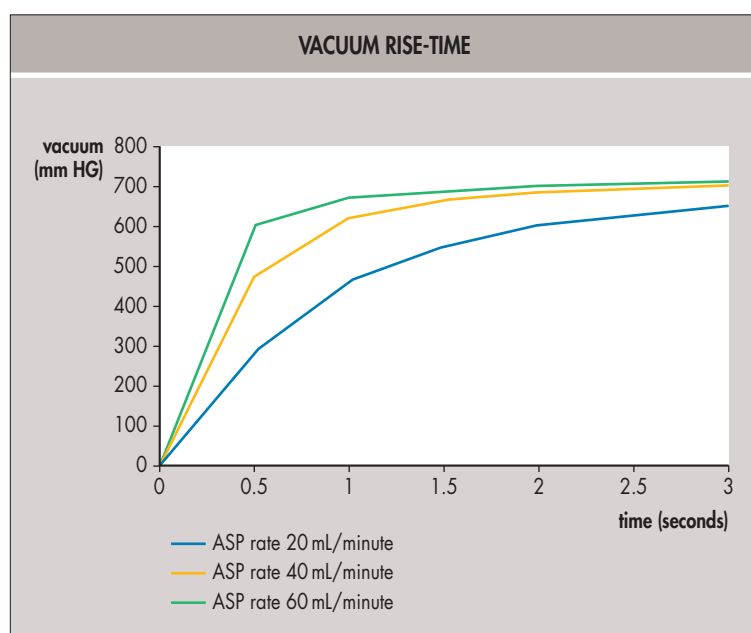
### Flow-Based (Peristaltic)

Roller pumps that rotate against compressible tubing or membrane generate flow; this “milks” fluid along the lumen and creates a pressure gradient between pump and anterior chamber (AC). Recent design changes in the pumps and sophisticated microprocessor controls have resulted in powerful and well-controlled pump systems. The rate at which fluid is aspirated through the unoccluded phaco tip is set at the machine console in milliliters per minute (mL/min). A low value allows events within the AC to happen slowly; a high value speeds up events and generates more “pulling power.” Fine adjustments of flow, achieved by changing the speed at which the pump turns, allow for personal surgical style or different operating conditions. Recent advanced systems sense when the tip is occluded partially and then make adjustments to the pump to compensate for reduced aspiration.

The second pump parameter that can be adjusted is the vacuum level at which, once achieved, the pump stops. When the tip becomes occluded, the pump continues to turn and move fluid into the cassette, increasing the vacuum level in the tubing between tip and cassette. Once the preset vacuum has been reached, the pump effectively stops (or turns slowly intermittently to compensate for vacuum loss) for as long as that vacuum level holds. The rate at which the maximum set vacuum level is reached is directly proportional to the flow rate (Fig. 5.9.2).

### Vacuum-Based

These systems generate an adjustable level of vacuum in a chamber in the machine; usually, a Venturi pump is used. It is the pressure difference between this chamber and the tip that generates flow. Once the tip is occluded, fluid continues to be removed from the tubing until the pressure within it equals that in the vacuum chamber. It is possible, however, to introduce a damping effect into the system so that the equilibration



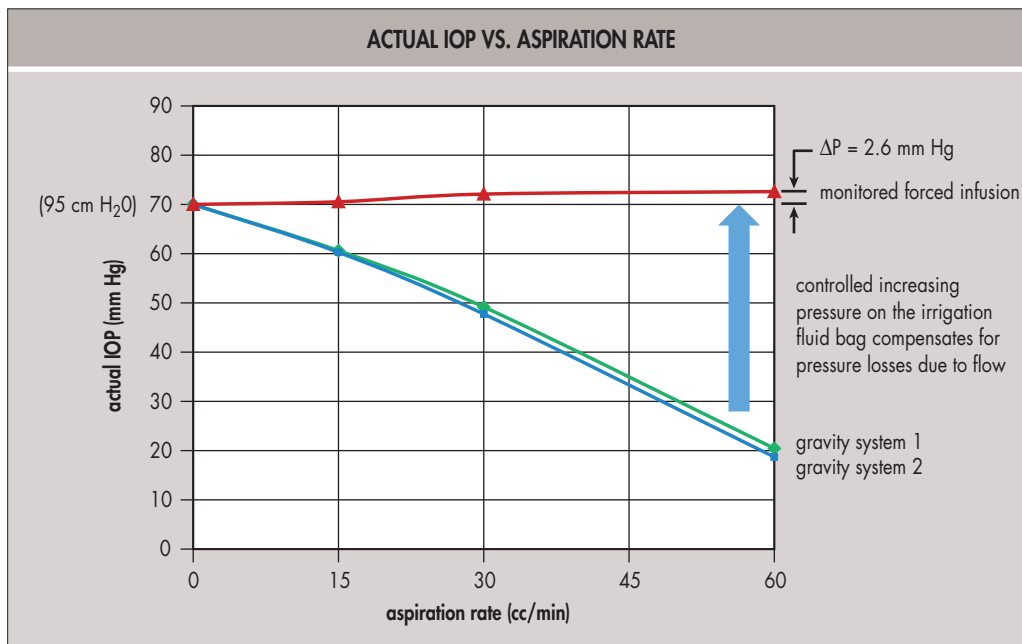
**Fig. 5.9.2** Vacuum rise-time as a function of aspiration rate. Graph showing the effect of increasing aspiration rate (pump speed) on the time to reach certain vacuum levels.

of pressures does not take place instantaneously. In a standard vacuum system, because the flow rate is generated by the pressure gradient, increasing the vacuum results in increased flow, whereas reducing vacuum lowers the flow. These two parameters cannot normally be modulated independently, although with at least one advanced machine, this is now possible.

## Anterior Chamber Hydrodynamics

It is important to understand the correct meaning of various terms used to describe the fluid dynamics of phaco. “Vacuum (Limit)” is taken to mean the preset maximum vacuum level indicated on the console. In neither peristaltic nor vacuum-based systems is this vacuum present in the AC, although some degree of vacuum must be present along the aspiration line (including in the phaco handpiece) to generate outflow. Normally, “flow” is used to mean aspiration flow rate, which is evacuation flow out of the eye. Fluid also flows out of the eye at a variable rate through the incisions, often called the *incision leakage flow*. To avoid confusion, if flow into the eye is being described, it is necessary to use the term “inflow.” In traditional phaco systems, the rate of fluid inflow is determined by the height difference between the drip chamber of the fluid reservoir (usually a hung bottle) and the eye. Inflow has been passive in traditional phaco machines; it is reduced in varying amounts by the resistance of the tubing and by any compression of the inflow sleeve around the phaco tip. The recently introduced “Centurion” phaco machine (Alcon) has an active inflow system allowing much more precise control of the AC dynamics and intraocular pressure. The system monitors the pressure in the inflow line, the vacuum pressure being generated in the outflow line and the aspiration flow rate, in real time, and adjusts the pressure being applied to the bag containing the inflow fluid in order to generate sufficient inflow to maintain (within limits) the intraocular pressure (IOP) chosen by the surgeon.

In any system (gravity-fed or with active fluidics) it is essential that the inflow potential (the maximum possible under free-flow conditions) at least equals, and if possible exceeds, the maximum transient outflow (combined incisional flow and machine-generated flow); otherwise AC collapse occurs (see “Postocclusion Surge” later). In a gravity-fed system (the traditional system), as the fluid bottle or bag is generally fixed during a given step in the procedure, the height of the bottle is set so that it will generate sufficient inflow during postocclusion surge to prevent AC collapse. For most surgeons, this is set at 80–95 cm above eye level, although some surgeons set the bottle even higher. When the phaco (or I/A) handpiece is in the eye with irrigation active (foot pedal position 1) then the eye is pressured to 80–95 cm H<sub>2</sub>O, which equates to 59–70 mm Hg. In an ex-vivo model it has been shown that during unoccluded aspiration (foot-pedal position 2) the IOP drops significantly because of resistance to inflow in a gravity-fed system. With an aspiration flow rate of 30 cc/min for example, with a fixed bottle height of 95 cm, the IOP drops from 70 mm Hg to 50 mm Hg<sup>6,7</sup> (Fig. 5.9.3). The effect of this is that during normal surgery with a



**Fig. 5.9.3** Actual intraocular pressure (IOP) with different aspiration flow rates. Graph showing how IOP drops with increasing aspiration in a gravity-fed system (two different manufacturers' machines). Monitored forced infusion system can overcome this. (Taken with permission from Boukhny M, Sorensen GP, Gordon R. Novel phacoemulsification system using feedback-based IOP target control. Presented at ASCRS Annual Meeting, Boston, April 25–29, 2014.)

gravity-based phaco system with these typical settings, the IOP will fluctuate during cataract removal between 70 and 50 mm Hg, depending on the foot-pedal position and the degree of tip occlusion. Only very briefly during postocclusion surge will it drop significantly lower than 50 mm Hg. The same ex-vivo study showed that the monitored forced infusion system produced no significant IOP changes with aspiration flow rates up to 60 cc/min.

In traditional longitudinal phaco, an active phaco tip (power-applied) produces forces that push material away from it. This is countered by the vacuum that holds the material to the tip. The torsional mode of the Infiniti (Alcon) generates a sweeping horizontal movement without repulsion, and lower vacuums can be used. When a surgeon uses a technique that involves sculpting (e.g., “divide and conquer”<sup>8</sup> or “stop and chop”<sup>9</sup>), a relatively low flow ( $\leq 25$  mL/min) with no tip occlusion is required (Video 5.9.1). The low flow allows sculpting near or even onto the capsule, without the risk of drawing the capsule into the port, and a tip slope of 30° or 45° allows the surgeon both to see the tip and to minimize occlusion potential. For subsequent nucleus fragment consumption (or initially in chop techniques), a high flow (20–40 mL/min) is required to pull the nucleus toward the tip, along with high vacuum (200–600 mm Hg) to hold it in contact for emulsification (Video 5.9.2). Occlusion in these circumstances is enhanced by rotation of the tip so that the opening is aligned with the edge of nucleus being grasped.

Many phaco systems now offer the surgeon the opportunity to adjust the fluidics performance, particularly vacuum rise-time, once occlusion has been achieved. One use is to have relatively low aspiration flow rates during the acquisition of nucleus fragments but set the machine to significantly increase the flow rate (and hence speed of achieving the preset vacuum) once the tip is occluded. Another example would be the reduction in flow rate on occlusion that some surgeons use when dealing with very soft cataracts or epinucleus.

## Fluidics of Microincisional Phaco

Since 2001, many surgeons have adopted the concept of microincisional phaco. This was first performed in a biaxial mode<sup>10</sup>; the infusion was dissociated from what became a “bare” aspiration tip by use of a separate cannula inserted through a separate incision. Each incision is only 1–1.5 mm wide, and there are a number of IOLs that can be inserted through sub-2-mm incisions. The reduced maximum incision size results in smaller changes to corneal curvature induced by the surgery. In coaxial phaco, the infusion ports in the infusion sleeve around the phaco tip are positioned close to the aspiration port and, therefore, can create turbulent flow that can disrupt the attractive force generated by aspiration. In theory, with biaxial phaco these forces are now separated and should result in better followability.

Critics of biaxial surgery point to the degraded fluidics that may be produced by a nonconforming bare solid cannula passing through a corneal incision; either incisional leakage must be significant, or the incision is so tight as to risk significant tearing of corneal stroma and Descemet's

membrane. New sleeves for coaxial microincision phaco have now been developed that allow coaxial phaco to be performed through 1.8-mm incisions.

Whether using biaxial or coaxial microincision techniques, it is important that surgeons understand the importance of fluidics and ensure that the inflow potential through the reduced sleeve, or the separate infusion instrument is greater than the maximum outflow during postocclusion surge with their particular combination of machine, needle, and vacuum settings.

## POSTOCCLUSION SURGE

With any pump design, in the occluded state, vacuum is generated in the lumen of the tubing. When the occlusion breaks, fluid rushes into the tubing to equilibrate the pressure difference between the AC and the lumen—“postocclusion surge” (Fig. 5.9.4). During the period of occlusion, the walls of the tubing tend to collapse in proportion to the increase in vacuum, and dissolved gas is pulled out of solution. On release of the occlusion the tubing re-expands and often rebounds, and the gas bubbles contract resulting in postocclusion surge. The difference between the outflow surge and the compensating inflow from the irrigation bottle determines the stability of the AC. Tubing with increased stiffness is said to have reduced compliance. Cassettes in the irrigation/aspiration line also have compliance, and a tendency exists for modern versions to have as much as possible of the fluid pathway in the cassette made of rigid material.

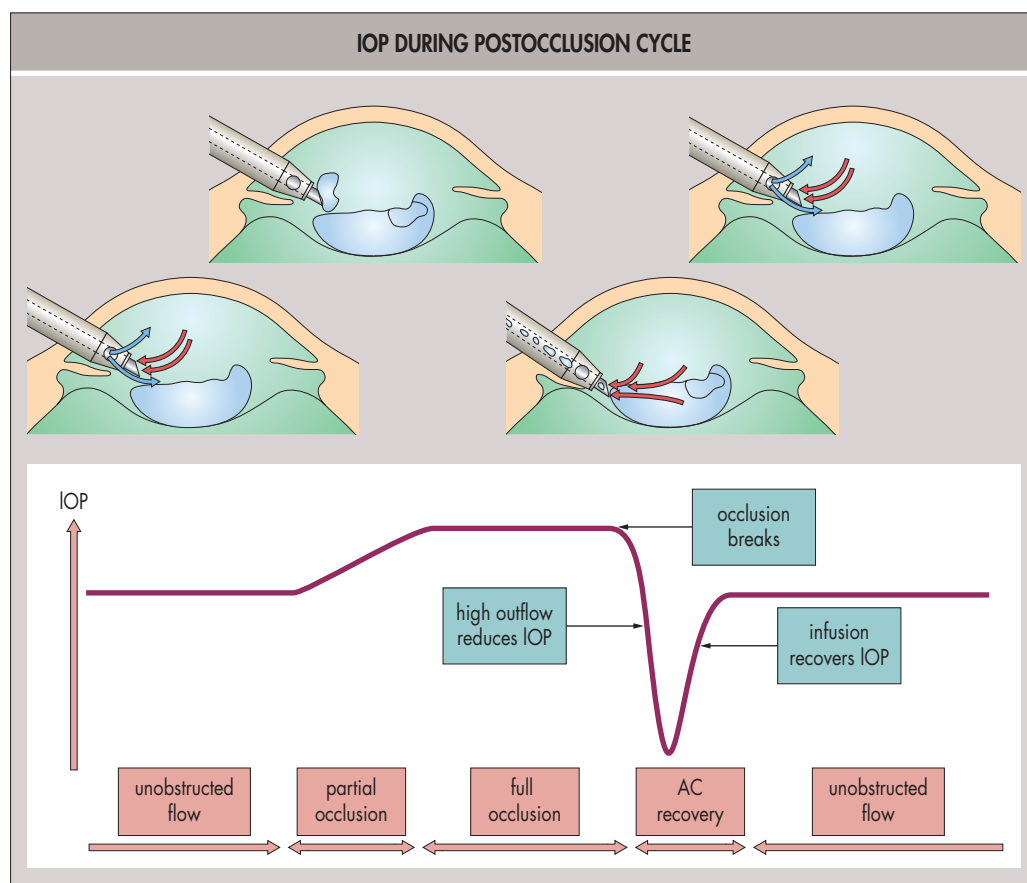
Phaco systems use a variety of other strategies to reduce the problems associated with postocclusion surge. The internal diameter of both the phaco needle (and any restrictions, such as seen in the flared needle) and outflow tubing modulate the outflow surge. Less compliant outflow tubing and cassettes reduce the rebound effect. Fig. 5.9.5 shows the impact of reducing tubing and cassette compliance in three generations of phaco equipment from a single manufacturer over a 10-year period. The effective inflow diameter (the gap between the outer wall of the tip and the inner wall of the sleeve in coaxial phaco, or the internal diameter and outflow port diameters of the irrigation instrument in biaxial phaco), along with the bottle height/irrigation pressure, determines the amount of inflow and how well it compensates for outflow surge. Manufacturers have different approaches to reducing the problems of postocclusion surge. These include reducing the vacuum after a given (surgeon-selected) time of full occlusion on the assumption that the occlusion is about to break. Others reduce the aspiration flow rate immediately after a sudden drop in vacuum is detected. When the vacuum at the tip suddenly decreases on occlusion break, a significant time lag occurs before the pressure-change information is propagated along the tubing to the phaco console. At least one manufacturer is exploring the possibility of having a pressure sensor in the handpiece to eliminate this time lag and thus speed up any programmed response to postocclusion surge.

However good the machine, surgeons need to understand the impact that choice of needle size/shape along with sleeve diameter and bottle height may have on AC stability.

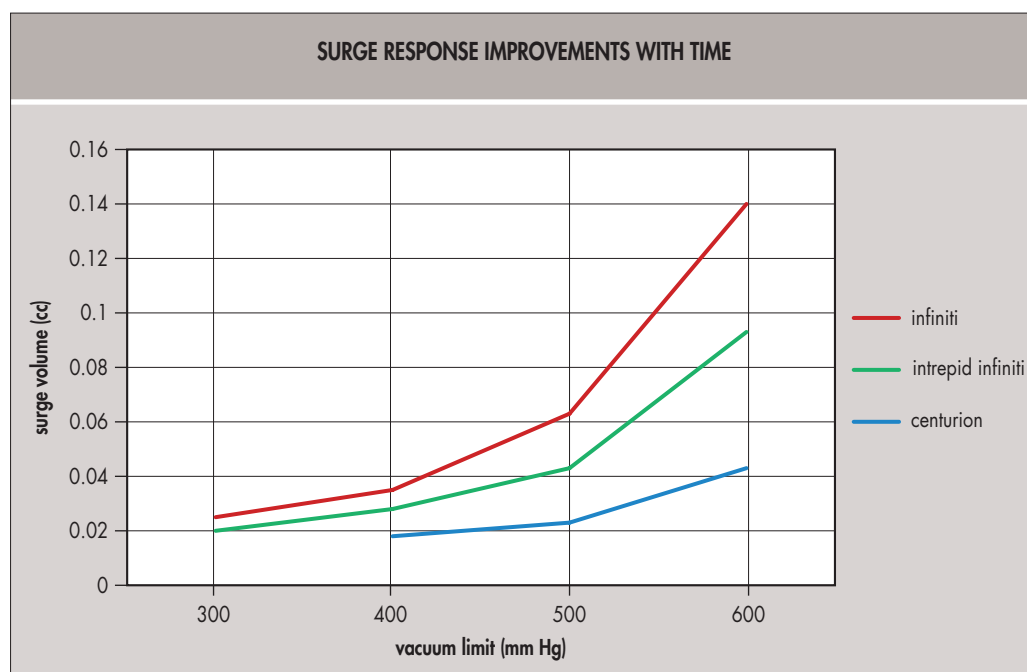
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5.9.1

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**Fig. 5.9.4** Intraocular pressure (IOP) during postocclusion surge. IOP initially maintained by bottle height. Slight rise when tip occluded. When occlusion breaks, large pressure difference between tubing and anterior chamber (AC) results in rapid outflow of fluid causing IOP to drop rapidly until infusion restores "normal" IOP.



**Fig. 5.9.5** Reduction of postocclusion surge resulting from reduced outflow compliance with time. Postocclusion surge volumes at different vacuum limits for original Infiniti phaco machine (2003), Infiniti with "Intrepid" reduced compliance cassette and tubing (2006) and Centurion phaco machine (2013) with new cassette and tubing (Adapted with permission from data provided by Alcon.)

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# Refractive Aspects of Cataract Surgery

Emanuel S. Rosen

# 5.10

**Definition:** Modern cataract surgery not only promises prevention of induced refractive errors by the surgical process but also the opportunity to enhance the eye's refractive status.

## Key Features

- Importance of the corneal shape before operation.
- Value of corneal topography.
- Prevention of induced corneal astigmatism.
- Treatment of astigmatism.
- Intraoperation.
- By incisions.
- By implant choice.
- Postoperation.
- By corneal laser surgery.
- By toric lens implantation.
- By piggyback lens implantation.

## INTRODUCTION

When Sir Harold Ridley implanted a human eye with a replacement lens (intraocular lens [IOL]) in 1949, he initiated a change in the role of cataract surgery.<sup>1</sup> As IOL implantation technology matured over the following years, cataract surgery became more than just removing a clouding crystalline lens; it allowed for the replacement IOL to be adjusted to correct intrinsic refractive error, or ametropia. In other words, there are two strategies for surgical intervention: first removing the impediment of a cataractous lens and then simultaneously incorporating an IOL of measured dioptric power to neutralize existing ametropia.

Of course, there are many other aspects to the refractive aspects of cataract surgery. Accurate biometry is vital (refer to that aspect of cataract management in the discussions in this section). Cataract surgery in eyes that have previously undergone corneal refractive surgery require special formulas to calculate the correct IOL power after keratometric values have been changed by that surgery. Management of astigmatism is a fundamental refractive need in cataract surgery and will be considered here. With the advent of clinical aberrometers and their application in refractive surgery, cataract replacement is now taking advantage of the deeper understanding of the relationship, in a refractive sense, between the cornea and the lens. Near, intermediate, and distance vision needs have to be satisfied by lens replacement, a task fulfilled by emergent multifocal IOL technology, pseudo-accommodative IOLs, and the future fulfillment of truly accommodating IOLs. The bases for refractive correction, as an aspect of cataract surgery, are accurate biometry on the one hand and corneal topography on the other.

The focus of cataract surgery is to correct the immediate aphakia. Current techniques and implants offer the opportunity to individualize patients' postoperative spherical and astigmatic errors and thus achieve overall patient satisfaction with regard to refraction.

Intraoperative techniques are the first to be applied (1) to ensure that astigmatism is not induced and (2) to neutralize it intraoperatively, if possible. Residual astigmatism after cataract surgery can be corrected by using four different techniques. These are (1) classic limbal relaxing incisions, which are easy to perform but have limited precision; (2) corneal laser refractive surgery (photorefractive keratotomy [PRK]); or (3) laser-assisted in situ keratomileusis (LASIK), additionally allowing for correction of spherical components; and (4) more recently, the use of a piggyback toric intraocular lens in the ciliary sulcus.<sup>2</sup>

## VALUE OF CORNEAL TOPOGRAPHY

Fig. 5.10.1 illustrates the importance of preoperative corneal topography in ensuring that the eye to be operated upon is fully understood: "Understand before you treat."

Corneal topography contributes significantly to our understanding of the requirements of cataract refractive surgery. It enables adjustments for astigmatism, when required, either intraoperatively or after the operation, while also detecting serious corneal issues before the operation to avoid unexplained poor postoperative visual acuity.

## INTRAOPERATIVE MANAGEMENT OF PREOPERATIVE CORNEAL ASTIGMATISM TO PREVENT INDUCTION OF CORNEAL ASTIGMATISM

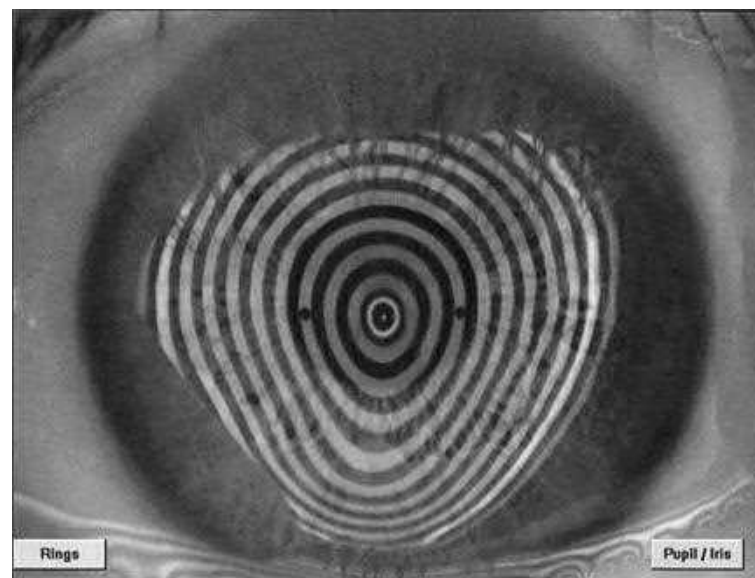
### Corneal Incisions

In a randomized clinical trial and noncomparative interventional case series, Tejedor and Murube<sup>3</sup> investigated the best location for clear corneal incision (CCI) in phacoemulsification ("phaco"), depending on pre-existing corneal astigmatism.

In summary, for cataract CCIs:

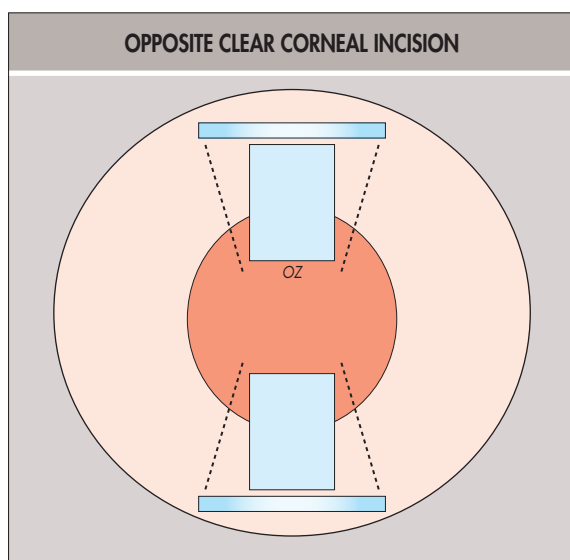
- A superior incision is recommended for at least 1.5 D of astigmatism with a steep meridian at 90°.
- A temporal incision is recommended for astigmatism less than 0.75 D and steep meridian at 180°.
- A nasal incision is recommended for at least 0.75 D of astigmatism with a steep meridian at 180°.

Beltrame et al.<sup>4</sup> compared astigmatic and topographic changes induced by different oblique cataract incisions in 168 eyes having phaco, which were randomly assigned to one of three groups: (1) 3.5 mm CCI, 60 eyes (Figs. 5.10.1–5.10.7 for similar examples); (2) 5.5 mm sutured CCI, 54 eyes; and

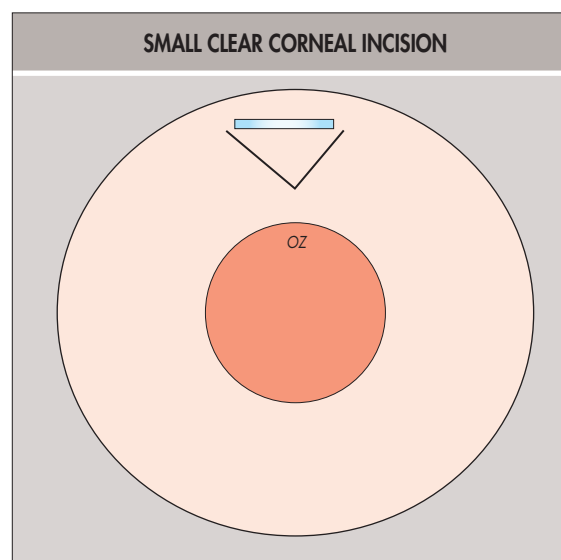


**Fig. 5.10.1** Pellucid marginal corneal degeneration. An example where preoperative corneal topography would have revealed the defect that resulted in "unexplained" poor visual results after surgery.

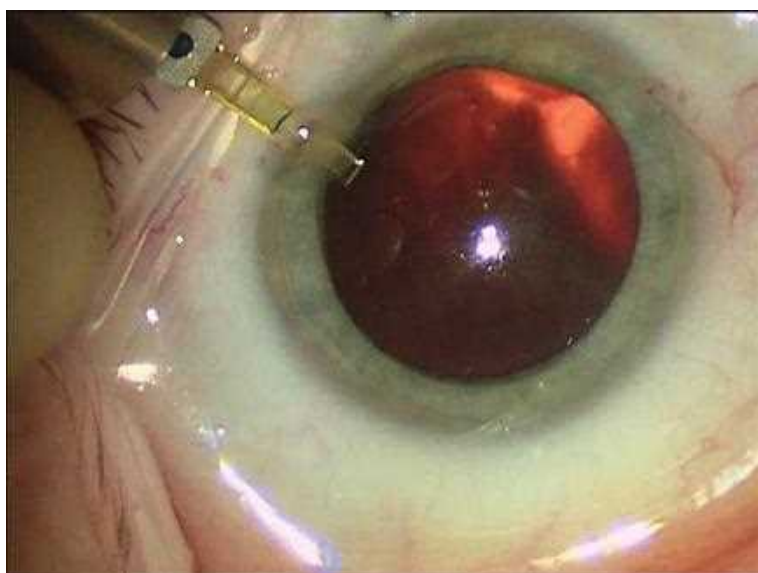




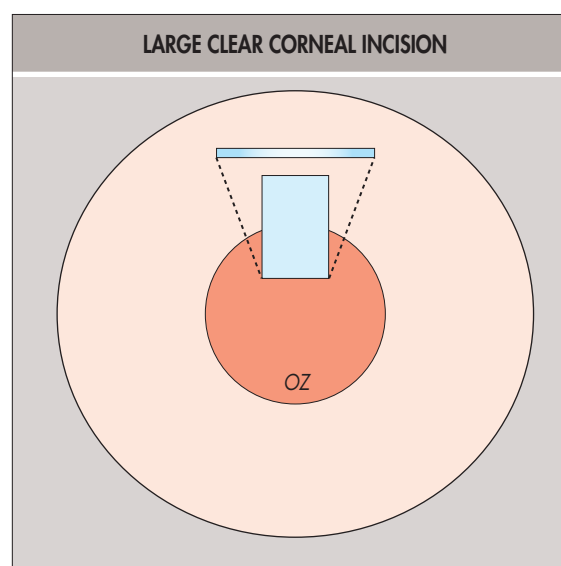
**Fig. 5.10.2** Opposite clear corneal incision to correct preoperative astigmatism. Diagram to illustrate symmetry of incisions designed to correct each half of the steep meridian "bow tie."



**Fig. 5.10.4** Small clear corneal incision—no central effect. OZ, optical zone.



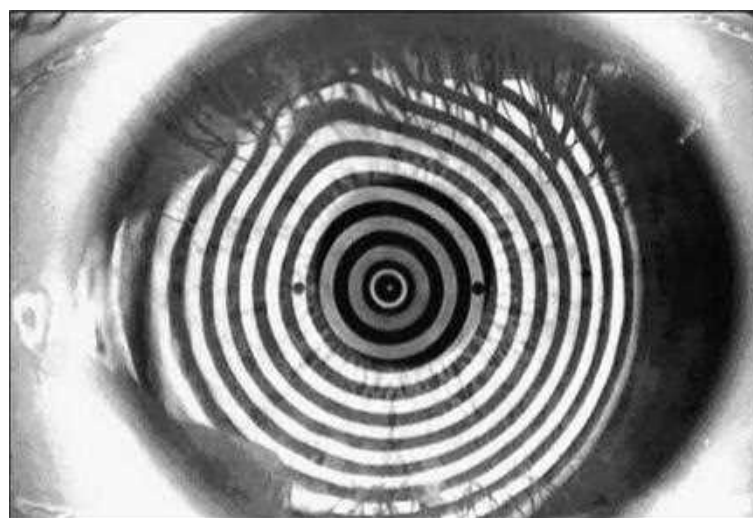
**Fig. 5.10.3** Clear corneal incision (2.5 mm).



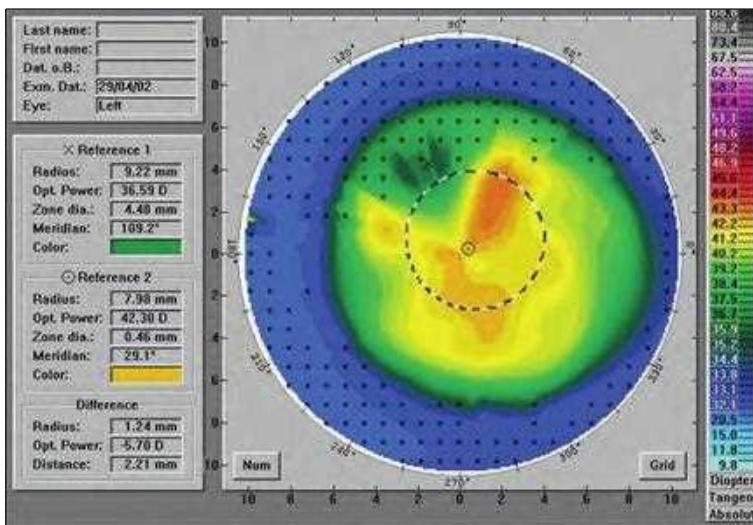
**Fig. 5.10.5** Large clear corneal incision—more effect. OZ, optical zone.

(3) 5.5 mm scleral tunnel, 54 eyes. Incisions lay on the 120° semi-meridian. Corneal topography was performed preoperatively and 1 week, 1 month, and 3 months postoperatively. Simulated keratometric readings were used to calculate astigmatism amplitude and surgically induced astigmatism (SIA). Postoperative topographic changes were determined by subtracting the preoperative numeric map readings from the postoperative numeric map readings. At 3 months postoperatively, the mean SIA in the right and left eyes, respectively, was  $0.68 \pm 1.14$  D (SD) and  $0.66 \pm 0.52$  D in the 3.5 mm CCI group,  $1.74 \pm 1.4$  D and  $1.64 \pm 1.27$  D in the 5.5 mm CCI group, and  $0.46 \pm 0.56$  D and  $0.10 \pm 1.08$  D in the scleral tunnel group. Right and left eyes showed similar SIA amplitude but different SIA meridian orientation. SIA was significantly higher in the 5.5 mm CCI group than in the other two groups 1 and 3 months postoperatively ( $P < 0.01$ ). All groups showed significant wound-related flattening and non-orthogonal steepening at two opposite radial sectors. Topographic changes were significantly higher in the 5.5 mm CCI group and significantly lower in the scleral tunnel group.

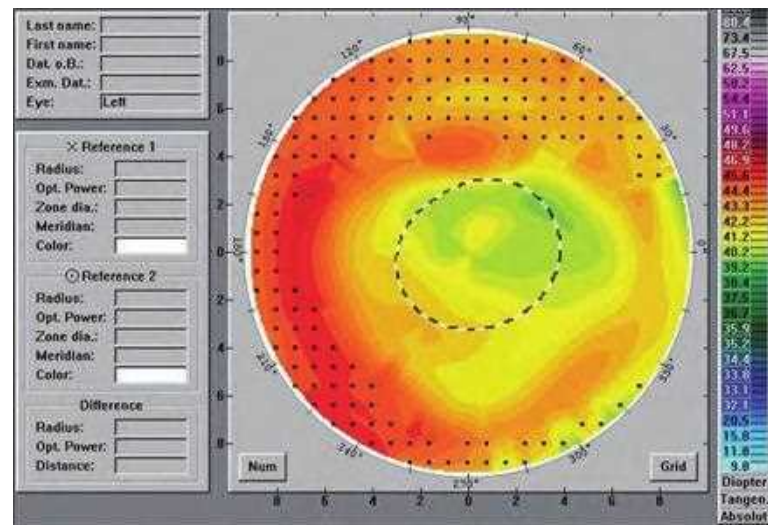
Right and left eyes showed similar SIA amplitudes but different SIA meridian orientations and topographic modifications, probably because of the different supero-temporal and supero-nasal corneal anatomic structures. The 5.5 mm CCI induced significantly higher postoperative astigmatism, SIA, and topographic changes.



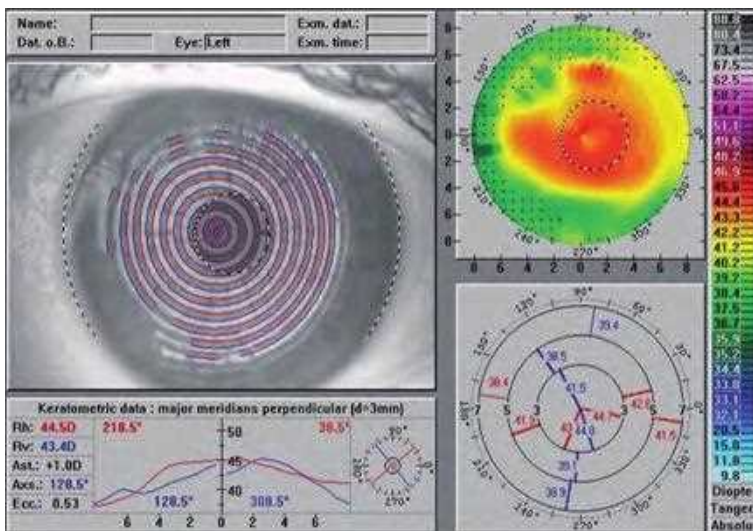
**Fig. 5.10.6** Topography map of 3-mm clear corneal incision. Peripheral flattening of cornea but no central effect.



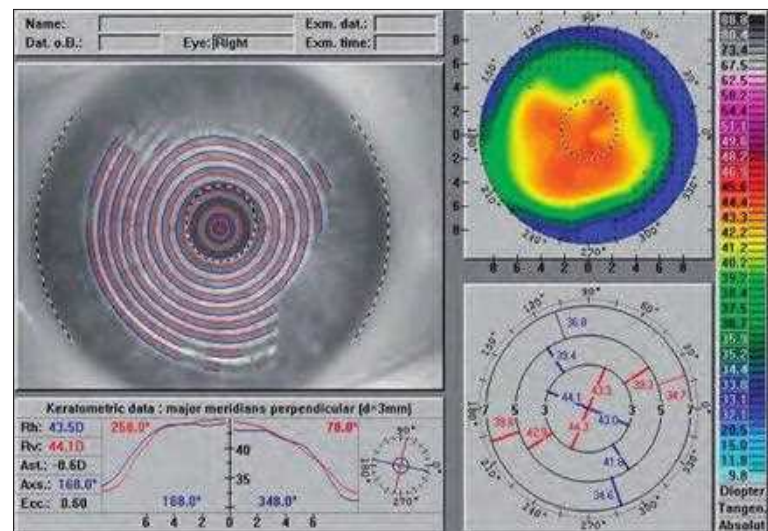
**Fig. 5.10.7** Topography map of 2.5-mm clear corneal incision. No peripheral flattening of the cornea or central effect.



**Fig. 5.10.9** Topography map of 3.7-mm clear corneal incision. (See the videokeratograph in Fig. 5.10.8.) The map illustrates the central effect of a larger peripheral clear corneal incision, with resulting nonorthogonal astigmatic hemi-meridia.



**Fig. 5.10.8** Videokeratograph of a 3.7-mm clear corneal incision. Note the localized flattening of the cornea close to incision, also affecting the optical zone.



**Fig. 5.10.10** Postoperative topography map following opposite clear corneal incision for 5 D astigmatism. Note the four hemi-meridia but no manifest or topographic astigmatism.

## TO TREAT PREOPERATIVE CORNEAL ASTIGMATISM

### Astigmatic Incisions

The cornea does not have axes but has only meridians, and all references to corneal incisions for the relief of astigmatic error in the cornea should be made to the “steep meridian.”

### Limbal Relaxing Incisions

Kaufmann et al.<sup>5</sup> compared limbal relaxing incisions (LRIs) with placement of the corneal cataract incision on the steepest keratometric meridian for the reduction of pre-existing corneal astigmatism at the time of cataract surgery. In a prospective single-center study, patients having 1.5 D or more of keratometric astigmatism were randomly assigned to two surgical techniques: on-steep meridian incisions (SMIs) consisting of a single CCI centered on the steepest corneal meridian; or LRIs consisting of two arcuate incisions straddling the steepest corneal meridian and a temporal CCI. After 6 months, the flattening effect was 0.35 D (range 0–0.96 D) and 1.10 D (range 0.25–1.79 D), respectively ( $P = 0.004$ ), thus confirming that the amount of astigmatism reduction achieved at the intended meridian was significantly more favorable with use of the LRI technique and remained consistent throughout the follow-up period.

### Opposite Clear Corneal Incisions

Lever and Dahan<sup>6</sup> were the first surgeons to demonstrate that in cataract surgery, the CCI has a small flattening effect on corneal curvature, which can be used to reduce pre-existing astigmatism (PEA). Adding an identical, penetrating CCI opposite the first one enhances the flattening effect. The extent of flattening affecting the optical zone of the cornea is dependent on the width of the clear corneal tunnel incision and the way it is constructed. Although a general algorithm can be devised, in general, it is incumbent upon each surgeon to devise his or her own algorithm, as the location of the incision, the knife used, and the length of the tunnel are difficult to standardize. Suffice it to say, the wider the incision and the more centrally it is placed, the greater will be its effect. The local flattening of the incision only has a central effect if it is wide enough. Figs. 5.10.2–5.10.15 illustrate all the incisions, their effects, and the healing process as depicted by corneal topography. It is recommended that surgeons wishing to utilize the technique should study the effects of their own CCIs through the medium of corneal topography and thereby derive a personal nomogram.

Paired opposite CCIs (OCCIs) are placed on the steepest meridian to achieve a reduction in the dioptric power of the central cornea. One CCI is used to perform cataract surgery, and the opposite CCI is made to ensure symmetry of the flattening effect and, therefore, to modulate PEA. Lever and Dahan<sup>6</sup> used 2.8- to 3.5-mm OCCIs in 33 eyes having PEA greater

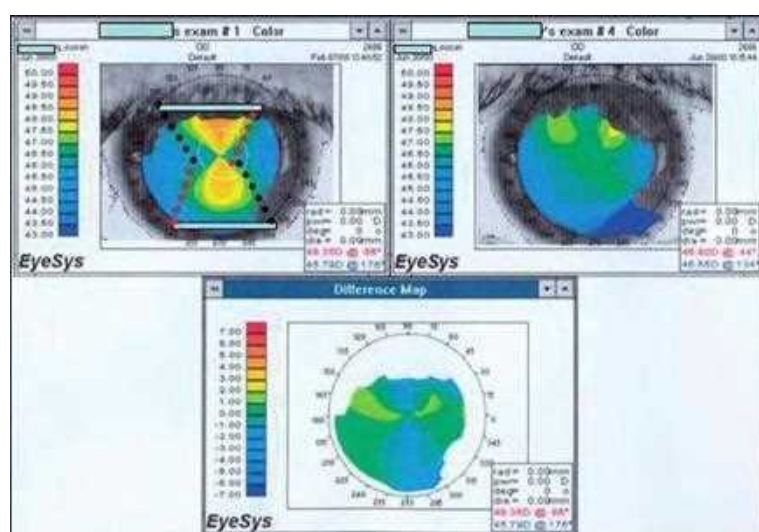


than 2.00 D and undergoing cataract surgery. The mean astigmatism correction achieved with this technique was 2.06 D. This technique is simple and effective and yields stable results that rival those of arcuate keratotomy. The OCCI technique has a potential application for the correction of astigmatism in general refractive surgery.

Qam-mar and Mullaney<sup>7</sup> evaluated the effect of OCCIs in correcting astigmatism on the steep corneal meridian axis in 14 patients with cataracts. They achieved a mean correction of astigmatism of  $1.23 \pm 0.49$  D (range 0.30–2.20 D). The mean surgically corrected astigmatism by vector analysis was  $2.10 \pm 0.79$  D (range 0.80–3.36 D). As other studies have shown,<sup>6–9</sup> paired OCCIs on the steep corneal meridian correct astigmatism in eyes undergoing cataract surgery with the use of routine surgical instruments.

The features of OCCIs may be summarized as follows:

- OCCIs cause negligible effect on spherical equivalence and, therefore, do not influence biometric calculations.
- Paired incisions are used for symmetric effect.
- Asymmetric OCCIs are used for asymmetric (“bow tie”) astigmatism.
- OCCIs are to be placed on a steep corneal meridian.



**Fig. 5.10.11** Preoperative, postoperative, and difference topography maps to illustrate opposite clear corneal incision (OCCI) effect. OCCI OD  $-15.5/+3.0 \times 90$  Plano post-op (4.5 mm OCCI); effect of each OCCI illustrated by dotted lines.

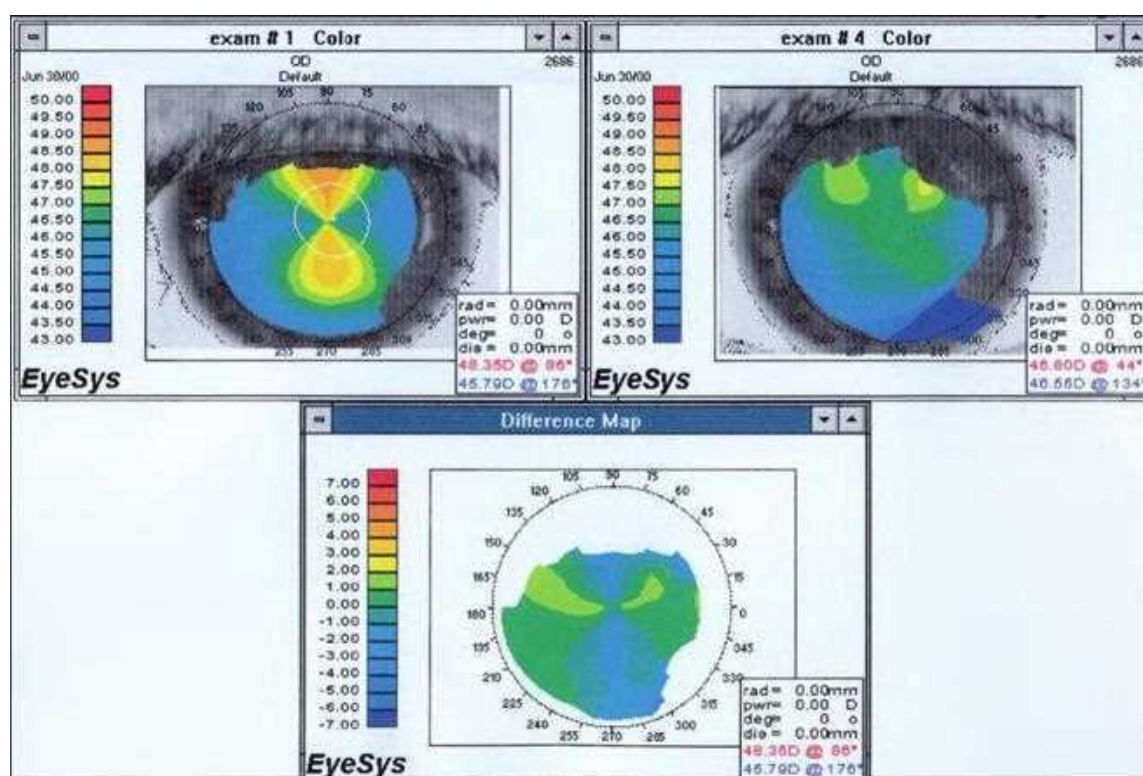
- The bulk of the cornea is preserved in case of need for correction of minor astigmatism with arcuate keratotomies.
- OCCIs also may be referred to as opposite penetrating astigmatic keratotomies (OPAKs).

## TORIC INTRAOCULAR LENS IMPLANTATION

Toric intraocular lenses can be used as an alternative or adjunct to corneal astigmatic incisions for correcting PEA in patients with cataracts. They are a particularly attractive option in those cases where LRIs or OCCIs are not powerful or predictable enough. Phaco extraction of a cataract through a small (astigmatically neutral) incision with toric intraocular lens implants (TIOLs) is an attractive alternative for patients with cataract and significant corneal astigmatism ( $> 1.5$  D). The elimination or reduction of preoperative astigmatism provides many patients with the prospect of clear distance vision without the aid of glasses.<sup>9–11</sup>

TIOLs for the correction of corneal astigmatism in cataractous and pseudophakic eyes. Accurate rotational stability and axial alignment are critical to the success of TIOL surgery. Factors that may influence the rotational stability of the TIOL include IOL design (plate haptic), overall haptic diameter, IOL material, and the eye's axial length. TIOL alignment meridian, size, and integrity of the capsulorrhexis, capsular bag dimensions, and postoperative healing/shrinkage. Despite accurate preoperative biometry and intraoperative alignment, patients may lose the benefits of astigmatism correction if the TIOL rotates after the operation.<sup>12–14</sup> Cataract surgery with TIOL allows the correction of high degrees of regular corneal astigmatism. Toric lens cataract surgery also is valuable as a secondary procedure, for example, after keratoplasty, with resultant higher degrees of regular residual astigmatism.<sup>15</sup>

Spontaneous rotation of a TIOL can occur and will require correction by surgical intervention to restore the IOL to its correct neutralizing alignment in astigmatism. An example of this is the case of a 23-year-old female with myopic astigmatism who underwent TIOL implantation. Preoperative uncorrected visual acuity (UCVA) was 20/800 and 20/1200, respectively, with  $-7.75 -4.25 \times 0^\circ$  and  $-8.25 -5.25 \times 180^\circ$ . In the left eye, an UCVA of 20/30 was achieved. After 3 months of successful implantation of TIOL in the left eye, the patient presented with a sudden decrease in visual acuity in this eye. UCVA was 20/100 with a refraction of  $+2.50 -4.50 \times 165^\circ$ . The toric marks showed a  $30^\circ$  rotation from the original position and required repositioning of the TIOL, resulting in a final UCVA of 20/25, which remained stable at 6 months' follow-up. A TIOL can undergo considerable rotation, and inevitably this will compromise visual acuity. Its relocation, therefore, is required, and more often than not, this will prove to be an effective procedure to recover visual acuity.<sup>16</sup>

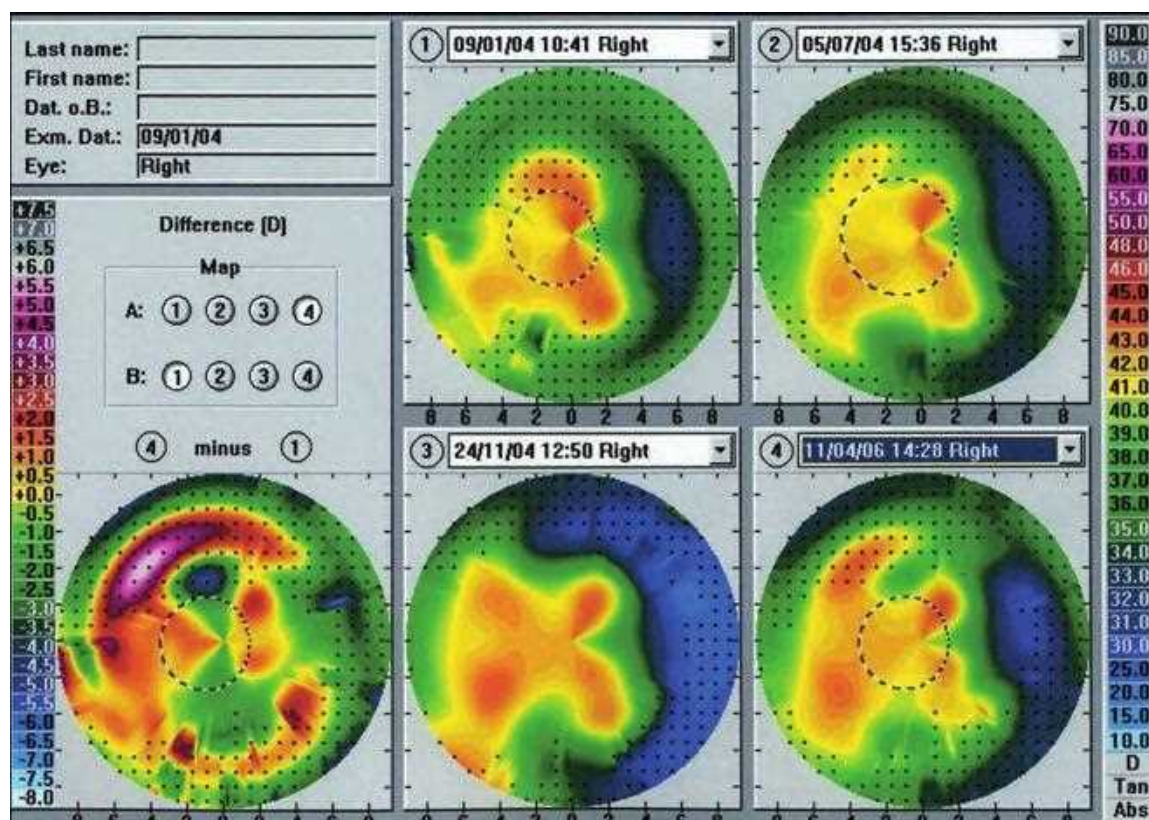


**Fig. 5.10.12** Preoperative, postoperative, and difference topography maps to illustrate opposite clear corneal incision effect. Opposite clear corneal incision (OCCI) OD  $-15.5/+3.0 \times 90$  Plano post-op (4.5 mm OCCI).









**Fig. 5.10.15** OD (right eye) pre-op +10.25/−4.5 × 175 ≡ 6/6–2 postoperative +0.25 ≡ 6/5 uncorrected visual acuity (UCVA) 6/5. Topography maps illustrating sequential healing responses of cornea to opposite clear corneal incision effect. Difference map illustrates flattening of original astigmatism. Manifest refraction virtually plano. Final map illustrates typical four hemi-meridia with spherical optical zone.

## LIGHT-ADJUSTABLE INTRAOCULAR LENS IMPLANT

Residual refractive errors after cataract and lens implant surgery are treated with corneal incisional surgery, excimer laser corneal surgery, or toric IOL primary or secondary implantation (piggyback lens implants), but a one-step planned refractive outcome remains desirable. The light-adjustable intraocular lens implant (LAL) offers the prospect of consulting room, postoperative, refractive adjustment of the provisional refractive outcome of the primary surgery, even though with secondary adjustment steps but without the requirement for further surgical intervention. The LAL incorporates a photosensitive silicone macromer in a medical-grade silicone polymer matrix. The photosensitive IOL component is 100 µm molded onto the posterior surface of the silicone optic of the IOL. This posterior layer has a higher concentration of ultraviolet (UV) light absorber compared with the anterior portion of the implant optic. Selective irradiation of the LAL uses a specific UV (365 nm) beam to irradiate the IOL and produces a controlled spherical and/or cylindrical power change; this is undertaken a few weeks postoperatively, when the eye's refraction has stabilized after the cataract surgery. In the interim period, the patient has to wear UV-filtering glasses to prevent unwanted UV radiation entering the eye before it is appropriate to apply the selective exposure, after which the refractive power of the implant is locked in. Postoperative studies with longer-term follow-up are impressive.<sup>26–28</sup>

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# Small Incision and Femtosecond Laser-Assisted Cataract Surgery

Mark Packer

# 5.11



**Definition:** Small incision cataract surgery is the extraction of the lens through a corneal incision designed to be self-sealing.

## Key Features

- The refinement of incision placement and architecture, as well as the reduction of final incision size occasioned by the implantation of a foldable, injectable intraocular lens, permits the reduction of postoperative astigmatism and enhancement of refractive cataract surgery.
- Continuous curvilinear capsulorhexis facilitates sculpting techniques, such as divide and conquer, trending to today's preferred horizontal and vertical chopping methods.
- Hydrodissection to lyse cortical–capsular connections.
- Hydrodelineation to permit phaco within the protective layer of the epinucleus improves the safety and efficiency of phaco.
- Power modulations, such as millisecond level control of ultrasound power application, allow for reduction of the energy required for cataract extraction, protection of the cornea from thermal injury, and enhancement of the rapidity of postoperative visual rehabilitation.
- Femtosecond laser-assisted surgery represents a relatively new technology that some surgeons have adopted for cataract extraction.

## Associated Feature

- The separation of irrigation from aspiration made possible through biaxial microincision phaco represents an advance in control of the fluidic behavior of the intraocular environment, permitting greater versatility in every step of the cataract extraction procedure.

## INTRODUCTION

The principal technical features of phaco include the following:

- Watertight, self-sealing corneal incisions.
- Intact, round, centered capsulorhexis with a diameter smaller than that of the intended intraocular lens (IOL) optic.
- Efficient ultrasound power modulation and fluidics to protect the capsule, iris, and cornea.
- Fastidious cortical cleanup, resulting in a clean capsular bag.
- Atraumatic IOL insertion through an incision of 1.5–2.4 mm.

“Phaco” refers to the techniques and technology required for the fragmentation and extraction of the crystalline lens through a small corneal incision and the implantation of an intraocular lens (IOL), resulting in rapid visual rehabilitation and reduced need for optical correction.

Since the time of its introduction in the late 1960s, phaco has evolved into a highly effective method of cataract extraction. Incremental advances in surgical technique and the simultaneous redesign and modification of technology have permitted increased safety and efficiency. Among the advances that have shaped modern phaco are incision construction, continuous curvilinear capsulorhexis, cortical cleaving hydrodissection and hydrodelineation, and nucleofractis techniques.

The United States patent #3589363, filed July 25, 1967, lists Anton Banko and Charles D. Kelman as inventors of “an instrument for breaking apart and removal of unwanted material, especially suitable for surgical

operations such (as) cataract removal, including a handheld instrument having an operative tip vibrating at a frequency in the ultrasonic range with an amplitude controllable up to several thousandths of an inch.”<sup>1</sup>

Even until recently, the fundamental mechanisms by which the system known as “phaco” operates has remained controversial. Although some authors have described the surgical advantages of a unique type of cavitation energy, others have denied any role for cavitation energy in phaco.<sup>2</sup>

## INCISION CONSTRUCTION AND ARCHITECTURE

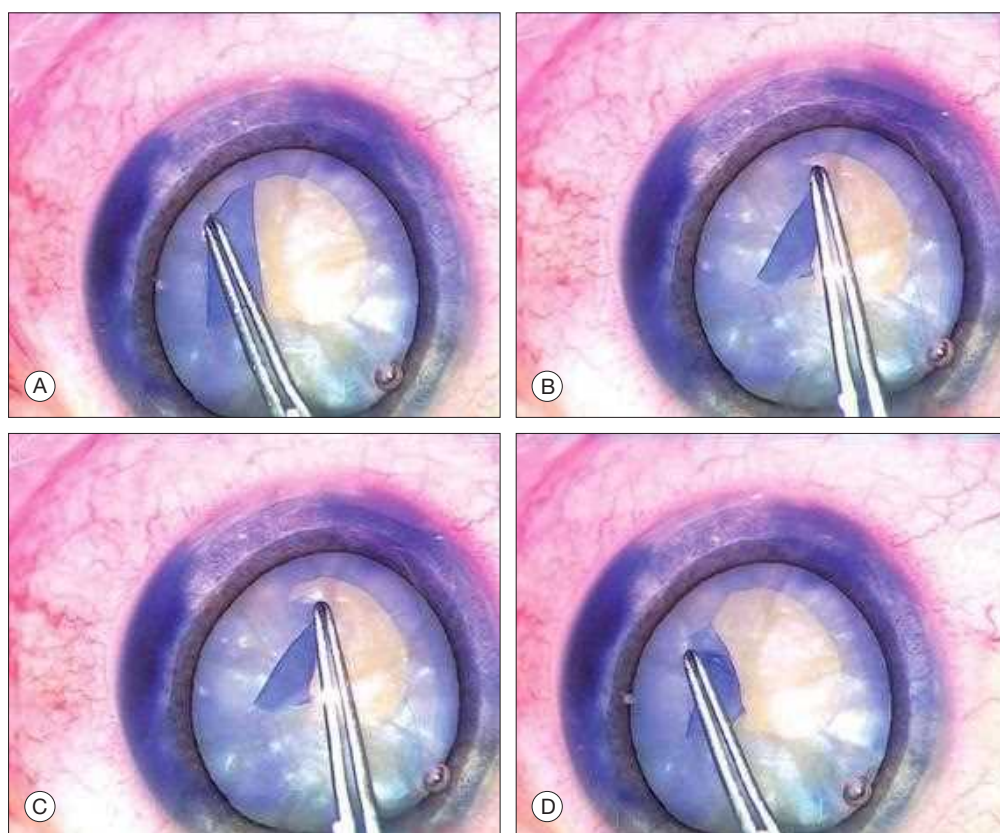
Since 1992, when Fine described the self-sealing temporal clear corneal incision (CCI), the availability of foldable IOLs has furthered the trend away from scleral tunnel incisions to clear corneal incisions.<sup>3</sup> Rosen demonstrated through topographic analysis that CCIs 3 mm or less in width do not induce significant astigmatism.<sup>4</sup> This finding led to increasing interest in T-cuts, arcuate cuts, and LRIs for managing pre-existing astigmatism at the time of cataract surgery. Surgeons recognized many other advantages of the temporal CCI, including better preservation of the conjunctiva, increased stability of refractive results because of decreased effects from lid blink and gravity, ease of approach, elimination of the bridge suture and iatrogenic ptosis, and improved drainage from the surgical field via the lateral canthal angle.

Surgeons originally adopted single-plane incisions utilizing a 3-mm diamond knife. After pressurizing the eye with viscoelastic through paracentesis, the surgeon placed the blade on the eye so that it completely applanated the eye, with the point of the blade positioned at the leading edge of the anterior vascular arcade. The knife was advanced in the plane of the cornea until the shoulders, 2 mm posterior to the point of the knife, touched the external edge of the incision. Then, the point of the blade was directed posteriorly to initiate the cut through Descemet's membrane in a maneuver known as the *dimple-down technique*. After the tip entered the anterior chamber, the initial plane of the incision was re-established to cut through Descemet's membrane in a straight-line configuration.

Williamson was the first to utilize a shallow 300–400  $\mu$ m grooved CCI.<sup>5</sup> Langerman later described the single-hinge incision, in which the initial groove measured 90% of the depth of the cornea anterior to the edge of the conjunctiva.<sup>6</sup> Surgeons employed adjunctive techniques to combine incisional keratorefractive surgery with CCIs. Osher described the construction of arcuate keratotomy incisions at the time of cataract surgery for correction of pre-existing corneal astigmatism. Kershner used the temporal incision by starting with a nearly full-thickness T-cut, through which he then made his corneal tunnel incision.<sup>7</sup> Finally, the recommendation of LRIs by Gills and Nichamin advanced what ultimately became most popular means of reducing pre-existing astigmatism.<sup>8,9</sup>

Following phaco, lens implantation, and removal of residual viscoelastic, stromal hydration may be performed to seal the incisions by gently irrigating balanced salt solution into the stroma at both edges of the incision with a 26- or 27-gauge cannula. An intraoperative Seidel test may be used to ensure sealing. Studies of sequential optical coherence tomography of postoperative CCIs have demonstrated that the edema from stromal hydration lasts up to 1 week.<sup>10</sup>

CCIs, by nature of their architecture and location, are associated with unique complications. Chemotic ballooning of the conjunctiva may occur as a result of irrigating fluid streaming into an inadvertent conjunctival incision. In this case, the conjunctiva may be snipped to permit decompression. Incisions that are too short can result in an increased tendency for iris prolapse and poor sealability. A single suture may be required to



**Fig. 5.11.1** Backward traction on the capsular flap forms the basis of a predictable technique for rescuing the capsulorrhexis from a radial tearout. As shown here in the case of an opaque cataract with trypan blue capsule stain, the tear has extended too far to the periphery (A). Therefore, the flap is unfolded and laid back in the plane of the capsulorrhexis from where it was torn (B). The flap is then pulled with reverse tangential force until the capsule tears back toward the center (C). Construction of the capsulorrhexis may then continue (D).

secure the wound. In contrast, a long incision may result in striae in the cornea that compromise the surgeon's view during phaco. Coarse manipulation of the phaco tip may result in epithelial abrasions or tears in Descemet's membrane, compromising self-sealability. Of great concern is the risk of incisional burns.<sup>11</sup> When incisional burns develop in CCIs, rapid contraction of tissue and loss of self-sealability occur. Suture closure of the wound may induce excessive astigmatism.

The literature supports the view that suboptimal construction of CCIs may lead to poor coaptation, inadequate sealing, and ingress of bacteria, thereby increasing the risk of acute postoperative bacterial endophthalmitis.<sup>12</sup> However, four large published series have found no greater likelihood of infection with corneal versus other types of incisions.<sup>13–16</sup> Regardless of the type of incision, the principle to be followed is that appropriate incision construction and watertight closure are obligatory. Besides poor wound closure, other significant factors that have been associated with higher risk of postoperative infection include posterior capsule rupture, vitreous loss, older age, prolonged surgery, immunodeficiency, active blepharitis, lacrimal duct obstruction, inferior incision location, and male gender.<sup>17</sup>

## CONTINUOUS CURVILINEAR CAPSULORRHEXIS

Implantation of the IOL in an intact capsular bag facilitates the permanent rehabilitative benefit of cataract surgery. For many years, surgeons considered a “can opener” capsulectomy to be satisfactory for both planned extracapsular cataract extraction and phaco. However, in 1991, Wasserman et al. performed a postmortem study that showed that the extension of one or more V-shaped tears toward the equator of the capsule produced instability of the IOL and resulted in malpositioning of the IOL.<sup>18</sup> Gimbel and Neuhann popularized continuous curvilinear capsulorrhexis (CCC) in the later 1980s.<sup>19–21</sup>

The basic principles of manual CCC include the following:

- The continuous capsular tear should be performed in a stable anterior chamber under pressurization by an ophthalmic viscosurgical device (OVD).
- The tear should be initiated at the center of the capsule so that the origin is included within the circle of the tear.
- The continuous tear may proceed either clockwise or counterclockwise in a controlled and deliberate fashion, the surgeon regripping with the forceps or repositioning the point of the cystotome/bent needle on the inverted flap to control the vector of the tear.

A tear that begins moving peripherally or radially is a signal that an existing condition requires immediate attention. Further progress of the

tear should be stopped and the depth of the anterior chamber assessed. Frequently, the cause of the peripheral course of the tear is shallowing of the anterior chamber. Adding more OVD to deepen the anterior chamber opposes the posterior pressure, making the lens capsule taut, widening the pupil, and permitting inspection of the capsule (Video 5.11.1).

One important technique for redirection of the capsulorrhexis has been described by Little.<sup>22</sup> In this technique, to rescue the capsulorrhexis from a peripheral tearout, the force applied to the capsular flap is reversed but maintained in the plane of the anterior capsule. It is necessary to first unfold the capsular flap so that it lies flat against the lens cortex, as it did prior to being torn. Force can then be applied with the capsule forceps by holding the capsular flap as close to the root of the tear as possible and pulling backward in a retrograde direction along the circumferential path of the completed portion of the capsulorrhexis. Traction should be applied in the horizontal plane of the capsule and not upward. The initial pull should be circumferentially backward and then, while holding the flap under tension, directed more centrally to initiate the tear. The forward progress of the capsulorrhexis will uniformly and predictably redirect toward the center of the capsule (Fig. 5.11.1). If the capsule will not tear easily and the entire lens is being pulled centrally, this rescue maneuver should be abandoned to avoid a wrap-around capsular tear or zonular dialysis. Other rescue techniques, such as completing the capsulorrhexis from the opposite direction or making a relieving cut in the flap edge and continuing in the same direction, represent reasonable alternatives.

The use of trypan blue to stain the anterior capsule in the absence of a good red reflex constitutes an important adjunctive technique for capsulorrhexis construction. The dye may be injected into the chamber through paracentesis under air. The air and residual dye are then exchanged for viscoelastic. Despite the absence of a red reflex, the capsule is easy to see.

The technique of CCC has provided important advantages both for cataract surgery and IOL implantation. Because endolenticular or in situ phaco must be performed in the presence of an intact continuous capsulectomy opening, capsulorrhexis has served as a stimulus for modification of phaco techniques. The edge of a well-constructed rhexis completely overlaps the edge of the IOL, ensuring positional stability and enhancing refractive predictability.

## HYDRODISSECTION AND HYDRODELINEATION

Hydrodissection has traditionally meant injection of fluid into the cortical layer of the lens to separate the nucleus from the cortex and the capsule. Following the adoption of capsulorrhexis, hydrodissection became a critical step to mobilize, disassemble, and remove the nucleus. Fine first described



cortical cleaving hydrodissection, which is designed to cleave the cortex from the capsule and leave the cortex attached to the epinucleus.<sup>23</sup> Cortical cleaving hydrodissection often eliminates the need for cortical cleanup as a separate step in cataract surgery.

In this technique, the anterior capsular flap is initially elevated with a 26-gauge blunt cannula. Firm and gentle continuous irrigation results in a fluid wave that cleaves the cortex from the posterior capsule. The lens bulges forward because fluid is trapped by equatorial cortical–capsular connections. Depressing the central portion of the lens with the side of the cannula forces fluid around the equator and lyses the cortical–capsular connections. Adequate hydrodissection is demonstrated by rotation of the nuclear–cortical complex. The demonstration of free rotation of the lens within the capsule represents a critical step in phaco.

Hydrodelineation describes separation of the epinuclear shell from the endonucleus by irrigation. The epinucleus acts as a protective cushion within which phaco forces can be confined. Further, the epinucleus keeps the bag on stretch throughout the procedure, making capsule rupture less likely.

To perform hydrodelineation, a 26-gauge cannula is placed in the nucleus, off center to either side, and directed at an angle downward and forward toward the central plane of the nucleus. When the nucleus starts to move, the endonucleus has been reached. At this point, the cannula is directed tangentially to the endonucleus, and a to-and-fro movement of the cannula is used to create a tunnel within the epinucleus. The cannula is backed out of the tunnel approximately halfway, and gentle but steady pressure on the syringe allows fluid to enter the distal tunnel without resistance. A circumferential golden or dark ring will appear, outlining the endonucleus.

Occasionally, an arc, rather than a complete ring, will result, surrounding approximately one quadrant of the endonucleus. In this instance, the procedure can be repeated in multiple quadrants until a golden or dark ring confirms complete circumferential separation of the endonucleus from the epinucleus.

## NUCLEOFRACTIS TECHNIQUES

The recognition that the lens nucleus could be divided and removed from within the protective layer of the epinucleus while preserving the capsulorrhexis influenced the development of a plethora of phaco techniques.

### Divide and Conquer

In the divide-and-conquer technique originally described by Gimbel,<sup>24</sup> a deep crater is sculpted into the center of the nucleus, including the posterior plate. However, phaco fracture, described by Shepherd, is often referred to as a “divide and conquer” technique.<sup>25</sup> In this technique, the surgeon sculpts a groove parallel to the incision one and a half to two times the diameter of the phaco tip, with the tip in a bevel-up position, using moderate power and low vacuum. Using the phaco handpiece and a second instrument, the surgeon then rotates the nucleus by 90° and sculpts a second groove perpendicular to the first. Sculpting continues until the red reflex is seen at the bottom of the grooves. A bimanual cracking technique is used to create a fracture through the nuclear rim in the plane of one of the grooves. The nucleus is then rotated by 90°, and additional fractures are made until four separate quadrants are isolated. A short burst of phaco power with increased vacuum then is used to embed the phaco tip into one quadrant, which is pulled into the center for emulsification. The second instrument can help elevate the apex of the quadrant to facilitate its mobilization.

### Phaco Chop

Nagahara first introduced the “phaco chop” technique by using the natural fault lines in the lens nucleus to create cracks without creating prior grooves (Presentation at the American Society of Cataract and Refractive Surgery Film Festival, 1993). The phaco tip is embedded in the center of the nucleus after the superficial cortex is aspirated. In horizontal chopping, a second instrument, the phaco chopper, is then passed to the equator of the nucleus, beneath the anterior capsule, and drawn to the phaco tip to fracture the nucleus. The two instruments are separated to widen the crack. In vertical chopping, a sharp-tipped instrument is inserted directly into the nucleus beside the embedded phaco needle, and the two instruments are again separated as in horizontal chopping. The nucleus is rotated, and this procedure is repeated until several small fragments are created, which are then emulsified.

## POWER MODULATIONS

Fine described the “choo-choo chop and flip” technique in 1998 and subsequently correlated the reduction of ultrasound energy made possible by power modulations with superior uncorrected visual acuity on the first post-operative day.<sup>26,27</sup> Effective phaco time (EPT), absolute phaco time (APT), and cumulative dissipated energy (CDE) have become standard metrics for the utilization of ultrasound energy. Although EPT, APT, and CDE cannot be compared across different machines made by different manufacturers, when using the same machine, they can be compared from one case to the next as a sign of surgical efficiency.

In Fine’s technique, a 30° straight phaco tip is used bevel down. After aspirating the epinucleus uncovered by capsulorrhexis, a horizontal chopper is placed in the golden ring by touching the top center of the nucleus with the tip and pushing the tip peripherally so that it slides beneath the capsulorrhexis. The chopper is used to stabilize the nucleus by lifting and pulling toward the incision slightly, after which the phaco tip “lollipops” the nucleus in either pulse mode at 2 pulses per second or at the 80-millisecond burst mode. Burst mode utilizes fixed power and duration with variable interval. In pulse mode, there is variable power with fixed duration and interval. These power modulations reduce total ultrasound energy and increase hold. Once the tip is buried in the center of the nucleus, vacuum is maintained in foot position 2. The nucleus is scored by bringing the chopper to the side of the phaco needle. It is chopped in half by pulling the chopper to the left and slightly down while moving the phaco needle, still in foot position 2, to the right and slightly up (Fig. 5.11.2). Then, the nuclear complex is rotated by 90°. The chop instrument is again brought into the golden ring, the hemi-nucleus is lollipopped, scored, and chopped with the resulting wedge now lollipopped on the phaco tip and evacuated. The nucleus is rotated so that wedges can be scored, chopped, and removed by high vacuum assisted by short bursts or pulses of phaco. The size of the wedges is varied according to the density of the nucleus.

After evacuation of all endonuclear material, the epinuclear rim is trimmed in each of the three quadrants, mobilizing the cortex. As each quadrant of the epinuclear rim is rotated to the distal position in the capsule and trimmed, the cortex in the adjacent capsular fornix flows over the floor of the epinucleus and into the phaco tip. The floor is pushed back to keep the bag on stretch until three of the four quadrants of the epinuclear rim and cortex have been evacuated. The epinuclear rim of the fourth quadrant is then used as a handle to flip the epinucleus. As the remaining portion of the epinuclear floor and rim is evacuated from the eye, the entire cortex is often evacuated with it.

If there is remaining cortex after removal of all the nucleus and epinucleus, there are three options. The phaco handpiece can be left high in the anterior chamber while the second handpiece strokes the cortex-filled capsular fornices. Frequently, this results in floating the cortical shell as a single piece and aspirating it through the phaco tip (in foot position 2) because cortical cleaving hydrodissection has cleaved most of the cortical–capsular adhesions.

Alternatively, if one wishes to complete cortical cleanup with the irrigation–aspiration handpiece prior to lens implantation, the residual cortex can almost always be mobilized as a separate and discrete shell and removed without turning the aspiration port down to face the posterior capsule.

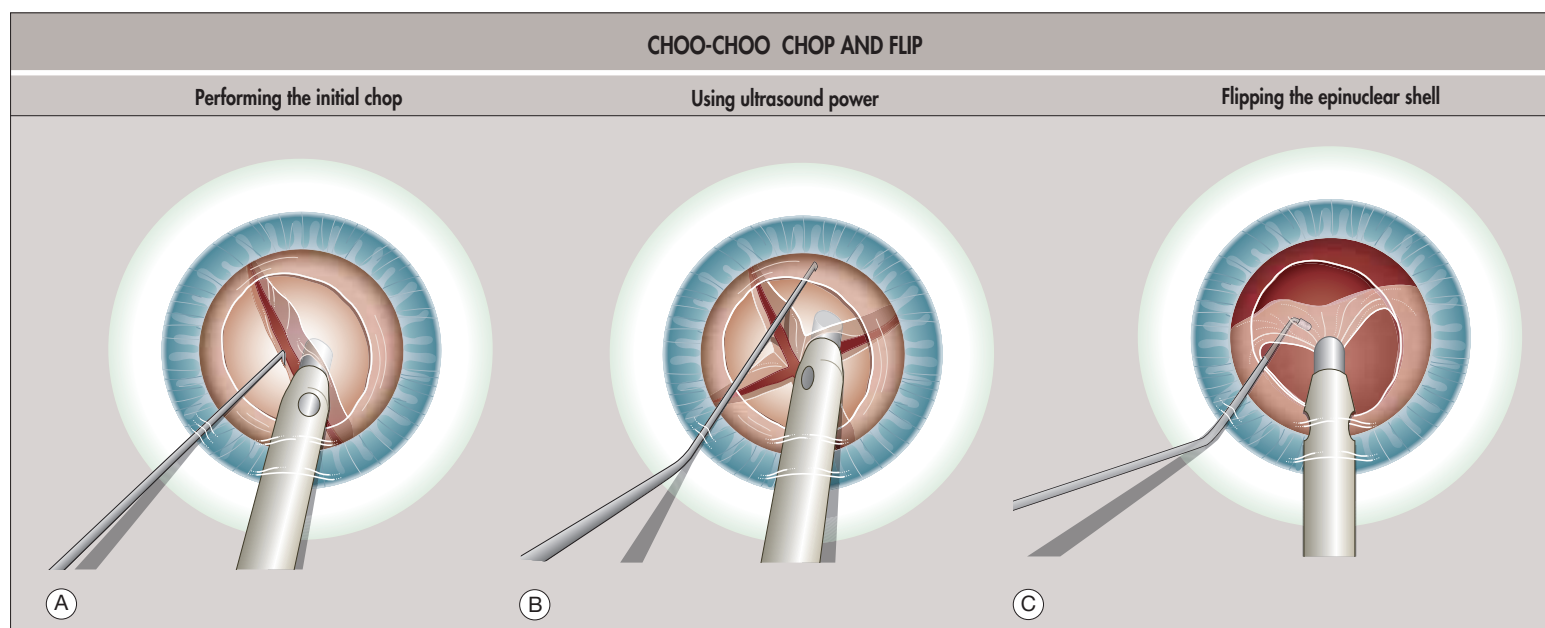
The third option is to visco-dissect the residual cortex by injecting a dispersive viscoelastic through the posterior cortex onto the posterior capsule. The viscoelastic material spreads horizontally, elevating the posterior cortex and draping it over the anterior capsular flap. At the same time, the peripheral cortex is forced into the capsular fornix. The posterior capsule is then deepened with a cohesive OVD, and the IOL is implanted, leaving anterior residual cortex anterior to the IOL. Removal of residual OVD material accompanies mobilization and aspiration of the residual cortex.

Nonlinear delivery of ultrasonic or sonic frequencies, such as torsional and elliptical phaco, has further improved operating efficiency. Chopping techniques in combination with power modulations and nonlinear ultrasound power delivery minimize morbidity and enhance the rapidity of visual rehabilitation.

## BIAXIAL MICROINCISION CATARACT SURGERY

Advances in ultrasound engineering during the late 1990s led to the application of millisecond-level control and variable duty cycles in phaco, vastly reducing the risk of thermal injury from the phaco needle and permitting removal of the irrigation sleeve. Separation of irrigation from aspiration





**Fig. 5.11.2** The surgeon performs the initial chop of the nucleus by deeply embedding the phaco needle in the center of the nucleus using ultrasound power, and then maintaining a hold on the nucleus with high vacuum in foot pedal position 2 without ultrasound as the horizontal chopper is brought from the golden ring to the side of the phaco needle to score the nucleus. The surgeon then completes the chop by separating the instruments with a slight upward movement of the phaco tip and a slight downward movement of the chopper (A). Each quadrant of nuclear material is in turn impaled, chopped, mobilized, and consumed with high vacuum and low amounts of ultrasound power (B). Finally, the epinuclear shell is flipped with a helpful push from the chopper (C).



during phaco came to be known as *biaxial microincision cataract surgery* (B-MICS) (Video 5.11.2).

The advantages of B-MICS include better followability because of the separation of infusion and aspiration, access to 360° of the capsular bag with either infusion or aspiration by switching instruments from one hand to the other, the ability to use the flow of irrigation fluid as a tool to move material within the capsular bag or anterior chamber (particularly from an open-ended irrigating chopper or manipulator), prevention of iris billowing and prolapse in cases of intraoperative floppy iris syndrome, and significantly decreased risk of vitreous prolapse in the case of a posterior capsular tear, zonular dialysis, or subluxated cataract, thanks to maintenance of a pressurized stream of irrigation.

Perhaps the greatest advantage of the biaxial technique lies in its ability to remove the subincisional cortex without difficulty. As originally described by Brauweiler, by switching infusion and aspiration handpieces between two microincisions, 360° of the capsular fornices are easily reached, and cortical cleanup can be performed quickly and safely.<sup>28</sup>

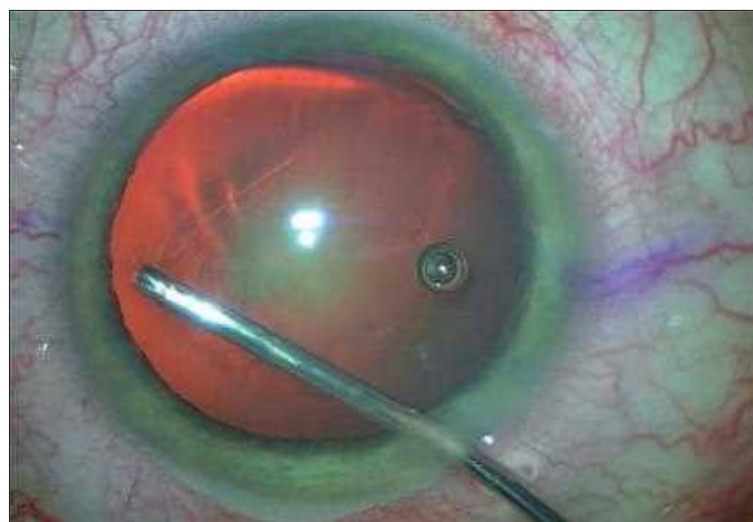
Since dispersive OVDs do not easily extrude through these small incisions, the anterior chamber is more stable during capsulorhexis construction, and there is much less likelihood of an errant tear. This added margin of safety is particularly noticeable in cases of zonular compromise, such as pseudo-exfoliation and traumatic zonular dialysis (Fig. 5.11.3). The added chamber stability also can make a difference in control of the capsulorhexis in both high myopia and high hyperopia with an extremely deep or a very shallow anterior chamber, respectively (Video 5.11.3).



## B-MICS VERTICAL CHOP TECHNIQUE

After hydrodissection and hydrodelineation, the phaco needle is first embedded proximally with high vacuum and 40% power. In the other hand is a vertical chopper that will be used to split the nucleus. As vacuum builds to occlusion a rapid rise time enables the phaco needle to quickly grasp the endonucleus. At the point occlusion is reached, the aspiration flow rate drops to zero. The surgeon then moves into foot position 2 so that high vacuum is maintained and the power drops to zero. The blade of the irrigating vertical chopper is brought down just distal to the phaco tip. As a full-thickness cleavage plane develops, dividing the nucleus in two, the instruments are separated to insure a complete chop (Fig. 5.11.4).

The lens is then rotated with the irrigating chopper so that the first hemi-nucleus can be chopped. If there is a disparity in size, the larger half is moved distally. The phaco needle is now embedded to the right by using high vacuum and low levels of power. A quadrant size piece is chopped off and consumed (Fig. 5.11.5). The remaining quadrant of the first hemi-nucleus is then impaled with the phaco tip and aspirated. Total EPT to this point is zero, showing minimal usage of ultrasound.



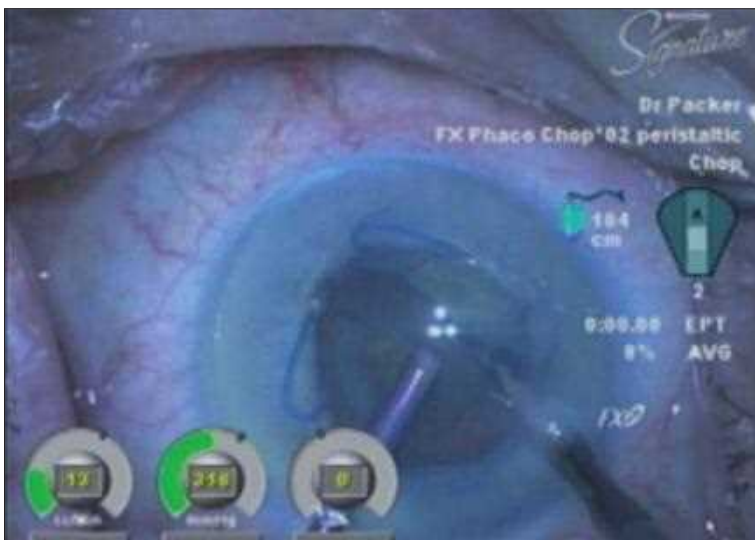
**Fig. 5.11.3** The capsulorhexis is nearly complete in this eye with a history of trauma and 90° of zonular dialysis visible temporally. The wrinkling of the capsule is a clear sign of the lack of zonular tension. Nevertheless, because of the increased control allowed by the micro-incisions, which prevent extrusion of viscoelastic, the capsulorhexis will be centered, round, and smaller in diameter than the intraocular lens (IOL) as intended.

To address the second half of the nucleus, it is first rotated with the irrigating chopper so that it is in the distal capsule. The phaco needle is embedded in the smaller hemi-nucleus, and this is subdivided with the irrigating chopper, again using high vacuum and low levels of power (Fig. 5.11.6). As the final quadrant is grasped and pulled centrally for aspiration, the sharp blade of the irrigating chopper is turned sideways as a safety precaution (Fig. 5.11.7).

When addressing the epinucleus, the vacuum and aspiration flow are reduced. Once three quadrants of the epinuclear shell have been rotated and trimmed, the final quadrant is used to flip the epinuclear bowl into the phaco needle. After aspiration of the epinucleus, the capsule is almost entirely clean of cortex (Fig. 5.11.8).

B-MICS with a vertical chop technique allows for efficient lens extraction with rapid visual rehabilitation. This procedure demonstrates some of the tangible benefits of separating inflow from outflow, use of irrigation fluid as an instrument to mobilize material, and reduced effective phaco time (Video 5.11.4).

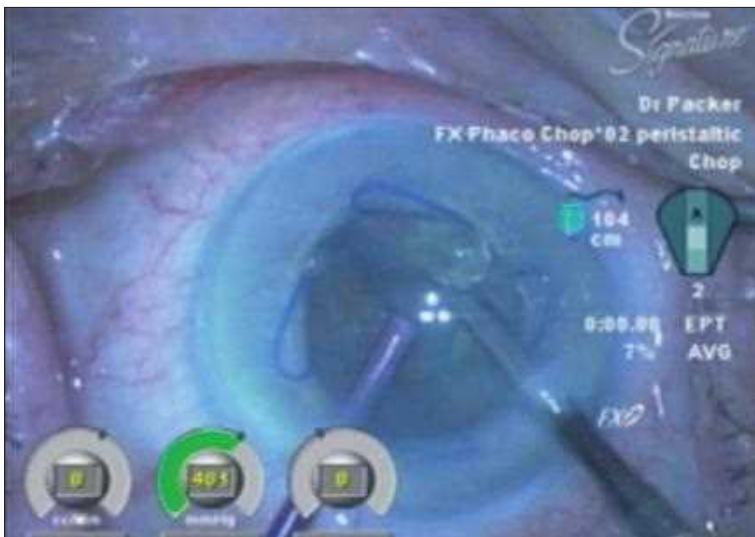




**Fig. 5.11.4** The phaco tip is embedded in the proximal nucleus bevel down; the nucleus is then held with high vacuum as the irrigating chopper slices vertically downward distal to the phaco tip. The chopper and the phaco tip are then separated as shown, to divide the nucleus.



**Fig. 5.11.7** The final segment of nucleus is grasped with high vacuum and brought centrally.



**Fig. 5.11.5** A quadrant-sized piece of nucleus is chopped and brought centrally, where it will be emulsified and aspirated.



**Fig. 5.11.8** At the conclusion of epinucleus aspiration, the capsule is almost entirely free of cortex.



**Fig. 5.11.6** A wedge of nucleus is chopped from the remaining hemi-nucleus.

## FEMTOSECOND LASER-ASSISTED CATARACT SURGERY

Femtosecond lasers have a unique ability to create discreet photodisruption of tissue with minimal collateral effects. This enables very precise cutting in ocular tissues, including the cornea, the lens capsule, and the crystalline lens.

Femtosecond lasers are indicated for the following surgical steps:

- Anterior capsulectomy.
- Lens fragmentation.
- Corneal arcuate incisions for treatment of astigmatism.
- Clear corneal incisions.

### Anterior Capsulectomy

Laser capsulectomy brings precision and reproducibility to the process of creating a capsular opening. Studies have shown that laser capsulectomies are significantly closer to the intended diameter than manual CCCs ([Table 5.11.1](#)).<sup>29,30</sup> However, concerns have arisen with regard to their resistance to tearing, which may be related to the surgeon's learning curve.

The size of the capsulectomy may influence the progression of posterior capsular opacification (PCO). Current practice requires that capsulectomy be in contact with the optic of the IOL around its circumference.



TABLE 5.11.1 Capsulectomy Data by Group

Differences are significant ( $P = 0.03$ ).

Group	Capsulectomy/Capsulorrhexis Diameter (mm)		
	Attempted	Measured	Attempted–Achieved
Laser ( $n = 49$ )			
Mean	5.23	5.08	0.16
SD	0.06	0.18	0.17
CCC ( $n = 24$ )			
Mean	5.36	4.95	0.42
SD	0.55	0.53	0.54

CCC, continuous curvilinear capsulorrhexis; SD, standard deviation.

From Tackman RN, Kuri JV, Nichamin LD, Edwards K. Anterior capsulectomy with an ultrashort-pulse laser. *J Cataract Refract Surg* 2011;37:819–24.)

TABLE 5.11.2 Percentage of Cases Achieving the Required Refractive Outcome

Deviation	6 Months After Surgery	
	Laser	Manual
0.00	13.5%	3.4%
$\leq 0.50$	81.1%	74.6%
$\leq 1.25$	100.0%	96.6%

From Uy H, Hill WE, Edwards K. Refractive results after laser anterior capsulotomy. *Invest Ophthalmol Vis Sci* 2011;52:5695.

However, significant variations in the extent of this contact or areas where there is no contact may cause the lens to decenter and tilt as the capsule contracts postoperatively.

Kranitz and Nagy reported improved overlap of the capsulectomy edge on the optic of the IOL and less horizontal decentration of the IOL in cases where laser capsulectomy had been used.<sup>31,32</sup> It has been proposed that the consistency of laser capsulectomy may increase the consistency of effective lens position (ELP) and hence the ability to hit the targeted postoperative refractive result. Early data presented by Uy and Hill confirm this effect.<sup>33,34</sup> In a study of 44 cases undergoing laser capsulectomy and 62 cases undergoing manual CCC, a significantly higher proportion produced the intended refractive outcome at 6 months by a factor of 4. Table 5.11.2 shows results supporting the hypothesis that laser capsulectomy has a positive effect on the consistency of ELP.

## Lens Fragmentation

Fragmentation of the lens prior to cataract surgery is intended to reduce or eliminate the need to use ultrasound energy during disassembly of the nucleus. In the ideal situation, the nucleus would simply be removed by aspiration. However, it might be anticipated that harder nuclei will require some ultrasound emulsification.

In the quest for optimal outcomes, different cutting patterns and algorithms (shot placement, energy, and pulse repetition frequency) may all influence the efficiency of the fragmentation. Nichamin has shown some of the patterns that were evaluated during an early phase of the development of lens fragmentation.<sup>35</sup> It was found that different patterns had different degrees of effectiveness, depending on the hardness of the cataract being treated. Overall, the pie pattern proved the most effective over the range of cataract grades from 1–5+.

Packer and Uy have presented data on the effectiveness of phaco-fragmentation by comparing the total ultrasound energy required for disassembly of the nucleus after laser lens fragmentation with that required during conventional ultrasound phaco surgery. Their results are shown in Tables 5.11.3 and 5.11.4.<sup>36</sup>

The reduction in the use of ultrasound energy may lead to other benefits, such as less corneal edema, faster visual recovery, and a reduction in the rate of endothelial cell loss. Packer and Uy reported that endothelial cell density changes from baseline are less following laser lens fragmentation compared with conventional ultrasound phaco. Table 5.11.5 summarizes these results.

TABLE 5.11.3 Analysis of Mean (SD) CDE as a Function of Nuclear Cataract Grade

Treatment Groups	For Grade 0 Mean (SD) N	For Grade 1 Mean (SD) N	For Grade 2 Mean (SD) N	For Grade 3 Mean (SD) N	For Grade 4 Mean (SD) N
Laser treatments	1.9 (3.2) 3	0.0 (0.0) 4	3.0 (4.0) 29	9.3 (9.4) 25	24.0 (18.8) 27
Control group	7.8 (–) 1	4.4 (2.4) 7	8.2 (6.1) 24	15.2 (13.0) 15	41.2 (24.7) 7
% Difference (control vs laser)	–75.6%	–100.0%	–63.4%	–38.8%	–41.7%

TABLE 5.11.4 Numbers of Subjects and Statistical Significance by Cataract Grade

Grade $\leq 1$		Grade 1		Grade 2		Grade 3		Grade 4	
Laser	Phaco	Laser	Phaco	Laser	Phaco	Laser	Phaco	Laser	Phaco
$N = 7$	$N = 8$	$N = 4$	$N = 7$	$N = 29$	$N = 24$	$N = 25$	$N = 15$	$N = 27$	$N = 7$
$P = 0.006$		$P = 0.006$		$P < 0.001$		$P = 0.069$		$P = 0.052$	

TABLE 5.11.5 Changes in Endothelial Cell Density Between Baseline and 3 Months After Surgery

	Grade 1		Grade 2		Grade 3		Grade 4	
	Laser	Phaco	Laser	Phaco	Laser	Phaco	Laser	Phaco
Mean % change	1.5	–7.0	0.1	–1.3	–0.1	–4.3	–2.4	–1.5
SD	14.4	9.7	14.9	11.1	10.5	8.7	11.9	8.3
P value	$0.10 > P > 0.05$		NS		$0.10 > P > 0.05$		NS	

SD, standard deviation.

## Corneal Incisions

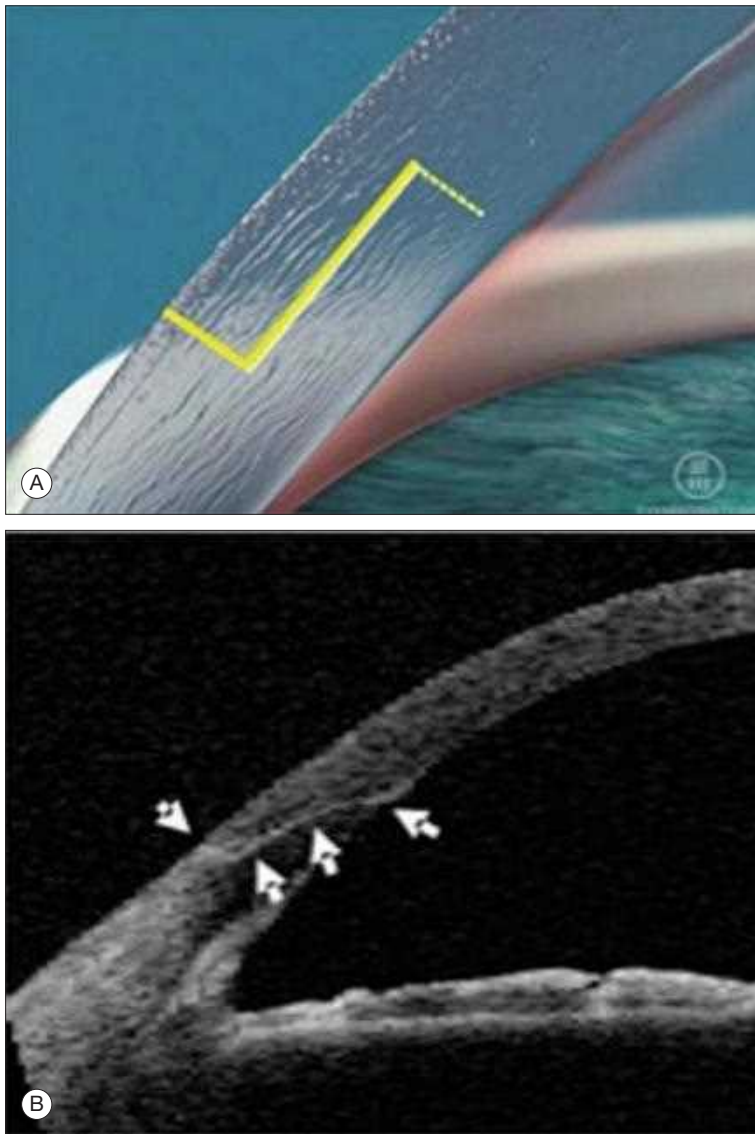
In an early study with cadaver eyes, Masket showed the ability of a single-plane laser incision to be self-sealing at significant intraocular pressures (IOPs) and indentations at certain wound tunnel lengths.<sup>37</sup> Palanker reported that three-plane laser incisions were self-sealing and watertight at physiological IOPs.<sup>38</sup> It is not clear whether this applies to the incision immediately after its creation or at the end of the surgical cases, following the use of the phaco handpiece and IOL insertion. Fig. 5.11.9 shows the planned corneal incision and the optical coherence tomogram of the wound obtained the day after surgery.

The effectiveness of laser LRIs or astigmatic keratotomy has yet to be established in the literature, although the precision of laser in creating incisions of the precise length and depth required suggests that the procedure should be more reproducible and reliable than manual methods. Several authors have shown reduction of astigmatism in patients who have undergone keratoplasty or in patients with a high degree of astigmatism with femtosecond laser arcuate keratotomy.<sup>39–42</sup> In addition, some authors have reported that femtosecond laser corneal relaxing incisions are effective in reducing corneal astigmatism during cataract surgery, and their long-term effectiveness should be evaluated.<sup>43</sup>

## CONCLUSIONS

Since the time of Charles Kelman's inspiration while in the dentist's chair (while having his teeth ultrasonically cleaned), progress in phaco technology and techniques has produced ever-increasing benefits, including more rapid visual rehabilitation and reduced dependence on contact lenses and glasses. Creative engineering and surgical ingenuity have acted synergistically to improve outcomes. Advances in technique and technology will continue to benefit our patients as we develop the exciting new future of small-incision cataract surgery.





**Fig. 5.11.9** Planned incision (A) with dotted line showing part to be opened at time of surgery with a surgical blade and optical coherence tomography (OCT) if incision the day after surgery (B).

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# Manual Cataract Extraction

Frank W. Howes

# 5.12

**Definition:** Removal of crystalline lens by nonautomated or manual techniques.

## Key Features

- Diversity of techniques for optimal cataract patient outcomes.
- Intracapsular cataract extraction or large-incision full lens extraction.
- Extracapsular cataract extraction or large-incision nucleus expression cataract surgery.
- Small-incision manual nucleus expression lens surgery (“mininuc” technique).

## INTRODUCTION

The techniques of manual cataract surgery remain invaluable in the management of certain crystalline lens and zonular pathologies inappropriate for phacoemulsification (“phaco”).

The decision regarding the choice of procedure is based on a spectrum of factors related to the socioeconomic environment (equipment availability) and the operative experience (surgeon and team) on the one hand and to the ophthalmological condition of the patient on the other.

## Historical Issues

Manual cataract surgery techniques (initially intracapsular cataract extraction [ICCE] followed by extracapsular cataract extraction [ECCE]) have been the mainstay of cataract surgery for the majority of the last century. Much of the value of the manual techniques has been the lower costs and minimal instrumentation with which the surgery can be performed. These techniques provide excellent rehabilitation of blindness caused by cataract at the expense of only recovery time and stability of refraction over the first year.<sup>1</sup>

ICCE held favor over ECCE in view of the latter’s potential for complications (inflammation, iritis, phacoanaphylaxis, secondary membranes, glaucoma<sup>2</sup>) until the 1950s. The development of systems that provided simultaneous irrigation while aspirating was the key to the return of the extracapsular systems. These systems allowed for better removal of lenticular material (ECCE). These principles reached a high level of technological sophistication (and expense) in the phaco techniques. The attempts at cost containment led to the development of manual nucleus expression surgery through smaller incisions, or the so-called mininuc technique.<sup>3–6</sup>

## MANUAL (LARGE-INCISION) CATARACT SURGERY

These techniques require strict attention to wound construction for optimal optical outcome.

## Incision

An incision of 8–12 mm of arc length around the limbus (corneal, limbal, scleral, or a combination of all) is required to manually express the nucleus from the capsular bag in ECCE, whereas an incision of 12–14 mm around the limbus is required in ICCE. Variation in the incision position has a profound influence on the postoperative occurrence of cylindrical error.<sup>7</sup> The more corneal the section is placed, the stronger is the influence on the cylindrical error. The more scleral the section is placed, the less is the

cylindrical induction, particularly if a three-plane (Fig. 5.12.1), valve-type incision is utilized. Combinations of both scleral and corneal sections can be used to correct pre-existing cylindrical errors.<sup>8</sup> These sections can be rotated appropriately to reduce cylindrical error in any meridian.

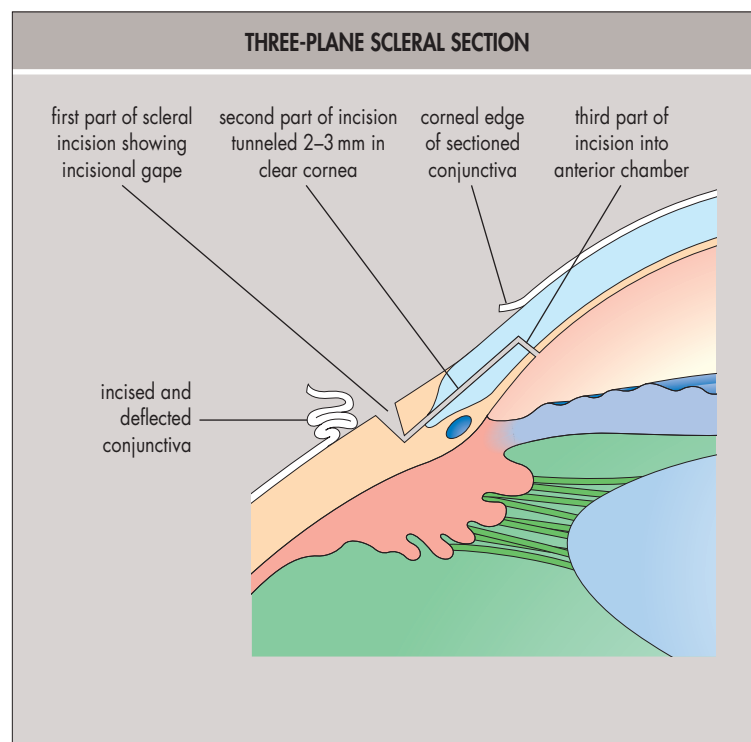
When the incision is fashioned, the third plane of the incision (see Fig. 5.12.1) should be completed only when the anterior capsulectomy has been performed. This allows the anterior chamber to maintain depth, with or without viscoelastic material, while the anterior capsulectomy is undertaken. Once this is done, the internal incision may be completed.

## Wound Closure

During closure of a wound cut in the three-plane format, the sutures must not be overtightened; the edges are merely opposed (incisional gape)<sup>9</sup> (see Fig. 5.12.1). The valve effect of the incision seals the wound. In cases in which leakage is excessive, closure can be obtained by intracameral air.

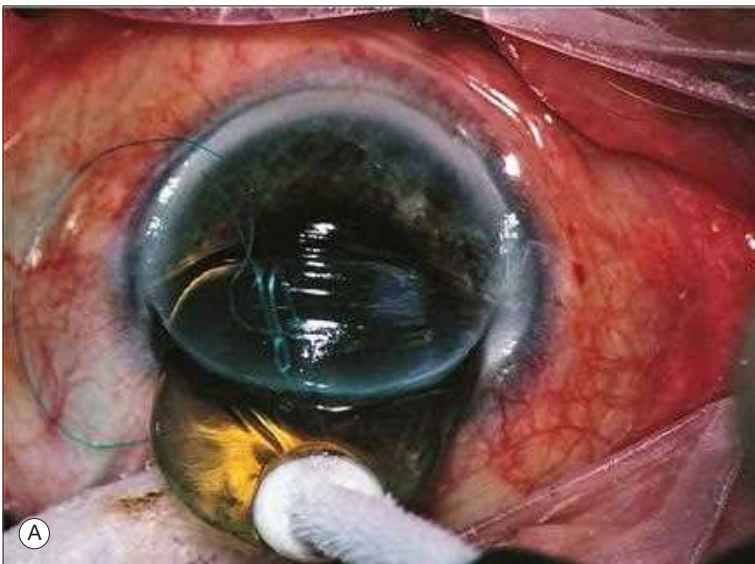
Further opportunity for cylinder modification arises when sutures are removed. This allows controlled dehiscence of the wound. Dehiscence induces negative cylindrical effect at the meridian of the suture removal. A rough guide to timing suture removal is as follows:

- After 1 month, if major wound dehiscence is required to correct cylindrical error (3–6 diopters).
- After 2 months, if minor dehiscence is required to correct cylindrical error (2–3 diopters).
- At 3–6 months, to resume preoperative cylinder.
- After 6 months, to maintain surgically induced cylinder correction, if appropriate.



**Fig. 5.12.1** Three-plane scleral section. This incision is formed with the use of a sharp microsurgical knife for the initial vertical segment, followed by use of a curved dissecting blade to form the intralaminar section of the incision. The final vertical portion of the incision is best cut with corneal microscissors. Tissue elasticity produces the incisional gape evident.





**Fig. 5.12.2** Intracapsular delivery of the lens after it has been brought forward through the pupil with the cryoprobe. (A) The pupil constricts spontaneously as soon as the maximal diameter of the lens is through. In the lower left of the figure, the moist swab is shown as the swab and the lens are sliding. (B) The cornea has a concave surface, showing that the eye is soft without forward pressure from the vitreous body. The anterior chamber is reformed with a physiological solution. (From Roper-Hall MJ. Stallard's eye surgery. 7th ed. London, UK: Wright; 1989.)

## INTRACAPSULAR CATARACT EXTRACTION

### General Comments<sup>10</sup>

Currently, the need for ICCE is restricted to the need for removal of the entire crystalline lens. This is necessary when the zonular fibers are no longer present or when they are of insufficient strength to withstand the phaco process or to provide adequate stability for an intraocular lens.

Zonular dissolution, an essential step in the past, is thus unnecessary for today's indications for ICCE. The cryoprobe (tip freeze adherence driven by gaseous expansion) remains the most valuable tool for ICCE (Fig. 5.12.2).

### Specific Techniques

#### Iris Management

Full pupillary dilation is necessary for the lens to pass through. Posterior synechiae may need division or a miotic pupil may need stretching, but invariably the pupil is sufficiently elastic to permit passage of the lens. A small peripheral iridectomy should be cut at some stage in the procedure to avoid pupil block. Occasionally, a radial iridotomy (from peripheral iridotomy to pupil margin) is necessary for access to the lens surface for cryo-application and optimal "ice ball" formation. It is important to have a dry lens bed, free of both iris and cornea, for safe removal of the lens without collateral damage. (An assistant elevating the cornea with traction on a suture placed in mid-incision [incision as described above] will free the surgeon's nondominant hand to dry the lens and move the iris away with a microswab and operate the cryoprobe with the dominant hand to apply the "ice ball" and appropriate swaying traction to remove the lens.)

#### Vitreous Presentation or Prolapse

After careful removal of the lens, the vitreous face is likely to remain intact if unnecessary globe pressure is avoided. Should vitreous emerge from the entry wound, proper excision is necessary to avoid any vitreous traction syndrome. Vitrectomy may be necessary, depending on the intraocular lens of choice. Identification of prolapsed vitreous will be enhanced by injection of particulate triamcinolone.

#### Intraocular Lenses

Because the capsular bag has been removed, the choice of intraocular lens (IOL) support is limited to the angle, iris, or ciliary sulcus (fixated by suture). This should be done with ophthalmic viscosurgical device (OVD) protection.

An angle-supported lens must be fitted carefully to the individual chamber diameter so that it neither distorts nor moves for endothelial protection. An iris-supported lens, either anteriorly or posteriorly fixed, provides safe optical rehabilitation when adequate iris is available. Ciliary sulcus lens placement requires transscleral support by suture fixation and

is useful when there is either iris damage (e.g., from trauma) or trabecular damage (e.g., associated with glaucoma). Adequate vitreous clearance is a prerequisite in the case of all of these placement sites, particularly with ciliary sulcus fixation.

## EXTRACAPSULAR CATARACT EXTRACTION

Extracapsular surgery entails more steps compared with intracapsular surgery in that the capsular bag is left in the eye, held in position by zonular fibers. To initiate the process, a hole is made in the crystalline lens in a central position in the visual axis (anterior capsulotomy). The remainder of the process involves careful removal of the contents.

### Anterior Capsulotomy

The techniques of anterior capsulotomy have changed over the past 30 years.<sup>11</sup>

#### "Can Opener" Capsulotomy

The simplest type of capsular opening or capsulotomy is the "can opener" type, in which a number of very close, pinpoint perforations are created in a central, circular tract in the anterior capsule. Centripetal traction is placed on the central piece of capsule to create a tear along the perforations. The loose piece is then carefully removed. One advantage of this technique is the relative accuracy that can be achieved when visibility is poor (e.g., for a dense cataract with a poor red reflex or a very small pupil that requires the perforations to be made under the pupillary margin).

#### Linear Capsulotomy and Intercapsular Techniques

Linear capsulotomy techniques enable external expression while the anterior capsule is utilized to protect the corneal endothelium. In this method, a curvilinear incision is made in the upper third of the anterior lens capsule to create a slit or envelope opening into the lens capsular bag. After nucleus mobilization and expression and cortical material removal, the IOL can be inserted into the remaining capsular bag. The capsulotomy is completed by performing a continuous curvilinear capsulorhexis across the remaining capsule to complete the circular central opening.

#### Capsulorhexis

Capsulorhexis, or continuous curvilinear capsulotomy, is a quick and, once learned, easy technique for anterior capsule removal. It provides the best security for the IOL within the capsular bag.<sup>12</sup> The initial capsulotomy can be made centrally with a cystotome, or bent needle, or by utilizing the tip of a fine capsulorhexis forceps. Once the capsule has been opened, a piece of anterior capsule is grasped and torn in a circular manner, with continuous change of the tearing vectors to achieve the round opening (capsulotomy) in the anterior capsule.

### Size, Type, and Position of Capsulectomy

The capsulectomy needs to be large enough for the passage of the nucleus. The size of the nucleus is age dependent but can be modified by hydrodissection and hydrodelineation using an appropriate cannula.<sup>13</sup> If the nucleus is deemed too big for passage through the capsulectomy (e.g., after an unsuccessful hydrodelineation or after too small an initial capsulorrhexis), relaxing incisions in the capsulorrhexis are necessary to reduce the possibility of capsular dislocation and zonular damage during nucleus expression. During hydrodissection, if the anterior capsular opening is large enough, part of the equatorial rim of the nucleus can be expressed into the anterior chamber, then rotated into the anterior chamber and into the incision, and thus removed from the eye. OVD material between the corneal endothelial surface and the nuclear surface is necessary to prevent endothelial damage.

The size and shape of the capsulorrhexis can be varied by the surgeon. A large capsulectomy facilitates surgery, but when this exceeds approximately 6.5 mm in diameter, the capsulorrhexis becomes difficult to control because of the presence of the insertion of the zonules.<sup>14</sup> When the anterior capsular ridge is crossed, the danger of a peripheral radial irretrievable split<sup>15</sup> is possible (particularly if the anterior chamber is not kept deep; a shallow anterior chamber creates tension on the anterior zonular ligament). Peripheral splits are usually blocked by the zonular fibers, but unwanted posterior capsular tears may be caused by this mechanism.

### Nucleus Expression

The scleral lip of the incision should be depressed to allow the leading pole of the nucleus to present into the incision. Gentle pressure at the 180° opposing limbus then expresses the nucleus. The appropriate pressure may be applied with a broad-based instrument, such as a vectis or squint hook.

Alternatively, internal expression with the use of an irrigating vectis is effective, as long as the nucleus has undergone hydrodissection and partial hydroexpression. The space between the nucleus and the posterior capsule or cortex is opened with the irrigation function of the vectis. Viscoelastic material also is useful in defining and holding these spaces and in preventing posterior capsular and endothelial damage.

### Cortical Washout

The remaining cortex is removed using an irrigation–aspiration technique. The tip of the irrigation–aspiration cannula (Simcoe) should be kept in view to avoid unwanted capsular engagement. Difficulties can arise if the globe pressure causes the anterior chamber to become shallow, closing the fornix of the capsular bag. Partial closure of the wound and irrigation produces a deep and safe anterior chamber within which to work. Cleaning of the posterior capsule and removal of remaining resistant cortical remnants can be achieved by aspiration using a fine cannula with a polished tip.

### Intraocular Lens Insertion

Insertion of the IOL is performed under direct vision, with the second haptic inserted either by circular dialing of the IOL or by direct placement with the use of fine forceps.<sup>16</sup> When the capsular bag is damaged by complication, the sites of IOL placement become the same as those noted in the ICCE section. In some circumstances where sufficient capsular support still exists in spite of capsular damage, posterior chamber implantation can be considered (ciliary sulcus placement).

### Mininuc Technique<sup>3-6,17</sup>

#### Anterior Chamber Maintainer

An anterior chamber maintainer (ACM) (Fig. 5.12.3) is inserted through the clear cornea to the anterior chamber between the 4 o'clock and 8 o'clock positions, parallel to and near the limbus. The height of the infusion bottle determines the intraocular pressure (IOP). The continuous flow is responsible for the anterior chamber maintenance system.

#### Capsulorrhexis

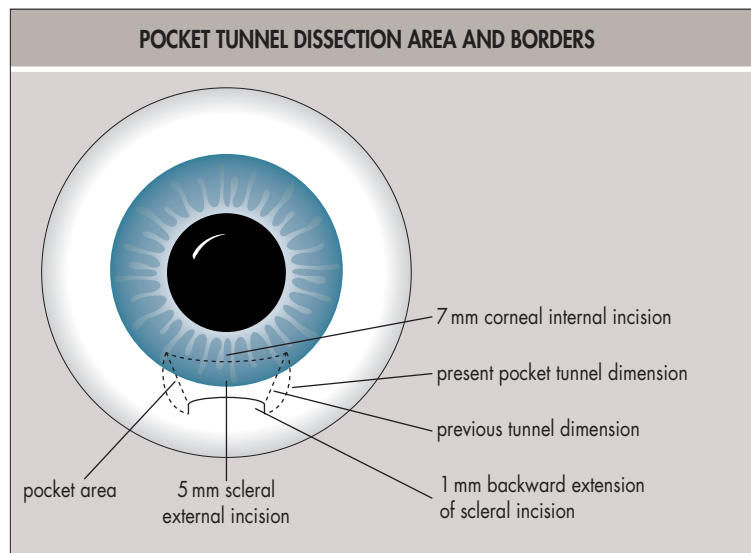
The IOP is increased to 40 mm Hg (5.3 kPa). This pressure pushes the lens backward, which facilitates the formation of capsulorrhexis and prevents accidental radial capsule tear to the periphery.<sup>15</sup> A 5- to 6-mm capsulorrhexis is preferred.

#### Sclerocorneal Pocket Tunnel

The scleral entrance incision to the sclerocorneal pocket tunnel is frown shaped and 5 mm long and is placed 1 mm behind the limbus (Fig. 5.12.4).



**Fig. 5.12.3** Anterior chamber maintainer located at the 6 o'clock position, parallel and adjacent to the limbus, in clear cornea. The incision is made into the cornea with a stiletto 1.1 mm wide and beveled 1.5–2 mm.



**Fig. 5.12.4** Pocket tunnel dissection area and borders.

At both ends of the incision, perpendicular backward continuation incisions that are 1 mm long are cut. This extension helps accommodate the thickness of the nucleus as it passes through the tunnel. The tunnel is dissected anteriorly for 3–4 mm (1 mm in the sclera, 1 mm in the limbus tissue, and 2 mm in the clear cornea). Also, the scleral dissection is enlarged on both sides of the tunnel beyond the 1 mm backward scleral incision to make a pocket-like dissection (hence the term “pocket tunnel” rather than simply “tunnel”). The keratome internal incision is placed parallel to the curvature of the limbus and is 20% longer than the scleral outer incision. The pocket tunnel facilitates nucleus expression.

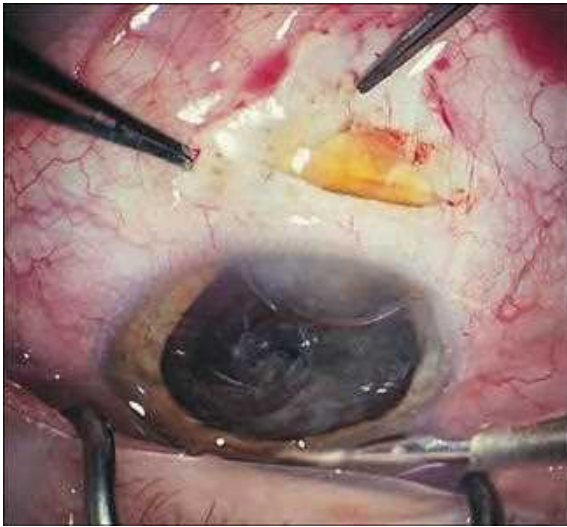
### Nucleus Manipulation

Hydrodissection is performed in two separate, anatomically distinct parts of the lens: the first just under the capsule and the second between the hard-core nucleus and the epinucleus.<sup>17</sup> Usually, the hydrodissection under the capsule partially moves the nucleus to the anterior chamber at the 12 o'clock position. If the nucleus does not move anteriorly, the hydrodissector cannula is lodged perpendicularly around the equator of the nucleus and then moved behind the nucleus. The positive IOP in the anterior segment pushes the posterior capsule away, creating a counterforce to the anterior movement of the hydrodissector cannula while the hard-core small nucleus is being separated from the epinucleus and the cortex. In this way, the smallest possible hard-core nucleus is isolated, to be delivered through the intact capsulorrhexis. At this stage, the nucleus is ready for expression.

### Nucleus Expression

A plastic glide (4 mm wide, 0.2 mm thick) is introduced through the tunnel under the nucleus. Slight pressure is induced on the glide at the inner limbal area, and the pressure is used to guide the nucleus that is to be engaged in the sclerocorneal pocket tunnel. This pocket is made to accommodate the nucleus at this stage. When the nucleus is well lodged





**Fig. 5.12.5** The nucleus is lodged in the pocket tunnel and hydroexpressed out of the eye. The glide is located behind the nucleus. External expression is performed on the glide away from the external incision of the pocket tunnel.

in the pocket and no leakage of balanced salt solution (BSS) is observed, slight scleral pressure is induced. The further the nucleus is expressed (Fig. 5.12.5), the more backward is the location of the scleral pressure. If the external pressure on the sclera is located near the internal incision throughout, an area of leakage is created rather than prevented, and nucleus expression cannot be completed. The IOP during nucleus expression is 40–45 mm Hg (5.3–6.0 kPa), helping hydroexpression of the nucleus.

### Cortex Removal and Intraocular Lens Implantation

Cortex removal and IOL implantation are facilitated by the deep anterior chamber formation induced by the ACM system. Insertion of the IOL is performed under direct vision, in a similar manner to ECCE, as described above. With a smaller incision than those in both ECCE and ICCE, the techniques of foldable lens insertion, as used in phaco surgery, can be employed.

## COMPLICATIONS

Complications of cataract surgery tend to be similar among all of the techniques used, although the incidences of the complications of the different techniques vary (Box 5.12.1). In the majority of cases, these complications occur in relation to capsular damage, with consequential anterior segment vitreous and iris involvement, occasionally involving the incision as well. Poor technique may lead to inflammatory conditions when lens nucleus material has not been completely removed or incisions have been closed poorly. Complications tend to be sequential, increasing the importance of producing a good result at the first surgery. Experience in each technique minimizes complications.

## DISCUSSION

The drive toward smaller-incision surgery has continued, and with new techniques of smaller-incision nuclear expression surgery combined with

### BOX 5.12.1 Complications of Cataract Surgery

Optical power aberrations (sphere and cylinder)  
Capsule rupture without vitreous loss  
Capsule rupture with vitreous loss  
Vitreous capture in incisional wound  
Iris prolapse  
Iris capture in incisional wound  
Nucleus loss into the posterior segment  
Intraocular lens loss into the posterior segment  
Inability to primarily implant intraocular lens because of the above  
Glaucoma (aphakic, inflammatory, malignant, pupil block)  
Corneal endothelial damage  
Chronic inflammatory disease  
Cystoid macular edema  
Retinal detachment  
Hypotony  
Choroidal edema and effusion  
Choroidal hemorrhage  
Infection

the introduction of anterior capsule staining techniques, advanced grades of cataract surgery have been performed successfully.<sup>18</sup> These techniques continue to prove useful in developing countries, where cost constraints are a factor in the delivery of sight-saving cataract surgery.<sup>19</sup> The results compare favorably with modern phaco surgery.<sup>20</sup>

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# Combined Procedures

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# 5.13



**IN THIS CHAPTER**  
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**Definition:** Cataract surgery simultaneously combined with other ocular surgery.

## Key Features

- Combined surgery for glaucoma and cataract is a valid option in management.
- Minimally invasive glaucoma surgery (MIGS) frequently is combined with cataract surgery.
- Descemet's stripping automated endothelial keratoplasty (DSAEK), rather than penetrating keratoplasty, combined with cataract surgery is now the treatment of choice for coexisting cataract and corneal endothelial disease.
- Refractive outcome from combined DSAEK–Descemet's membrane endothelial keratoplasty (DMEK) and cataract removal is much more predictable than with penetrating keratoplasty.
- Combined phacovitrectomy, rather than sequential surgery, is used increasingly for some conditions, such as macular hole and pucker, even when pre-existing lens opacities are minimal, especially in those older than ages 50–60 years.

## INTRODUCTION

Cataract develops mainly as a response to aging but also as a result of chemical or biological insults to the eye. The conditions that are commonly associated with cataract and that lend themselves to combined surgical approaches are glaucoma, corneal opacity, effects of penetrating trauma, and vitreoretinal disorders.

## COMBINED GLAUCOMA SURGERY

### Overview

The prevalence of significant cataract in people ages 65–74 years is greater than 20%, and the prevalence of chronic glaucoma is about 4.5% in people over age 70 years.<sup>1,2</sup> The 5-year incidence of nucleus cataract in people with open-angle glaucoma and older than 50 years is estimated to be 20%. Patient adherence to treatment with topical glaucoma medication, the most common form of glaucoma treatment, is low.<sup>3</sup>

For these reasons, combining cataract surgery and glaucoma surgery in a single operation appears to be a valid management option. There has been a rapid expansion in recent years in the number of devices, implants, and techniques that are less invasive and are safer than those used in traditional glaucoma surgery. In minimally invasive glaucoma surgery (MIGS), these techniques are increasingly being combined with cataract surgery.

An important consideration is that cataract surgery alone results in an intraocular pressure (IOP) drop of up to 5 mm Hg in patients with glaucoma.<sup>4</sup> Complications after glaucoma surgery may increase the risk of an adverse outcome.<sup>5</sup>

## Trabeculectomy and Cataract Surgery

Phacoemulsification (“phaco”) combined with glaucoma surgery probably produces better IOP control with fewer complications compared with manual extraction plus glaucoma surgery, although there are no large well-controlled, randomized studies on this.<sup>4,6,7</sup> However, IOP reduction and subsequent control seem to be less effective with combined surgery than with trabeculectomy alone—possibly as a result of more prolonged breakdown of the blood–aqueous barrier associated with cataract surgery.<sup>8</sup> When combined surgery is considered, a single-site approach may be less time consuming, but a two-site approach allows the surgeon to use the familiar temporal clear corneal approach to the cataract. There is ongoing debate as to whether a single-site or two-site approach gives better control, and several studies have reported no significant difference in the IOP-lowering effect.

## Nonpenetrating Glaucoma Surgery and Cataract

Nonpenetrating glaucoma surgery (deep sclerectomy with or without viscocanaloplasty) can be combined with phaco. Some studies have reported that these techniques are as effective as trabeculectomy when combined with phaco,<sup>9–11</sup> but longer-term studies are required to support this claim.

## Minimally Invasive Glaucoma Surgery

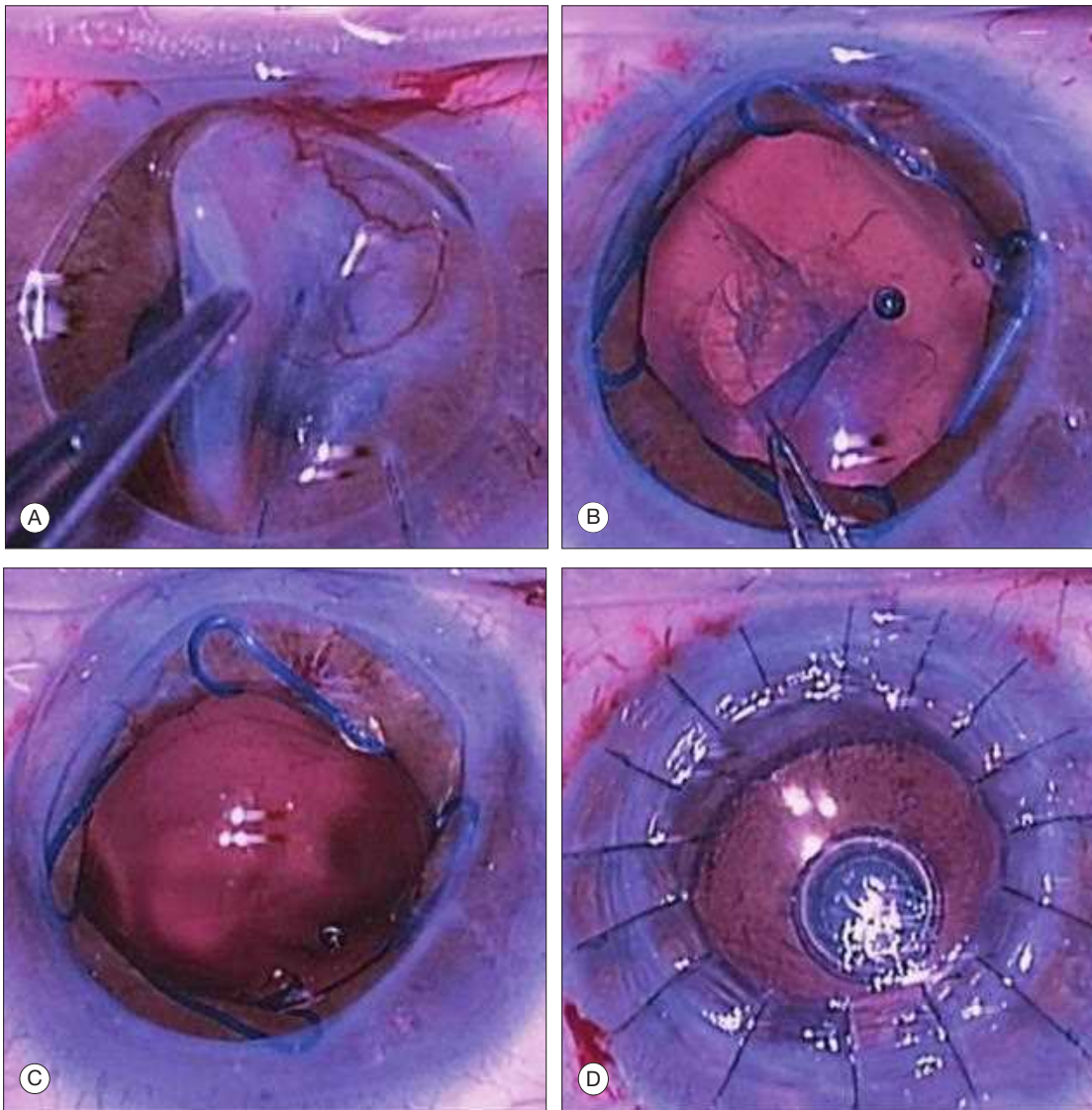
MIGS is potentially less traumatic and has a higher safety profile compared with conventional surgery. These techniques should involve an ab interno conjunctiva-preserving approach and consequently produce a modest reduction in IOP. Often combined with phaco, in which case it is termed “phacoplus,” the aim of surgery is to reduce the need for topical medications in patients with mild-to-moderate glaucoma. Most studies performed in patients who undergo MIGS in combination with phaco. Because of the large number of patients in this group, the potential market for these products is large. Few trials of sufficient quality exist at present to make firm recommendations. Reviews of the literature are cautious at best.<sup>12,13</sup> These treatments do offer alternatives to patients with glaucoma, and if studies demonstrate clinical effectiveness over the long term, these techniques may become more universally adopted.

## Aqueous Shunts

Aqueous shunts, such as the Baerveldt or Ahmed valve, are indicated in the treatment of more complex refractory glaucoma cases where surgery is required. Phaco can be performed effectively at the time of shunt surgery, although the decision to combine the two procedures has to be made on a case-by-case basis because only small retrospective case series reports are available.<sup>14</sup>

## Outcomes

Phaco surgery can be incorporated into many glaucoma procedures. IOP reduction following phacotrabeculectomy is greater than that following cataract surgery alone, although not as great as following trabeculectomy alone.<sup>15</sup> Increasingly, the role of MIGS may offer patients with cataract and early glaucoma the option not to use topical medication following combined surgery, although further study on this is required.



**Fig. 5.13.1** (A) Patient with combined corneal and lens opacities. This degree of corneal opacity demands an “open sky” approach to cataract removal. (B) Here, an iris expander device and an “open sky” technique of cataract extraction are used. (C) “Open sky” cataract extraction performed. (D) Combined cataract extraction with intraocular lens (IOL) implantation and penetrating keratoplasty.

## LENS SURGERY COMBINED WITH KERATOPLASTY

### Historical Review

Anterior or posterior lamellar corneal surgery is now much more common compared with penetrating keratoplasty (PKP). Eyes that require keratoplasty often have an associated increased risk of cataract because of the underlying pathology (Fig. 5.13.1); this includes corneal perforation as a result of trauma or infection. Also, age-related corneal degeneration, such as Fuchs’ corneal degeneration, often coexists with age-related cataract. These factors resulted in the development of a variety of techniques for combined primary cataract surgery and keratoplasty (“triple procedure”), or IOL exchange combined with keratoplasty. Combined cataract surgery and lamellar corneal surgery is often referred to as the “new triple procedure.”

### Surgical Options

A retrospective analysis of eyes that underwent PKP for Fuchs’ endothelial dystrophy, with an average follow-up period of 6 years,<sup>16</sup> showed an incidence of significant cataract in 75% of patients over 60 years of age. In those who subsequently required lens surgery, 13% lost transplant clarity postoperatively. Two recent reports following Descemet’s stripping endothelial keratoplasty (DSEK) showed the presence of cataract in 40% at 1 year in one study and cataract extraction rate of 31% and 55% at years 1 and 3, respectively, in patients over 50 years of age.<sup>17,18</sup> Similarly, studies following Descemet’s membrane epithelial keratoplasty (DMEK) showed a 76% progression of cataract.<sup>19</sup> Following DSEK/DSAEK the endothelial cell loss rate can be as high as 56% in the first year,<sup>20</sup> although with standardized technique, the endothelial cell loss has been reduced to less than 35%. In patients undergoing DMEK, the endothelial cell count loss at 1 year is in

the range of 25%.<sup>19</sup> Multiple reports have suggested that combined cataract surgery and endothelial grafts (DSAEK and DMEK) were not associated with any increased complication rate or endothelial cell loss.<sup>21,22</sup> Therefore, an argument exists for not subjecting such a cornea to multiple surgeries. The decision in individual cases depends on the balance of the risks and benefits. One key decision for the clinician is whether it is possible to determine if the main barrier to good vision is the cornea or the lens. Another is the likelihood of development of frank decompensation if keratoplasty is not carried out. A combined approach may be the best choice in either circumstance.

Choice of IOL depends on individual circumstances. In the event that cataract surgery is part of the primary procedure, a standard IOL can be placed in the capsular bag. If sufficient capsular and/or zonular support exists, then the best option is a capsule or sulcus-placed posterior chamber IOL. If adequate support is not available, then the choice is a posterior chamber IOL, either transclerally sutured or iris sutured.<sup>23,24</sup>

Biometry and IOL power calculation is problematic if PKP or lamellar keratoplasty is combined with cataract surgery. The refractive impact of DSEK, however, is reasonably consistent, with a hyperopic shift of 0.75–1.5 D,<sup>25</sup> although this is much less with thinner grafts. With the use of DMEK, where little or no stroma is transplanted, the surgery causes even less change in the refractive power.<sup>26</sup>

### Specific Techniques

The techniques of keratoplasty are dealt with elsewhere. A significant recent trend is toward either anterior or posterior lamellar keratoplasty, and significant benefit is obtained by the cataract surgeon in these closed-chamber techniques. The ongoing audit of keratoplasty conducted by the Corneal Graft Registry of the National Health Service (NHS) – Blood and Tissue, in the United Kingdom, has shown that during 2010, 26%





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of the surgeries performed were deep posterior lamellar keratoplasty, 15% were deep anterior lamellar keratoplasty (DALK), and 56% were DSEK, with the number of endothelial keratoplasty procedures increasing.

Phaco surgery can be difficult because of the poor visibility as a result of the corneal disease. Selected cases with stromal opacity (see Fig. 5.13.1A) may be suitable for a routine phaco procedure after DALK and use of an ophthalmic viscosurgical device in the bed to restore anterior chamber and capsule visibility.<sup>27</sup> In cases of endothelial disease where the stromal clarity is reasonable, a combined phaco with DSEK/DMEK is now the preferred technique (Video 5.13.1). This offers much quicker visual rehabilitation and more predictable refractive outcome than combined PKP and phaco.<sup>28</sup>

Such an approach is not always possible, and “open sky” removal of the lens may be required. The altered anterior-chamber and lens-iris diaphragm dynamics, abnormal light reflexes present in the “open sky” situation (see Fig. 5.13.1),<sup>29</sup> and difficulty in controlling the anterior and posterior capsule increases the risk of surgical complications. Capsulorhexis can be difficult because of decreased anterior pressure caused by the “open sky.” Careful use of scissors can be of help. The nucleus is expressed manually after thorough hydrodissection. Manual irrigation-aspiration of the cortex is carried out with the use of a cannula, such as the Simcoe cannula.

When specific endothelial keratoplasty techniques are combined with cataract surgery, certain additional risks, such as pupil abnormalities and lens subluxation or dislocation, arise either because of the effect of the air tamponade or anterior chamber depth modulation needed in these surgeries.

## Complications

Apart from the possible inherent complications of keratoplasty, the combined procedure carries an increased risk of cystoid macular edema. Other complications of combined procedures are the variability of refractive outcome and the delayed visual rehabilitation compared with straightforward cataract surgery. Weighed against this, however, is the additional risk of graft failure inherent in the alternative of a two-stage procedure.

## Outcomes

There are currently no definitive studies providing hard evidence of the benefit of one approach over another, but with the development of standardized techniques of corneal graft surgery, the new triple procedure shows very similar results to the two-stage approach.

## COMBINED PHACOVITRECTOMY

### Introduction

Both age-related cataract and secondary cataract are a common feature in many patients with vitreoretinal disorders. The widespread acceptance of phaco in the late 1980s and 1990s and the availability of combined phaco and vitrectomy machines with single cassettes offered the possibility of efficient combined surgery, with secure wound construction and stable intracapsular IOL fixation. Although pars plana fragmatome lensectomy is still performed in specific scenarios, combined phaco with IOL implant and vitrectomy (phacovitrectomy) is now an established technique to deal with concomitant cataract when vitrectomy is performed. Studies have shown that combined phacovitrectomy can be carried out with low morbidity and good results.<sup>30</sup> As confidence with the technique has grown, indications for combined surgery have expanded.

### Indications and Advantages Over Sequential Noncombined Surgery

When first introduced, phacovitrectomy was reserved for cases where cataract precluded an adequate fundal view during vitrectomy surgery. However, phacovitrectomy now is increasingly used when lens opacities are mild or even nonexistent, particularly in patients over 50–60 years of age.<sup>31</sup> In these cases, cataract surgery is not necessary to successfully complete the vitrectomy but is done to avoid the need for subsequent cataract surgery and hasten visual recovery. Vitrectomy surgery, particularly in the age group of over 50 years, often results in the development of significant lens opacities, especially if long-acting gases are used, as in macular hole surgery.<sup>32,33</sup>

Phacovitrectomy in these situations offers a number of advantages over vitrectomy followed by subsequent cataract surgery in two steps. Only one operation is needed, avoiding the surgical difficulties and morbidity associated with cataract extraction following vitrectomy. These include small pupil size, deep anterior chamber with reverse pupil block, and increased mobility of the lens-iris diaphragm with an increased risk of posterior capsule tears.

Combining phaco and vitrectomy also improves postoperative retinal visualization, allowing accurate retinal assessment and treatment, and visual recovery is not delayed by subsequent cataract development. Phacovitrectomy allows more complete anterior vitrectomy and access to the anterior retina and vitreous base without the risks associated with lens touch.<sup>34</sup>

## Disadvantages

Macular hole and macular pucker are the most common clinical scenarios where “nonessential,” optional phacovitrectomy is considered because of the high frequency of cataract formation after surgery in these cases in the age group affected. However, not all patients are ideal candidates for phacovitrectomy. For some patients, vitrectomy, followed by sequential cataract surgery, if needed, is a better option. In patients with diabetes, lens opacities following vitrectomy are paradoxically less common than in those without diabetes.<sup>35</sup> Among patients with diabetes, there seems to be a higher incidence of posterior synechiae, posterior capsule opacity, and inflammatory anterior uveitis following phacovitrectomy, especially if retinopathy is very active; a large amount of intraoperative laser is needed, or gas tamponade is used.<sup>36</sup> Therefore, although phacovitrectomy is frequently carried out successfully in patients with diabetes who have significant lens opacities,<sup>37</sup> these patients are not always ideal candidates for phacovitrectomy.

The absence of accurate preoperative biometry secondary to vitreoretinal pathology, with variable axial length measurements and fixation, also could be regarded as a relative contraindication to nonessential phacovitrectomy. Fellow-eye measurements can be used, but incorrect axial length estimations will result in errors in IOL choice and potentially significant unplanned ametropia. Similarly, scleral buckling and use of silicone oil alter the final refractive outcome in an unpredictable way. Phacovitrectomy in eyes with elevated maculae, as occurs with epiretinal membrane and macular holes, has been reported to be associated with a myopic shift in the planned refraction. This is most likely to be related to measuring a short axial length preoperatively with the use of ultrasonography, but it also may be related to gas-induced, anterior chamber depth changes.<sup>38</sup> The use of partial coherence interferometry (PCI) to measure axial length (which uses the retinal pigment epithelium [RPE] reflection, rather than the inner retinal surface) can overcome some of these errors.<sup>39</sup> However, if PCI is used in eyes with thickened maculae, the graphical display should be inspected. If the inner retinal reflectivity is high (e.g., with a dense epiretinal membrane), the device can occasionally interpret this reflective peak as the RPE. In this situation, the graph cursor can sometimes be adjusted to the lower RPE peak manually.<sup>40</sup> Details on adjustment and other potential errors in measurement can be found in manufacturers’ device manuals. If axial length is measured by using ultrasonography, aiming approximately 0.5 dioptres hypermetropic or correcting for the preoperative macula thickening based on optical coherence tomography (OCT) measurements, can reduce the effect.<sup>38,41</sup>

Similarly, with macula involving retinal detachment, care needs to be taken to ensure that the true axial length is measured rather than from the detached retina. Sometimes, the scan cursor can be manually changed to the RPE peak with optical biometry, but if any doubt exists, the true axial length should be measured by using combined vector-A/B-scan biometry.<sup>42,43</sup>

## Specific Techniques

Lens surgery can be carried out successfully via either a clear corneal incision (CCI) or scleral tunnel incision. If valved sclerostomy ports are used, they can be inserted prior to phaco to avoid the risk of wound leak during later insertion. If nonvalved ports are used, then all but the infusion port may be more optimally placed after phaco to avoid loss of vitreous cavity fluid and exacerbated lens iris diaphragm retropulsion syndrome, especially in already vitrectomized eyes.<sup>44</sup> If a corneal incision is used, then the tunnel should be kept relatively short to avoid interference with the posterior segment view. Similarly, temporal incisions are less axial and less likely to interfere with the fundal view than superior ones. A suture can be



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used to secure the wound to avoid wound leak during scleral indentation (Video 5.13.2).

Posterior segment intraocular gas pressure can cause significant problems in phacovitrectomy. Anterior displacement of the optic of the IOL by posterior gas pressure can lead to optic capture by the iris. Similarly, displacement of the anterior capsule onto the iris can lead to postoperative posterior synechiae formation. There are some possible strategies to reduce the incidence of these problems. Sustained postoperative dilatation should be avoided, but some clinicians use short-acting mydriatics to discourage synechiae formation. Capsulorrhexis size should be large enough to avoid problems with rhexis phimosis but should aim to just overlap the optic edges by 0.5 mm to hold the optic posteriorly. Capsulorrhexis can occasionally be difficult in eyes with vitreous hemorrhage and no red reflex. In these cases, capsule staining and/or use of the endoillumina-tor in the anterior chamber can facilitate visualization. Alternatively, some vitrectomy can be carried out first, if possible, to improve the red reflex before rhexis is undertaken. IOL optic diameter should be large to reduce the risk of optic capture. Lenses with broad haptic fixation offer the advantages of avoiding optic capture and superior IOL centration.

IOL insertion can be performed either before or after vitrectomy is completed. Peripheral vitreous base view can be impaired in pseudophakic eyes, and there is an argument for withholding IOL insertion until after the posterior segment surgery has been completed. IOLs with rounded, tapering edges and a gradual reduction in optic power offer advantages for “trans-IOL” vitrectomy by avoiding the occurrence of “jack-in-the-box” prismatic effects when viewing the posterior segment through the edge of the IOL. Posterior capsule opacity appears to be more common after phacovitrectomy, and primary capsulectomy with the vitrectomy cutter can be performed to avoid another threat to delayed visual recovery.<sup>45</sup> Acrylic folding IOLs have several advantages over silicone IOLs with less IOL condensation during fluid–air exchange and also reduced possibility of silicone oil adherence if oil is subsequently used.

## Conclusion

Phacovitrectomy is an effective technique to allow combined cataract extraction and vitrectomy. Its use is now being extended to patients with

minimal lens opacities before they undergo, for example, macular hole surgery, to avoid delaying visual recovery secondary to postoperative cataract.

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# Cataract Surgery in Complex Eyes

Jesse M. Vislisl, Gary S. Schwartz, Stephen S. Lane

# 5.14

**Definition:** Cataract surgery in eyes with other pathologies.

## Key Features

- Zonular integrity is evaluated at the slit lamp preoperatively by assessing for lens decentration, phacodonesis, and iridodonesis.
- Uveitis may complicate cataract surgery as a result of poor dilation, posterior synechiae, zonular laxity, and exaggerated postoperative inflammation.
- Preoperative endothelial cell density less than 1000/mm<sup>2</sup>, central corneal thickness greater than 640  $\mu$ m, and corneal epithelial edema indicate increased risk for postoperative corneal decompensation in patients with Fuchs' corneal dystrophy.
- Femtosecond laser-assisted cataract surgery may have distinct advantages for certain complex eyes because of ease in capsulorhexis creation, assistance with nucleofractis, and reduced postoperative endothelial cell loss.

## Associated Features

- A large capsulorhexis ( $\geq 5.5$  mm in diameter) facilitates removal of nuclear fragments and reduces postoperative anterior capsular phimosis in the setting of zonular laxity.
- Areas of weakened zonules may be stabilized intraoperatively and postoperatively by using capsular hooks, capsular tension rings, and capsular tension segments.

## INTRODUCTION

Modern cataract surgery can normally be performed with minimal anesthesia, manipulation of ocular tissue, and postoperative morbidity. Although most surgeons perform routine surgery using the same basic techniques for all patients, in some circumstances, the surgical technique must be altered because of specific preoperative conditions in complex eyes.

## ZONULAR INSTABILITY

When cataract surgery and intraocular lens (IOL) placement are planned for a patient with history of ocular trauma, intraocular surgery, pseudo-exfoliation syndrome, or systemic conditions associated with zonulopathy (e.g., Marfan's syndrome), it is important for the surgeon to evaluate the status of the zonules. Zonular instability increases the risk of intraoperative complications and the likelihood of IOL subluxation postoperatively.<sup>1,2</sup>

Zonular integrity may be evaluated at the slit lamp preoperatively by looking for the presence of lens decentration, phacodonesis, or focal iridodonesis. This may be facilitated by having the patient quickly shift the direction of gaze or by gently shaking the slit lamp table with a fist. When necessary, it often is possible to directly visualize the zonular ligament fibers by using a gonioscope. If a patient has a history of ocular trauma, the eye should also be examined for iridodialysis and vitreous in the anterior chamber, either of which makes zonular dehiscence likely.

During surgery, care must be taken to preserve as many of the remaining supporting zonules as possible. If discrete areas of zonular dehiscence are present, a cohesive ophthalmic viscosurgical device (OVD) may be used to force a dispersive OVD into the area of zonular loss and prevent vitreous prolapse into the anterior chamber. The anterior capsule may initially dimple under the cystotome tip in the presence of zonular laxity, rather than being immediately punctured. If difficulty is encountered when beginning the anterior capsular tear, two 27-gauge needles may be used in

a crossing fashion to create countertraction and assist with initiation of the rhexis. After the capsulorhexis is begun, pseudo-elasticity of the capsule may be experienced because of the reduction in counterresistance offered by the zonules to oppose the tearing forces applied by the surgeon.<sup>3</sup> In cases of marked zonular loss, capsular hooks or retractors may be utilized to stabilize the bag and facilitate completion of the rhexis.<sup>4</sup> If these are unavailable, nylon iris fixation hooks can be used in a similar manner, although the tips may tend to inadvertently tear the capsule. After starting the rhexis, the surgeon gently retracts the capsular edge with hooks in the direction of the area of dehiscence. After the rhexis is completed, the hooks may be left in place while hydrodissection and phacoemulsification ("phaco") are performed. A large rhexis (at least 5.5 mm in diameter) is made to facilitate removal of nuclear fragments and prevent postoperative anterior capsular phimosis. Careful and complete hydrodissection is performed so that the nucleus rotates easily within the capsular bag with minimal zonular stress. Bimanual rotation may be utilized to further reduce zonular stress by simultaneously rotating the nucleus using two instruments located 180° apart.

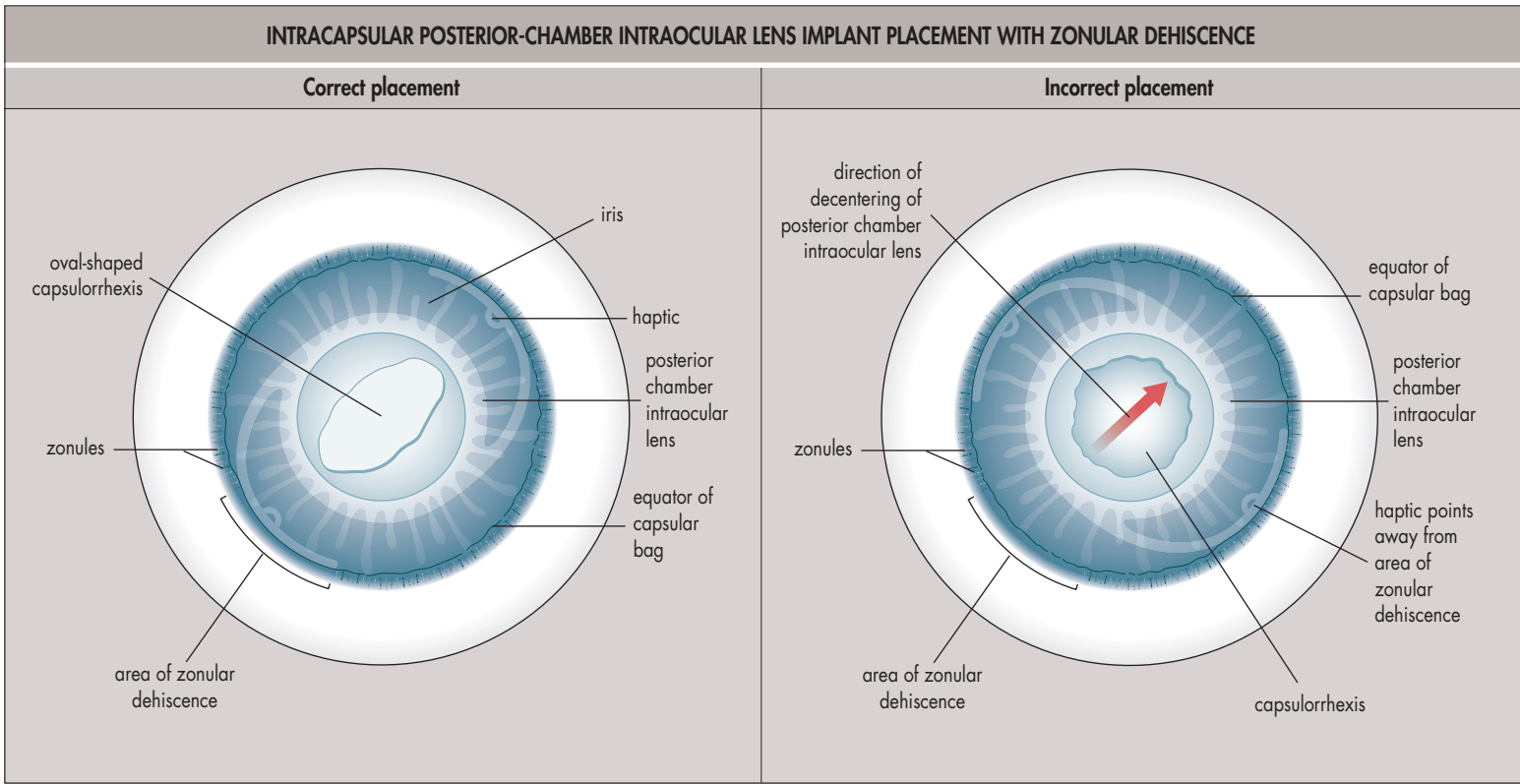
A horizontal chop technique is preferable for nuclear disassembly in situations of zonular laxity because it causes minimal strain on the zonular fibers. If grooving is performed within the capsular bag, the main incision should be created in a position so that the phaco needle carves toward the area of dehiscence to prevent induction of forces that extend the area of zonular loss. If the surgeon feels that zonular support is inadequate for intracapsular manipulation, the nucleus may be prolapsed from the capsular bag, and phaco can be performed within the anterior chamber.

Once the nucleus and epinucleus have been removed, cortical cleanup must be performed delicately. Stripping the cortex in tangential fashion with forces perpendicular to the radial zonular fibers has been shown to exert reduced force on the zonule.<sup>5</sup> With the nucleus removed, the capsular bag is floppier in nature, and the area of the dehiscence may be drawn toward the aspiration tip. In such cases, the surgeon may have more control when the irrigation and aspiration ports are separated to perform bimanual irrigation-aspiration. In this way, the irrigation tip can be used to hold back the capsular fornix of the area of dehiscence while the aspiration tip safely removes cortex.

After complete removal of the cataract, an appropriate IOL must be selected. Whenever possible, the IOL is placed within the capsular bag. Intracapsular IOL placement without a capsular tension segment or ring may be appropriate for patients who have small areas of zonular dehiscence. In such cases, a three-piece posterior-chamber intraocular lens (PCL) should be placed so that one of the haptics is oriented toward the area of dehiscence, thus extending the bag in that direction (Fig. 5.14.1). If the haptics are rotated so that they are 90° away from the dehiscence, the optic is more likely to decenter in a direction away from the area of dehiscence.

Mild, diffuse, zonular laxity and zonular dehiscence up to 4 clock hours may be managed by placing a capsular tension ring within the capsular bag. Areas of dehiscence greater than 4 clock hours may be managed by using capsular tension segments to provide additional capsular support. Capsular tension segments and some tension rings, such as the Cionni ring, have eyelets to allow fixation to the scleral wall with a polypropylene or Gore-Tex suture.<sup>6</sup> These devices are left in place postoperatively and have been shown to help expand and center the capsular bag, thus preventing the lens implant from migrating away from areas of zonular dehiscence.

If capsular support is felt to be inadequate for intracapsular lens placement, an alternative technique should be utilized (Table 5.14.1). A sulcus-supported PCL can be placed so that the haptics are 90° away from the area of dehiscence (Fig. 5.14.2). This orientation prevents the haptics from slipping posteriorly into the vitreous chamber. If a continuous curvilinear capsulorhexis has been performed, it is advantageous to prolapse



**Fig. 5.14.1 Intracapsular Posterior-Chamber Intraocular Lens (PCL) Implant Placement With Zonular Dehiscence.** With correct placement within the capsular bag, one haptic is positioned toward the area of dehiscence to extend the capsule peripherally, stabilize the region, and maintain optic centration. Note that the capsulorrhexis is ovoid in shape because it has been pulled by the haptic in the direction of the dehiscence. With incorrect placement, the haptics are oriented 90° away from the dehiscence. In this situation, the PCL may decenter away from the area of dehiscence in the direction of the arrow.

TABLE 5.14.1 Options for Intraocular Lens Placement After Cataract Extraction			
Procedure	Optic Position	Haptic Position	Haptic Fixation
Intracapsular posterior-chamber intraocular lens (PCL) implant	Capsular bag	Capsular bag	Capsular bag fornices
Intracapsular PCL with reverse optic capture*	Posterior chamber	Capsular bag	Capsular bag fornices
Sulcus-supported PCL	Posterior chamber	Ciliary sulcus	Ciliary sulcus
Sulcus-supported PCL with optic capture*	Capsular bag	Ciliary sulcus	Ciliary sulcus
Transscleral fixated PCL	Posterior chamber	Ciliary sulcus	Trans-scleral fixation
Iris-sutured PCL	Posterior chamber	Ciliary sulcus	Iris sutures
Anterior chamber lens	Anterior chamber	Anterior chamber	Anterior chamber angle
Aphakia	None	None	None

\*The “optic capture” and “reverse optic capture” techniques require an appropriately sized and intact continuous curvilinear capsulorrhexis.

the optic posteriorly into the capsular bag while the haptics remain in the sulcus. This technique often results in more stable optic centration in the presence of zonular dehiscence.

If insufficient capsule is present to support both haptics, a PCL may be sutured to the iris or transsclerally fixated by using suture or other means (Fig. 5.14.3).<sup>7,8</sup> Since transscleral and iris fixation procedures are technically difficult to perform, some surgeons may opt for placement of an anterior chamber lens instead. Modern anterior chamber lenses have proven to be safe,<sup>9</sup> although many surgeons still prefer to keep the IOL as close as possible to the physiological location of the natural crystalline lens.

Femtosecond laser-assisted cataract surgery (FLACS) may have considerable advantages in patients with zonular laxity. In this setting, creation of the rhexis is performed by using disruptive laser energy, rather than tearing forces, and thus is not dependent on countertraction from healthy zonules. In addition, much of the nucleofractis technique is performed atraumatically by the laser and thus further zonular loss from the mechanical action of the phaco tip is avoided.

## UVEITIS

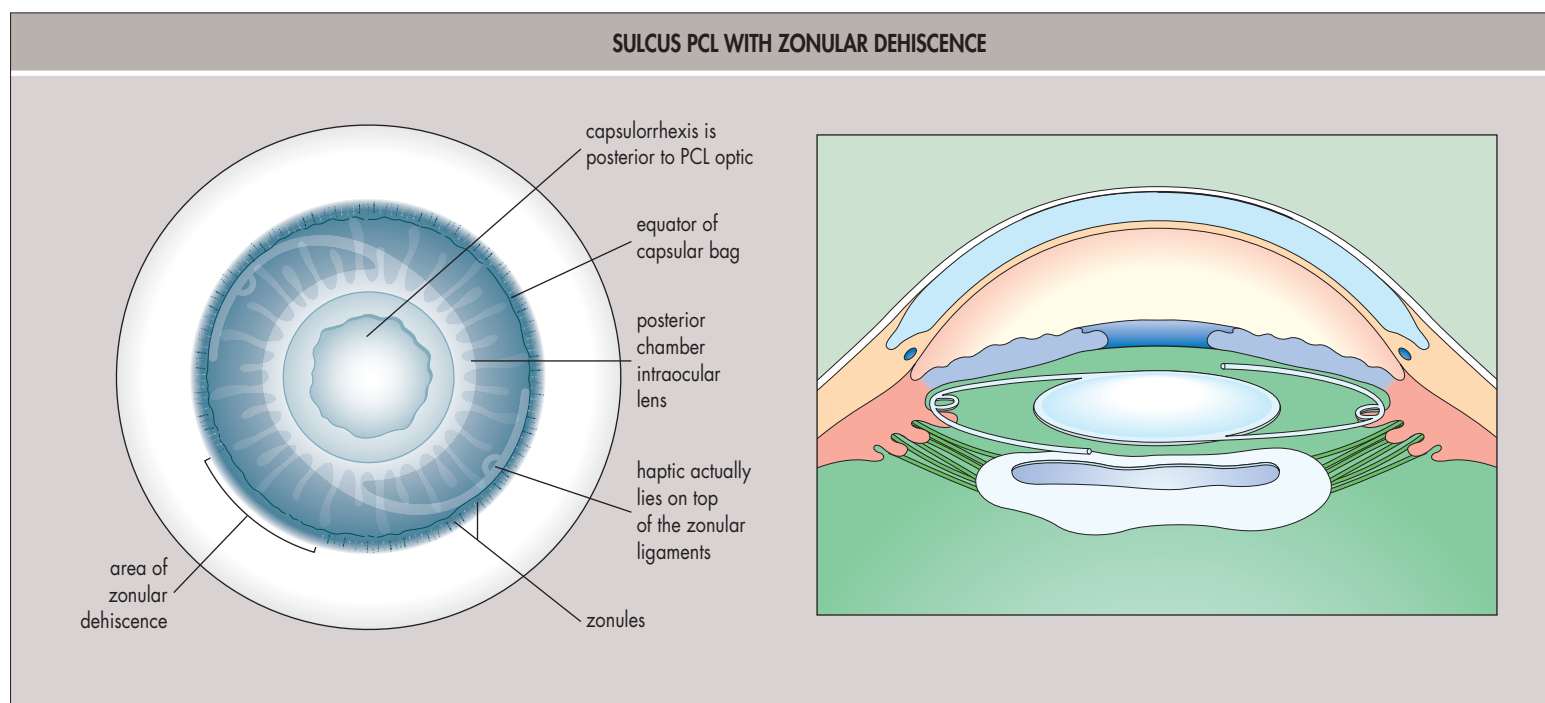
Cataract extraction with IOL insertion in patients with uveitis is often made more difficult because of poor dilation, posterior synechiae, zonular laxity, and higher levels of postoperative inflammation. If possible, a patient should not undergo surgery until the uveitis has been quiescent for at least 3 months. Even so, patients with a significant history of uveitis should receive oral prednisone 10 mg/kg daily for up to 1 week prior to surgery followed by a 2- to 3-week taper. In addition, select patients may benefit from intravenous methylprednisolone sodium succinate 125–250 mg during the surgery. Patients with chronic uveitis secondary to herpes simplex or varicella-zoster virus infections should be treated with perioperative oral antivirals at full treatment doses.

Small-incision phaco is the procedure of choice for patients who have a history of uveitis.<sup>10</sup> The smaller incision results in less iris manipulation than large-incision nucleus expression and results in less postoperative inflammation and faster healing. In addition, creating the wound in the avascular clear cornea results in less inflammation compared with a scleral tunnel incision because the limbal and conjunctival blood vessels are spared.

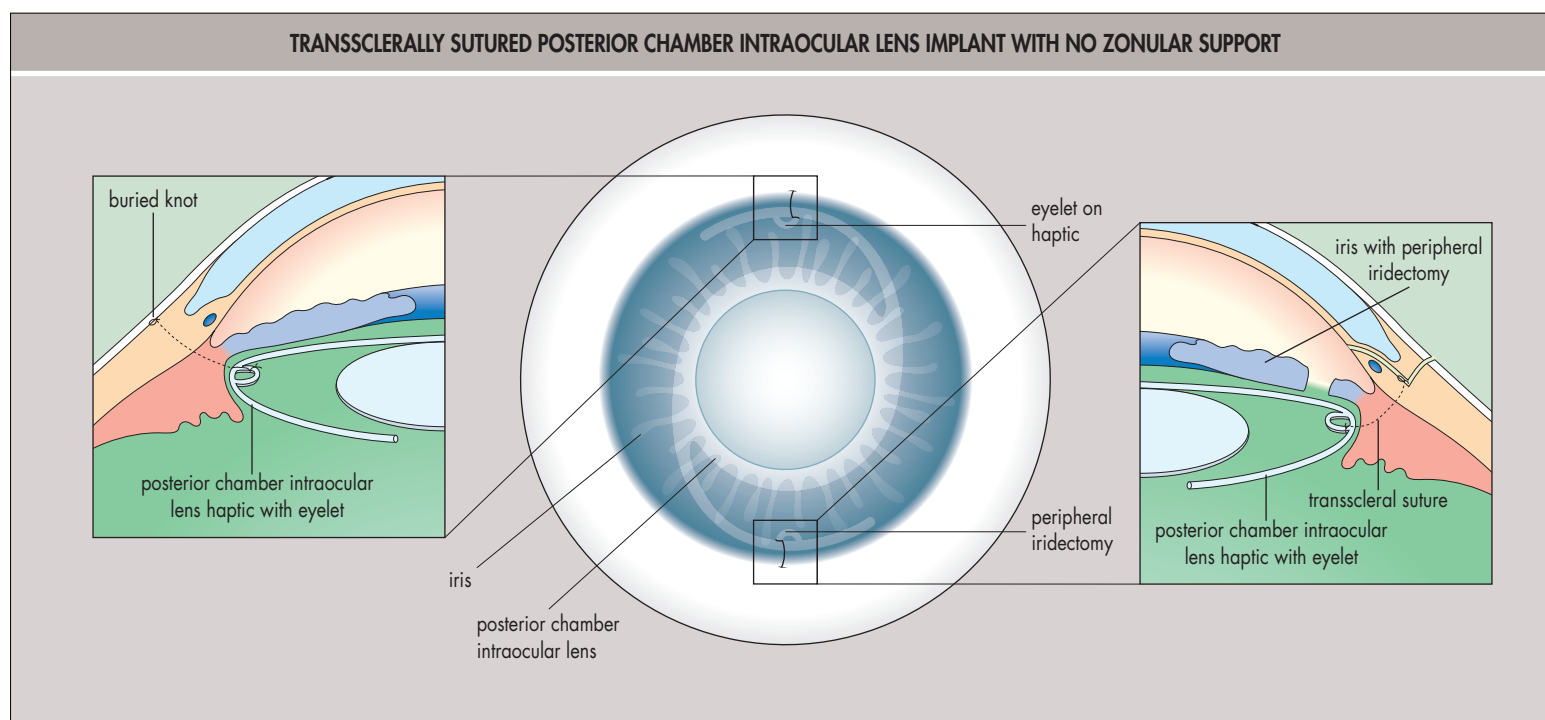
When necessary, posterior synechiolysis may be performed with use of a cyclodialysis spatula or viscodissection. The pupil may need to be enlarged if dilation is inadequate. The surgeon has the choice of manually stretching the pupil by using two instruments usually found on the surgical tray or by using an instrument specifically designed for pupillary dilation (e.g., the Beehler pupil dilator or the Malyugin ring). Pupillary membranes, if present, may need to be incised and stripped to further assist with dilation.

Acrylic lens implants are preferred and usually well tolerated by patients with uveitis.<sup>11</sup> Silicone lenses are discouraged in this setting because they may accumulate inflammatory precipitates postoperatively. In addition, it is best to avoid anterior chamber lenses, iris-sutured PCLs, and sulcus-supported PCLs, as they have a tendency to cause postoperative inflammation as a result of contact with the iris and the ciliary body. Whenever possible, a capsule-supported PCL is used. If capsular support is not present at the time of IOL implantation, a transsclerally fixated PCL may be placed, or the patient may be left aphakic.

In vitro and in vivo studies have demonstrated an advantage of heparin surface-modified polymethyl methacrylate (PMMA) lenses compared with regular PMMA lenses when looking at the adhesion of inflammatory



**Fig. 5.14.2 Sulcus Posterior-Chamber Intraocular Lens (PCL) Placement With Zonular Dehiscence.** The PCL is properly placed in the ciliary sulcus with the haptics oriented 90° away from the area of dehiscence. Placement in this orientation will decrease the likelihood that the haptics will prolapse posteriorly through the area of dehiscence and into the vitreous cavity.



**Fig. 5.14.3 Transscleral Sutured Posterior-Chamber Intraocular Lens (PCL) With No Zonular Support.** When no capsular or zonular support is present, a PCL may be secured by using two transscleral polypropylene or Gore-Tex sutures passed through eyelets on the haptics. The knots are rotated into the sclera to decrease the risk of long-term complications from knot erosion through the conjunctiva.

cells.<sup>12</sup> For this reason, heparin surface-modified PMMA lenses probably have an advantage over regular PMMA lenses in patients with history of uveitis. However, because of the necessity for a larger incision when using PMMA lenses, it remains unclear whether heparin surface-modified lenses have an advantage over foldable silicone or acrylic IOLs when otherwise small-incision phaco may be performed.

## COMPROMISED ENDOTHELIUM

Some patients, such as those with Fuchs' endothelial dystrophy, have a compromised corneal endothelium at the time of cataract surgery. The trauma of intraocular surgery causes further endothelial cell loss, potentially resulting in prolonged, and even irreversible, corneal edema. Pachymetry and specular microscopy may be performed as part of the preoperative

assessment on any patients with suspected endothelial dysfunction. Pre-operative risk factors for corneal decompensation in the setting of Fuchs' dystrophy include endothelial cell density less than 1000/mm<sup>2</sup>, central corneal thickness greater than 640 μm, and the presence of corneal epithelial edema.<sup>13</sup>

The surgeon should strive to minimize damage to the corneal endothelial cells during surgery. Rather than making the incision through temporal clear cornea, a more posterior, scleral tunnel approach may reduce endothelial disruption. A dispersive OVD will be more protective to the corneal endothelium than a cohesive OVD. The surgeon may wish to periodically refill the anterior chamber with OVD throughout the procedure. Phaco energy and time should be kept to a minimum, thus a chopping nucleofractis technique is preferred. Nuclear fragments should be emulsified as posteriorly as possible with the tip of the phaco hand piece directed away



from the cornea. FLACS is advantageous in these cases because it requires less phaco energy and causes less postoperative reduction in endothelial cell density.<sup>14</sup> Despite all these measures taken, however, corneal decompensation may still occur. Patients with corneal edema may benefit from topical hyperosmotic agents or corneal transplantation postoperatively. It is critical that adequate informed consent (including a discussion of the possibility of post-cataract surgery corneal transplantation) is obtained prior to the procedure. A myopic refractive target is advised if it seems likely that subsequent endothelial keratoplasty (EK) will be required, to counter the usual hyperopic refractive shift that accompanies EK procedures.

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# Pediatric Cataract Surgery

Michael O'Keefe, Caitriona Kirwan, Elie Dahan<sup>†</sup>

# 5.15

**Definition:** Cataracts occurring in the pediatric age group, arbitrarily defined as birth to adolescence.

## Key Features

- Two main approaches are used to remove cataracts in children: pars plana and corneolimbic approach.
- Intraocular lenses, contact lenses, and spectacles are the most readily available means to correct aphakia in children.
- Advances in contact lens technology results in improved visual outcomes.
- Use of intraoperative triamcinolone and better surgical techniques reduces inflammation.
- Postoperative glaucoma remains a major problem.

## INTRODUCTION

Cataracts in childhood not only reduce vision but also interfere with normal visual development.<sup>1-3</sup> The management of pediatric cataracts is far more complex than the management of cataracts in adults. The timing of surgery, the surgical technique, the choice of the aphakia correction, and amblyopia management are of utmost importance in achieving good, long-lasting results in children.<sup>4-10</sup> Children's eyes are not only smaller than adults' eyes, but their tissues are much more reactive as well. The inflammatory response to surgical insult seems more pronounced in children, often because of iatrogenic damage to the iris. During the past 2 decades, the refinements that have occurred in adult cataract surgery have contributed to the further development of pediatric cataract surgery (PCS).<sup>2,4-8</sup> Certain adaptations and modifications in surgical technique are required to achieve results similar to those achieved in adults.<sup>2-8</sup> Furthermore, postoperative amblyopia management forms an integral part of visual rehabilitation in children.<sup>1-10</sup>

## HISTORICAL REVIEW

Discission of soft cataracts was first described by Aurelius Cornelius Celsus, a Roman physician who lived 2000 years ago. Discission remained the method of choice until the middle of the twentieth century. The technique consisted of lacerating the anterior capsule and exposing the lens material to aqueous humor for resorption and/or secondary washout. Repeated discissions often were required to manage the inevitable secondary cataracts.<sup>2</sup> Many early complications (e.g., plastic iritis, glaucoma, and retinal detachments) were associated with these early techniques.<sup>2,11</sup> With the advent of vitrectomy machines and viscoelastic substances, as well as the refinements in cataract surgery, these complications have been reduced markedly over the past 2 decades.<sup>2</sup>

## PREOPERATIVE EVALUATION AND DIAGNOSTIC APPROACH

A careful history assists the clinician in selecting the investigations needed for determining the cataract's etiology.<sup>2</sup> Information on problems during pregnancy (e.g., infections, rashes or febrile illnesses, exposures to drugs, toxins, or ionizing radiation) should be elicited. Family history of cataracts

### BOX 5.15.1 Laboratory Tests for Bilateral Nonhereditary Pediatric Cataracts

Complete blood count  
Random blood sugar  
Plasma calcium and phosphorus  
Urine assay for reducing substances after milk feeding  
Red blood cell transferase and galactokinase levels  
If Lowe's syndrome is suspected, screening for amino acids in urine  
Toxoplasmosis titer  
Rubella titer  
Cytomegalovirus titer  
Herpes simplex titer

in childhood or other ocular abnormalities can be relevant. Both parents and all siblings should be examined with a slit lamp to determine any lens abnormalities. When family history is positive, consultation with a geneticist is recommended. A thorough examination by a pediatrician to assess the child's general health and to elicit information about other congenital abnormalities may be helpful.

Laboratory tests in children who have bilateral cataracts in nonhereditary cases are listed in Box 5.15.1. Most unilateral pediatric cataracts are idiopathic and do not warrant exhaustive laboratory tests.

The ophthalmological part of the evaluation starts with a complete ocular examination, which includes an assessment of visual acuity, pupillary response, and ocular motility. Biomicroscopy follows and might necessitate sedation or even general anesthesia in very young patients. Indirect fundus examination with dilated pupils is made unless the cataract is complete. A- and B-scan ultrasonography is carried out in both eyes to compare axial lengths and to discover any posterior segment abnormalities.

## ALTERNATIVES TO SURGERY

The development of metabolic cataracts, such as those found in galactosemia, can be reversed if they are discovered in the early phases. With the elimination of galactose from the diet, the early changes in the lens, which resemble an oil droplet in the center of the lens, can be reversed.<sup>12</sup> Later on, lamellar or total cataracts develop and require surgery.

When lens opacities are confined to the center of the anterior capsule or the anterior cortex, dilatation of the pupils with cyclopentolate 1% twice daily can improve vision and postpone the need for surgery. Photophobia and partial loss of accommodation are side effects of this measure.

## ANESTHESIA

General anesthesia is presently the only anesthetic option in PCS. It is extremely important to request deep anesthesia throughout the procedure to minimize iatrogenic damage to iris and cornea.<sup>5,7,8</sup> Children's sclera is particularly elastic; therefore, any tension on the extraocular muscles results in loss of anterior chamber depth and increased intraocular pressure (IOP). A useful marker for anesthesia depth is the position of the eye during surgery. If the cornea moves upward or downward, the anesthesia is too light and should be deepened. When this guidance is followed, surgery is easier to perform.

## GENERAL TECHNIQUES

Unlike in adults, pediatric cataracts are soft. Their lens material can be aspirated through incisions that are 1–1.5 mm long at the limbus or can

<sup>†</sup>Deceased



be subjected to lensectomy through the pars plana. When intraocular lens (IOL) implantation is intended, a larger limbal wound is needed to introduce the IOL. With the use of foldable implants, the incision is not more than 3 mm. A scleral tunnel is better than a clear corneal incision (CCI). Unlike in adults, the wound should be securely sutured with 10.0 vicryl sutures to prevent wound dehiscence with iris incarceration—a common complication in children.<sup>2,4,5,7,8,10</sup>

## SPECIFIC TECHNIQUES

Two main approaches exist for the removal of cataracts in children: the pars plana approach and the corneolimbal approach.

Both techniques have advantages and disadvantages. The pars plana approach was developed with the advent of vitrectomy machines in the late 1970s.<sup>13,14</sup> It was intended to deal mainly with very young infants in whom surgery is more difficult. With the continuing refinements in cataract and implant surgery in adults, the pars plana approach gradually is being abandoned in favor of the limbal approach because the latter allows better preservation of the capsular bag for lens-in-the-bag IOL placement.<sup>2,5,7,8</sup>

### Pars Plana Approach

The pars plana approach is indicated mainly for neonates and infants under 2 years of age, particularly for those who have bilateral congenital cataracts, in which case immediate IOL implantation is not intended.<sup>2</sup> The technique requires a guillotine-type vitrectomy and balanced salt solution (BSS) containing epinephrine (adrenaline) 1:500 000. The location of the pars plana in infants can be 1.5–3.5 mm from the limbus. In the last decade, surgeons have largely abandoned the 20-gauge vitrectomy apparatus in favor of the 23-gauge or the 25-gauge version. A lensectomy–anterior vitrectomy is completed, sparing a 2- to 3-mm peripheral rim of anterior and posterior capsules. These capsule remnants are used to create a shelf to support a posterior chamber IOL that may be implanted later on in life.<sup>15</sup> It is important to avoid vitreous incarceration in the wounds by turning off the infusion before withdrawing the vitrectomy cutter from the eye. This precaution reduces the chances of suffering retinal traction and detachment later in life.<sup>16</sup>

This technique is rapid and allows for a permanently clear visual axis. The postoperative course is normally less complicated than that after the limbal approach because fewer maneuvers occur in the anterior chamber. Consequently, the iris and the corneal endothelium suffer less iatrogenic damage. In cases of children with bilateral cataracts, where an anesthetic risk exists because of unstable medical status, both eyes can be operated on sequentially at the same surgery, but treating both eyes as separate operations. This is now a procedure practiced by some pediatric ophthalmologists even when there is no anesthesia-related risk. This has the additional advantage of reducing the risk of relative amblyopia and freeing up operating room time, thus reducing trauma to the child.<sup>17</sup>

### Corneolimbal Approach

The corneolimbal approach is the most widely used surgical technique. A long tunnel limbal incision reduces the risk of iris prolapse. Sometimes, the pupil is meiotic and will not dilate well. This requires intracameral phenylephrine 2.5% and/or iris hooks. Viscoelastic materials are necessary to maintain the anterior chamber depth. Some use an anterior chamber maintainer (ACM) to maintain the chamber, and it can provide a steady intraoperative IOP and helps keep the pupil dilated throughout the procedure because of positive hydrostatic pressure.

Two limbal incisions are made with a 23-g micro-vitreo-retinal blade (MVR; Alcon Laboratories Inc., Fort Worth, TX). These allow for use of a bimanual technique with one cannula infusing fluid to the anterior chamber and the opposite one aspirating the lens material.

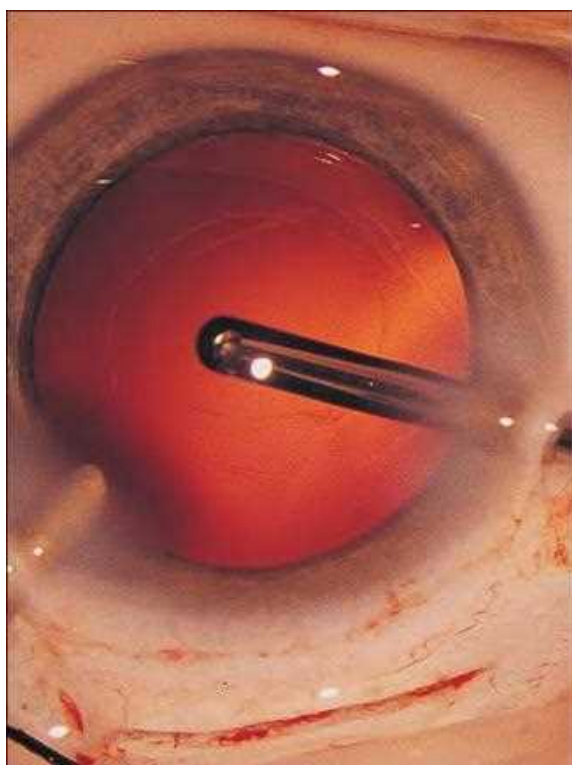
Various techniques have been described to open the anterior capsule. The younger the child, the more difficult it is to perform a capsulorrhexis. Infants have a very elastic anterior capsule that easily tears toward the periphery. A manual capsulorrhexis using a push/pull technique has been described.<sup>18</sup> A more practical alternative is to use a vitrectomy probe to create a small central opening in the anterior capsule (Fig. 5.15.1). This hole can be enlarged gradually by biting into the anterior capsule with the vitrector until the desired 4- to 5-mm opening is achieved. Another alternative is the Oertli diathermy system, which has the effect of creating a controlled central 5-mm round capsulotomy<sup>19</sup> (Fig. 5.15.2). Gentle hydrodissection and hydrodelineation free the lens material, which can be aspirated by using the bimanual technique or with the vitrector. The



**Fig. 5.15.1**  
Anterior Capsulotomy Performed With Use of a Vitrectomy Probe in a Case of Congenital Cataract. Note the use of the anterior chamber maintainer for a deep anterior chamber and a well-dilated pupil.



**Fig. 5.15.2** Oertli diathermy system for performing capsulotomy.



**Fig. 5.15.3**  
**Elective Posterior Capsulectomy and Deep Anterior Vitrectomy.** This is performed with the use of a vitrectomy probe, after all the lens material has been aspirated within the capsular bag.

management of the posterior capsular bag is determined by the age of the patient and as to whether an implant should be inserted. Most surgeons agree that infants under 6 years of age should receive an elective posterior capsulectomy and anterior vitrectomy.<sup>20</sup> Posterior capsulorrhexis is performed manually or with a vitrector.

Its diameter should be at least 4 mm (Fig. 5.15.3). The anterior vitrectomy should be generous, removing one third of the vitreous to ensure a permanently clear visual axis. Smaller posterior capsulectomies and shallow anterior vitrectomies close, especially in neonates. Posterior capsulectomies, either alone or combined with shallow anterior vitrectomy, does not guarantee a permanent clear visual axis because lens epithelial cells regrow and can form new membranes.

A modification of the technique includes a translimbal capsulorrhexis and lens aspiration, then insertion of the IOL into the capsular bag. The wound is closed, and the anterior chamber is maintained with either viscoelastic or ACM. The surgeon then goes through the pars plana to perform a posterior capsulorrhexis and anterior vitrectomy by using a vitrector. Leaving the posterior capsule intact, especially in neonates and children under 2 years of age, results in very early posterior capsule opacification. The use of yttrium–aluminum–garnet (YAG), either immediately after surgery or later, has had limited success. Because of logistics, it is not possible unless the surgeon has access to a horizontal laser system.

## CHOICES FOR CORRECTION OF APHAKIA IN CHILDREN

Spectacles, contact lenses, and IOLs are the most readily available means to correct aphakia in children.

### Spectacles

Aphakic spectacles provide satisfactory correction only in cases of bilateral aphakia in which anisometropia does not represent a problem.<sup>2</sup> Most of the patients develop good visual acuity with the use of spectacles, provided that the eyes are not excessively microphthalmic.<sup>2</sup> The disadvantages of spectacles are cosmetic concerns and the poor optical quality of high-plus lenses.

### Contact Lenses

During the 1970s and 1980s, contact lenses were described as the method of choice to correct unilateral and bilateral aphakia in childhood.<sup>2,9,10</sup> Contact lenses provide better optical correction compared with spectacles, and their dioptric power can be adjusted throughout life. However,

## BOX 5.15.2 Guidelines for the Choice of Intraocular Lens Dioptic Power

### Children Less Than 2 Years Old

- Do biometry, and undercorrect by 20%, or
- Use axial length measurements only
- Axial length, IOL dioptric power
  - 17 mm, 25 D
  - 18 mm, 24 D
  - 19 mm, 23 D
  - 20 mm, 21 D
  - 21 mm, 19 D

### Children Between 2 and 8 Years Old

- Do biometry, and undercorrect by 10%

the management of contact lenses in children can be very difficult and costly because of frequent loss of lenses, recurrent infections, and poor follow-up. The Infant Aphakia Treatment Study (IATS)<sup>21</sup> was a multicenter randomized clinical trial comparing cataract surgery with or without IOL implantation in infants ages 1–6 months with clinical congenital cataracts. The IATS authors concluded that there was no significant difference in the median visual acuity between eyes that underwent primary IOL implantation and those left aphakic. However, significantly more adverse events occurred, and a need existed for additional intraoperative procedures in the IOL group. Those authors concluded that primary IOLs should be reserved for those cases where, in the opinion of the surgeon, the use of handling of a contact lens would result in significant periods of uncorrected aphakia. During the last 2 decades, many technical problems have been overcome. One such recent advance is the introduction of extended wear silicone elastomer and custom rigid gas permeable contact lenses that are a great advance.<sup>22</sup> Some problems, such as cost of replacement and need for frequent replacement because of changes in refractive error and lens loss, have persisted.

## Intraocular Lenses

The IOL option was originally advocated in cases of unilateral pediatric cataracts because it facilitates amblyopia management by providing more permanent correction.<sup>2,4,5,7,8,10,13</sup> Implanting an IOL in a growing eye is not an ideal solution. The aim in the IOL option, unlike in the contact lens alternative, is to correct most, but not all, of the aphakia; the residual refractive error has to be corrected with the use of spectacles, which can be adjusted throughout life.

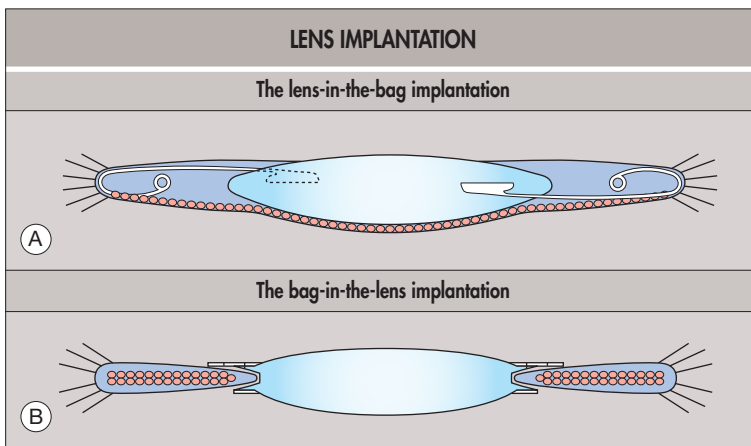
The implantation of anterior chamber angle supported IOLs in children was discontinued in the mid-1980s. Devastating complications, such as secondary glaucoma and corneal decompensation, were attributed to these IOLs, especially in younger patients. Posterior chamber intraocular lens (PCL) implantation represents, by far, the best method for the correction of aphakia.

### Selection of Intraocular Lenses

The choice of the dioptric power of IOL for young children is the main difficulty faced by the ophthalmologist.<sup>2</sup> Pediatric IOLs are not yet readily available,<sup>23,24</sup> and the rapid growth of the eye during the first 2 years of life makes an effective choice difficult.<sup>2,4,7,8,25–27</sup> (Box 5.15.2). Nevertheless, in the 1990s, increasingly positive reports were published on the use of PCLs in children and even in neonates.

The material from which the IOL is made must have a long track record of safety. Polymethyl methacrylate (PMMA) IOLs have been in use for more than 50 years; PMMA is probably the safest material to be used in children until similar follow-up data on other biomaterials become available. Nevertheless, during the last decade, many surgeons have switched to the use of foldable hydrophobic IOLs in children. The actual size of the capsular bag and the ciliary sulcus in children has been ascertained by the work of Bluestein et al.<sup>24</sup> PCLs, which were originally oversized, have been reduced from 13–14 mm to 12–12.5 mm in diameter in most modern models. In children, it is even more important to implant an IOL of the correct size.<sup>24</sup> Pediatric IOLs should not exceed 12 mm in overall diameter, considering that the average adult ciliary sulcus diameter rarely exceeds 11.5 mm. Ideally, the pediatric IOL should be available in diameters of the range 10.5–12 mm.<sup>24</sup> The choice of IOL size is determined mainly by the site of implantation (i.e., lens-in-the-bag or ciliary sulcus).





**Fig. 5.15.4** Schematic drawing of the lens-in-the-bag implantation (A) and the bag-in-the-lens implantation (B).

Both the biometry and the age of the child determine the choice of the IOL dioptric power. Two main age groups exist with regard to PCS: patients younger than 2 years and patients between 2 and 8 years of age. In the first group, the axial length and the keratometric (K) readings change rapidly, whereas in the second group the changes are slower and more moderate.<sup>25–27</sup> To counteract the large myopic shift that occurs, it is advisable to undercorrect in children with IOLs so that they can grow into emmetropia or mild myopia in adult life.<sup>25–27</sup>

Those who are under 2 years of age should receive 80% of the power needed for emmetropia at the time of surgery. Because the K readings also change rapidly during the first 18 months of life, it is practical to rely on the axial length only when the IOL dioptric power is chosen for infants (Box 5.15.2). The postoperative residual refractive error is corrected by spectacles, which can be adjusted as will as the child grows. Infants and toddlers can tolerate up to 6 D of anisometropia, which disappears within 2–3 years.<sup>27</sup> Most of the infants who have unilateral pseudophakia need a patch over the sound eye for half their waking hours for the first year and for 80% to 90% of the waking day until age 4 or 5 years. Patches alleviate the symptoms of anisometropia but at the same time affect the chances of development of good binocularity.<sup>26</sup>

For the age range of 2–8 years, the IOL dioptric power should be 90% of that needed for emmetropia at the time of surgery (see Box 5.15.2). The induced anisometropia is moderate and lessens with the expected myopic shift that occurs in adolescence.<sup>25–27</sup>

### Implantation in Children Under 2 Years of Age

Intraocular implantation is controversial in infants. However, implantation in those beyond 6 months and beyond 1 year of age is widely practiced, particularly in unilateral cases. The most popular approach involves cataract aspiration and capsulectomy through the corneal sclera wound. The implant is inserted through the corneal sclera wound into the capsular bag. Elective posterior capsulectomy and anterior vitrectomy are performed through the pars plana. The results of the IATS and improved contact lens technology may see a shift away from IOL in the age group.<sup>21</sup>

### Implantation in Children Above 2 Years of Age

For children older than 2 years, the IOL should be inserted because the eye has reached nearly the adult size, although its sclera is much softer. Gimbel<sup>28</sup> has described a special IOL implantation technique for this group of patients. This technique requires extreme dexterity because both anterior and posterior capsulorhexes are performed. The IOL haptics are placed in the bag fornices, while the optic is protruded through both capsulorhexes to be captured beneath the posterior capsule remnants. Tassignon recently developed a new technique for a special IOL called *bag-in-the-lens*.<sup>29</sup> The technique consists of creating an anterior and posterior capsulorhexes. The specially designed IOL has, at its periphery, a groove that contains both anterior and posterior capsule rims (Fig. 5.15.4). Although technically demanding, promising early results indicate that this technique may eliminate the need for elective anterior vitrectomy.

### Postoperative Treatment

The eyes of infants and younger children are highly reactive to surgery. These eyes produce excessive fibrin, and as a result, an intense inflammatory response occurs soon after surgery. The pupil remains meiotic, and

corneal edema occurs. The inflammation is worse if the surgery has been traumatic. A combination of intense topical and systemic corticosteroids is used for the first few weeks with use of atropine or cyclopentolate to dilate the pupil. The medications are tapered over about 4–6 weeks. The use of triamcinolone 4 mg in 0.1 mL has significantly reduced the inflammation and lessened the need for intense topical and systemic corticosteroids.<sup>30</sup>

## COMPLICATIONS

Intraoperative complications are related to the age of the child at surgery, anesthesia, and surgical technique. The anterior chamber tends to collapse, the iris can protrude through the wound, and the pupil constricts. Deep anesthesia, good surgical technique, ACM, iris hooks, and proper vitrectomy help minimize these problems.

### Postoperative Complications

Early complications include fibrinous uveitis, high IOP, incarceration of iris in the wound, and endophthalmitis. Late complications include dislocation of the IOL, chronic iritis, glaucoma, and retinal detachment. The rate of glaucoma or suspected glaucoma in the IATS 1 year after surgery was 12% at 1 year and 30% at 5 years follow-up, with no difference between eyes that were aphakic and those that were pseudophakic.<sup>21</sup> Many reasons have been reported as a cause of glaucoma; delaying surgery until the infant is 6 weeks old is thought to reduce the risk.<sup>31,32</sup>

### Amblyopia Management

The child's parents must understand that surgery is only the start of visual rehabilitation and that rehabilitation must continue throughout childhood.

Unilateral cases are the most difficult to manage.<sup>2,4,5,7–10</sup> Amblyopia treatment starts soon after surgery, after postoperative inflammation subsides and the medium becomes clear. The initial treatment must be aggressive to boost vision in the deprived eye. Occlusion of the sound eye is carried out for half the waking day for the first year. Therefore, occlusion should be maintained 80% to 90% of the waking day. Soon after surgery for bilateral aphakia, spectacles are prescribed, a bifocal lens of +3 should be prescribed at 2 years. For unilateral aphakia and pseudophakia, patching should be continued until the child is 4–5 years of age. The patch wear time can be reduced gradually but should not be abandoned until the child reaches 8–9 years of age.

### Options to Correct Myopic Shift

The growth of aphakic and pseudophakic eyes is unpredictable. This particularly applies to pseudophakic eyes.<sup>33</sup> A myopic shift of 7 D or more is not uncommon. IOL exchange when an implant has been in place for more than a year is extremely difficult and carries significant risks. However, contact lenses,<sup>22</sup> refractive surgery,<sup>34</sup> and secondary IOLs to correct the myopia are now the preferred options. Both the techniques and the outcome of these various options have produced good visual outcomes with low risk of complications.

## OUTCOME

The visual outcome depends largely on the type of cataract, the laterality of the pathology, the timing of intervention, the quality of surgery, and, above all, the management of amblyopia. It is possible to achieve nearly normal vision even in cases of unilateral congenital cataracts, provided the amblyopia management is aggressive.<sup>2–10,24</sup> Binocularity usually is poor in these cases, but some gross stereopsis can be expected.<sup>35</sup> Children with aphakia and pseudophakia certainly should be followed up throughout their childhood and preferably throughout life.<sup>36</sup>

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# Complications of Cataract Surgery

Thomas Kohnen, Li Wang, Neil J. Friedman, Douglas D. Koch

# 5.16



**Definition:** All unwanted events during or after conventional cataract surgery with potential threat to the normal structure and/or function of the eye.

## Key Features

- Intraoperative complications, depending on incision, perforation, detachment of structures, burns, anterior capsule, posterior capsule, zonulae, capsulorhexis, iris problems, subluxation, sulcus structure, hemorrhage.
- Postoperative complications, depending on wound characteristics, epithelial characteristics, corneal irregularities and problems, intraocular hemorrhage, glaucoma, problems with architecture of the implanted intraocular lens, problems with the retina, dislocation of the lens.

## Associated Feature

- Understanding the mechanism of several complications in cataract surgery and performing the correct steps to minimize further unwanted negative results.

## INTRODUCTION

Phacoemulsification (“phaco”), sutureless, self-sealing tunnel incisions, and foldable intraocular lenses (IOLs) have changed cataract surgery dramatically over the past 2 decades. Postoperative astigmatism and inflammation are typically minimal; visual recovery and patients’ rehabilitation are accelerated. The published literature indicates that modern cataract surgery, although certainly not free of complications, is a remarkably safe procedure, regardless of which extraction technique is used.<sup>1</sup>

Using rigid criteria for scientific validity, Powe et al.<sup>1</sup> analyzed 90 studies published between 1979 and 1991, addressing visual acuity ( $n = 17\,390$  eyes) or complications ( $n = 68\,316$  eyes) following standard nuclear expression cataract extraction with posterior chamber IOL implantation, phaco with posterior chamber IOL implantation, or intracapsular cataract extraction with anterior chamber IOL implantation. Strikingly, the percentage of eyes with postoperative visual acuity of 20/40 or better was 89.7% for all eyes and 95.5% for eyes with no pre-existing ocular comorbidity. The incidence of sight-threatening complications was less than 2%.

In this chapter, the key elements in the prevention, recognition, and management of the major intraoperative and postoperative complications of cataract surgery are discussed.

## INTRAOPERATIVE COMPLICATIONS

### Cataract Incision

The cataract incision serves as more than just the port of access to the anterior segment; it is a critical step of the operation that affects ocular integrity and corneal stability. The traditional limbal or posterior limbal incision has been largely replaced by tunnel constructions, which can be located in the sclera, limbus, or cornea and are characterized by their

greater radial length and an anterior entry into the anterior chamber to create the self-sealing internal corneal valve. Advantages of tunnel incisions are increased intraoperative safety, decreased postoperative inflammation and pain, increased postoperative watertightness, and reduced surgically induced astigmatism.<sup>2</sup>

### Tunnel Perforation

Tearing of the roof of the tunnel predisposes to excessive intraoperative leakage, which compromises anterior chamber stability, and to postoperative wound leakage. If the tear occurs at either edge of the roof, surgery usually can be completed using the initial incision, proceeding slowly and observing the wound carefully as instruments are introduced or manipulated in the eye. It usually is preferable to suture the incision at the conclusion of surgery, even if the wound is watertight, to restore a more normal architecture and prevent external wound gape.

If, however, the roof is perforated in the center of the flap, and this is noted before the anterior chamber is entered, creation of a new incision should be considered. If the cut is extremely small (e.g.,  $< 0.5$  mm), sometimes the same procedure as for lateral roof tears (see above) can be used. Before IOL insertion, the opposite margin of the wound is enlarged, and to prevent further tearing, the incision is made larger than normal for IOL insertion. Suture closure usually is advisable to restore normal wound architecture.

If the floor of the tunnel is perforated, which can happen during scleral tunnel dissection, surgery usually can be performed through this wound; care must be taken to avoid trauma to any prolapsing uveal tissue. The perforation should be closed with sutures or fibrin glue.

### Descemet’s Detachment

Detachment of Descemet’s membrane can be a major postoperative complication, resulting in persistent corneal edema and decreased visual acuity. To prevent Descemet’s detachment, the surgeon should carefully observe the inner lip at each phase of the procedure. To avoid blunt stripping of Descemet’s membrane during enlargement of the wound, a sharp metal or diamond blade is recommended.

If detachment is caused by viscoelastic injection, the agent must be removed by using a blunt cannula. Intraoperatively, repositioning of Descemet’s membrane usually can be achieved by injecting balanced salt solution (BSS) or occasionally air or an ophthalmic viscosurgical device (OVD) through the paracentesis site. With the experience we have gained over the last 5 years with Descemet’s membrane endothelial keratoplasty (DMEK) air or gas injection (20% sulfahexafluoride [ $\text{SF}_6$ ]) can perfectly reattach a stripped Descemet’s membrane.

If a visually significant Descemet’s detachment is present postoperatively, the authors of this chapter prefer to intervene after 2–3 weeks; however, late spontaneous reattachment 2–3 months (in one case, 10 months) postoperatively has been reported.<sup>3,4</sup> To reattach Descemet’s membrane, the patient is positioned at the slit lamp after several drops of anesthetic agent and antibiotics have been administered. A paracentesis incision is made inferotemporally. A 27- or 30-gauge cannula is attached to a syringe with a filter, and the syringe is filled with  $0.5\text{--}1\text{ cm}^3$  of air or, for eyes that have an unsuccessful injection of air alone, an expansive gas (e.g.,  $\text{SF}_6$ ). Using the cannula, approximately 50% of the aqueous is drained, and the chamber is reformed with injection of the gas. Another technique





**Fig. 5.16.1 Corneal Burn Following Phacoemulsification (Phaco).** In this patient with an apparent filtering bleb, phaco was performed through a temporal, clear corneal incision (CCI). Posterior capsular rupture was suspected; the surgeon injected a highly retentive ophthalmic viscosurgical device beneath and in front of the nucleus to minimize the risk of posterior dislocation of the nucleus. Phaco was instituted with low flow and vacuum settings, and a severe corneal burn was immediately produced because of obstruction of the phaco tip by the viscoelastic material. The incision was closed with several interrupted sutures. Many of these pulled through the injured tissue, and as a result, additional suturing was required several days later. Postoperatively, the patient has 5 D of surgically induced astigmatism that has persisted for more than 5 years.

for repairing Descemet's detachments using intracameral gas injection at the slit lamp microscope has been reported.<sup>5</sup> A 25-gauge needle on a 3-mL syringe filled with the gas and another 25-gauge needle are advanced through the corneoscleral limbus at opposite clock hours with the bevel up and the needles oriented parallel to the iris plane. The plunger on the syringe is depressed to inject the gas and fill the anterior chamber while aqueous humor is allowed to egress from the opposing 25-gauge needle. More complicated cases may require direct suturing.<sup>6</sup>

## Thermal Burns

Part of the energy produced by the phaco tip is dissipated as heat. This heat is conducted into the eye along the titanium tip and then cooled by the ongoing flow of the irrigation-aspiration fluid. If for any reason the flow is blocked, a corneal burn can occur within 1–3 seconds. The most common cause is inadequate flow through the phaco tip because it has been obstructed by a retentive OVD; this problem arises from use of low flow and vacuum settings. The critical warning sign is the appearance of milky fluid that is produced around the tip as emulsification commences.

To avoid corneal burns, phaco and irrigation-aspiration functions should always be tested before the eye is entered. Some of the viscoelastic material that overlies the nucleus can be aspirated before the start of emulsification to ensure that aspiration is adequate. To prevent constriction of the irrigating sleeve, an incision size that is appropriate for each particular phaco tip should be selected. If a burn does occur, meticulous suturing of the wound with multiple radial sutures (Fig. 5.16.1) is required. A bandage contact lens may assist with wound closure. Severe postoperative astigmatism can result. The smaller incision size and new-generation phaco tips continue to contribute to a reduction in the incidence of corneal burns.

## Anterior Capsulectomy

### Preventing Radial Tears in the Anterior Capsule

For phaco, the preferred method of anterior capsulectomy is capsulorrhexis. It is now recognized that radial tears in the anterior capsule can pose significant risks because of their tendency to tear into the equatorial region of the lens<sup>7</sup> and extend into the posterior capsule. This causes posterior capsular rupture, loss of lens material, and IOL decentration. The surgeon's goal, therefore, must be to retain an intact capsulorrhexis. A common cause of radial tears is irretrievable loss of the capsulorrhexis tear peripherally beneath the iris. To prevent this, the following steps should be considered:

- The anterior chamber should be reinflated with an OVD.
- The vector forces of the tear should be changed to redirect the tear in a more central direction.
- If the tear is lost beneath the iris, the capsulorrhexis should be restarted from its origin, proceeding in the opposite direction (if possible, this

new capsulorrhexis should end with the incorporation of the original tear in an outside-in direction; however, the original tear is often too peripheral to permit this, and a single radial tear is created).

An alternative approach to a “lost” capsulorrhexis is to convert to a “can opener” capsulectomy. It may, indeed, be safer to have multiple tears, rather than a single one, because forces that extend these tears can be distributed to multiple sites, which reduces the likelihood of a tear extending equatorially.

### Excessively Small Capsulorrhexis

If the diameter of the capsulorrhexis opening is excessively small, the tear should be directed more peripherally and continued beyond the original point of origin before completion of the capsulorrhexis; this procedure removes an annulus of capsule and enlarges the opening. If the capsulorrhexis has been terminated and the opening is too small, a new tear can be started by making an oblique cut with Vannas scissors or a sharp needle. It usually is preferable to enlarge the capsulorrhexis after IOL implantation, to minimize the risk of radial tears during lens implantation.

### Minimizing Complications When Radial Tears Are Present

If radial tears are present, several modifications in surgical technique should be considered to minimize the risk of tear extension into the posterior capsule:

- Hydrodissection or hydrodelineation is performed gently to minimize distention of the capsular bag.
- Cracks during emulsification are made gently away from the area(s) with radial tears. Alternatively, as much of the nucleus as possible is sculpted within the capsular bag, and the rest is removed at the iris plane. The height of the infusion bottle is kept low to prevent overinflation of the anterior chamber (which can cause the tear to extend peripherally).
- The IOL should be placed with the haptics 90° away from the tear. One-piece polymethyl methacrylate (PMMA) lenses tend to maintain better centration in these situations. Rotation of the IOL should be minimized. The OVD should be removed in small aliquots while gentle infusion of BSS is performed through a side-port incision.
- It is important to avoid anterior chamber collapse at any phase of the operation when radial tears are present. Anterior bulging of the posterior capsule can place increased stress on a radial tear, which predisposes its extension into the equator and posterior capsule. To avoid this, the chamber is deepened each time the phaco or irrigation-aspiration tip is removed from the eye; this is done by injecting fluid, OVD, or perhaps air through the paracentesis incision with a syringe while the instrument is removed from the incision.

## Nucleus Expression Cataract Extraction

Complications related to nucleus expression are covered in Chapters 5.11 and 5.12.

## Complications During Phaco

### Hydrodissection

Hydrodissection was developed to permit easy rotation of the nucleus in the capsular bag and to facilitate removal of various layers of the lens by eliminating their adhesion to surrounding tissues. Two major complications of hydrodissection are inadequate hydrodissection and overinflation of the capsular bag. The former results in a nucleus that does not rotate, and this predisposes to zonular dehiscence if excessive force is exerted on the nucleus. This can be avoided by making an additional hydrodissection, particularly in quadrants that have not been hydrodissected before. U-shaped cannulas are useful to hydrodissect subincisional regions of the lens not accessible with straight or angulated cannulas.

Overinflation of the capsular bag can predispose to prolapse of the nucleus into the anterior chamber, which might compromise the ease or safety of nucleus emulsification. A serious complication of overinflation is posterior capsular rupture, with loss of the nucleus into the vitreous. This is more likely to occur in eyes with long axial lengths, (hyper)mature cataracts, or with fragile posterior capsules, such as those found in patients who have posterior polar cataracts.<sup>8</sup>

### Iris Prolapse or Damage

Iris prolapse is usually caused when the anterior chamber is entered too posteriorly, such as near the iris root. If this is noted early in the case

and interferes with the easy introduction of instruments into the eye, it is advisable to suture the incision and move to another location.

A second and more ominous cause of iris prolapse is an acute increase of intraocular pressure (IOP) accompanied by choroidal effusion or hemorrhage. In this instance, the surgeon should attempt to identify the cause and lower the IOP. Digital massage on the eye, pressing directly on the incision, may successfully lower the pressure. It is useful to examine the fundus to ascertain whether a choroidal effusion or hemorrhage exists. With choroidal effusion, aspiration of vitreous can be helpful, as can the administration of intravenous mannitol. If a choroidal hemorrhage occurs or if the increased IOP from an effusion is resistant to treatment, it usually is best to terminate the surgery. The wound is sutured carefully; intraocular miotics are administered, and a peripheral iridectomy may be performed to help reposition the iris. For effusions, surgery can be deferred until later in the day or the next day, when the fluid dynamics of the eye have returned to a more normal state. If a limited choroidal hemorrhage has occurred, it is best to wait 2–3 weeks before attempting further surgery.

Trauma to the iris from prolapse or emulsification with a phaco tip can produce an irregularly shaped pupil and iris atrophy and can predispose to posterior synechiae formation. If iris damage is produced inferiorly through contact with the phaco tip, loose strands of tissue should be cut to reduce the likelihood of these being aspirated into the phaco tip. Another option is to use a single iris hook to retract the inferior iris, holding it away from the phaco tip for the duration of the procedure.

### Floppy Iris Syndrome

This complication has been observed during phaco in patients receiving  $\alpha_1$ -antagonist agents, such as tamsulosin (Flomax). The symptoms include billowing and floppiness of the iris, prolapse of the iris to the main and side incisions, and progressive constriction to the pupil during surgery.<sup>9</sup>

When treating patients who receive  $\alpha_1$ -antagonist agents, the surgeon can try to avoid severe intra- and postoperative complications by preoperative use of atropine, intraoperative epinephrine (adrenaline), lower phaco vacuum and aspiration settings, the use of supercohesive OVDs, and various iris hooks and pupil dilators.<sup>10</sup>

### Trapped Nucleus

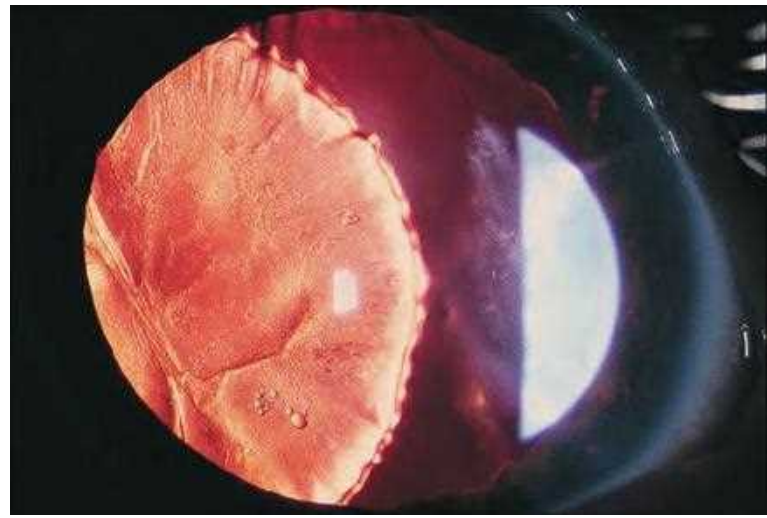
In this situation, the nucleus seems to be trapped within the capsular bag; it resists rotation, elevation, or both. This usually indicates a nucleus that requires further hydrodissection, which should be repeated in regions not previously hydrodissected (e.g., laterally and inferiorly with angled or straight cannulas, superiorly with U-shaped cannulas; if these cannulas are not available, additional paracentesis sites can be created in strategic locations).<sup>11</sup> If this fails to achieve adequate mobilization of the nucleus, viscodissection can be performed. An OVD is injected in the plane of the hydrodissection, which usually results in elevation of the nuclear remnant. When re-entering the eye with the phaco tip, irrigation should not be used until a second instrument has been inserted through the stab incision and placed below the nucleus; when irrigation and aspiration begin and the OVD is removed, the second instrument prevents the nuclear piece from falling back into the posterior chamber.

If the capsulorrhexis is small and the nuclear circumference is intact, nuclear elevation through the capsulorrhexis may not be possible. Additional sculpting might be required to thin the nucleus centrally or to remove some of the peripheral nucleus. After the nucleus has been sufficiently thinned, an instrument, such as a Sinskey hook or spatula, can be teased posteriorly through the remaining nuclear tissue. This enables elevation of a portion of the nucleus and thereby facilitates access to the remainder.

### Subluxated Lens

The surgical approach for subluxated lenses (Fig. 5.16.2) is determined by lens stability, lens position, and nuclear density.<sup>12</sup> In a subluxated lens with adequate zonular support, phaco (or nuclear expression) can be performed. OVD is injected as needed throughout the surgery to tamponade the vitreous in areas of zonular dehiscence. Extensive hydrodissection and viscodissection should be carried out. Depending on the density of the nucleus, either phaco in the capsular bag or anterior chamber phaco under a retentive viscoelastic is performed. Any form of zonular stress should be minimized, particularly with nuclear rotation. Although not the topic of this chapter, femtosecond laser-assisted capsulectomies can help in these situations because they produce minimal stress to the zonules.

If phacodonesis is present but the lens has not fallen posteriorly, a soft nucleus sometimes can be removed by phaco-aspiration, whereas a



**Fig. 5.16.2 Subluxated Lens.** This patient had a subluxated lens caused by ocular trauma. The crystalline lens was removed using a pars plana approach, and a sulcus-sutured intraocular lens was implanted.

hard nucleus should be extracted by using an intracapsular approach. Pars plana vitrectomy is an excellent option for these cases as well; it certainly is preferred when the lens is subluxated posteriorly.

The location of the IOL placement depends on the status of the capsular bag after cataract removal. If zonular disruption is minimal (fewer than 3 clock hours), the IOL can be implanted into the capsular bag with the haptic orientated in the meridian of the zonular defect. If the zonular disruption is larger, options include the following:

- Ciliary sulcus implantation, possibly with scleral or iris fixation of one or both haptics.
- Insertion of one haptic into the capsular bag and suturing of the second haptic into the sulcus.
- Endocapsular ring implantation to stabilize the capsular bag or a Cionni ring to suture the capsular bag/ring complex to the sclera.<sup>13–15</sup>
- Anterior chamber lens implantation (angle-supported or iris fixated).<sup>16</sup>
- An angle-supported anterior chamber lens, which is acceptable if no anterior chamber angle pathology, glaucoma, or uveitis is present.<sup>14</sup>
- Posterior chamber lens implantation (as iris fixated retropupillary Artisan type).<sup>17</sup>

### Ruptured Posterior Capsule

Posterior capsule rupture is the most common serious intraoperative complication of cataract surgery.<sup>18</sup> Proper management, however, can result in minimal morbidity to the patient. A posterior capsular rent is more likely to occur in eyes with small pupils, hard nuclei, or pseudo-exfoliation syndrome. Recent reports suggest that the visual prognosis of patients who have broken posterior capsules is excellent. The key factors are to minimize ocular trauma, meticulously clean prolapsed vitreous from the anterior segment, if present, and ensure secure fixation of the IOL.

### Before Nucleus Removal

A capsular break noted before nucleus extraction is a potential disaster. The first objective is to prevent the nucleus from being dislodged into the vitreous cavity. An OVD can be injected posterior and anterior to the nucleus to prevent its posterior displacement and to cushion the corneal endothelium. Another alternative is to insert an instrument through a pars plana incision 3 mm posterior to the limbus into the vitreous, which Kelman had described as “posterior assisted levitation” (Charles Kelman, personal communication). The nucleus is pushed gently anteriorly so that it can be captured in front of the iris and safely removed from the eye. Once the nucleus or its remnants have been repositioned in the anterior chamber, the choice is to convert or to continue the emulsification. The latter course can be more hazardous and predisposes to enlarging the rent and possibly losing the nucleus into the vitreous. In most circumstances, the nucleus should be managed by sufficiently enlarging the wound to facilitate easy extraction of the nucleus on a lens loop. However, in the case of a small break or when only a small amount of nucleus is left, it may be possible to cover the posterior capsular opening with a retentive OVD and complete the phaco. A Sheets glide can also be used as a “pseudo-posterior capsule” to facilitate completion of phaco.



Vitreous loss almost always accompanies posterior capsular rupture that occurs before nucleus removal. Whenever feasible, vitrectomy should be performed before the nuclear pieces are removed. Clearly, this should not be done if it makes loss of the nucleus into the vitreous more likely.

### During Cortical Irrigation–Aspiration

When capsular rupture occurs during aspiration of the cortex (which is, in fact, the most common cause),<sup>7,19</sup> a key factor is the status of the vitreous. If no vitreous is present in the anterior segment, vitreous loss often can be averted. An OVD can be injected through the capsular opening to push the vitreous posteriorly. Cortical removal can be completed using low-flow irrigation. Options include using a manual system; a dry approach, aspirating with a cannula in the chamber filled with OVD; a bimanual approach through two paracentesis openings; and automated irrigation–aspiration with all settings reduced.<sup>20</sup> The cortex should be stripped first in the region farthest from the rent, and the direction of stripping should be toward the rent. Because it can be hazardous to remove the cortex in the region of the rent, the cortex is sometimes better left in the eye, to avoid the possibility of enlarging the rent and precipitating vitreous loss. One option to prevent extension of the rent is to convert the tear into a small posterior capsulorrhexis, which eliminates any radially orientated tears that could extend with further surgical manipulation.

If vitreous is present in the anterior segment, vitrectomy should be performed first, with the necessary caution being taken to prevent extension of the rent. Depending on the type of capsular tear, the vitrectomy is performed through either the limbal incision or the pars plana. The former approach is used when the tear is located near the incision, which permits vitrectomy with minimal risk of enlargement of the tear. A pars plana approach is preferred when the tear is remote from the incision and, therefore, less accessible anteriorly. In either case, irrigation is provided with an infusion cannula in the paracentesis opening, or a 23-gauge trocar is inserted through the pars plana. After a thorough anterior vitrectomy, the remaining cortical material can be removed using one of the techniques described earlier or using the vitrector in the aspiration mode without cutting.

### Intraocular Lens Insertion

Careful inspection of the anatomy of the capsule and zonules is required to determine the appropriate site for IOL implantation. There are five choices: capsular bag; iris fixated (retropupillary or prepupillary); ciliary sulcus; sutured posterior chamber; and anterior chamber.

#### Capsular Bag

If the rent is small and relatively central, and if the anterior capsular margins are well defined, the posterior chamber IOL can be implanted into the capsular bag. If possible, conversion of posterior capsule tears to posterior continuous curvilinear capsulorrhexis (CCC) is recommended.<sup>21</sup> With the use of an OVD, posterior CCC is initiated by grasping the advancing tear in the posterior capsule with forceps, and then applying CCC principles. This technique is applied to avoid an anticipated extension of the inadvertent linear or triangular tear during maneuvers, such as a required vitrectomy or lens placement. The surgeon should ensure that the haptics are orientated away from the rent (to avoid haptic placement or subsequent migration into the vitreous) and that the lens is inserted gently to avoid enlargement of the rent.

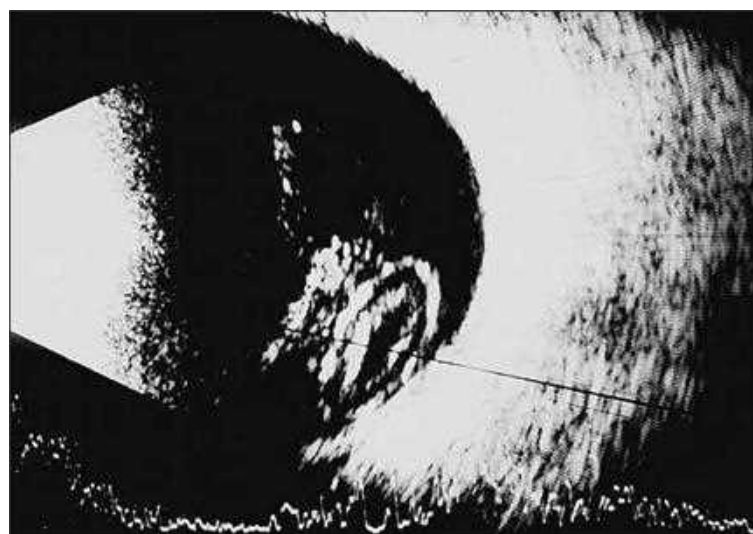
#### Iris Fixated (Retropupillary or Prepupillary)

This type of fixation can be chosen for cases of aphakia, defect posterior capsule, or tissue weakness. The great advantage of iris-fixated IOLs is that no capsular bag is necessary for fixation. These lenses, known as *Artisan/Verisyse lenses*, have claws which fix them on the iris stroma and are often implanted in patients with aphakia because of failed cataract surgery, pseudo-exfoliation syndrome (PEX), or connective tissue weakness (Video 5.16.1).

The implantation itself is a difficult technique because of the danger of potential loss of the IOL in the vitreous. Potential complications, such as endothelial cell loss, decentration, loss of enclavation, and iris damage, have to be considered.

Koss and Kohnen found no significant loss of endothelial cells after implantation of anterior chamber iris-claw lenses in aphakic eyes. The distance from lens to endothelium remained constant pre- and postoperatively.<sup>22</sup>

Recent studies have shown an increase in visual acuity after retroiridal or sclerafixated implantation of an IOL due to aphakia, luxation, or zonula insufficiency.<sup>23,24</sup> When implanting IOLs in eyes with zonular insufficiency,



**Fig. 5.16.3 Dropped Nucleus.** B-scan ultrasonography 1 day after dislocation of a lens nucleus into the vitreous cavity in a patient with high myopia.

stabilization with a capsular tension ring has to be considered to avoid further postoperative complications.<sup>25</sup>

Postoperative examinations should include measurement of IOP and endothelial cell count.

#### Ciliary Sulcus

If the rent exceeds 4–5 mm in length or extensive zonular loss occurs, the capsular bag probably is not adequate for IOL support. In such cases, the ciliary sulcus is opened with an OVD, and the iris is retracted in all quadrants to assess the status of the peripheral capsule and zonules. The IOL is inserted with its haptics oriented away from the area of the rent and positioned in areas of intact zonules and capsule.

Another alternative, if the anterior capsulorrhexis is intact, is sulcus placement of the IOL, with capture of the optic through the capsulorrhexis. Finally, some surgeons advocate iris suture fixation of one or both haptics to prevent IOL decentration. After the IOL optic is captured through the pupil, McCannel sutures are used to secure the haptic(s) to the iris, and then the optic is repositioned through the pupil.

#### Sutured Posterior Chamber

If loss of more than 4–5 clock hours of capsule or zonules occurs, the ciliary sulcus may be inadequate for lens stability. The lens can be fixated to the sclera or to the iris using single or dual 10-0 polypropylene or more recently Gore-Tex sutures. If one region of solid peripheral capsule and zonules exists, one haptic can be inserted into the sulcus in this area, and the opposite haptic can be sutured to the sclera or the iris.

#### Anterior Chamber

A Kelman-type multiflex anterior chamber IOL design is a good option for patients who do not have glaucoma, peripheral anterior synechiae, or chronic uveitis. A peripheral iridectomy should be performed in these patients to prevent pupillary block. Iris fixated Artisan anterior chamber type IOLs have even less complications.

### Dropped Nucleus

Loss of nuclear material into the vitreous cavity (Fig. 5.16.3) is one of the most potentially sight-threatening complications of cataract surgery.<sup>26</sup> Clinical and cadaver eye studies implicate posterior extension of breaks in the capsulorrhexis as a common cause of this complication.<sup>7,27</sup> Therefore, the surgeon would be wise to use increased caution when phaco is performed with capsulorrhexis tears.<sup>28</sup> Posterior polar cataract, which predisposes to posterior capsular dehiscence, is another risk factor for dropped nucleus.<sup>29</sup>

Loss of the nucleus into the vitreous cavity can be avoided by recognizing the early signs of posterior capsular rupture. These include unusual deepening of the anterior chamber, decentration of the nucleus, or loss of efficiency of aspiration, which suggests occlusion of the tip with vitreous. If capsular rupture is noted, the steps outlined earlier should be taken to prevent nucleus loss.

Some controversy exists with regard to the appropriate management of loss of the nucleus into the vitreous. Most surgeons recommend completing the procedure with careful anterior vitrectomy and removal of



See clip:  
5.16.1



remaining accessible lens material. In general, IOL implantation is permissible; one exception might be loss of an extremely hard, dense nucleus that would require removal through a limbal incision. If a significant amount of nuclear material has been retained, vitreoretinal surgery needs to be performed 1–2 days postoperatively. Patients whose eyes have small residual nucleus fragments may be observed and referred if increased IOP or uveitis refractory to medical treatment develops. Some surgeons advocate irrigating the vitreous with fluid in an attempt to float the nucleus back into position. An obvious concern is that this additional turbulence could increase vitreous traction on the retina resulting in retinal tears and retinal detachment.

## Anterior Segment Hemorrhage

The presence of intraocular blood prevents the surgeon's visualization during the procedure, stimulates postoperative inflammation, and synechia formation, and accelerates capsular opacification. To minimize the risk of bleeding, discontinuation of anticoagulant therapy before surgery can be considered if it does not pose a significant medical risk to the patient.<sup>30</sup> The sites of anterior segment hemorrhage are either the wound or the iris. Steps to minimize or eliminate bleeding from the wound include the following:

- Careful cautery of bleeding vessels in the vicinity of the incision.
- Creation of an adequate internal corneal valve to minimize the likelihood of scleral blood entering the anterior chamber.
- Performing a clear corneal incision.
- Avoid iris trauma, which can lead to iris bleeding.

Intraocular bleeding can be stopped by taking the following measures:

- Temporarily elevating the IOP with a balanced salt solution or an OVD.
- Injecting a dilute solution of preservative-free epinephrine 1:5000 (or a weaker solution).
- Direct cautery (if the bleeding vessel can be identified) with a needle-tipped cautery probe.

The most serious complication of cataract surgery is expulsive hemorrhage, which is actually a spectrum of conditions ranging from suprachoroidal effusion to mild hemorrhage to severe hemorrhage with expulsion. A sign of any of these conditions is shallowing of the anterior chamber with posterior pressure that resists further deepening of the chamber, sometimes accompanied by a change in the red reflex. These conditions typically occur intraoperatively but also may occur postoperatively, usually when the IOP is below normal (Fig. 5.16.4). Choroidal effusion also may be a precursor to suprachoroidal hemorrhage, which presumably occurs from the rupture of a blood vessel that is placed under stretch. Risk factors for suprachoroidal hemorrhage include hypertension, glaucoma, nanophthalmos, high myopia, and chronic intraocular inflammation.<sup>31</sup>

If sudden shallowing of the anterior chamber occurs and the eye becomes firm, the retina should be examined, if possible, to ascertain the cause. If a dark choroidal elevation is noted, a choroidal hemorrhage is likely, and the incision should be closed as quickly as possible. The worst scenario is expulsion of intraocular contents through the wound. With tunnel incisions, the wound typically is self-sealing and resists expulsion of a significant amount of tissue. This self-sealing construction can save



**Fig. 5.16.4 Choroidal Effusion.** This patient experienced deep ocular pain 1 day postoperatively. A choroidal hemorrhage was noted on close examination. This resolved over several months, leaving no permanent sequelae.

an eye from complete loss of intraocular contents. However, the surgeon can assist by using a finger tamponade on the wound while hyperosmotic solution is given intravenously. The wound should be closed and the anterior chamber deepened further, if possible, using a balanced salt solution or an OVD.

In the event of severe ongoing prolapse of tissue through the incision, a posterior sclerotomy should be performed; this must be done quickly. Time permitting, a conjunctival peritomy is made 3–4 mm posterior to the limbus. Using a microsurgical steel knife, a radial incision approximately 2 mm in length is made, scratching through the sclera to the level of the suprachoroidal space. Usually, blood begins to ooze from this site. As this occurs, infusion of fluid and OVD into the anterior chamber is commenced in an attempt to restore normal anterior segment anatomy. This bleeding site can be left open, or it can be sutured once the rate of hemorrhage has diminished, the incision has been closed, and the normal anterior chamber depth has been restored. The goal in these cases is to preserve the eye; cataract surgery can always be completed at a later date, typically 2 or more weeks later.

It is recommended that postoperative examinations should be performed 1 day, 7–10 days, and 4–6 weeks after cataract surgery.

## POSTOPERATIVE COMPLICATIONS

### Wound Dehiscence

With small-diameter tunnel incisions, wound dehiscence is relatively uncommon. The creation of an internal corneal valve typically prevents the major complications of wound leakage, inadvertent filtering bleb, and epithelial downgrowth. The wound healing process varies according to the site of the posterior entry. Scleral limbal incisions heal by the ingrowth of episcleral vascular tissue. New fibrovascular tissue is deposited with an orientation parallel to the edges of the incision and perpendicular to existing collagen bundles. Over the ensuing few years, collagen remodeling occurs, so that the new collagen becomes oriented parallel to existing collagen bundles, which increases the strength of the healed area.<sup>32</sup> Ultimately, the strength of the healed area is approximately 70%–80% that of the native tissue. For corneal incisions, closure of the external wound takes place by apposition or, in areas of wound gape, by epithelial ingrowth. A gradual process of remodeling then occurs; this consists of fibrocytic metaplasia of keratocytes with deposition of new collagen, again parallel to the incision, followed, over a number of years, by remodeling similar to that seen with scleral incisions. In the absence of vascular tissue, this process occurs much more slowly than in scleral or limbal tissue. Postoperative abnormalities in wound structure are produced by defects in the tunnel architecture or by defective wound healing because of systemic disorders, pre-existing tissue abnormalities (e.g., excessively thin or weak tissue), or incarceration of material, such as lens, vitreous, or iris, in the wound, which inhibits the normal healing process.

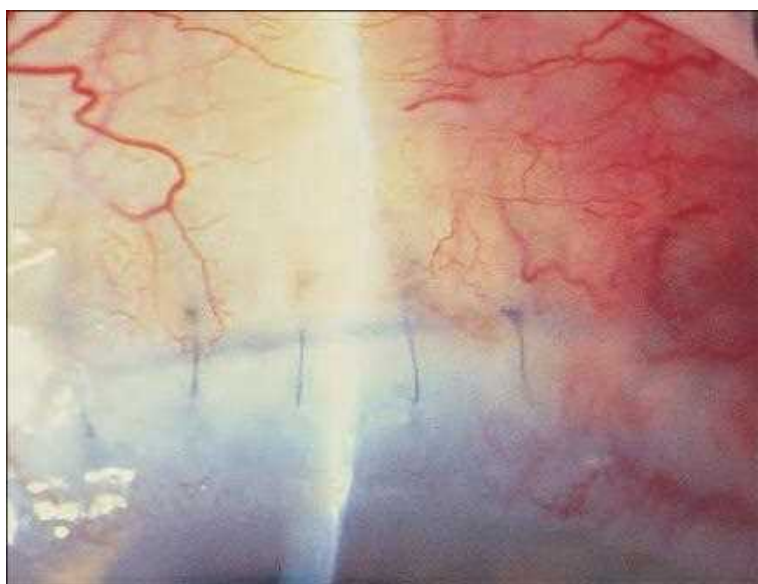
### Wound Leakage

A wound leak that occurs in the immediate postoperative period usually is the result of inadequate suture closure for a specific wound configuration. This entity is rare with tunnel constructions. Scleral pocket incisions have a longer tunnel and can readily be demonstrated to be watertight at the conclusion of surgery. Corneal incisions as small as 3.5 mm in width seal remarkably well, even though intraoperative pinpoint posterior lip pressure in these eyes often can induce a wound leak. Some surgeons perform hydration of the corneal stroma to prevent a wound leak that can be elicited with posterior lip pressure; however, this hydration clears within a few minutes to hours, and it is uncertain whether it has any actual clinical value.

Wound leaks in scleral incisions typically are covered by conjunctiva and usually resolve within a few days; occasionally, they lead to the formation of a filtering bleb. Medical management of scleral or corneal wound leaks may include the following:

- Decreasing or discontinuing corticosteroid therapy.
- Administration of prophylactic topical antibiotics.
- Pressure patching.
- Use of a collagen shield, bandage lens, or disposable contact lens.
- Administration of aqueous inhibitors.

It usually is necessary to suture a wound if the leak persists after 5–7 days, or if there is a flat anterior chamber, iris prolapse, extensive external tissue gape, or excessive against-the-wound astigmatism (Fig. 5.16.5).



**Fig. 5.16.5 Wound Dehiscence.** This patient had 5 D of against-the-wound astigmatism following nuclear expression. The surgeon resutured the wound 4 weeks postoperatively, but the astigmatism immediately recurred. Note the thin, fragile sclera, sometimes characterized as scleral “melting.”

### Inadvertent Filtering Bleb

Formation of a filtering bleb after cataract surgery occurs if the wound leaks under a sealed conjunctival flap. If early filtration is recognized, progression might be prevented by discontinuation of corticosteroid treatment. If the patient is asymptomatic, the physician can observe the bleb. Elimination of the bleb can be considered if it causes irritation, tearing, or infection. Blebs that tend to be more symptomatic are tall and cystic and encroach over the corneal surface. Options for late closure include cryotherapy, chemical cautery, neodymium:yttrium–aluminum–garnet (Nd:YAG) laser,<sup>33</sup> or surgical closure. The latter can be a complex procedure because of endothelialization of the fistula. The surgical approach requires excision of the conjunctival bleb, scraping or cryotherapy of the cells that line the fistula, and closure of the fistula, which sometimes requires a scleral patch graft.

### Epithelial Ingrowth

Epithelial ingrowth or downgrowth is a rare but serious complication of intraocular surgery. It occurs most commonly after intracapsular cataract extraction and less often following nucleus expression; it is extremely rare after phaco. Surface epithelium that invades the intraocular structures, such as over the cornea, iris, ciliary body, lens capsule, and Bruch's membrane,<sup>34</sup> can cause corneal decompensation, chronic anterior uveitis, and intractable secondary angle-closure glaucoma. Conditions for the onset of this entity are highly variable, but it appears to be more common in patients who undergo multiple intraocular procedures or have postoperative wound dehiscence.

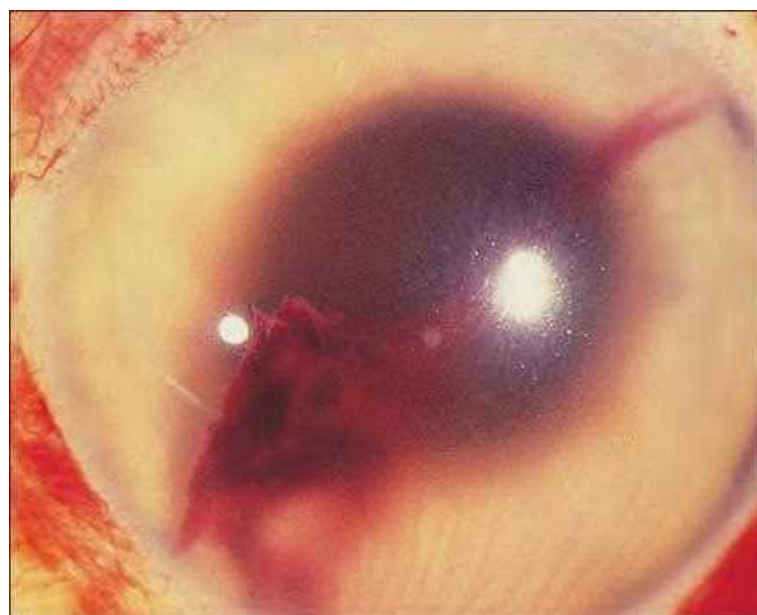
The presence of epithelial downgrowth may be confirmed by irradiation of the affected iris with an argon laser (epithelial tissue turns white with argon ablation, compared with the dark or brown appearance of normal iris) or diagnosed with specular micrography (noting a sheet of abnormal tissue that obliterates the normal endothelial mosaic); however, the definitive diagnosis is dependent on the histopathological confirmation of epithelial tissue in the eye. Treatment consists of complete destruction of all intraocular epithelial tissue by using cryotherapy, iridocyclectomy, or pars plana vitrectomy. Unfortunately, the prognosis for this postoperative complication is poor, except for a well-defined cyst that can be excised en bloc.<sup>35</sup>

### Postoperative Astigmatism

Complications related to postoperative astigmatism are covered in Chapters 5.4 and 5.18.

### Corneal Edema and Bullous Keratopathy

Factors that predispose to corneal edema following cataract surgery include the following:



**Fig. 5.16.6 Postoperative Hyphema.** This hyphema was produced by hemorrhage from the scleral incision in a patient who had a small postoperative wound leak. The hyphema resolved once the incision closed, which led to cessation of ongoing bleeding and restoration of normal intraocular pressure.

- Prior endothelial disease or cell loss.
- Intraoperative mechanical endothelial trauma.
- Excessive postoperative inflammation.
- Prolonged postoperative elevation of IOP.

Preoperatively, patients should be examined carefully for evidence of Fuchs' dystrophy or other conditions that produce a low endothelial cell count. Patients who have marginal corneal endothelial function may complain of poorer vision in the morning because of corneal edema produced by hypoxia overnight. Although most patients who have Fuchs' dystrophy have guttae that are readily visible with slit-lamp examination, in rare instances, patients can have low endothelial cell counts in the absence of guttae. It often is advisable to obtain an endothelial cell count in the fellow eye. Finally, corneal pachymetry can be helpful to assess such patients because those with a corneal thickness in excess of approximately 0.63 mm presumably have marginally compensated corneas and are at great risk of developing permanent postoperative corneal edema. If the corneal thickness is greater than 0.63 mm but no corneal edema is evident, the authors generally perform cataract surgery alone and advise patients of the increased risk of developing postoperative corneal decompensation. If frank epithelial and stromal edema is present, a combined cataract extraction with posterior lamellar or (only rarely nowadays) penetrating keratoplasty (PKP) may be advisable.

Several measures can be taken intra- and postoperatively to minimize the risk of corneal injury. Some surgeons may consider nuclear expression safer than phaco, and others may consider femtosecond laser-assisted surgery (FLACS) safer.<sup>36</sup> Techniques to remove the nucleus in the posterior chamber seem to minimize endothelial cell loss.<sup>37</sup> Evidence suggests that highly retentive OVDs are more protective when surgical removal of the nucleus is carried out near the endothelium. Postoperatively, inflammation should be aggressively treated with topical corticosteroids, and IOP should be maintained below 20 mm Hg. Mechanical factors, such as Descemet's detachment or retained nuclear fragments in the angle touching the endothelium, should be addressed. For symptomatic relief, hypertonic saline ointment is sometimes helpful as a temporary measure. Sequential corneal pachymetry is an excellent way to document the resolution of postoperative corneal edema, which may take up to 3 months; it is usually advisable to wait at least this long before recommending penetrating keratoplasty.

### Hyphema

A postoperative hyphema is caused by bleeding from the wound or iris (Fig. 5.16.6). As the hyphema resolves, the IOP should be controlled. Surgical reintervention to remove a blood clot is indicated if severe, medically resistant pressure elevation exists for several days. The duration of tolerated pressure elevation depends on the patient's age and the status of the optic nerve. Making clear corneal incisions (CCIs) reduces the incidence of postoperative hyphema.

Late hyphema or microhyphema most often is caused by chafing of the IOL against the iris or ciliary body (uveitis–glaucoma–hyphema [UGH] syndrome).<sup>38</sup> This most typically occurs because of loss of fixation of the sulcus-fixated posterior chamber IOL; micromovements of the lens cause chafing against a vessel, which produces the postoperative bleeding. Treatment consists of IOL exchange and ensuring that the new lens is well fixated; this might require suture fixation to the sclera or implantation of an anterior chamber lens. A rare cause of postoperative bleeding is hemorrhage from vascularization of the internal margin of the incision (Swans syndrome)<sup>39</sup>; this can be diagnosed by noting neovascularization of the wound using gonioscopy; it is treated by argon laser photocoagulation.

## Endocapsular Hematoma

Endocapsular hematoma is the postoperative entrapment of blood between the posterior surface of the IOL and the posterior capsule.<sup>40</sup> It is a variant of hyphema, with the exception that the blood can become entrapped within the capsular bag for months or even permanently. Fortunately, in most instances, the amount of blood is minimal and either does not significantly impair vision or is absorbed over a few weeks or months.<sup>41</sup> When the accumulation is extensive and persistent, Nd:YAG laser posterior capsulectomy is curative when used to enable immediate blood flow into the vitreous, where the blood can be resorbed.

## Intraocular Pressure Elevation

Elevation of IOP following cataract surgery is a common occurrence. Fortunately, it is usually mild and self-limiting and may or may not require prolonged antiglaucoma therapy. Causes of acute pressure elevation are retention of viscoelastic substances, obstruction of the trabecular meshwork with inflammatory debris, and pupillary or ciliary block. Patients who have pre-existing glaucoma are at much greater risk of developing acute, significant pressure elevation. Prevention of this problem includes careful removal of the OVD at the time of surgery, control of intraocular bleeding, and the use of intra- and postoperative antiglaucomatous agents. Intracameral injection of 0.01% carbachol at the conclusion of surgery is effective, as is the postoperative administration of pilocarpine gel; topical beta-blockers; apraclonidine; and topical, intravenous, or oral carbonic anhydrase inhibitors. If marked elevation of IOP is present on the first postoperative day, this can be immediately controlled by “venting” the anterior chamber. After topical anesthetic agents and antibiotics have been administered, a forceps or other fine instrument is used to depress the posterior lip of the paracentesis incision, which allows the egress of a small amount of OVD and aqueous.<sup>42</sup> This is repeated as necessary until the IOP is brought into the low-normal range. The patient can then be treated with topical antiglaucoma therapy and followed carefully to ensure that pressure is controlled.

Chronic IOP elevation can be caused by corticosteroid use, retained lens (particularly nuclear) material, chronic inflammation, peripheral anterior synechiae formation, endophthalmitis, and ciliary block. The correct diagnosis of the underlying cause is required to institute appropriate therapy.

## Capsular Block Syndrome

Capsular block syndrome (CBS) is initially defined as the entrapment of an OVD in the capsular bag because of apposition of the anterior rim of the capsulorrhexis with the anterior face of the IOL.<sup>43,44</sup> This may be more common with acrylic IOLs because of their slightly “stickier” surface. Postoperatively, the bag becomes more distended (perhaps through osmotic imbibition of aqueous), and the IOL is pushed anteriorly to create a myopic refractive shift. This can be prevented by meticulous removal of the OVD from the bag at the conclusion of surgery. To accomplish this, it is helpful to gently depress the IOL optic to displace the OVD trapped behind the IOL.<sup>45</sup> Treatment requires Nd:YAG laser puncture of the anterior capsule peripheral to the edge of the capsulorrhexis, which permits the OVD to escape into the anterior chamber. Alternatively, if the pupil is relatively small and the anterior capsule is not accessible to laser treatment, a small posterior capsulectomy can be performed, which permits the OVD to drain into the vitreous. Another alternative is bimanual aspiration–irrigation of the material from the capsular bag after the IOL has been dislocated with the irrigation instruments.

A new classification of CBS includes intraoperative CBS, early postoperative CBS, and late postoperative CBS.<sup>46</sup> Intraoperative CBS occurs during rapid hydrodissection using a large amount of BSS and has been discussed in the section on hydrodissection. Early postoperative CBS represents the

initial type of CBS, with accumulation of the OVD in the capsular bag, as discussed earlier. Late postoperative CBS refers to eyes with accumulation of a milky-white substance in the closed capsular bag.<sup>47–49</sup> Reduction of vision with this type of CBS is rare, and Nd:YAG laser capsulectomy can be performed, if necessary.

## Intraocular Lens Miscalculation

Complications related to IOL miscalculation are covered in Chapter 5.4.

## Intraocular Lens Decentration and Dislocation

Common causes of IOL decentration and dislocation are asymmetrical loop placement, sunset syndrome, loss of zonular support for a lens fixated in the capsular bag, and pupillary capture of the IOL optic.<sup>50</sup>

### Asymmetrical Haptic Placement

Pathological studies indicate that asymmetrical loop placement is an extremely common occurrence, particularly when “can opener” capsulectomies are performed. The incidence of this complication has been greatly reduced with the advent of capsulorrhexis, which permits excellent visualization of the capsular edge and ensures that a lens placed in the capsular bag is retained there. An IOL with asymmetrical loop placement becomes symptomatic if the lens is decentered sufficiently relative to the pupil; symptoms include polyopia, glare, induced myopia (from looking through the peripheral portion of the IOL), and loss of best spectacle-corrected visual acuity (BSCVA). Depending on the severity of the symptoms, treatment includes IOL repositioning or IOL exchange. In some instances, topical miotics can be prescribed; however, few patients prefer this mode of management.

### Sunset Syndrome

Sunset syndrome occurs when a sulcus-fixated posterior chamber IOL dislocates through a peripheral break in the zonules, typically inferiorly. Sunset syndrome is usually an acute, nonprogressive event. Treatment options again depend on the severity of the patient’s symptoms. The authors have found that simple IOL repositioning is often unsuccessful and predisposes to recurrence. Therefore, several other options are recommended:

- Repositioning the lens, combined with iris fixation sutures.
- IOL exchange with a larger, more rigid lens.
- Scleral fixation of a posterior chamber lens.
- Replacement with an anterior chamber lens.

### Lens-Bag Decentration

In rare instances, a lens that is placed in the capsular bag can dislocate as a result of bag decentration caused by zonular rupture or dehiscence. Treatment of this condition, if sufficiently severe, requires IOL exchange with some form of scleral fixation or implantation of an anterior chamber lens.

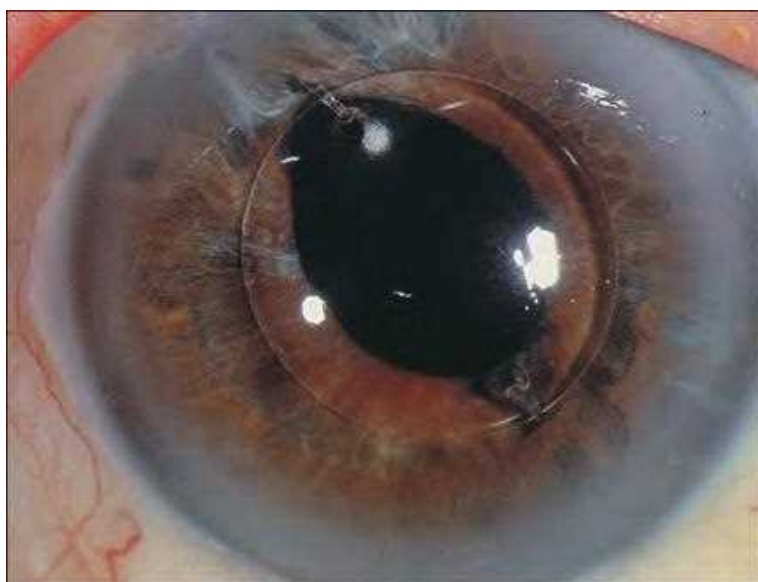
### Pupillary Capture

Pupillary capture of the IOL optic consists of the posterior migration of some portion of the iris beneath the IOL optic (Fig. 5.16.7). Predisposing factors are “can opener” capsulectomy and sulcus implantation of the posterior chamber IOL, particularly in the absence of angulated haptics. In rare instances, however, pupillary capture can occur with capsular fixation of the lens after capsulorrhexis, especially when the capsulorrhexis is large.<sup>51,52</sup> Pupillary capture can produce acute and chronic iritis, posterior synechiae formation, visual loss from deposition of inflammatory cells on the IOL surface, and, if the lens is displaced sufficiently eccentrically and anteriorly, chronic endothelial trauma with corneal decompensation. Pupillary capture diagnosed within a few days of its occurrence can be treated pharmacologically or by manually repositioning the optic into the posterior chamber. Chronic pupillary capture may be more difficult to manage, because firm synechiae form between the iris and posterior capsule. In such situations, the IOL should be repositioned if there are visual symptoms, chronic uveitis, or corneal endothelial trauma. Chronic cellular precipitates on the IOL surface can often be managed by the administration of topical corticosteroids and occasional Nd:YAG laser “dusting” of the anterior IOL surface.<sup>53</sup>

## Sulcus-Fixated Intraocular Lens Dislocation

Another subtle but important form of IOL dislocation is loss of fixation of the sulcus-fixated IOL. This can produce recurrent microhyphema or





**Fig. 5.16.7 Pupillary Capture of the Intraocular Lens.** Predisposing factors in this patient included a “can opener” capsulectomy, intraoperative iris trauma, and nonangulated haptics.

hyphema, as well as chronic iritis and even pigmentary glaucoma. The loss of lens fixation often is subtle, but it can be diagnosed at the slit lamp by observing the third and fourth Purkinje images. If the patient is asked to look eccentrically and then refix centrally, these images can be seen to flutter or wobble excessively (pseudo-phacodonesis), which indicates lack of adequate IOL fixation. Intraoperatively, this can be verified by touching the IOL with an instrument; there is obvious IOL instability.

Pigment dispersion syndrome (PDS) can occur after uneventful cataract surgery and implantation of a posterior-chamber single-piece IOL with a sharp-edge design after sulcus position of these IOLs. Several days after IOL implantation, marked pigment dispersion can be seen on the iris and in the trabecular meshwork, associated with an elevation in IOP. Thorough examination showed that the implanted IOL is in the ciliary sulcus. After surgical repositioning of the IOLs into the capsular bag, the pigment dispersion regressed and the IOP returned to normal limits.<sup>54</sup>

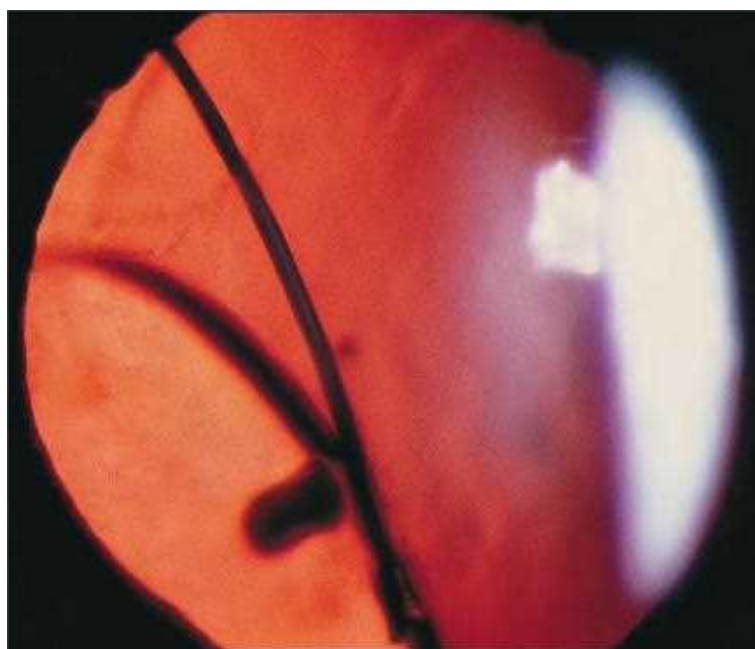
## Posterior and Anterior Dislocation

In rare instances, a posterior chamber lens can fall posteriorly and either become suspended in the anterior vitreous (Fig. 5.16.8) or dislocate completely into the vitreous cavity. In the former instance, IOL exchange is advisable, because the lens is within reach and can produce visual symptoms or chafe on uveal tissue. Management of a complete posterior IOL dislocation is more controversial. Although this condition is well tolerated in some eyes, in others, the lenses can become entrapped in the vitreous base and cause vitreous traction and retinal tears, or they can produce visual symptoms by intermittently moving into the visual axis.

Even more rarely, anterior dislocation of a posterior chamber lens into the anterior chamber may occur.<sup>55</sup> This can be prevented with a small and continuous capsulorhexis and in-the-bag implantation of the lens.

## Intraocular Lens Exchange

Several principles of IOL exchange need to be emphasized. It is generally preferable to exchange lenses that have haptics that are poorly designed, too short, or deformed from lens malposition in the eye. Patients who have a marginal corneal endothelium status, generally should be subjected to the least traumatic surgery possible, such as iris repositioning with iris fixation sutures rather than IOL exchange, particularly if the latter requires anterior vitrectomy. It is important to distinguish between IOL decentration and pupil displacement. In some instances, the patient's symptoms result from an eccentrically displaced pupil in the face of a relatively well-positioned IOL. Clearly, surgery, if indicated, should address the underlying problem by reconstructing the pupil. This can be done by suturing the pupil in the peripheral region and opening the pupil centrally with several small sphincterotomies. If certain complications are associated with the site of the dislocated IOL (e.g., recurrent microhyphema with a posterior chamber IOL or peripheral anterior synechiae with an anterior chamber IOL), it may be advisable to place the new lens in a new site.



**Fig. 5.16.8 Intraocular Lens Dislocation.** During surgery, a capsular rupture was noted. A lens was, however, implanted in the posterior chamber. On the morning after surgery, the lens was found to be dislocated posteriorly and inferiorly, and the patient was referred for treatment. At the time of lens exchange, it appeared that insufficient capsular support was present, and a new lens was sutured into the ciliary sulcus.

Finally, if sufficient intact posterior capsule exists, an attempt can be made to reopen the capsular flaps to permit fixation of the new lens within the capsular bag; this, clearly, is the most desirable location.

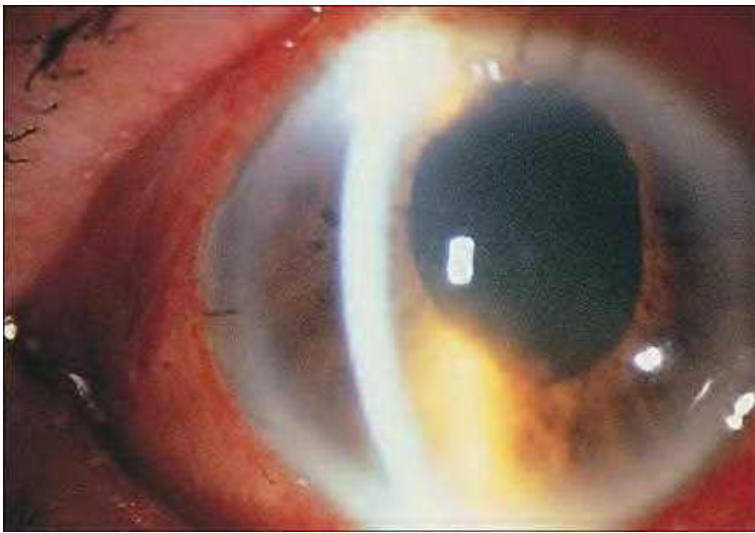
## Cystoid Macular Edema

Cystoid macular edema (CME) is the most common cause of unexpected visual loss following cataract surgery.<sup>56,57</sup> Fluorescein angiographic CME can occur in up to 50% of patients at 4–8 weeks postoperatively, but clinical CME occurs in less than 3% of patients. Recent studies have shown that macular swelling can be clinically insignificant but can be detected, for example, with optical coherence tomography (OCT).<sup>58</sup> The typical time of onset of clinical CME is 3–4 weeks postoperatively. Predisposing factors are intraoperative complications (e.g., vitreous loss or severe iris trauma), vitreous traction at the wound, diabetic retinopathy,<sup>59</sup> and pre-existing epiretinal membrane. In cases without predisposing factors, CME typically resolves over several weeks, although most surgeons prefer to treat this topically with nonsteroidal and corticosteroid drops.<sup>60</sup> Other modes of treatment that have been employed include sub-Tenon's corticosteroid injection, and administration of systemic nonsteroidal anti-inflammatory drugs with corticosteroids. In patients who have epiretinal membranes, CME may take months to resolve. When associated with diabetic retinopathy, CME often is resistant to medical therapy and can persist indefinitely; macular laser photocoagulation is sometimes helpful to document angiographically the leaking vessels and microaneurysms. Patients who have ongoing structural abnormalities, such as vitreous traction or extensive iris chafing, are less likely to experience spontaneous resolution of CME and may benefit from surgical correction of the precipitating factor.

## Endophthalmitis

Endophthalmitis can occur in an acute or chronic form. It is characterized by ciliary injection, conjunctival chemosis, hypopyon, decreased visual acuity, and ocular pain. The acute form generally develops within 2–5 days of surgery and has a fulminant course (Fig. 5.16.9). Common causative organisms are Gram-positive, coagulase-negative micrococci, *Staphylococcus aureus*, *Streptococcus* species, and *Enterococcus* species.<sup>61,62</sup>

Chronic endophthalmitis is caused by organisms of low pathogenicity, such as *Propionibacterium acnes* or *Staphylococcus epidermidis*. It typically is diagnosed several weeks or longer after surgery. Signs include decreased visual acuity, chronic uveitis with or without hypopyon formation, and, in some instances, plaque-like material on the posterior capsule. Histopathologically, this material consists of the offending microorganism embedded in residual lenticular tissue.



**Fig. 5.16.9 Postoperative Endophthalmitis.** This patient developed acute postoperative endophthalmitis after clear cornea cataract surgery and implantation of a polymethyl methacrylate (PMMA) posterior chamber intraocular lens. During cataract surgery, a capsular break occurred, and an anterior vitrectomy was performed. The patient was treated successfully with vitrectomy and injection of intravitreal antibiotics combined with postoperative topical antibiotic therapy. Final visual acuity was 20/50 (6/15).

Treatment of endophthalmitis consists of culturing aqueous and vitreous aspirates, followed by administration of intravitreal,<sup>63</sup> topical, and subconjunctival antibiotics, as discussed elsewhere. In the Endophthalmitis Vitrectomy Study, no evidence was found of any benefit from the use of systemic antibiotics.<sup>64</sup> Pars plana vitrectomy helped increase the final visual outcome only in those patients who had an initial visual acuity of light perception or worse.<sup>64</sup> (For further discussion of endophthalmitis, see Chapter 7.9.)

## Posterior Capsular Opacification

Secondary cataract formation is a major complication of IOL implantation after extracapsular cataract extraction (ECCE; or phaco). The incidence is in the range of 18%–50% in adults followed up for as long as 5 years; in infants and juveniles, an opacification rate of 44% was found within 3 months of surgery after in-the-bag IOL implantation with an intact posterior capsule.<sup>65</sup> Posterior capsular opacification (PCO) is caused by proliferation and migration of residual lens epithelial cells. These can produce visual loss through two mechanisms:

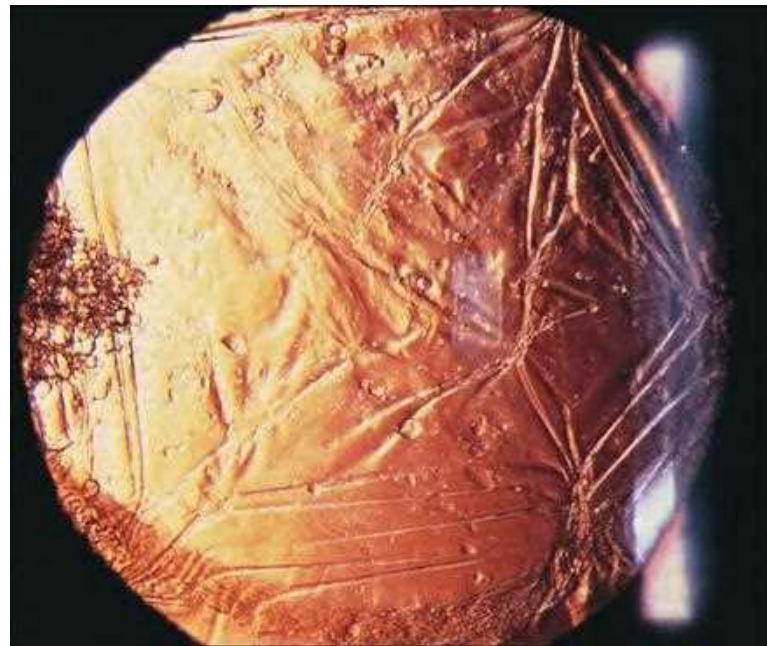
- Formation of swollen, abnormally shaped lens cells called Elschnig's pearls, which migrate over the posterior capsule into the visual axis (Fig. 5.16.10).
- Transformation into fibroblasts, which may contain contractile elements (myofibroblasts) and cause the posterior capsule to wrinkle (see Fig. 5.16.8).

Standard treatment of PCO consists of opening the capsule with Nd:YAG laser. Complications of this treatment include acute and, in rare instances, chronic IOP elevation, pitting of the IOL, and retinal detachment. Factors that predispose to retinal detachment include an axial length greater than 24.5 mm, male gender, and pre-existing retinal pathology.<sup>66–68</sup>

A related and unusual abnormality is the formation of striae in the posterior capsule in the absence of abnormal proliferation of lens epithelial cells. In some patients, this produces a Maddox-rod effect; the typical symptoms are linear streaks that radiate from lights, and their orientation is 90° from the meridian of the striae. The cause is stretching of the capsular bag by the IOL, which produces the striae aligned with the axis of the lens haptics. Typically, this is present on the first postoperative day but may not be mentioned by the patient until later. In many eyes, the striae resolve in the first or second week after surgery as capsular contraction occurs, which counteracts the stretch forces of the IOL haptics. If the condition persists and is sufficiently symptomatic, it can be corrected readily with a laser posterior capsulotomy. For further discussion of PCO, see Chapter 5.17.

## Retinal Detachment

Retinal detachment is a well-recognized complication of cataract surgery, occurring in 0.2% to 3.6% of persons after extracapsular cataract surgery.



**Fig. 5.16.10 Posterior Capsular Opacification.** Elschnig's pearl formation and capsular wrinkling causing a severe decrease of visual acuity.

The incidence of retinal detachment increases fivefold if an intracapsular procedure is performed.<sup>69</sup> Predisposing factors include Nd:YAG laser capsulotomy, axial length greater than 24.5 mm, myopic refractive error, lattice degeneration, male gender, intraoperative vitreous loss, postoperative ocular trauma, posterior vitreous detachment, and history of retinal detachment in the fellow eye.<sup>67,70,71</sup> Steps to prevent retinal detachment include the following:

- A careful preoperative fundus examination.
- Preservation of the integrity of the posterior capsule at the time of surgery.
- Education of patients with regard to the symptoms of retinal tears and detachment.
- Regular postoperative dilated fundus examinations.

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# Secondary Cataract

Liliana Werner

# 5.17

**Definition:** Secondary cataract, also known as *posterior capsule opacification* (PCO), is the most common complication after cataract surgery, resulting from migration and proliferation of residual lens epithelial cells (LECs) onto the central posterior capsule, leading to decrease in visual function, and ultimately in visual acuity. Opacification within the capsular bag also may present as anterior capsule opacification (ACO) or interlenticular opacification (ILO).

## Key Features

- Caused by migration and proliferation of residual lens epithelial cells.
- Treatment is most commonly neodymium:yttrium–aluminum–garnet (Nd:YAG) laser.
- May be exacerbated or ameliorated via surgical techniques and specific lens design.

## INTRODUCTION

Secondary cataract or posterior capsule opacification (PCO) is the most common postoperative complication of cataract surgery. Its incidence has decreased over the past few decades as the understanding of its pathogenesis has evolved. Advances in surgical technique and intraocular lens (IOL) design and materials all have contributed to the gradual decline in PCO incidence. However, it remains a major cause of decreased visual acuity after cataract surgery, occurring at a rate of between 3% and 50% in the first 5 postoperative years.<sup>1</sup>

## PATHOGENESIS

PCO results from migration and proliferation of residual lens epithelial cells (LECs) onto the central posterior capsule. When the cells invade the visual axis as pearls, fibrotic plaques, or wrinkles, the patient experiences a decrease in visual function and, ultimately, in visual acuity.<sup>2</sup> The epithelium of the crystalline lens consists of a sheet of anterior epithelial cells (“A” cells) that are in continuity with the cells of the equatorial lens bow (“E” cells). The latter cells comprise the germinal cells that undergo mitosis as they peel off from the equator. They constantly form new lens fibers during normal lens growth. Although both the anterior and equatorial LECs stem from a continuous cell line and remain in continuity, it is useful to divide these into two functional groups. They differ in terms of function, growth patterns, and pathological processes. The anterior or “A” cells, when disturbed, tend to remain in place and not migrate. They are prone to a transformation into fibrous-like tissue (pseudo-fibrous metaplasia).

In contrast, in pathological states, the “E” cells of the equatorial lens bow tend to migrate posteriorly along the posterior capsule (e.g., in posterior subcapsular cataracts, and the pearl form of PCO). In general, instead of undergoing a fibrotic transformation, they tend to form large, balloon-like bladder cells (the cells of Wedl). These are the cells that are clinically visible as “pearls” (Elschnig’s pearls). These equatorial cells are the primary source of classic secondary cataract, especially the pearl form of PCO. In a clinical study by Neumayer et al., significant changes in the morphology of Elschnig’s pearls were observed within an interval of only 24 hours. Appearance and disappearance of pearls, as well as progression and regression of pearls within such short intervals illustrate the dynamic behavior of regenerative PCO.<sup>3</sup>

The “E” cells also are responsible for formation of a Soemmerring’s ring, which is a doughnut-shaped lesion composed of retained/regenerated cortex and cells that may form following any type of disruption of the anterior lens capsule. This lesion was initially described in connection with ocular trauma. The basic pathogenic factor of the Soemmerring’s ring is the anterior capsular break, which may then allow exit of central nuclear and cortical material out of the lens, with subsequent Elschnig’s pearl formation. A Soemmerring’s ring forms every time any form of extracapsular cataract extraction (ECCE) is done, as manual, automated, or phacoemulsification (“phaco”) procedures. For practical purposes, it is useful to consider this lesion as the basic precursor of classic PCO, especially the “pearl” form. The LECs have higher proliferative capacity in the young compared with the old; therefore, the incidence of PCO formation is higher in younger patients.

The same cell types mentioned above are involved in other processes of opacification within the capsular bag (Fig. 5.171). These include anterior capsule opacification (ACO)<sup>4,5</sup> and interlenticular opacification (ILO).<sup>6,7</sup> The latter is the opacification of the space between two or more IOLs implanted in the bag (piggyback implantation).

## Treatment and Prevention

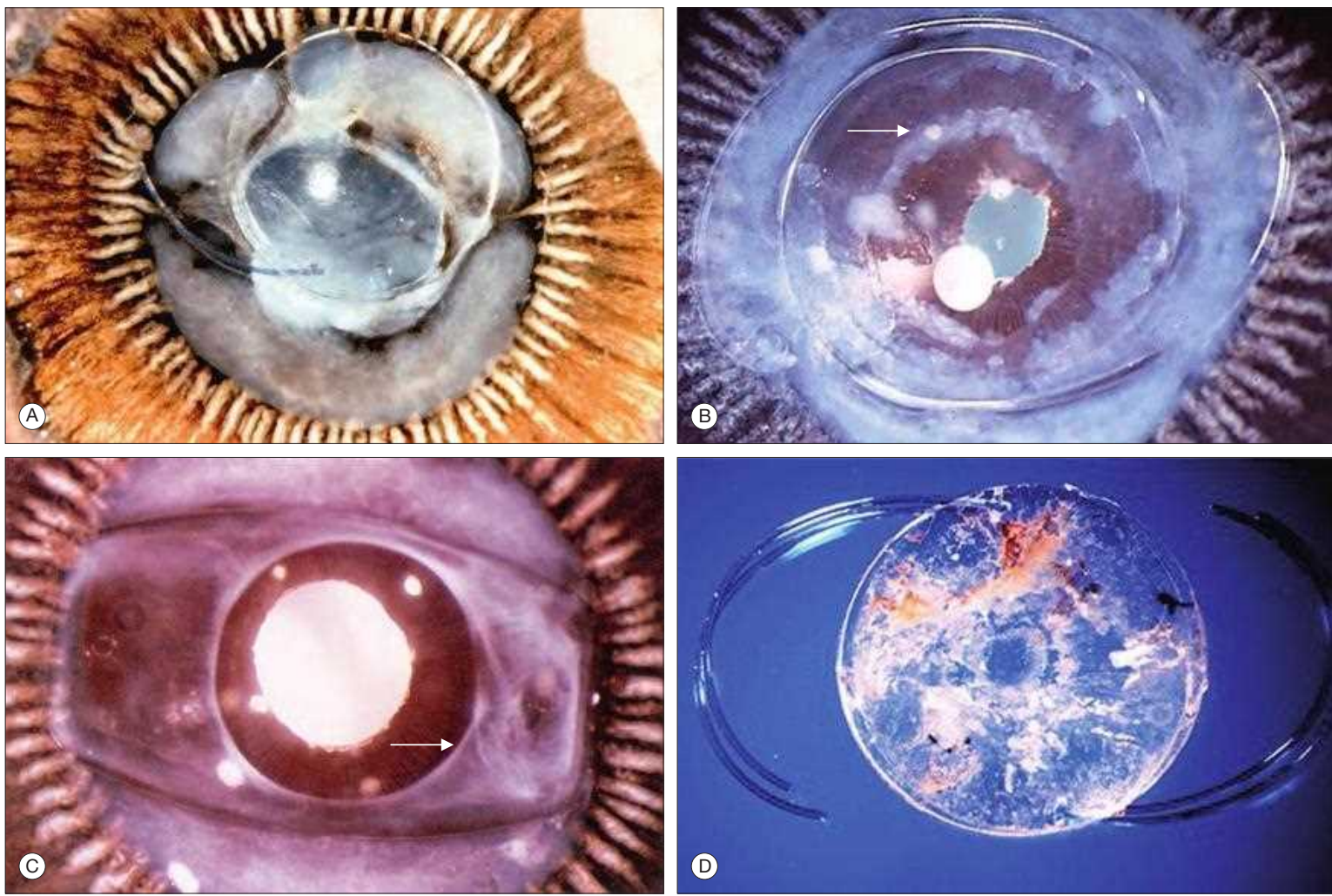
The treatment of PCO is typically neodymium:yttrium–aluminum–garnet (Nd:YAG) laser posterior capsulectomy. This is a simple procedure in most cases but is not without risks. Complications include IOL damage, IOL subluxation or dislocation, retinal detachment, and secondary glaucoma.<sup>8</sup> Therefore, prevention of this complication is important, not only because of the risks associated with its treatment but also because of the costs involved in the procedure. Extensive research has been performed on the inhibition of LEC proliferation and migration by pharmacological agents through various delivery systems, or IOL coatings, in vitro and in vivo animal studies.<sup>9–11</sup> Use of pharmacological and nonpharmacological agents for this purpose in an unsealed system may increase the risk of toxicity to surrounding intraocular structures, especially corneal endothelial cells. The Perfect Capsule, a silicone device that reseals the capsular bag allowing isolated safe delivery of irrigating solutions into its inner compartment, therefore, was developed.<sup>12</sup> Immunotherapy and gene therapy, as well as physical techniques to kill/remove LECs, have been investigated.<sup>13,14</sup> We evaluated in our laboratory the efficacy of an Nd:YAG laser photolysis system in removing LECs by using eyes from human cadavers. Light microscopy and immunohistochemistry revealed that the laser photolysis system removed LECs from the anterior lens capsule and capsule fornix. Along with the cells, laminin, fibronectin, and cell debris remained in the untreated areas but were removed by the treatment, which may be useful for PCO prevention.<sup>14</sup>

While basic research on an effective mechanism for PCO eradication is evolving, the practical surgeon can apply some principles to prevent it.<sup>15</sup> Studies done in our laboratory, as well as clinical studies done in other centers, have helped in the definition of three surgery-related factors that help in the prevention of PCO:

- Hydrodissection-enhanced cortical cleanup.
- In-the-bag IOL fixation.
- Performance of a capsulorrhexis slightly smaller than the diameter of the IOL optic (Fig. 5.172).

The same studies helped in the definition of three IOL-related factors for PCO prevention:

- Use of a biocompatible IOL to reduce stimulation of cellular proliferation.
- Enhancement of the contact between the IOL optic and the posterior capsule.
- An IOL with a square, truncated optic edge.



**Fig. 5.17.1 Different Forms of Opacification Within the Capsular Bag.** (A) Human eye from cadaver (posterior or Miyake-Apple view) implanted with a rigid lens, showing asymmetric fixation and decentration. A doughnut-shaped, white lesion can be seen for 360° in the equatorial region of the capsular bag (Soemmerring's ring), and the posterior capsule is fibrotic. (B) Human eye from cadaver (posterior view) implanted with a rigid lens. Soemmerring's ring is also present. A posterior capsulotomy had been performed for posterior capsule opacification, and proliferation of Elschnig's pearls can be seen at the edges of the capsulotomy (arrow). (C) Human eye from cadaver (posterior view) implanted with a foldable, plate silicone lens. The anterior capsule is fibrotic (arrow). Although Soemmerring's ring formation can be seen, the posterior capsule is not opacified. (D) Pair of foldable, hydrophobic acrylic lenses explanted because of interlenticular opacification. The lenses are fused together through the material within the interlenticular space.

### Hydrodissection-Enhanced Cortical Cleanup

Howard Fine introduced this technique and coined the term cortical cleaving hydrodissection. The edge of the anterior capsule is slightly tented up by the tip of the cannula while the fluid is injected. The technique is used by many surgeons to facilitate cortex and equatorial LEC ("E" cell) removal, also enhancing the safety of the operation. Experimental studies used different solutions during the hydrodissection step of the phacoprocedure (e.g., preservative-free lidocaine 1%, antimetotics, etc.).<sup>16</sup> Further studies are necessary to establish the safety and utility of these solutions in terms of PCO prevention.

Although a careful cortical cleanup and elimination of as many "E" cells as possible is fundamental to reducing the incidence of PCO, the role of anterior capsule polishing and elimination of "A" cells remains to be demonstrated. Indeed, Sacu et al. have performed a randomized, prospective study to evaluate the effect of anterior capsule polishing on PCO.<sup>17</sup> The anterior capsule was extensively polished in one eye and was left unpolished in the other eye. Digital slit lamp photographs taken 1 year postoperatively by using a standardized photographic technique showed that anterior capsule polishing caused no significant difference in the outcome of PCO. Some authors actually believe that the postoperative fibrous metaplasia of remaining "A" cells would push the IOL against the posterior capsule, and that would explain the relatively low PCO rates of eyes implanted with silicone lenses having rounded optic edges.<sup>18</sup>

### In-the-Bag IOL Fixation

The hallmark of modern cataract surgery is the achievement of consistent and secure in-the-bag or endocapsular IOL fixation. The most obvious advantage of in-the-bag fixation is the accomplishment of good lens

centration. However, endocapsular fixation functions primarily to enhance the IOL-optic barrier effect, as will be discussed later. In a series of human cadaver eyes implanted with different IOLs and analyzed in our laboratory, central PCO and Nd:YAG rates were both influenced by IOL fixation, that is, less PCO and Nd:YAG capsulectomies in eyes where the IOLs were in the bag.<sup>15</sup>

Marie-José Tassignon proposed a variation of the in-the-bag IOL fixation concept for PCO prevention, named "bag-in-the-lens" implantation.<sup>16</sup> This involves the use of a twin-capsulorrhexis IOL design and performance of anterior and posterior capsulorrhexes of the same size. The biconvex lens has a circular equatorial groove in the surrounding haptic, for placement of both capsules after capsulorrhexis. If the capsules are well stretched around the optic of this lens, the LECs will be captured within the remaining space of the capsular bag, and their proliferation will be limited to this space, so the visual axis will remain clear (Fig. 5.17.3). Experimental and clinical studies showed that bag-in-the-lens implantation was highly effective in preventing PCO when the anterior and posterior capsules were properly secured in the IOL groove.

### Capsulorrhexis Size

There is evidence that PCO is reduced if the capsulorrhexis diameter is slightly smaller than that of the lens optic so that the anterior edge rests on the optic. This helps provide a tight fit of the capsule around the optic analogous to "shrinkwrapping," which has beneficial effects in maximizing the contact between the lens optic and the posterior capsule. In a retrospective clinical study performed at the John A. Moran Eye Center, University of Utah, on patients implanted with different IOLs, including lenses with round or square optic edges, the degree of postoperative PCO was





**Fig. 5.17.2 Human Eye Obtained From Cadaver (Posterior View) 19 Months After Implantation of a Single-Piece Hydrophobic Acrylic Lens.** This is an example of application of the three surgery-related factors for prevention of posterior capsule opacification. The lens was symmetrically implanted in the bag, via capsulorrhexis smaller than the optic diameter of the lenses (ideally, the capsulorrhexis margin should cover the edge of the lens for 360°). No significant Soemmerring's ring formation is present.



**Fig. 5.17.3 Clinical Photograph Taken 6 Months After Cataract Surgery With "Bag-in-the-Lens" Implantation in a 64-Year-Old Patient.** The area corresponding to the optic of the lens is completely free of opacities. (Courtesy Dr. Marie-José Tassignon, Belgium.)

correlated with the degree of anterior capsule overlap.<sup>19</sup> Considering all patients, including the patients distributed in different IOL groups, there was always a significant negative, linear correlation between the degree of overlap and PCO.

### Biocompatible Intraocular Lens

Many definitions for the term "biocompatibility" exist. With regard to PCO, materials with the ability to inhibit stimulation of cell proliferation are more "biocompatible." The "sandwich" theory states that a hydrophobic acrylic IOL with a bioadhesive surface would allow only a monolayer of LECs to attach to the capsule and the lens, preventing further cell proliferation and capsular bag opacification. We performed two

immunohistochemical studies on the adhesion of proteins to different IOLs that had been implanted in human eyes from cadavers.<sup>20,21</sup> Analyses of histological sections have demonstrated that fibronectin mediates the adhesion of this hydrophobic acrylic lens to the anterior and posterior capsules. Analyses of explanted lenses have confirmed the presence of greater amounts of fibronectin on the surfaces of the same lens. However, even though differences among materials exist, in terms of PCO prevention it appears that the geometry of the lens, with a square posterior optic edge is the most important factor (see IOL optic geometry below).

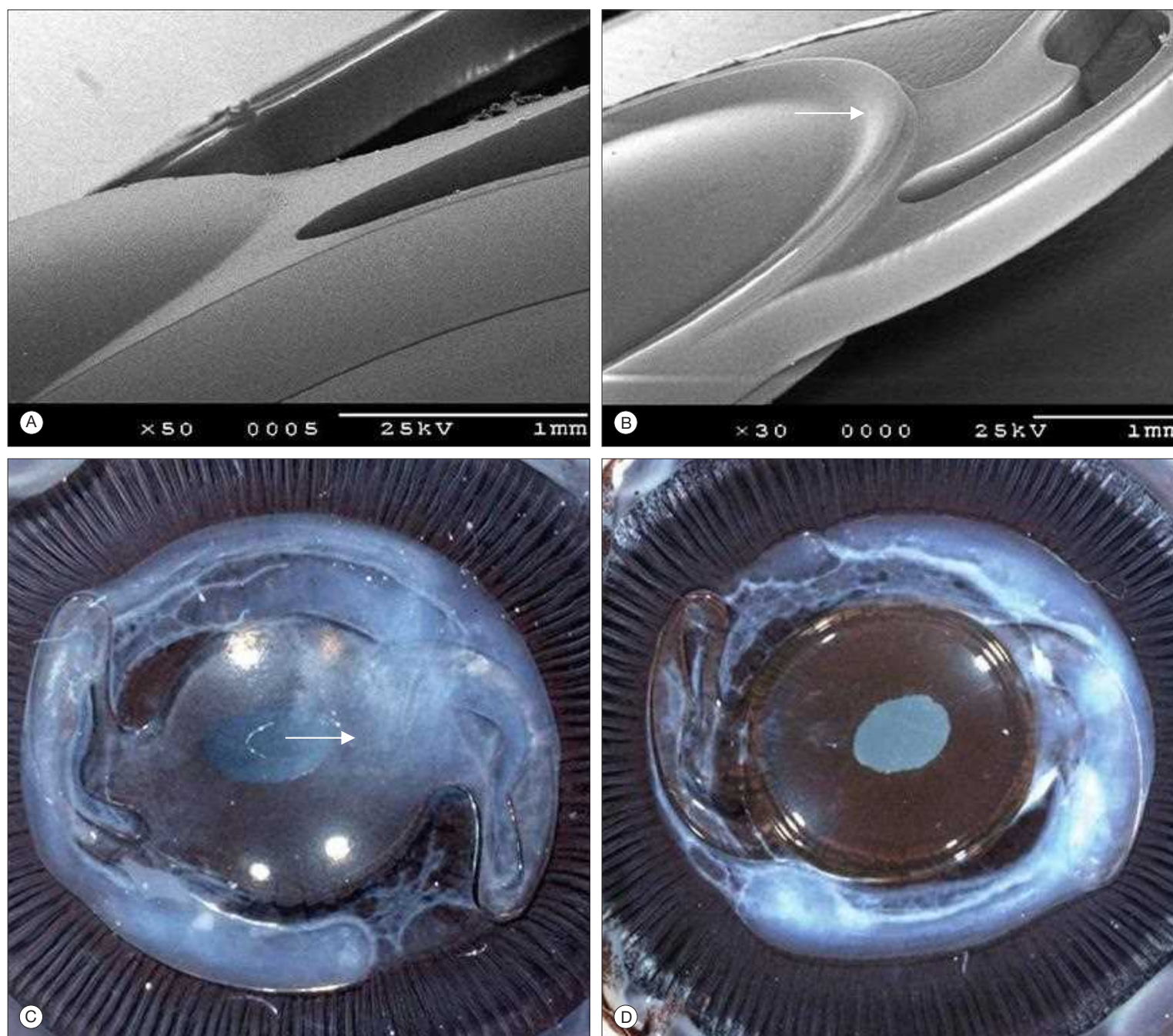
The adhesiveness of the material may have a more direct impact on the development of ACO. This generally occurs much earlier in comparison to PCO, sometimes within 1 month postoperatively. When the continuous curvilinear capsulorrhexis (CCC) is smaller than the IOL optic, the anterior surface of the optic's biomaterial maintains contact with the adjacent posterior aspect of the anterior capsule. Any remaining anterior LECs ("A" cells) in contact with the IOL have the potential to undergo fibrous proliferation; thus, ACO is essentially a fibrotic entity. Studies in our laboratory using pseudo-phakic eyes obtained from cadavers showed that ACO is more common with silicone IOLs, especially the plate designs, because of the larger area of contact between these lenses and the anterior capsule (see Fig. 5.171C).<sup>4</sup> However, the same studies showed that the plate design resists contraction forces within the capsular bag better than three-piece silicone lenses with flexible haptics (polypropylene).<sup>5</sup> These latter showed the higher rates of capsulorrhexis phimosis and IOL decentration as a result of excessive capsular bag fibrosis. Therefore, a tendency exists in IOL manufacture favoring haptic materials with higher rigidity, such as polymethyl methacrylate (PMMA), polyimide (Elastimide), and poly(vinylidene) fluoride (PVDF). In the same studies, ACO was less significant with hydrophobic acrylic lenses having an adhesive surface.

ACO has been considered a clinical problem when anterior capsular shrinkage associated with constriction of the anterior capsulotomy opening (capsulorrhexis contraction syndrome or capsular phimosis) accompanies excessive anterior capsule fibrosis. This has been especially observed in conditions associated with zonular weakness (e.g., pseudo-exfoliation and advanced age, and with chronic intraocular inflammation. Besides phimosis of the CCC opening, excessive zonular traction, and its sequelae, IOL dislocation and retinal detachment can occur because of excessive capsular fibrosis. Excessive opacification of the anterior capsule is problematic in that it hinders visualization of the peripheral fundus during retinal examination. Otherwise, a certain degree of ACO is sometimes considered an advantage because it can prevent potential dysphotopsia phenomena caused by the square edge of some IOL optic designs. Additionally, anterior capsule fibrosis with contraction of the capsular bag will push the IOL optic against the posterior capsule, helping in the prevention of PCO according to the "no space, no cells" theory. This mechanism would explain the relatively low PCO rates with some silicone lenses, in the absence of a square optic edge profile, as noted above (hydrodissection-enhanced cortical cleanup).<sup>18</sup>

The adhesiveness of the IOL material may also have an influence on ILO formation. To date, all cases of ILO that we have analyzed in our laboratory seem to be related to two hydrophobic acrylic IOLs being implanted in the capsular bag through a small capsulorrhexis, with its margins overlapping the optic edge of the anterior IOL for 360°.<sup>6</sup> When these lenses are implanted in the capsular bag through a small capsulorrhexis, the bioadhesion of the anterior surface of the front lens to the anterior capsule edge and of the posterior surface of the back lens to the posterior capsule prevents the migration of the cells from the equatorial bow onto the posterior capsule. This migration may be directed toward the interlenticular space. In this scenario, the two IOLs are sequestered together with aqueous and LECs in a hermetically closed microenvironment. In addition, the adhesive nature of the material seems to render the opacifying material very difficult to remove by any surgical means (see Fig. 5.171D).

Based on the common features of different cases of ILO, some surgical methods were proposed for its prevention. The first option would be to implant both IOLs in the capsular bag but with a relatively large-diameter capsulorrhexis. The other possibility is to implant the anterior IOL in the sulcus and the posterior IOL in the bag with a small rhexis. These should help sequester the retained/proliferated equatorial LECs within the equatorial fornix. Reassessment of factors leading to ILO formation is important because of the development of dual-optic accommodating IOLs to be implanted in the capsular bag.<sup>7</sup> Additionally, piggyback implantation for correction of residual refractive errors appears to be increasing in popularity, including implantation of a multifocal IOL in patients with pseudo-phakia. However, in these cases the second (anterior) IOL is generally fixated in the ciliary sulcus.





**Fig. 5.17.4 Foldable, Hydrophilic Acrylic Lenses With Square Optic and Haptic Edges.** The lens in (B) was modified to incorporate an extra ridge all around the optic (enhanced square edge; arrow). (C,D) are photographs obtained from rabbit eyes (posterior view), experimentally implanted with the lenses in (A,B), respectively. Soemmerring's ring formation is observed in both eyes. The arrow in (C) shows the opacification of the posterior capsule, which started at the level of the optic-haptic junction. (From: Werner L, Mamalis N, Pandey SK, et al. Posterior capsule opacification in rabbit eyes implanted with hydrophilic acrylic intraocular lenses with enhanced square edge. *J Cataract Refract Surg* 2004;30:2403–9.)

### Contact Between the IOL Optic and the Posterior Capsule

Different factors can help maximize the contact between the IOL and the posterior capsule, contributing to the so-called “no space, no cells” concept. Optic/haptic angulation displacing the optic posteriorly and stickiness of the IOL optic material are the most important lens features for obtaining a tight fit between lens and capsule. Three-piece lenses manufactured from the different haptic materials currently available today have in general a posterior optic/haptic angulation ranging 5°–10°. To keep the advantages of the two above-mentioned factors, it is important to achieve endocapsular lens fixation and to create a capsulorrhexis smaller than the diameter of the lens optic.

Capsular tension rings may have a role in the prevention of PCO. Equatorial capsular tension rings have the ability to maintain the contour of the capsular bag and to stretch the posterior capsule. Thus, they have primarily been used in cases of zonular rupture or dehiscence, secondary to trauma, or when inherent zonular weakness is present, such as in pseudo-exfoliation syndrome. It has been demonstrated by high-resolution laser interferometric studies that a space exists between the IOL and the posterior capsule with different lens designs. With a capsular tension

ring in place, this space was found to be smaller or nonexistent. Thus, LECs would not find a space to migrate and proliferate onto the posterior capsule. Capsular tension rings also produce a circumferential stretch on the capsular bag, with the radial distention forces equally distributed. Formation of traction folds in the posterior capsule, which may be used as an avenue for cell ingrowth is thus avoided.

Capsular tension rings may also have a role in the prevention of opacification of the anterior capsule. The presence of a broad, band-shaped, capsular ring would keep the anterior capsule leaf away from the anterior optic surface and the posterior capsule. This would ultimately lead to less metaplasia of LECs on the inner surface of the anterior capsule with less fibrous tissue formation, as well as less opacification and contraction of this structure. IOLs with design features that also help maintaining the anterior capsule away from the anterior surface of the lens have been evaluated in our laboratory.<sup>7</sup> A capsular tension ring designed to prevent opacification within the capsular bag was evaluated in two centers, one in Japan (Nishi O) and the other in Austria (Menapace R).<sup>22</sup> Both centers reported a significant reduction in PCO and ACO with the rings, in comparison to the contralateral eyes implanted with the same lens design.<sup>22</sup>

### Intraocular Lens Optic Geometry

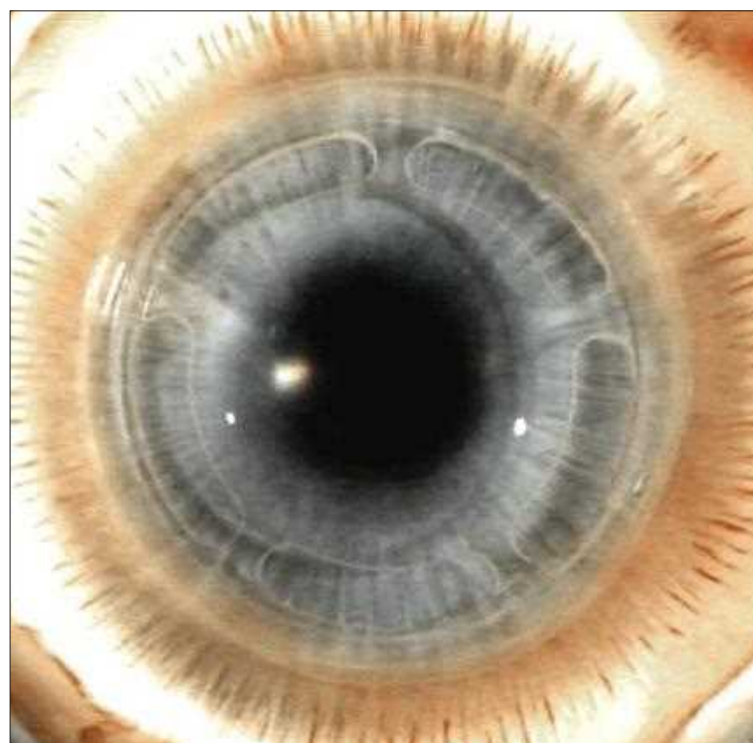
The square, truncated lens optic edge acts as a barrier, preventing migration of proliferative material from the equatorial region onto the posterior capsule.<sup>15</sup> The barrier effect is absent in lenses having rounded edges, and proliferative material from the equatorial region has greater free access to the posterior capsule, opacifying the visual axis. The barrier effect of the square optic edge is functional when the lens optic is fully in the bag, in contact with the posterior capsule. When one or both haptics are out of the bag, a potential space that is present allows an avenue for cellular ingrowth toward the visual axis. Different modern lenses manufactured from different materials currently on the market present this important design feature. Some of them have a square edge on the posterior optic surface, whereas the anterior optic edge has remained round to prevent dysphotopsia. Findings from experimental studies which demonstrate that the square edges of different lenses on the market are not equally “sharp,” even when the same class of materials is considered, are noteworthy.<sup>23,24</sup>

The optic-haptic junctions of square-edged single-piece lenses may represent a site for cell ingrowth and PCO formation.<sup>25</sup> At the level of those junctions, the barrier effect of the square edge appears to be less effective. We obtained better results regarding PCO formation with a hydrophilic acrylic single-piece lens having an “enhanced” square edge than with the standard model of the same design.<sup>25</sup> The enhanced edge provided the lens with a peripheral ridge around the lens optic for 360°. In the standard model, the square edge profile appeared to be absent at the level of the optic-haptic junctions (Fig. 5.174<sup>26</sup>). Therefore, the square optic edge is probably the most important IOL design feature for PCO prevention. It appears, however, that it should be present for 360° around the IOL optic in order to provide an effective barrier effect.

### INTRAOCULAR LENSES MAINTAINING THE CAPSULAR BAG OPEN OR EXPANDED

We have recently evaluated the outcome of capsular bag opacification with a new single-piece, disc-shaped hydrophilic acrylic IOL compared with a commercially available single-piece, hydrophobic acrylic IOL in the rabbit eye for 5 weeks (Fig. 5.175).<sup>27,28</sup> The peripheral rings of the disc-shaped lens, by expanding the capsular bag and preventing IOL surface contact with the anterior capsule, prevented ACO and PCO. We hypothesized that IOL designs maintaining an open or expanded capsular bag are associated with bag clarity. Mechanical compression of the inner bag surface (and residual LECs) by a relatively bulky device/IOL has been one of the possible mechanisms advanced to explain this finding. Another factor may be mechanical stretch of the bag at the level of the equatorial region (maintaining the overall bag contour), by some devices, such as the capsular bending ring of Nishi and Menapace,<sup>22</sup> and Hara’s equator ring.<sup>29</sup> Constant irrigation of the capsular bag’s inner compartment by the aqueous humor also may have an influence on the prevention of proliferation of residual LECs. Equatorial stretch and aqueous humor irrigation would help explain the PCO preventative effect, even in eyes where there was no contact between the IOL optic and the posterior capsule. Previous reports indicated that transforming growth factor- $\beta_2$  in the normal aqueous humor inhibits proliferation of LECs and corneal endothelial cells.<sup>30</sup> According to Nishi, constant irrigation by the aqueous humor may prevent certain cytokines that are involved in stimulating LEC proliferation from reaching a threshold concentration level within the bag compartment; one of these cytokines would be represented by interleukin-1.<sup>31</sup>

In summary, development of PCO is multifactorial, and its eradication depends on the quality of the surgery as well as on the quality of the IOL implanted. Each factor described here does not act in isolation; it is their interaction that produces the best results. Research on the prevention of any form of opacification/fibrosis within the capsular bag is increasing in importance, especially with the advent of specialized IOLs, such as accommodative lenses, which are designed to enable a forward movement of the optic on efforts of accommodation. The functionality of such lenses will likely require the long-term transparency and elasticity of the capsular bag. Further research to investigate new proposed mechanisms for capsular bag opacification prevention, such as with IOLs/devices maintaining an open capsular bag, is warranted.



**Fig. 5.175 Gross Photograph (Miyake-Apple View) of the Anterior Segment of a Rabbit Eye Implanted With a New Disk-Shaped IOL, Taken 5 Weeks Postoperatively.** The lens is a single-piece, hydrophilic acrylic, monofocal lens suspended between two complete haptic rings that are connected by a pillar of the haptic material. This design maintains the capsular bag expanded, with the anterior capsule separated from the anterior optic surface. Anterior and posterior capsules are overall clear. Minimal proliferation is limited to the space between the peripheral rings.

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# Outcomes of Cataract Surgery

Mats Lundström

# 5.18

**Definition:** Outcomes of cataract surgery include both objective and subjective measures. The objective outcomes are typically visual and refractive.

## Key Features

Objective measures of functional vision:

- Uncorrected visual acuity.
- Best-corrected visual acuity.
- Contrast sensitivity.
- Glare disability.
- Visual field.
- Color vision.

## INTRODUCTION

Outcomes of cataract surgery can be classified according to objective and subjective findings. Objective measures of functional vision include not only best-corrected visual acuity (BCVA) but also uncorrected distance visual acuity, contrast sensitivity, glare disability, visual field, and color vision. The refractive outcome is important because a cataract extraction is also a refractive procedure. Subjective findings are best evaluated through structured interviews or questionnaires.

## EVALUATION OF OUTCOMES

Functional vision assessment implies the ability to characterize parameters of vision and translate these into how well a patient is able to perform activities in daily life with respect to vision. To do this objectively, the parameters that characterize vision must first be determined. In both clinical practice and research, these parameters can be allocated to five major areas:

- Limiting resolution (high-contrast visual acuity).
- Contrast performance (contrast sensitivity and threshold).
- Performance at various background illuminations (glare disability).
- Field of view (visual field).
- Color performance (color vision).

It is important to fully evaluate the visual system in a patient who has a cataract by using these five parameters. In many cases, the patient does not present to the clinician with the diagnosis of cataract. The patient usually presents with complaints of decreased vision or visual disabilities. It is the clinician's responsibility to evaluate the patient's history and examine the patient to determine the cause of the reduced vision. After diagnosis of a cataract—or any other diagnosis—has been made, some of the five parameters that describe visual performance may be found to be less important.

To translate the visual performance or functional vision of a patient into the ability to perform a specific activity necessitates knowledge of the visual requirements needed to carry out that activity. The visual requirements needed to perform specific daily life activities are poorly mapped out. Therefore, the patient's self-assessed limitation in carrying out daily life activities that are dependent on vision is an important part of the outcomes evaluation. It has been suggested that self-assessed visual function is the most important part of the outcomes evaluation.<sup>1</sup> In the evaluation of outcomes of cataract surgery in daily practice, a proper follow-up time after surgery is crucial. Just as status 1 day after surgery may reflect whether the surgery was traumatic or not, sufficient time must elapse before the final refraction and patient satisfaction can be evaluated. The visual outcome

depends on the surgical procedure, the age of the patient, ocular comorbidities, and surgical complications, among other things. The refractive outcome depends on the surgical procedure, the preoperative status and examination, and the intended target refraction. The type of intraocular lens (IOL), pupil size, and surgical procedure are important for contrast sensitivity, glare, halos, and other visual disturbances. The patient's satisfaction with vision after surgery depends on the preoperative information given and the patient's expectations, as well as the visual outcome.

## FIVE PARAMETERS THAT DESCRIBE VISUAL FUNCTION

### Visual Acuity Testing

#### Standardized Visual Acuity Testing

Standardized visual acuity tests measure the ability of a patient to recognize standardized optotypes (usually Snellen acuity letters) at a specified visual angle, illumination, and contrast.<sup>2</sup> Visual acuity can be recorded in various notations, in which normal vision would be Snellen units 20/20 or 6/6, decimal notation 1.0, or logarithm of minimum angle of resolution (LogMAR) 0.0.

#### Potential Retinal Acuity Testing

A special type of acuity test used in cataract patients is the assessment of potential retinal acuity. This test is essential for patients who have pigment mottling in the macula and reduced vision, particularly in the presence of a cataract or other optical aberrations of the eye. In the cataract age group, the incidence of macular degeneration is at least 10% and may exceed 15%, depending on the age of the patient.<sup>3,4</sup> It is important that both the surgeon and the patient have a realistic expectation of the quality of postoperative vision, which helps both parties to accurately assess the risk-benefit ratio. Removal of a significant cataract always should be considered, even in the presence of an abnormal macula or if the predicted acuity is low.

### Contrast Sensitivity Testing

Contrast sensitivity testing is important for the assessment of both sensory disease and media opacities. With media opacities, such as cataracts, a general depression occurs in contrast sensitivity at all points, with a slightly greater depression at lower contrasts.<sup>5-7</sup>

### Glare Testing

Glare testing is useful in the assessment of media opacities, such as cataracts. The effects are negligible in sensory disorders, except for a few macular disorders, such as cystoid macular edema (CME), in which intraocular light scatter occurs in the superficial layers of the retina.<sup>8,9</sup> Even with this disorder, the changes in glare disability are minimal. Glare testing can be very sensitive and specific to media opacities, but more importantly, it gives visual acuity values or equivalents that relate to a person's vision in daylight, as opposed to vision in a testing room with high-contrast letters.

### Visual Fields

The integrity of visual fields is particularly important in patients with sensory disorders, such as glaucoma and optic neuropathies, and patients who have suffered strokes that have affected the visual pathways.<sup>10,11</sup> Unfortunately, these disorders also are common in the age group that suffers from cataracts and may go undetected until after the cataract surgery. Additionally, visual field defects that result from strokes may change the

risk–benefit ratio for cataract surgery, particularly if the stroke occurred recently.

## Color Vision

Color vision is specifically important in sensory disease, such as retinopathies and optic neuropathies, which often show characteristic color vision changes that help make the differential diagnosis and monitor the effect of therapy. In patients who have ocular media disorders, such as cataracts, the changes in color vision can usually be correlated with the color of the cataract. For example, a patient who has a brunescient (yellow-brown) cataract has significant deficiencies in the blue end of the visual spectrum (shorter wavelengths).<sup>12</sup> When color deficiencies do not correlate, sensory disorders should be suspected. Although color vision testing is very sensitive in some disorders, such as central serous maculopathy and CME, by “bleaching” or reducing the apparent brightness, other parameters, such as visual acuity, visual field, and contrast sensitivity, are also affected, which makes routine color testing unnecessary.

## OBJECTIVE FINDINGS OF CATARACT SURGERY OUTCOMES

### Best-Corrected Visual Acuity

The term *best-corrected visual acuity* implies that the patient’s eye has been optically corrected to achieve the best visual acuity. In most cases, this value is obtained with best spectacle refraction. In cases of irregular corneal astigmatism, the BCVA may be attained with a rigid contact lens, not with spectacles. In recent studies with known preoperative pathology excluded (best case analyses), between 97% and 98% of the patients who had received cataract surgery achieved BCVA equal to or better than 20/40 (6/12; 0.5).<sup>4,13</sup> A suggested standard was to achieve a final BCVA of 0.5 or better in 97% of all cataract extractions in eyes with no ocular comorbidity.<sup>4</sup> The corresponding number for all routine patients with cataract, including those with ocular comorbidity, was 94% in a recent report (Table 5.18.1).<sup>4</sup>

### Uncorrected Visual Acuity

The term *uncorrected visual acuity* (UCVA) refers to the patient’s vision in standard conditions with no extraocular optical correction. Unlike BCVA, several additional factors (e.g., pupil size, degree of refractive error, and amount of regular astigmatism) also influence the measured visual acuity.<sup>14–16</sup> UCVA is most useful in the evaluation of specialty lenses, such as multifocal and toric intraocular lenses (IOLs). The goal when using these lenses is to reduce or eliminate the patient’s dependence on glasses and to achieve good uncorrected distance visual acuity (UCDA) and near visual acuity. To achieve target refraction is crucial when using multifocal IOLs. Unfortunately, multifocal IOLs have a tendency to give more glare and halo compared with monofocal IOLs.<sup>17</sup> This applies to most types of IOLs with more than one focus, and to construct the optimal IOL for both near and distant vision is an area of active research. UCVA can be used as a quality characteristic of the surgical procedure, especially on the day after surgery.<sup>18</sup> For this purpose, however, it is relevant to use the target refraction if, for instance, postoperative myopia is planned.

### Target Refraction Prediction Error

Another factor in the determination of UCVA is the ability to achieve the target postoperative refraction. Most surgeons target the majority of their patients for postoperative refractions in the range of 0.0 to –0.50 D. With modern biometry equipment, newer IOL formulas, personalization of lens constants, and improvements in surgical technique, at least 90%

of patients should have sphero-equivalent refraction within  $\pm 1.00$  D of the intended target.<sup>19</sup> In a recent study on routine cataract surgery, about 90% of cataract extractions resulted in a final refraction within  $\pm 1.0$  D of the intended target refraction (see Table 5.18.1).<sup>4</sup> A suggested standard was a biometry error with a correct sign centered on 0 D and with 87% or more of the values within  $\pm 1$  D of error.<sup>4</sup>

Surgically induced astigmatism (SIA) may be intentional or not intentional. Small-incision cataract surgery results in less SIA than did earlier, larger-incision surgical techniques.<sup>20–22</sup> The magnitude of SIA may be less than 0.5 D on average, depending on incision site and incision size.<sup>23–25</sup> The best outcome of cataract surgery with respect to astigmatism is usually to achieve as low a postoperative astigmatism as possible. SIA can be used to achieve this result by varying the placement of the incision. SIA, thereby, can counteract preoperative astigmatism and result in reduced postoperative astigmatism.<sup>26,27</sup>

## Contrast Sensitivity

Following cataract surgery, in the absence of other ocular disease, the contrast sensitivity returns to normal.<sup>28,29</sup> Binocular contrast sensitivity may not be normalized until second eye surgery has been performed, given the occurrence of cataract in both eyes.<sup>30</sup>

## Glare

Studies have documented that the correlation of most of the instruments used for glare testing and outdoor vision testing show a dramatic improvement after cataract surgery.<sup>6,7,31–34</sup>

## Visual Fields

The visual field returns to normal after cataract surgery in the absence of ocular comorbidity.

## Color Vision

After cataract surgery in patients who have blue-color deficiencies caused by the cataract, the return to normal color vision is perceived as sensational by some patients but is not even noticed by others. Color vision returns to normal in the absence of other ocular disease.

## SUBJECTIVE FINDINGS OF CATARACT SURGERY OUTCOMES

### Patients’ Self-Assessment of the Visual Outcome

A large number of questionnaires for use in cataract surgery care have been published.<sup>35</sup> They usually cover activity limitations in daily life because of problems with vision and, therefore, are disease-specific questionnaires for establishing the health-related quality of life for cataract patients. On average, about 90% of patients undergoing cataract surgery achieve improved self-assessed visual function, according to a multicenter study using a modern questionnaire (see Table 5.18.1).<sup>36,37</sup>

Older patients (>85 years) also benefit from cataract surgery.<sup>38,39</sup> The positive impact of cataract surgery on patients’ self-assessed visual function seems to be long lasting, provided that no other ocular disease appears in the operated eye.<sup>40,41</sup> Self-assessed poor visual function after cataract surgery may result from an ocular comorbidity, a disturbing cataract in the fellow eye, or anisometropia.<sup>42</sup> Several factors are related to better subjective visual outcome. These include younger age, low preoperative visual acuity, high postoperative visual acuity, second-eye surgery, and no ocular comorbidity.<sup>43</sup>

## CATARACT SURGERY OF ONE OR BOTH EYES

Patients with bilateral cataract benefit from bilateral cataract extraction. Studies have shown that second-eye cataract surgery adds health-related quality of life for such patients.<sup>44,45</sup> A remaining cataract in the fellow eye after first-eye surgery may have a poor effect on binocular vision.<sup>30,42</sup>

A bilateral cataract extraction can be performed sequentially with a varying interval between the two surgeries so that some patients receive immediate sequential cataract surgery (ISCS), while others have delayed sequential cataract surgery (DSCS) with an interval between the surgeries of weeks or months. However, same-day bilateral cataract surgery requires

**TABLE 5.18.1 Outcome Measures Following Cataract Surgery: Achievements in Some Recent Studies (%)**

Measure	All Patients	Best Cases
BCVA $\geq 0.5$ (6/12)	94 <sup>4</sup>	97 <sup>13</sup>
Absolute mean prediction error $\leq 1$ D	91.5 <sup>4</sup>	97.3 <sup>4</sup>
Better patient reported visual function after surgery than before	91.5 <sup>37</sup>	
BCVA, best-corrected visual acuity.		

a strict set of operating rules, whereby each eye is treated as an entirely new operative procedure to avoid any possibility of cross contamination. Rapid rehabilitation of the patient is a worthy goal and a more economic process for all concerned.<sup>46</sup>

CATARACT SURGERY IN EYES WITH OCULAR COMORBIDITY

A substantial number of patients undergoing routine cataract surgery have coexisting eye diseases. A sight-threatening ocular comorbidity is the most frequent reason for a poor outcome after cataract surgery.<sup>21,42,47-51</sup> However, this does not mean that cataract extraction is unnecessary when there is an ocular comorbidity. Studies have shown that many patients with age-related macular degeneration and cataract benefit from cataract extraction.<sup>52,53</sup>

SUMMARY

All clinicians are aware that good history taking, a thorough examination, and quantification of the five areas that describe functional vision are all important in the determination of indications for surgery and outcome of surgery. Furthermore, it is extremely important to evaluate the indications for, and outcomes of, cataract surgery with respect to health-related quality of life. This is in the best interests of patients, but it should also be done because of the significant costs to health care linked to this procedure.

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# Structure of the Neural Retina

Hermann D. Schubert

## 6.1

**Definition:** The structure of the neural retina reflects its embryological development and its ultimate purpose: the absorption and processing of photons of visible light.

### Key Feature

- In a surgical specialty, knowledge of anatomy has to keep pace with that of imaging and procedures.

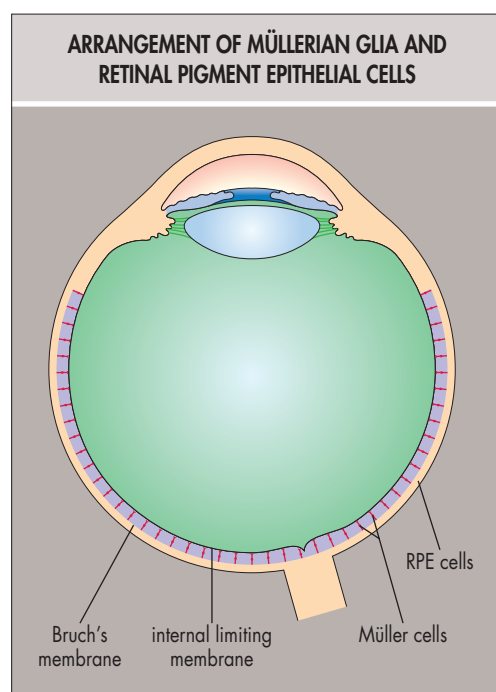
### INTRODUCTION

The primary purpose of the corneoscleral and uveal coats of the eye is to provide protection to the retina in addition to providing nourishment and enabling ocular movement. The retina is derived embryologically from the optic vesicle, an outpouching of the embryonic forebrain.<sup>1</sup> The bilayered neuroepithelial structure of the mature retina reflects the apex-to-apex arrangement of the original optic cup. It also forms the wall of a cavity, the vitreous cavity, which is filled with glycosaminoglycans and collagen. The ocular cavity is homologous to a leptomeningeal cistern<sup>2</sup> in that both vitreous and choroid are derived from mesenchyme that sandwiches the neuroepithelium on its path away from the brain. The ocular neuroepithelial cyst has two openings. Anteriorly lies the pupil, which is a full-thickness aperture, and posteriorly lies the optic nerve in which, similar to a coloboma, only derivatives of the inner retinal layers are found. Because the cell apices are oriented inwardly, the two layers of the optic cup and their derivatives are enveloped externally by basement membrane (Fig. 6.1.1).

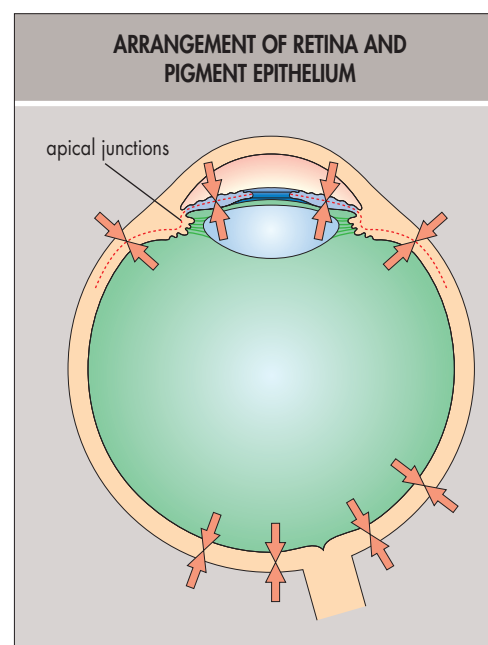
The relationship of the epithelial layers to each other is modified from anterior to posterior. Anterior to the ora serrata, the pigmented and nonpigmented epithelia of the iris and ciliary body are joined at their apices by a system of intercellular junctions (Fig. 6.1.2), which is continuous with the external limiting layer of the neural retina and the apical junctional girdles

of the retinal pigment epithelium (RPE; Fig. 6.1.3). At the ora serrata, the pigmented epithelium is continued as RPE; its basement membrane becomes Bruch's membrane. The nonpigmented epithelium of the ciliary body and pars plana is continued posteriorly as the neural retina; its basement membrane becomes the internal limiting membrane. The union of the epithelial layers delimits the anterior cul-de-sac of the subretinal space at the ora serrata.<sup>3</sup>

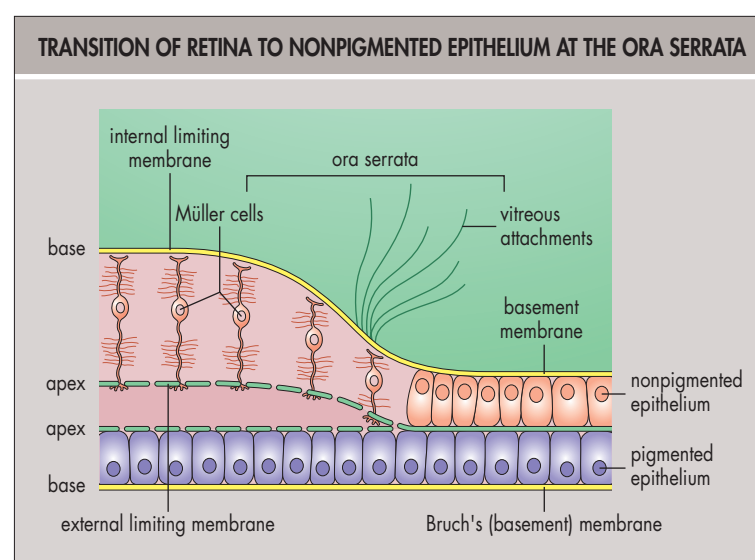
The apex-to-apex arrangement between the epithelia that clearly exists anterior to the ora is continued posteriorly by Müller cells that face and



**Fig. 6.1.1 Apex-to-Apex Arrangement of Müllerian Glia and Retinal Pigment Epithelial Cells.** Because the cell apices face each other, the neuroepithelia are enveloped externally by a basement membrane. Note that this basement membrane is elaborated by a single-layer neuroepithelium, in contrast to the internal limiting membrane, which is formed by Müller cells.

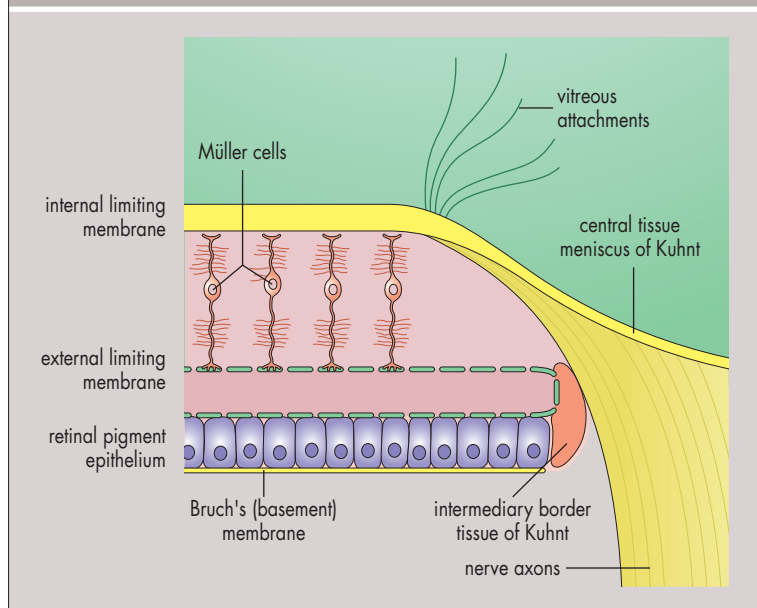


**Fig. 6.1.2 Apex-to-Apex Arrangement of Retina and Pigment Epithelium.** Apical attachments connect the iris and ciliary body epithelia (red dotted line).



**Fig. 6.1.3 Transition of Neural Retina to Nonpigmented Epithelium at the Ora Serrata.** The external limiting membrane, which consists of the attachment sites of photoreceptors and Müller cells, transforms into the apical junctional system of the pars plana epithelia. The internal limiting membrane becomes the basement membrane of the nonpigmented epithelium.

## STRUCTURES OF THE RETINA THAT BORDER THE OPTIC NERVE HEAD



**Fig. 6.1.4 Structures of the Retina That Border the Optic Nerve Head.** The junctional system of the external limiting membrane connects with the apical junctional system of the retinal pigment epithelium and is supported by the intermediary border tissue of Kuhnt.

intermittently contact the RPE (see Fig. 6.1.1). Here, the contact is maintained not by apical junctions (even though an interreceptor matrix exists) but by the pressure of the vitreous and by suction forces of the RPE. Müllerian glia are the main structural cells of the neural retina and are found throughout the retina from the ora to the optic nerve head.

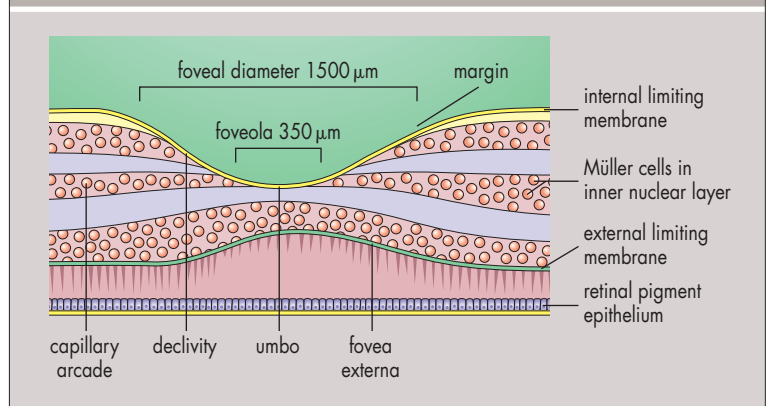
At the optic nerve head, the internal limiting membrane continues as the basement membrane of Elschnig, supported by the glial meniscus of Kuhnt (Fig. 6.1.4). The (glial) external limiting membrane joins the apices of the RPE to form the posterior cul-de-sac of the subretinal space at the optic nerve,<sup>3</sup> which is delimited by a glial border tissue, the intermediary border tissue of Kuhnt. This border tissue continues posteriorly at the choroidal level as the border tissue of Elschnig; both tissues separate the outer retina and choroid from the axons of the inner retina. The axons, in turn, fixate the posterior retina to the scleral lamina cribrosa and its glial system. The retina, therefore, is fixed to the choroid directly by the apical junctional system at the ora serrata (anterior cul-de-sac of the subretinal space) and indirectly, via the ciliary body and choroid, to its attachments at the scleral spur and sclera. At the nerve head, all neuroepithelial and choroidal layers are fixed by both the junctional tissues and the exiting axons. The corneoscleral coat protects, moves, and holds the retina in the appropriate position and allows the object of regard to be focused on the center of the retina.

## CENTER OF THE MACULA: UMBO

The fovea represents an excavation in the retinal center and consists of a margin, a declivity, and a bottom (Fig. 6.1.5). The bottom corresponds to the foveola, the center of which is called the *umbo*. The umbo represents the precise center of the macula, the area of retina that results in the highest visual acuity. Usually, it is referred to as the *center of the fovea* or *macula*. Although both terms are commonly used clinically, neither is a precise anatomical designation.

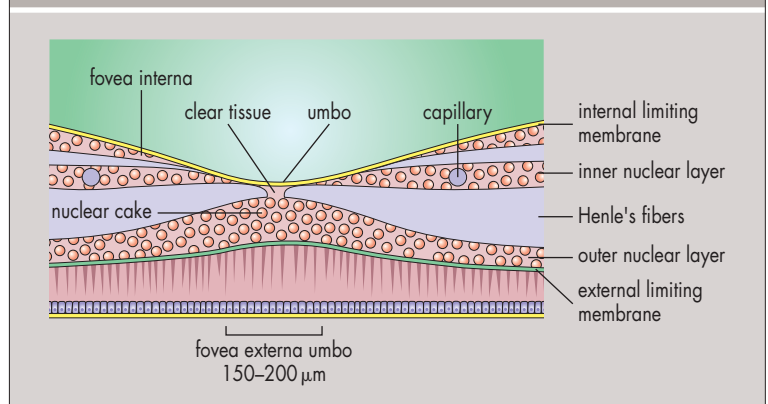
The predominant photoreceptor of the foveola and umbo is the cone. The foveal “nuclear cake” results from the centripetal migration of the photoreceptors and the centrifugal lateral displacement of the bipolars and ganglion cells during foveal maturation, which occurs 3 months before and 3 months after term.<sup>4,5</sup> Although their individual diameters are narrowed because of extreme crowding, central cones maintain their volume through elongation, up to a length of 70  $\mu\text{m}$ .<sup>5</sup> The central packing of cones takes place in an area of 1500  $\mu\text{m}$  diameter.<sup>4</sup> The greatest concentration of cones is found in the umbo, an area of 150–200  $\mu\text{m}$  diameter, referred to as the *central bouquet of cones*.<sup>5</sup> Estimates of central cone density are 113 000 and 230 000 cones/ $\text{mm}^2$  in baboons and cynomolgus monkeys, respectively. For the central bouquet, the density of cones may be as high as 385 000 cones/ $\text{mm}^2$ .<sup>6</sup> The inner cone segments (myoids) are connected

## FOVEAL MARGIN, FOVEAL DECLIVITY, FOVEOLA, AND UMBO



**Fig. 6.1.5 Foveal Margin, Foveal Declivity, Foveola, and Umbo.** The foveal diameter (from margin to margin) measures 1500  $\mu\text{m}$ , and the foveola is 350  $\mu\text{m}$  in diameter. The foveal avascular zone is slightly larger (500  $\mu\text{m}$ ) and is delimited by the capillary arcades at the level of the inner nuclear layer. The foveal excavation represents the fovea interna, which is lined by the internal limiting membrane. The fovea externa is represented by the junctional system of the external limiting membrane. Both fibers of Henle and the accompanying glia assume a horizontal and radial arrangement in the fovea.

## UMBO AND FOVEOLA



**Fig. 6.1.6 Umbo (Center) and Foveola.** The outer nuclear layer is separated from the inner nuclear layer by the horizontal-oblique fibers of Henle. Umbo and foveola between few nuclei feature clear müllerian fibers (clear tissue), delimited by fibers of Henle externally and by the internal limiting membrane internally. The central 150–200  $\mu\text{m}$  represents the umbo, where cone concentration is maximal.

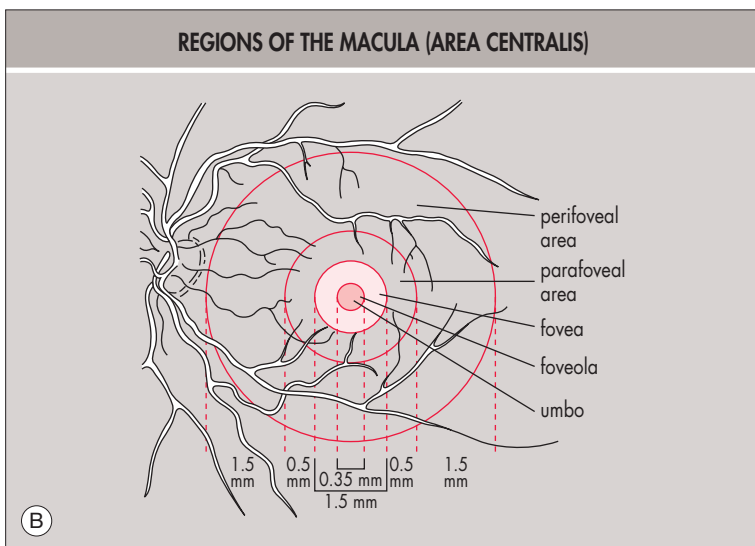
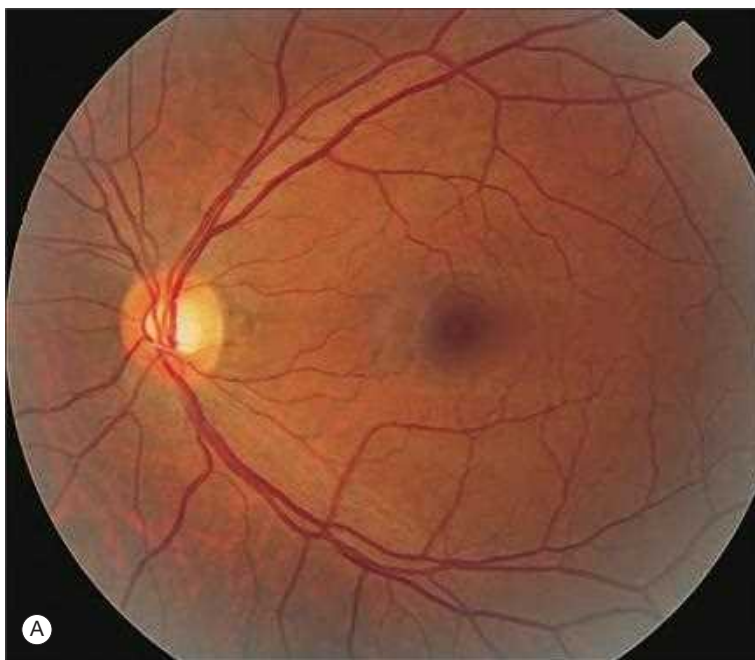
laterally by a junctional system, the external limiting membrane. Their inner fibers (axons) travel radially and peripherally as fibers of Henle in the outer plexiform layer (Fig. 6.1.6). As a result of their high concentration and crowding, the central cones have their nuclei arranged in multiple layers in a circular shape, which resembles a cake (*gateau nucleaire*).<sup>5</sup>

Cones, including their inner and outer segments, are surrounded and enveloped by the processes of müllerian glia, which concentrate on the vitreal side (*tissu clair*),<sup>5</sup> just underneath the internal limiting membrane.<sup>7</sup> Some glial cell nuclei are found in this inner layer, but most form part of the laterally displaced inner nuclear layer. Foveal development, therefore, involves the migration, elongation, concentration, and displacement of both neuronal cells and, most importantly, glial cells, the main structural element of the retina. Radiating striae found in the foveal internal limiting membrane are related to fibers of Henle but are probably mediated by glia that elaborate and are connected to the internal limiting membrane. The density of the foveal glia has been measured as 16 600–20 000 cells/ $\text{mm}^2$ .<sup>6</sup>

## FOVEOLA

The bouquet of central cones is surrounded by the foveal bottom, or foveola, which measures 350  $\mu\text{m}$  in diameter and 150  $\mu\text{m}$  in thickness (see Fig. 6.1.5). This avascular area consists of densely packed cones that are elongated and connected by the external limiting membrane. As a result of the elongation of the outer segments, the external limiting membrane is bowed vitreally, a phenomenon that has been termed *fovea*





**Fig. 6.1.7 Normal Fundus With Macula Encompassed by Major Vascular Arcades.** The macula, or central area, has the following components from center to periphery: umbo, foveola, fovea, parafovea, and perifovea.

*externa*. Both the umbo and the foveola represent the most visible part of the outer retina; however, to the level of the external limiting membrane, all cones and their axons are enveloped by the processes of Müller cells, which form the vitreal inner layer and elaborate and support the internal limiting membrane. Thus, the apex-to-apex arrangement of the optic cup is maintained by the processes of müllerian glia that face the apices of the pigment epithelial cells in the foveola. The high metabolic demands of central cones are met by direct contact with the pigment epithelium, as well as through the processes of glia, whose nuclei lie more peripheral in the inner nuclear layer and closer to the perifoveal vascular arcades (see Fig. 6.1.6).

In pathological conditions, loss of the normal foveolar reflex may indicate a glial disturbance (acute nerve cell damage, cloudy swelling) either primarily or mediated by the vitreous, which is tightly adherent to the thin internal limiting membrane. Loss of the foveal reflex may thus indicate traction or edema of glial cells and, secondarily, of cones. The inner glial layer may separate from the nuclear layer, which results in cyst-like schisis.

## FOVEA

The fovea consists of the thin bottom, a 22° declivity (the clivus),<sup>3</sup> and a thick margin (see Figs. 6.1.5–6.1.7). The bottom, or foveola, was described earlier. The declivity of 22° denotes the lateral displacement of the bipolars, horizontal and amacrine cells in the inner nuclear layer, which also includes the nuclei of its müllerian glia. The avascular foveola is surrounded by the vascular arcades, a circular system of capillaries. These

vessels are located at the level of the internal nuclear layer and leave an avascular zone of 250–600  $\mu\text{m}$  between them. The declivity also is associated with an increase in basement membrane thickness, which reaches a maximum at the foveal margin. Internal limiting membrane thickness and strength of vitreal attachment are inversely proportional; that is, adhesions are strongest in the foveola.<sup>3</sup> Not surprisingly, the foveal center is most affected in traumatic macular holes in which glial opercula suggest anterior–posterior traction as the cause. The margin of the fovea (*margo foveae*) is often seen biomicroscopically as a ring-like reflection of the internal limiting membrane, which measures 1500  $\mu\text{m}$  (disc size) in diameter and 0.55 mm in thickness (see Fig. 6.1.7).

## PARAFOVEA

The parafovea is a belt that measures 0.5 mm in width and surrounds the foveal margin (see Fig. 6.1.7). At this distance from the center, the retina features a regular architecture of layers, which includes 4–6 layers of ganglion cells and 7–11 layers of bipolar cells.<sup>8</sup>

## PERIFOVEA

The perifovea surrounds the parafovea as a belt that measures 1.5 mm wide (see Fig. 6.1.7). The region is characterized by several layers of ganglion cells and six layers of bipolar cells.<sup>8</sup>

## MACULA, OR CENTRAL AREA

The umbo, foveola, fovea, parafovea, and perifovea together constitute the macula, or central area.<sup>9</sup> The central area can be differentiated from the extra-areal periphery by the ganglion cell layer. In the macula, the ganglion cell layer is several cells thick; however, in the extra-areal periphery, it is only one-cell thick. The macular border coincides with the course of the major temporal arcades and has an approximate diameter of 5.5 mm (see Fig. 6.1.7), which comprises the diameter of the fovea (1.5 mm), twice the width of the parafovea ( $2 \times 0.5 = 1$  mm), and twice the width of the perifovea ( $2 \times 1.5 = 3$  mm).<sup>10</sup>

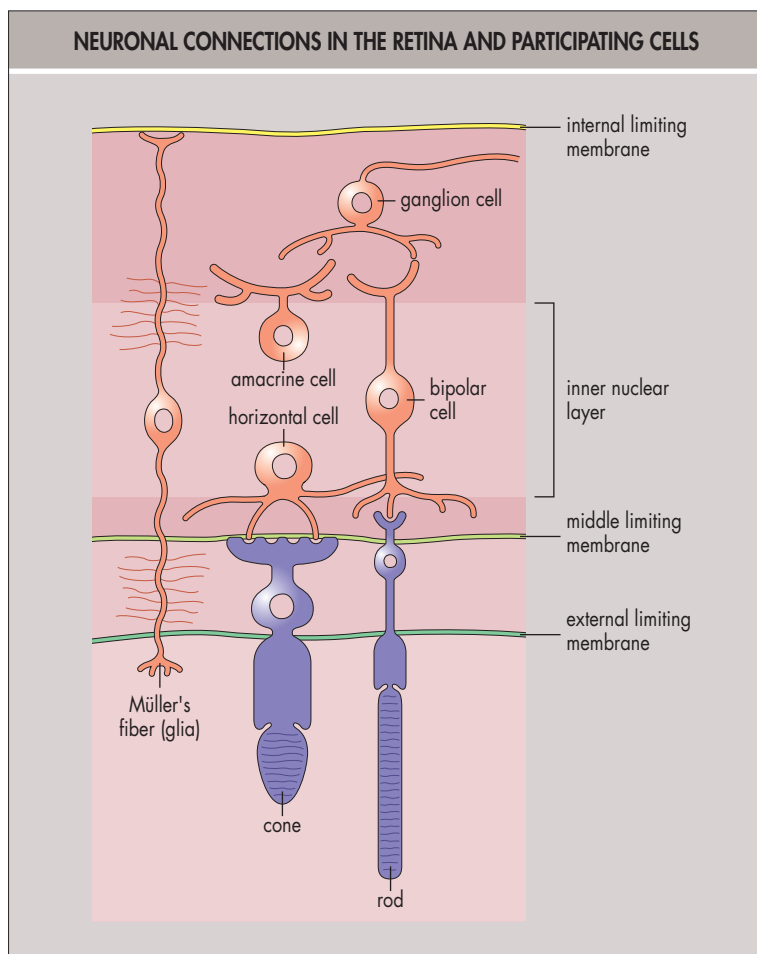
## EXTRA-AREAL PERIPHERY

The peripheral retina is divided arbitrarily into belts of near, middle, far, and extreme periphery.<sup>9</sup> The belt of the near periphery is 1.5 mm wide, and the belt of the middle periphery, or equator, is 3 mm wide. The far periphery extends from the equator to the ora serrata. The width of this belt varies, depending on ocular size and refractive error. The average circumference of the eye is 72 mm at the equator and 60 mm at the ora serrata, and the average width of this belt is 6 mm. Because peripheral retinal pathology is usually charted in clock hours, 1 clock hour corresponds to 5–6 mm of far peripheral circumference. Therefore, the far periphery of the retina may be divided into 12 squares that measure approximately  $6 \times 6$  mm. As a result of the insertion of the posterior vitreous base, most peripheral pathology falls into these squares. The ora serrata and pars plana are referred to as the *extreme periphery*.<sup>9</sup>

## LAYERS OF THE NEURAL RETINA

With the exception of the fovea, ora serrata, and optic disc, the neural retina is organized in layers, dictated by the direction of the müllerian glia, its structural backbone. Essentially, there is the photoreceptor layer plus the bipolar and ganglion cell layer, representing the outer first neuron and inner second and third neuron of the visual pathway. The müllerian glia elaborate the internal limiting membrane as its basement membrane and extend to the external limiting membrane, where it communicates with the apices of the RPE (Fig. 6.1.8).

The inner nuclear layer is home to the nuclei of the müllerian glia, the bipolar cells, and the horizontal and amacrine cells. The amacrine cells lie on the inside of the inner nuclear layer, and the horizontal cells lie on the outside (see Fig. 6.1.8). The inner nuclear layer has plexiform layers on either side, which connect it to the outer photoreceptor layer and the (inner) ganglion cell layer. From this simple anatomical consideration, it follows that rods and cones synapse with bipolar and horizontal cells in the outer plexiform layer. As a result of the increased length of fibers of Henle, the junctional system (the middle limiting “membrane”) is found in the inner third of the outer plexiform layer, which is the only truly plexiform portion of this layer. The bipolar cells and amacrine cells of the inner nuclear layer synapse with the dendrites of the ganglion cells in the inner



**Fig. 6.1.8 Neuronal Connections in the Retina and Participating Cells.** The inner nuclear layer contains the nuclei of the bipolar cells (second neuron) and müllerian glia. The amacrine cells are found on the inside and the horizontal cells on the outside of this layer, next to their respective plexiform connections.

plexiform layer. In embryogenesis, müllerian glia, along with their internal limiting membrane and orientation, antedate photoreceptor differentiation; this is analogous to the rest of the central nervous system, in which structural development precedes individual cell differentiation.

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# Retinal Pigment Epithelium

Michael F. Marmor

## 6.2

**Definition:** A melanin-containing epithelial layer that lies between the neural retina and choroid.

### Key Features

- Absorption of scattered light.
- Control of fluid and nutrients in the subretinal space (blood–retinal barrier function).
- Visual pigment regeneration and synthesis.
- Synthesis of growth factors to modulate adjacent structures.
- Maintenance of retinal adhesion.
- Phagocytosis and digestion of photoreceptor wastes.
- Electrical homeostasis.
- Regeneration and repair for degenerative disease.

### INTRODUCTION

The retinal pigment epithelium (RPE) is a vital tissue for the maintenance of photoreceptor function.<sup>1,2</sup> It is also affected by many diseases of the retina and choroid. Embryologically, the RPE is derived from the same neural tube tissue that forms the neural retina, but the cells differentiate into a transporting epithelium, the main functions of which are to metabolically insulate and support the overlying neural retina. As a cellular monolayer, the RPE is now an attractive target for therapeutic modification and transplantation.<sup>3</sup>

### STRUCTURE AND METABOLISM

#### Cellular Architecture and Blood–Retinal Barrier

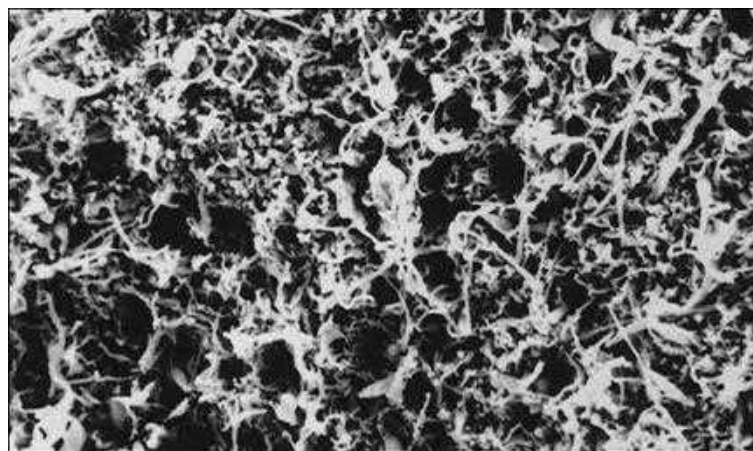
The RPE is a monolayer of interlocking hexagonal cells that are joined by tight junctions (zonulae occludens), which block the free passage of water and ions. This junctional barrier is the equivalent of the blood–retinal barrier of the neuroretina.

In the macular region, RPE cells are small (roughly 10–14  $\mu\text{m}$  in diameter), whereas toward the periphery, they become flatter and broader (diameter up to 60  $\mu\text{m}$ ). The density of photoreceptors also varies across the retina, but the number of photoreceptors that overlie each RPE cell remains roughly constant (about 45 photoreceptors per RPE cell).

In cross-section, the RPE cell is differentiated into apical and basal configurations. On the apical side (facing the photoreceptors), long microvilli reach up between (and envelop) the outer segments of the photoreceptors (Fig. 6.2.1). Melanin granules are concentrated in the apical end of the cell. The basal membrane has convoluted infolds to increase the surface area for the absorption and secretion of material. The cell structure is stabilized by a cytoskeleton of microfilaments and microtubules.

#### Pigments

The pigment that gives the RPE its name is *melanin*, found in cytoplasmic granules called *melanosomes*. In older age, melanin granules often fuse with lysosomes and break down, so the fundus in older adults typically appears less pigmented. The role of melanin in the eye remains somewhat speculative. The pigment serves to absorb stray light and minimize scatter within the eye, which has theoretical optical benefits. Visual acuity is, however, not degraded in the fundi of the very blond. Further, the appearance of the fundus can be misleading with respect to the RPE because the greatest racial differences are a result of choroidal pigmentation. Melanin also



**Fig. 6.2.1 Apical Surface of Human Retinal Pigment Epithelium as Seen Through a Scanning Electron Microscope.** Fine microvilli cover the surface and reach up between the photoreceptor outer segments (which have been peeled away in this view).

serves as a free radical stabilizer and can bind toxins and retinotoxic drugs, such as chloroquine and thioridazine, although it is unclear whether this effect is beneficial or harmful.

The other major RPE pigment is lipofuscin, which accumulates gradually with age, although it is not clear whether it is directly damaging to RPE cells as it is a component of both normal and pathological aging.

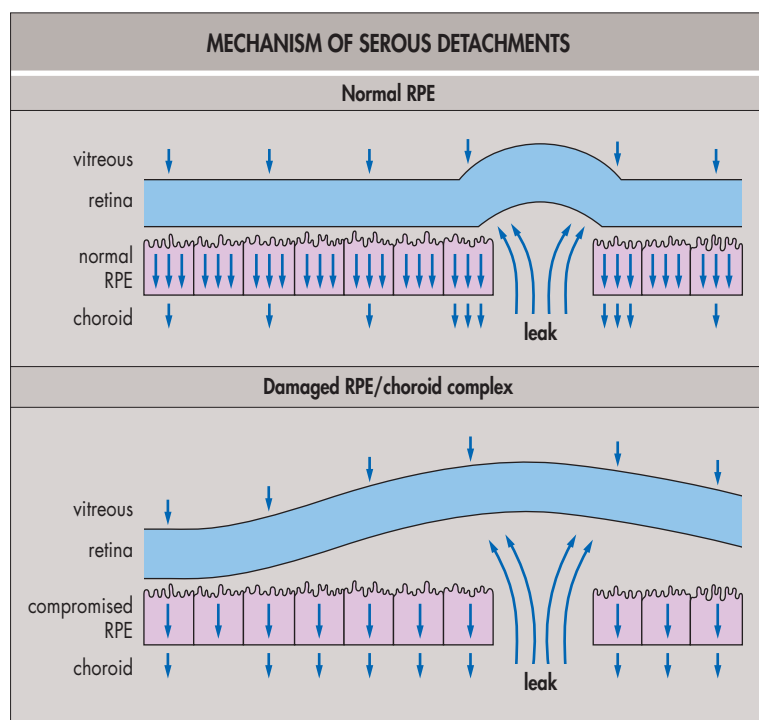
#### Metabolism and Growth Factors

A number of growth factors are elaborated by RPE cells and serve to modulate not only the behavior of the RPE but also the behavior of surrounding tissues.<sup>1,4</sup> Knowledge of these interactions is growing rapidly, and it is now recognized that the RPE is a critical part of a complex system of cellular cross-talk that controls vascular supply, permeability, growth, immunological responses, repair, and other processes vital to retinal function. Dysfunction within these systems contributes to disorders, such as age-related macular degeneration. Factors produced by the RPE include, among others, platelet-derived growth factor, which modulates cell growth and healing; pigment epithelium-derived factor, which acts as a neuroprotectant and vascular inhibitor; vascular endothelial growth factor, which can stimulate normal or pathological neovascular growth; fibroblast growth factor, which can be neurotropic; transforming growth factor, which moderates inflammation; ciliary neurotrophic factor, which supports and rescues cells; and other immune regulating components, such as Toll-like receptors and complement factors.

### MEMBRANE PROPERTIES AND FLUID TRANSPORT

#### Ion Channels and Transport Systems

The RPE membrane contains selective ion channels, and active or facilitative transport systems for ions and for metabolites, such as glucose and amino acids.<sup>5</sup> Different channels and transporters are present on the apical and basal membranes. The net effects of the asymmetrical transport systems are a movement of water across the RPE in the apical-to-basal direction and the generation of voltage across the RPE, as well as control of protein access to the subretinal space.



**Fig. 6.2.2 Mechanism of Serous Detachment.** When the retinal pigment epithelium (RPE) is normal, no serous detachment occurs beyond a focal site of leakage. When the RPE is compromised by choroidal or RPE disease that impairs outward fluid transport, a serous detachment forms until absorption across the exposed RPE balances the inward leak.

The ability of the RPE to transport water actively is very powerful, but water also moves out if the RPE barrier function is broken because of intraocular pressure and osmotic suction from the choroid. One clinical implication is that a small RPE break will not cause a serous detachment unless there is also a diffuse loss of RPE transport. Central serous chorioretinopathy involves broad dysfunction in the RPE-choroid complex (Fig. 6.2.2).<sup>6</sup>

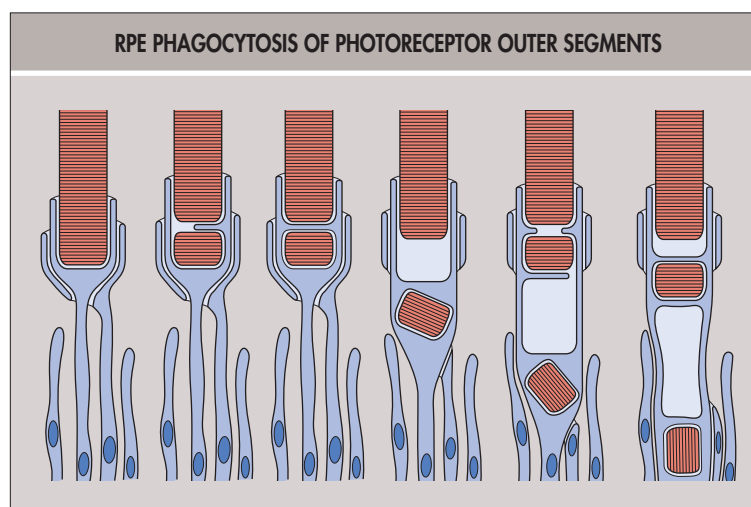
## Electrical Activity

The RPE generates no direct response to light. However, the asymmetrical transport properties of the apical and basal membranes generate a transepithelial voltage (called the *standing potential*), which can be modified secondarily by photoreceptor activity or by endogenously supplied substances.<sup>7</sup> Furthermore, light activation of photoreceptors also causes the release of a messenger substance that induces a basal RPE depolarization 5–10 minutes later. This late basal depolarization is recorded clinically as the “light response” of the clinical electrooculography (EOG). The light response is mediated through calcium-dependent chloride channels controlled, in part, by the bestrophin gene, which is altered in Best vitelliform dystrophy or autosomal recessive bestrophinopathy. The EOG is very subnormal in Best disease, but is not severely altered in most RPE disorders.<sup>7</sup>

## PHOTORECEPTOR–RETINAL PIGMENT EPITHELIUM INTERACTIONS

### Visual Pigment Regeneration

Absorption of light in the photoreceptors converts 11-*cis*-vitamin A to the all-*trans* form. This initiates transduction of light to a neural signal and begins a series of regenerative chemical changes to restore the supply of 11-*cis* vitamin A. Vitamin A is split off from the opsin molecule and carried by a transport protein to the RPE. In the RPE, vitamin A may be stored in an ester form, but eventually it is isomerized back to the 11-*cis* form by a critical enzyme RPE65, and then recombined with opsin.<sup>8</sup> Defects in several genes, including *RPE65*, *LRAT*, *RLPB* (*CRALBP*), and *RDH*, which control this regenerative cycle in the RPE, cause Leber congenital amaurosis or retinitis pigmentosa.



**Fig. 6.2.3 Retinal Pigment Epithelium (RPE) Phagocytosis of Photoreceptor Outer Segments.** The phagosome, containing the ingested material, enters the RPE cytoplasm, where it merges with lysosomes to facilitate digestion of the outdated membranes. (Adapted from Steinberg H, Wood I, Hogan MJ. Pigment epithelial ensheathment and phagocytosis of extrafoveal cones in human retina. *Philos Trans R Soc Lond* 1977;277:459–74.)

## Photoreceptor Renewal and Phagocytosis

Photoreceptors are continually exposed to radiant energy (light) and oxygen (from the choroid), which facilitates the production of free radicals that can damage membranes. Thus a process of cellular renewal is needed. Every day, upward of 100 discs at the distal end of the photoreceptors are phagocytosed by the RPE (Fig. 6.2.3), while new discs are synthesized.<sup>9</sup> The rods shed discs most vigorously in the morning at the onset of light, whereas cones shed more vigorously at the onset of darkness, and the outer segments are renewed roughly every 2 weeks. Within the RPE, the phagocytosed discs merge with lysosomes so that the material can be digested. Necessary fatty acids are recycled, whereas waste products are egested across the basal RPE membrane. Residual membrane debris, such as A2E, may contribute to the formation of lipofuscin and aging damage to the RPE.

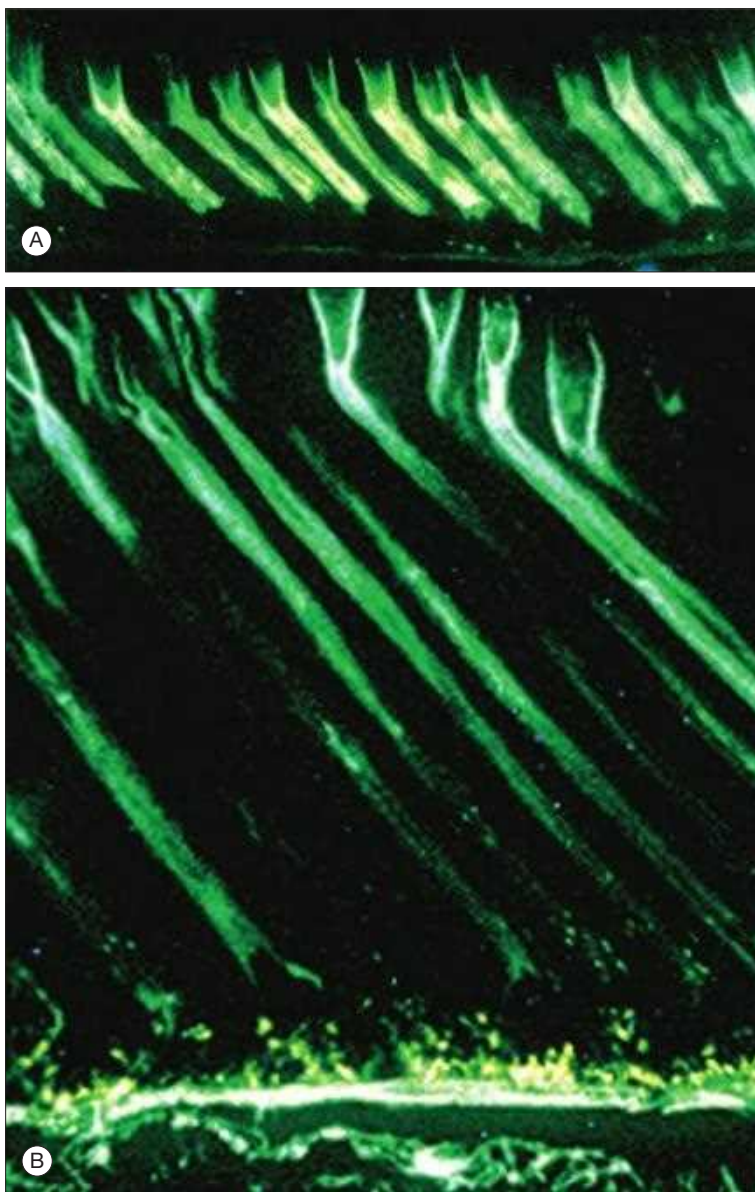
## Retinal Adhesion and Interphotoreceptor Matrix

Adhesion of the retina to the RPE is a complex process involving several interactive mechanisms. The neural retina is pressed in place by the vitreous gel, intraocular fluid pressure, and RPE water transport, which drive or pull water through the semipermeable tissue. There is some physical resistance to separation of outer segments from enveloping RPE microvilli. The strongest mechanism for bonding the retina to the RPE space appears to be the interphotoreceptor matrix (IPM), which is an elaborate chemical structure with distinct domains that surround the rods and cones (Fig. 6.2.4A).<sup>10</sup> When neural retina is freshly peeled from the RPE, the IPM material stretches dramatically before it breaks, which shows that it is firmly attached to both neural retinal and RPE surfaces (see Fig. 6.2.4B). However, the strength of the IPM adhesive system (as well as RPE fluid transport) is constantly and acutely dependent on metabolism.<sup>11</sup> Retinal adhesive force drops to near zero within minutes after death, and adhesive strength can be reversibly restored or enhanced by tissue oxygenation.

Retinal detachment disrupts fluid transport and the IPM, and even when the retina is surgically reattached, it can take several weeks for full recovery of IPM morphology, RPE/photoreceptor intercalation and normal adhesive strength.

## REPAIR, REGENERATION, AND THERAPY

The RPE is capable of local repair (unlike the neural retina), although injured cells may migrate and take on altered characteristics. After a focal laser burn, the RPE cells that surround the burn will divide and fill the defect to form a new blood–retinal barrier within 1–2 weeks. However, large RPE defects, such as geographical atrophy, do not heal. Because growth factors from the RPE normally serve to limit excessive proliferation of cells and vasculature, RPE injury becomes a part of the cycle of pathology that stimulates vascular or fibrous growth in many retinal conditions.



**Fig. 6.2.4 Cone Sheaths of the Interphotoreceptor Matrix, Shown by Fluorescent Staining With Peanut Agglutinin.** Cone tips indent the sheaths from above; the retinal pigment epithelium (RPE) is on the bottom. (A) The matrix sheaths are short in a normal eye. (B) They stretch dramatically before breaking as the retina is peeled from the RPE. This shows that matrix material bonds across the subretinal space. (Reproduced with permission from Hageman GS, Marmor MF, Yao X-Y, Johnson LV. The interphotoreceptor matrix mediates primate retinal adhesion. *Arch Ophthalmol* 1995;113:655–60.)

The RPE monolayer, however, can be cultured and transplanted, and RPE cells can be genetically engineered or physically stimulated to modify their metabolic activity. Thus, this tissue may also have an important role in the therapy of retinal disorders, ranging from dystrophies to aging. These new options depend directly on the physical and physiological characteristics of the RPE that have been reviewed above. For example, nondamaging laser therapy (low energy or micropulses) can stimulate a release of metabolic factors, including heat shock proteins that ameliorate injury. This approach is being explored for the treatment of several diseases, including macular edema and central serous chorioretinopathy.<sup>12</sup> Cellular damage to the RPE is specifically causative of several hereditary dystrophies, including retinitis pigmentosa that involves RPE genes, such as *RPE65* and *LRAT*, and Stargardt disease in which RPE damage leads to photoreceptor death. Many groups are now investigating the use of stem cell and RPE transplantation to put normal RPE back into eyes with these diseases.<sup>3</sup> The ability to culture and modify induced pluripotent stem cells (iPSC) allows for genetic modification to create designer RPE cells prior to transplantation,<sup>13</sup> although techniques for the culturing of cells, inserting cells to reach a large area of retina, and ensuring cell survival and function over a lifetime are still evolving. Finally, trials are beginning for genetic modification of the RPE (as well as other retinal cells) within the eye through transfection with viral and other gene carriers.<sup>14</sup>

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# Retinal and Choroidal Circulation

Caio Vinícius Saito Regatieri, Shiyong Roh, John J. Weiter

## 6.3



IN THIS CHAPTER  
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**Definition:** Retinal and choroidal blood vessels are responsible for nutrition of the posterior segment. It is essential to understand the choroidal and retinal circulatory systems to better recognize and treat disease states of the posterior segment.

### Key Features

- Retinal vascular anatomy.
- Choroidal vascular anatomy.
- Inner and outer blood–retinal barriers.
- Choroidal and retinal blood flow measurements.

## INTRODUCTION

Because many of the important diseases of the posterior segment are caused by changes in the vasculature of the retina and choroid, it is important to understand the circulatory systems involved to better recognize and treat disease states of the posterior segment. In this chapter, the anatomy and physiology of these circulatory systems are discussed.

## POSTERIOR SEGMENT VASCULAR ANATOMY

### Retinal Vascular Anatomy

The retinal blood vessels provide nourishment for the inner two thirds of the retina. The central retinal artery, which is the first branch of the ophthalmic artery, is an end artery that has no significant anastomoses.<sup>1</sup> In the area of the lamina cribrosa, its lumen measures about 170  $\mu\text{m}$  in diameter. Typically, just before its exit from the optic nerve, the central retinal artery divides into the superior and inferior papillary arteries, which, in turn, divide into nasal and temporal quadratic branches (Fig. 6.3.1A). The anatomic division of the retinal arteries into superior and inferior halves is usually maintained throughout the retina because normal retinal vessels rarely cross the horizontal raphe (see Fig. 6.3.1A). Cilioretinal arteries, derived from the posterior ciliary arteries, are variably present and emanate from the temporal rim of the optic nerve head toward the macula (see Fig. 6.3.1A).

Arteries and veins remain in the nerve fiber layer. Throughout the retina, the capillaries are arranged in laminar meshworks.<sup>2</sup> Depending on the thickness of the retina, the capillary meshwork can vary from three layers at the posterior pole to one layer in the periphery. The arterial intra-retinal branches supply three layers of capillary networks:

- The radial peripapillary capillaries.
- Superficial capillaries in the ganglion cell and nerve fiber layers.
- Deep, denser, capillaries in the inner nuclear layer.

Optical coherence tomography angiography (OCTA) reveals the microvasculature and the blood flow in the retinal capillaries in a noninvasive manner. Automated segmentation of the full-thickness retinal OCTA scans show in vivo the “superficial” and “deep” retinal vascular plexuses, and choriocapillaris. The superficial plexus shows a continuous and linear shape with a homogeneous wall. The vessels are evenly distributed and resemble a spider’s web. The deep network in healthy eyes has a regular distribution around the foveal avascular zone (FAZ), with more complex minute interconnections.

Like capillary networks elsewhere in the body, the retinal capillaries assume a meshwork configuration to ensure adequate perfusion to all inner retinal cells (see Fig. 6.3.1C).

A capillary-free zone is present around each of the larger retinal arteries and veins, but it is more prominent around arteries, where it measures up to 100  $\mu\text{m}$  in diameter. In the fovea and the far retinal periphery, retinal capillaries are absent. The FAZ is 400–500  $\mu\text{m}$  in diameter in normal eyes.

The venous drainage of the retina generally follows the arterial supply. Retinal veins (mainly venules) are present in the inner retina, where they occasionally interdigitate with their associated arteries. When two vessels cross, the artery usually lies anterior to the vein, and the two vessels share a common adventitial coat. Many more arteriovenous crossings occur temporally than nasally because the nasal vessels assume a much straighter course. The crossings are important because they represent the most common site of branch retinal vein obstructions. The retinal veins drain into the central retinal vein, which also acts as the major efferent channel for the vessels of the optic nerve (see Fig. 6.3.1A).<sup>2</sup>

### Choroidal Vascular Anatomy

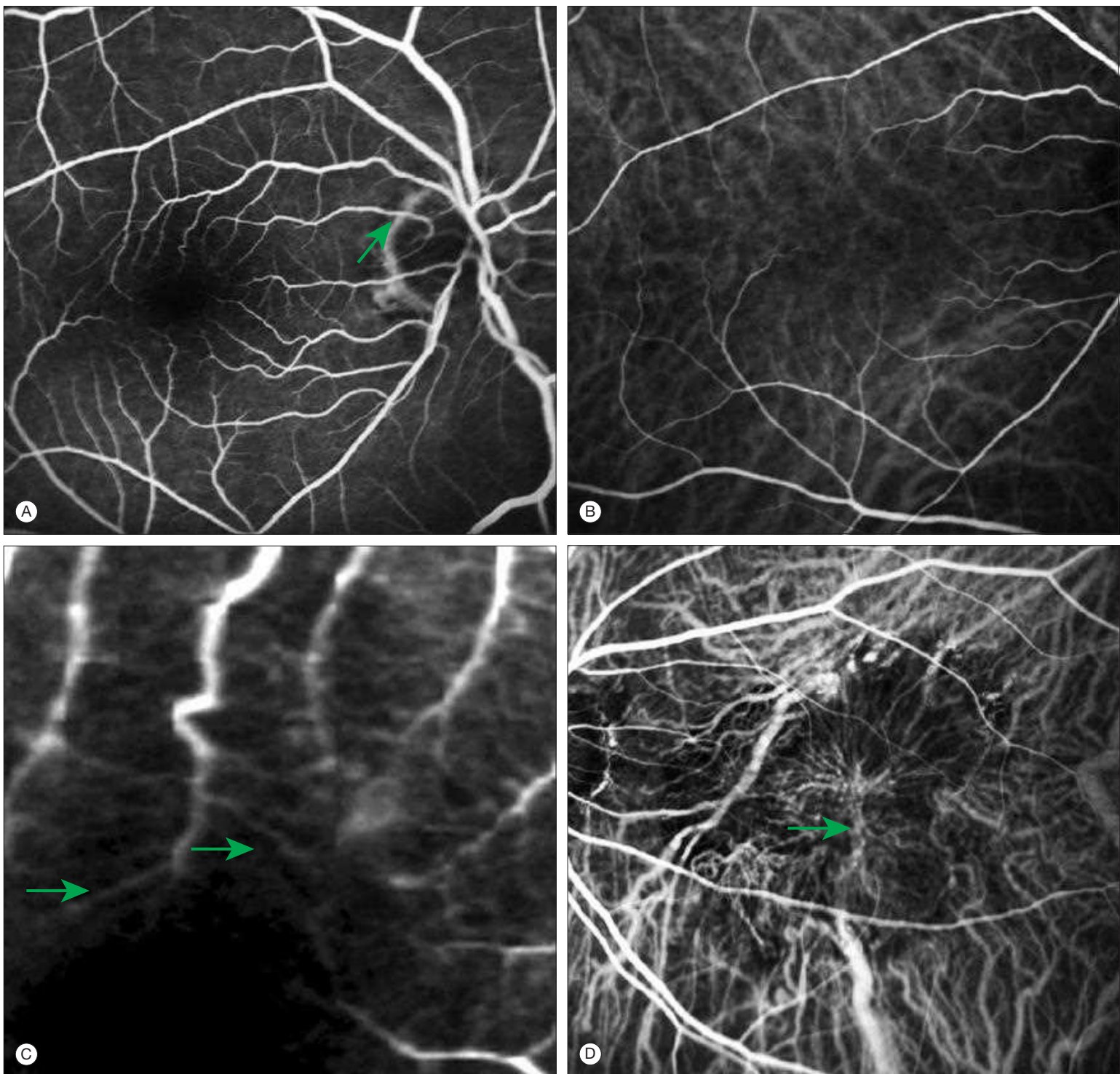
The choroid is, by far, the most vascular portion of the eye and, by weight, one of the most vascular tissues in the body. The choroid is responsible for the vascular support of the outer retina (see Fig. 6.3.1B). A structurally and functionally normal choroidal vasculature is essential for retinal function: Abnormal choroidal blood volume and/or compromised flow can result in photoreceptor and retinal pigment epithelium (RPE) dysfunction and death.<sup>3</sup> Other likely functions include light absorption, thermoregulation via heat dissipation, and modulation of intraocular pressure (IOP) via vasomotor control of blood flow. The choroid also plays an important role in the drainage of the aqueous humor from the anterior chamber via the uveoscleral pathway.

The blood supply to the choroid is from branches of the anterior and posterior ciliary arteries, branches of the ophthalmic artery. The overall structure of the choroid is segmental; this segmental distribution of blood begins at the level of the posterior ciliary branches and is mirrored in the vortex drainage system. As a result of the segmental distribution, the large and medium-sized choroidal arteries act as end arteries.

Histologically, starting from the retinal (inner) side, the choroid is divided into five layers:

- Bruch’s membrane.
- Choriocapillaris (layer of capillaries).
- Sattler’s layer (layer of medium diameter blood vessels).
- Haller’s layer (layer of large diameter blood vessels).
- Suprachoroida (transitional zone between choroid and sclera).<sup>4</sup>

The choriocapillaris is a highly anastomosed network of capillaries, forming a thin sheet apposed to Bruch’s membrane. The fibrous basement membrane of the capillary endothelial cells forms the outermost layer of Bruch’s membrane in humans. The choriocapillaris is about 10  $\mu\text{m}$  thick at the fovea, where there is the greatest density of capillaries, thinning to about 7  $\mu\text{m}$  in the periphery. The capillaries arise from the arterioles in Sattler’s layer, each of which gives rise to a hexagonal (or lobular) shaped domain of a single layer of capillaries, giving a patch-like structure to the choriocapillaris. The choriocapillaris has large diameter capillaries of 20–25  $\mu\text{m}$ , which allow the passage of multiple red blood cells at any moment in time. Unlike the retinal capillaries, the choriocapillaris has



**Fig. 6.3.1 Angiogram From Scanning Laser Ophthalmoscopy.** (A) Normal fluorescein angiogram shows the normal filling of retinal arteries and veins; note the cilioretinal artery (*green arrow*). (B) Normal indocyanine green angiogram shows the normal filling of choroidal vessels. (C) Magnified area from image A shows the retinal capillaries (*green arrows*) close to the foveal avascular zone. (D) Indocyanine green angiogram shows a choroidal neovascularization (*green arrow*) secondary to age-related macular degeneration (AMD).

fenestrations of 700–800 nm diameter, which allows more rapid transport of molecules (leakage).<sup>4</sup>

Besides the choriocapillaris, the choroid presents two other vascular regions: the outer Haller's layer of large blood vessels and the inner Sattler's layer of medium and small arteries and arterioles that feed the capillary network, and veins. The stroma (extravascular tissue) contains collagen and elastic fibers, fibroblasts, nonvascular smooth muscle cells, and numerous very large melanocytes that are closely apposed to the blood vessels. As in other types of connective tissue, there are numerous mast cells, macrophages, and lymphocytes.

### BLOOD–RETINAL BARRIER

The blood–retinal barrier (BRB) controls the exchange of metabolites and waste products between the vascular lumen and the neural retina and is

formed by the interaction of retinal glia and pericytes with the retinal vascular endothelium cells. In addition to the vascular contribution, the retina also possesses an epithelial barrier, the RPE, which controls the flow of fluid and nutrients from the highly vascularized choroid into the outer retina. Together, the vascular and epithelial components of the BRB maintain the specialized environment of the neural retina. Both the vascular endothelium (inner barrier) and the RPE (outer barrier) possess well-developed junctional complexes that include adherens and tight junctions.

The inner BRB controls permeability from the retinal blood vessels and consists of a well-developed junctional complex (adherens and tight junctions) in the vascular endothelial cells as well as no fenestration. The tight junctions restrict flux of a wide variety of substances, such as lipids and protein. The retinal capillaries are relatively impermeable, even to particles as small as sodium ions. The adherens junctions are essential to development of the barrier and influence the formation of the tight junction.



Together, the adherens junctions and tight junctions create the resistance barrier to the neural parenchyma. Although it is at the endothelium of the retinal capillaries that the barrier resides, the glial cells may play a role as metabolic intermediaries between the retinal capillaries and retinal neurons.<sup>5</sup> Thus, macromolecules and ions do not passively diffuse into the retina from the circulation but are associated with selective active transport into the retina.

The outer BRB is formed by tight junctions between cells of the RPE. The RPE resting on the underlying Bruch's membrane separates the neural retina from the fenestrated choriocapillaris and plays an important role in transporting nutrients from the blood to the outer retina. Although inter-RPE cell tight junctions are important in the control of paracellular movement of fluids and molecules between the choroid and retina, the polarized distribution of membrane proteins in the RPE is also important. The RPE plays an active role in supplying glucose to the photoreceptors and also retinol that is required for visual pigment synthesis.<sup>6</sup> The receptors that exist on the basal and lateral cell membranes of the RPE for nutrients have to be transported to the outer retina.

Although the retina is protected by the inner (retinal vascular endothelium cells) and outer (RPE) BRBs, *in vivo*, some leakage probably occurs. Most likely, this protein leakage is actively transported across the RPE into the choroid and/or removed through Schlemm's canal. Choroidal proteins exit the eye through emissary canals (openings in the sclera for vessels and nerves) or through the sclera, probably facilitated by the relatively high tissue pressure of the eye (IOP).<sup>6</sup>

In many clinically important pathological conditions, including diabetic retinopathy, retinal vein occlusion, and some inflammatory diseases, there is a breakdown of the inner BRB, leading to leakage of blood components to the neural retina. In addition, outer BRB breakdown can occur in conditions such as age-related macular degeneration (AMD) (see Fig. 6.3.1D), central serous chorioretinopathy, accelerated hypertension, and toxemia of pregnancy. Breakdown of the outer BRB results in serous retinal detachment or RPE detachment.

## RETINAL AND CHOROIDAL BLOOD FLOW

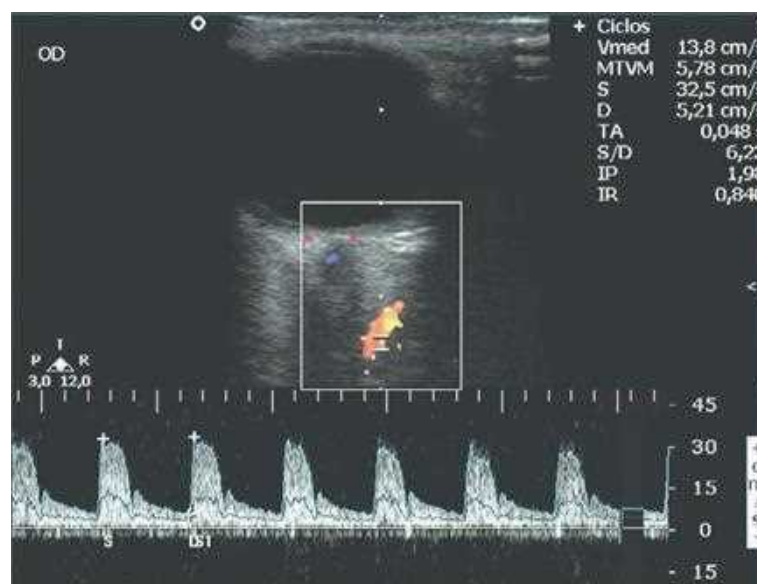
There are several techniques to analyze both qualitatively and quantitatively the retinal and choroidal blood flow, such as the following:

- Fluorescein angiogram with dye dilution (Video 6.3.1).
- Indocyanine green with dye dilution.
- Optical coherence tomography angiography.
- Laser Doppler velocimetry.
- Laser Doppler flowmetry.
- Scanning laser flowmetry.
- Color Doppler ultrasonography (Fig. 6.3.2).

These techniques have greatly enhanced the ability to quantify ocular perfusion defects in many disorders, including glaucoma, AMD, diabetic retinopathy and vascular occlusions, which are major causes of blindness in the developed world. However, methods for accurate, reproducible measurement of retinal and choroidal blood flow are still being perfected because of the difficult access to the retinal and choroidal circulation.

Quantitative retinal blood flow is studied mainly by the use of laser Doppler flowmetry and laser Doppler velocimetry, which are noninvasive techniques which permit the assessment of relative blood velocity, volume, and flow within a sampled volume of tissue. Using these techniques, it has been shown that the total retinal blood flow in healthy subjects is  $44.0 \pm 13.3 \mu\text{L}/\text{min}$ . The blood flow is highest in the temporal inferior quadrant, followed by that in the temporal superior quadrant, the nasal inferior quadrant, and the nasal superior quadrant. In all quadrants retinal blood velocities are linearly correlated to vessel diameters.<sup>7</sup>

Scanning laser ophthalmoscopic fluorescein angiography has also provided important information on retinal hemodynamics in normal individuals and those with glaucoma. In healthy individuals, arteriovenous passage times measured by scanning laser ophthalmoscopic angiography has been reported as averaging  $1.58 \pm 0.4$  seconds and mean dye velocity averaging  $6.67 \pm 1.59 \text{ mm}/\text{sec}$  in a large study of 221 individuals. In the same study, capillary flow velocity averaged  $2.89 \pm 0.41 \text{ mm}/\text{sec}$  in healthy subjects.<sup>8</sup> In patients with primary open-angle glaucoma, there is an 11% reduction in the mean dye velocity within the major retinal arteries. It has also been noted that arteriovenous passage time within retina is 41% slower in primary open-angle glaucoma.<sup>9</sup> Several studies have shown that patients with glaucoma suffer from inadequate ocular blood flow and that a relationship exists between ocular hemodynamics and progression of the disease.



**Fig. 6.3.2 Color Doppler Image of the Ophthalmic Artery.** The Doppler-shifted spectrum (time-velocity curve) is displayed at the bottom of the image. Red pixels represent blood movement toward to the transducer.

Unlike retinal arteries, retinal veins show no pulsations in blood velocity except at the point of exit from the globe.<sup>10</sup> The venous pressure of the intraocular veins exiting the eye depends on IOP and coincides with the pulse, which results in a pulsating venous perfusion pressure. The retinal venous outflow resistance is located mainly at the lamina cribrosa. The closed nature of the eye means that the pulsatile choroidal arterial inflow results in a pulse-related change in IOP, which causes a venous pulse. Depending on the relationship between IOP and venous pressure, this may result in a clinically visible pulse of the veins at their point of exit from the globe.

The choroid is primarily a vascular structure supplying the outer retina. The choroid circulation exhibits one of the highest rates of blood flow in the body. In fact, per tissue gram, the choroid has four times more blood flowing through it than does through the cortex of the kidney. Several studies showed that the choroid receives 65%–85% and the retina 5% or less of the ocular blood flow.

Using laser Doppler velocimetry, the choroidal blood flow is documented to be  $800 \mu\text{L}/\text{min}$ , 18 times higher than retinal blood flow. With advancing age, the choroidal blood velocity and choroidal thickness decrease significantly, and this may be related to the pathogenesis of AMD. Interestingly, mean blood pressure, smoking, and gender have no influence on choroidal blood flow parameters.

Studies assessing the choroidal circulation indicate a significant reduction of choroidal blood flow and volume in patients with glaucoma, AMD, and nonproliferative and proliferative diabetic retinopathy.

The major differences of the retinal and choroidal circulatory systems are shown in Table 6.3.1.

## RETINA AND CHOROIDAL CIRCULATION EVALUATED BY OCTA

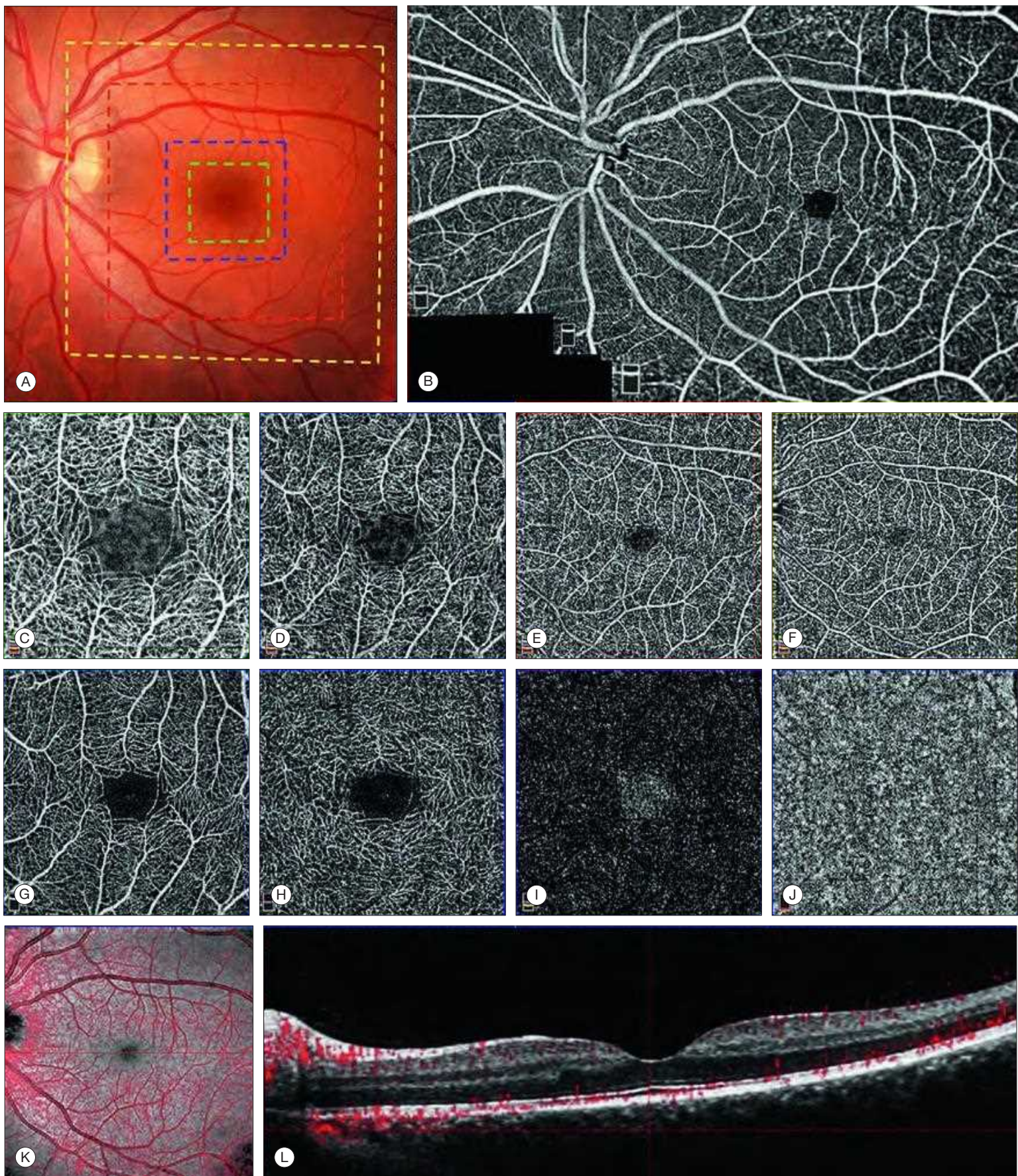
Fluorescein angiography and indocyanine green angiography have been the gold standard modalities for the evaluation of retinal and choroidal vasculature in the last three decades. The advantage of these imaging modalities lies in their ability to document retinal and choroidal vasculature through the dynamic assessment of contrast transit over time in the intravascular and extravascular spaces. However, their disadvantages include the absence of depth resolution, blurring of details by contrast leakage, and the inability to selectively evaluate different levels of the retinal and choroidal microvasculature. In addition, these angiographic methods require the use of intravenous dye, which may cause adverse reactions, such as nausea, vomiting, and, rarely, anaphylaxis.<sup>11</sup>

OCTA is a noninvasive imaging technique, which, in contrast to dye-based angiography, is faster and depth-resolved, allowing the evaluation of the vascular plexuses of the retina and choroid.<sup>12</sup> The OCTA software offers the option of  $2 \times 2 \text{ mm}$ ,  $3 \times 3 \text{ mm}$ ,  $6 \times 6 \text{ mm}$ , and  $8 \times 8 \text{ mm}$  OCTA images and automated segmentation of these full-thickness retinal scans into the “superficial” and “deep” inner retinal vascular plexuses,



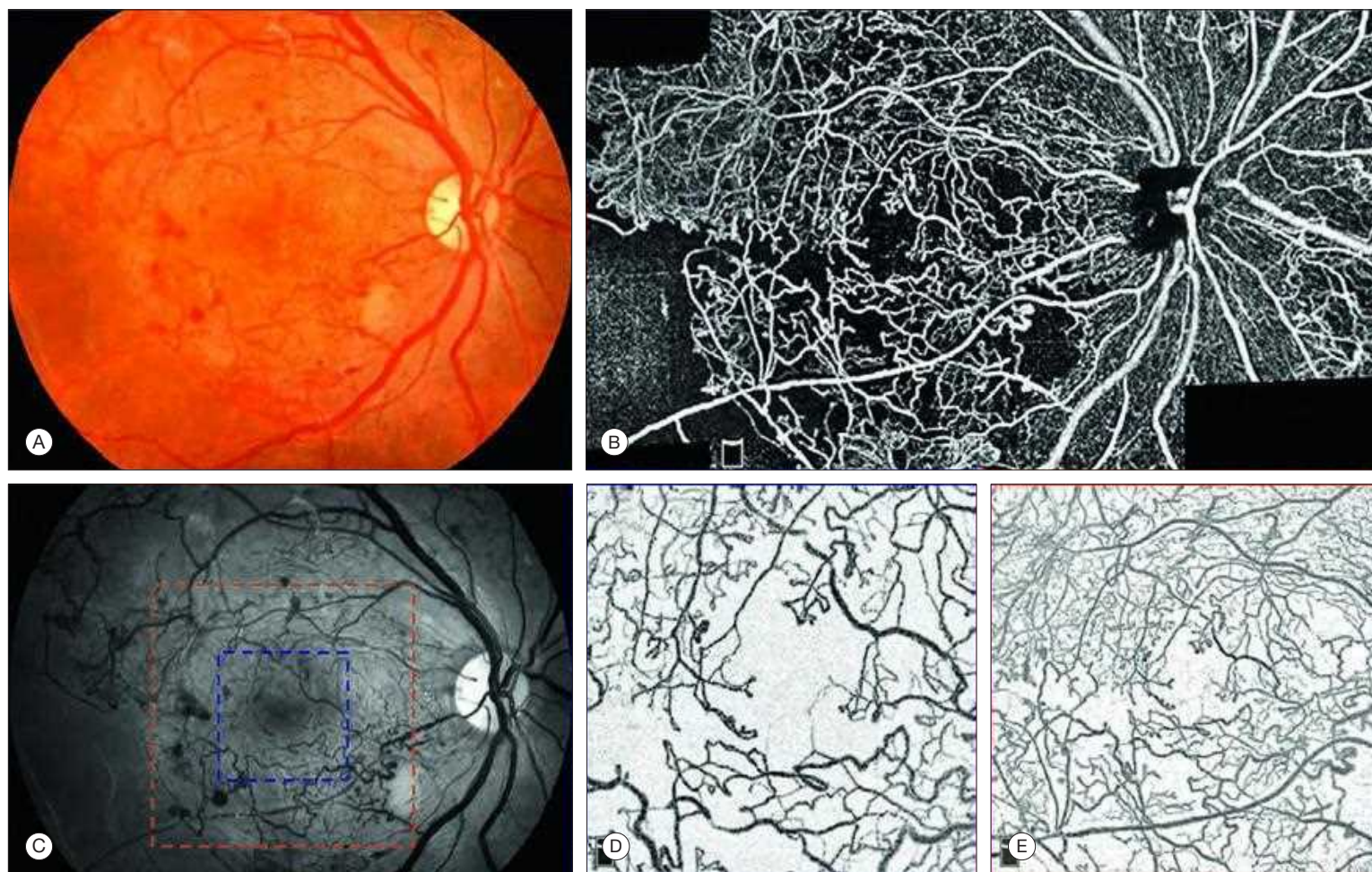
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6.3.1





**Fig. 6.3.3** (A) Color fundus photo (CFP). (B) Composite optical coherence tomography angiography (OCTA) image. (C) Full-thickness  $2 \times 2$  mm OCTA image (represented in the green square in CFP). (D) Full-thickness  $3 \times 3$  mm OCTA image (represented in the blue square in CFP). (E) Full-thickness  $6 \times 6$  mm OCTA image (represented in the red square in CFP). (F) Full-thickness  $8 \times 8$  mm OCTA image (represented in the yellow square in CFP). (G)  $3 \times 3$  mm OCTA image of the “superficial” inner retina. (H)  $3 \times 3$  mm OCTA image of the “deep” inner retina. (I)  $3 \times 3$  mm OCTA image of the outer retina shows absence of vasculature. The white represents noise. (J)  $3 \times 3$  mm OCTA image of the choriocapillaris is generally homogeneous. There is black shadowing from retinal vessels. (K) Angiographic reference image of the retina (6 retina 6 mm) and flow representation in red. (L) Cross-sectional OCTA flow image. (Courtesy Claudio Zett, PhD.)





**Fig. 6.3.4** (A) Color fundus photo (CFP). (B) Composite optical coherence tomography angiography (OCTA) image. (C) Red free. (D)  $3 \times 3$  mm OCTA image of the “superficial” inner retina (represented in the blue square in red free). (E)  $6 \times 6$  mm OCTA image of the “superficial” inner retina (represented in the red square in red free). (Courtesy Claudio Zett, PhD.)

**TABLE 6.3.1 Major Differences Between the Retinal and Choroidal Circulatory Systems**

Property	Retinal Circulation	Choroidal Circulation
Supply	Central retinal artery	Ciliary arteries
Blood flow	Normal for tissue	Highest in body
Tissue nourishment	Inner two thirds of retina	Outer one third of retina (photoreceptor and retinal pigment epithelium [RPE] complex)
Cellular junctions	Tight junctions between endothelial cells	Fenestrations in choriocapillaris
Nature of vasculature	End artery system	Functionally end artery system (lobular-shaped domain)
Blood flow regulation	Autoregulation	Controlled by the autonomic nervous system

outer retina, and choriocapillaris (Fig. 6.3.3). The OCTA segmentation of the superficial inner retina contains a projection of the vasculature in the retinal nerve fiber layer and the ganglion cell layer. The deep inner retina OCTA segmentation shows a composite of the vascular plexuses at the border of the inner plexiform layer (IPL) and inner nuclear layer (INL) and the border of the INL and outer plexiform layer.<sup>12</sup>

Published studies suggest that OCTA is efficacious in the evaluation of common ophthalmological diseases, such as age-related macular degeneration (AMD), diabetic retinopathy, occlusions of arteries and veins, and glaucoma. OCTA can detect changes in choroidal blood vessel flow and can elucidate the presence of choroidal neovascularization in a variety of conditions, especially in AMD.<sup>12</sup> It provides a highly detailed view of the retinal vasculature, which allows for accurate delineation of the FAZ in diabetic eyes and detection of subtle microvascular abnormalities in diabetic and vascular occlusive eyes (Fig. 6.3.4). OCTA is now proven to be an effective noninvasive tool to evaluate the retina and choroid circulation.

## REGULATION OF RETINAL AND CHOROIDAL BLOOD FLOWS

Regulation of blood flow through the choroid, as in the body in general, is under the control of the autonomic nervous system. Stimulation of the cervical sympathetic chain decreases choroidal flow, and sympathectomy increases it.<sup>13</sup> The choroid does not show evidence of autoregulation, the lack of which may have serious consequences. Changes in IOP are not reflected by compensatory changes in choroidal vascular pressure,<sup>13</sup> and sudden changes in IOP, as occur in the opening of the eye during surgery, can induce uveal effusion.

Because the autonomic tonus probably protects the eye from transient elevations in the systemic blood pressure under normal circumstances, if the nervous regulation breaks down in the presence of systemic hypertension, fluid may be forced through the retinal pigment epithelial barrier into the retina.<sup>14</sup> Such changes could contribute to the pathology of central serous chorioretinopathy, cystoid macular edema, and hypotony maculopathy. The ophthalmic artery and its branches are innervated richly with adrenergic fibers until the lamina cribrosa is reached.

From that point on, no nervous system control of the retinal circulation occurs.<sup>15</sup> The retinal circulation must therefore depend on local autoregulation to maintain a constant metabolic environment. The process of autoregulation in a vascular bed maintains constant or nearly constant blood flow through a wide range of perfusion pressures. Autoregulation of the retina is commonly used today in a much broader sense, to encompass the local homeostatic blood flow mechanisms that provide a constant metabolic environment in the retina despite various conditions that tend to upset this equilibrium. Blood flow in the retina appears to be primarily controlled by metabolic needs, especially the need for oxygen<sup>16</sup>; the accumulation of metabolic byproducts, such as carbon dioxide; and changes in pH. It is necessary to understand the factors that can influence autoregulation of the retinal circulation because these may have important clinical implications.<sup>17</sup>

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# Vitreous Anatomy and Pathology

J. Sebag

6.4

**Definition:** Vitreous is an extended extracellular matrix situated between the lens and the retina, approximately 4 mL in volume and 16.5 mm in emmetropic axial length.

## Key Features

- Optically clear.
- May modulate growth of the eye.
- Maintains media transparency.
- Serves as a reservoir for antioxidants.
- Plays a role in oxygen physiology of the eye.
- Separates from the retina during aging, in most cases resulting in innocuous posterior vitreous detachment (PVD).
- Anomalous PVD is a unifying concept in various vitreoretinopathies, including vitreo-maculopathies and rhegmatogenous retinal detachment.

## Associated Features

- PVD is a common cause of vitreous floaters and may degrade contrast sensitivity function, known as Vision Degrading Myodesopsia.
- Some surgeons advocate vitrectomy for symptomatic vitreous floaters to normalize contrast sensitivity function.
- PVD and vitrectomy increase oxygen levels contributing to cataractogenesis.
- Anomalous PVD is the inciting event in diseases of the vitreous-macular interface via vitreomacular traction and vitreoschisis and contributes to proliferative diabetic retinopathy, macular edema in diabetes and vein occlusions, and possibly exudative age-related macular degeneration.

## INTRODUCTION

Although vitreous is the largest structure within the eye, constituting 80% of the ocular volume, investigators of vitreous anatomy are hampered by two fundamental difficulties:

- Attempts to characterize vitreous morphology are efforts to visualize a tissue that is invisible “by design” (Fig. 6.4.1).
- The various techniques that were previously employed to study vitreous structure were flawed by artifacts induced by tissue fixatives, which caused precipitation of hyaluronan, formerly called *hyaluronic acid*.

The development of slit-lamp biomicroscopy by Gullstrand in 1911 was expected to enable clinical investigation of vitreous structure without the introduction of these artifacts. Nonetheless, a widely varied set of descriptions resulted. This phenomenon even persists in more modern investigations. Consider that in the 1970s, Eisner<sup>1</sup> described “membranelles” and Worst<sup>2</sup> described “cisterns”; in the 1980s, Sebag and Balazs<sup>3,4</sup> identified “fibers”; and in the 1990s, Japanese investigators<sup>5</sup> described “pockets” in the posterior vitreous,<sup>5,6</sup> although the largest one is very likely the same as Worst’s bursa premacularis.<sup>2</sup> What has been largely agreed upon is the molecular composition of vitreous.<sup>4,7–11</sup>

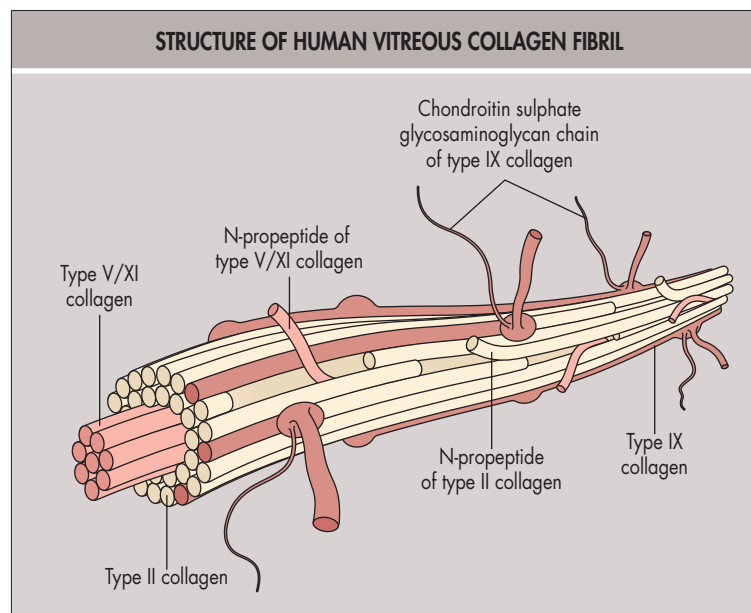
## MOLECULAR MORPHOLOGY

### Supramolecular Organization

Vitreous is composed of a dilute meshwork of collagen fibrils (Fig. 6.4.2) interspersed with extensive arrays of hyaluronan molecules.<sup>7–9</sup> The collagen



**Fig. 6.4.1 Vitreous Obtained at Autopsy on a 9-Month-Old Child.** The sclera, choroid, and retina were dissected off the transparent vitreous, which remained attached to the ora serrata. This was a neural retina that was firmly adherent to the vitreous base and could not be dissected. The vitreous was almost entirely gel (because of the young age of the donor) and thus was solid and maintained its shape, although situated on a surgical towel exposed to room air. (Courtesy The New England Eye Bank, Boston, MA.)



**Fig. 6.4.2 Structure of Human Vitreous Collagen Fibril.** Schematic diagram of the major heterotypic collagen fibrils of vitreous based on current knowledge of the structure and biophysical attributes of the constituent molecules. (With permission from Bishop P. The biochemical structure of mammalian vitreous. Eye 1996;10:64.)

fibrils provide a solid structure that is “inflated” by the hydrophilic hyaluronan.<sup>10</sup> Rheological observations also suggest the existence of an important interaction between hyaluronan and collagen.<sup>12</sup> Balazs hypothesized that the hydroxylysine amino acids of collagen mediate polysaccharide binding to the collagen chain through O-glycosidic linkages.<sup>10</sup> These polar amino acids are present in clusters along the collagen molecule, consistent with proteoglycans attachment to collagen in a periodic pattern.<sup>13</sup>

Hyaluronan–collagen interaction in the vitreous body may be mediated by a third molecule. In cartilage, “link glycoproteins” have been identified that interact with proteoglycans and hyaluronan.<sup>14</sup> Supramolecular complexes of these glycoproteins are believed to occupy interfibrillar spaces. Bishop<sup>8</sup> has elegantly described the potential roles of type IX collagen chondroitin sulfate chains, hyaluronan, and opticin in the short-range spacing of collagen fibrils and how these mechanisms might break down in aging and disease.

Many investigators believed that hyaluronan–collagen interaction occurs on a “physicochemical” rather than a “chemical” level.<sup>15</sup> Reversible complexes of an electrostatic nature between solubilized collagen and various glycosaminoglycans could, indeed, form because electrostatic binding between the negatively charged hyaluronan and the positively charged collagen likely occurs in vitreous.

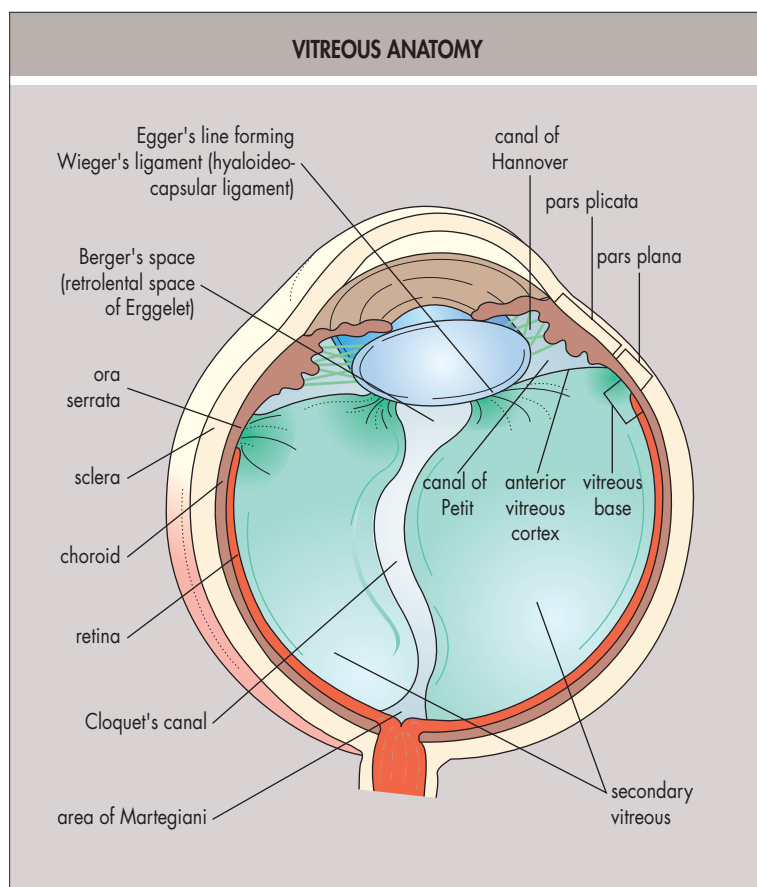
## VITREOUS ANATOMY

### Macroscopic Morphology

In an emmetropic adult human eye, vitreous is approximately 16.5 mm in axial length with a depression anteriorly just behind the lens (patellar fossa). The hyloideocapsular ligament of Weiger is the annular region (1–2 mm in width and 8–9 mm in diameter), where vitreous is attached to the posterior aspect of the lens. Erggelet's or Berger's space is at the center of the hyaloid capsular ligament. The canal of Cloquet arises from this space and courses posteriorly through the central vitreous (Fig. 6.4.3), which is the former site of the hyaloid artery in the embryonic vitreous.<sup>16</sup> The former lumen of the artery is an area devoid of collagen fibrils and surrounded by multifenestrated sheaths that were previously the basal

laminae of the hyaloid artery wall.<sup>4</sup> Posteriorly, Cloquet's canal opens into a funnel-shaped region anterior to the optic disc, known as the *area of Martegiani*.

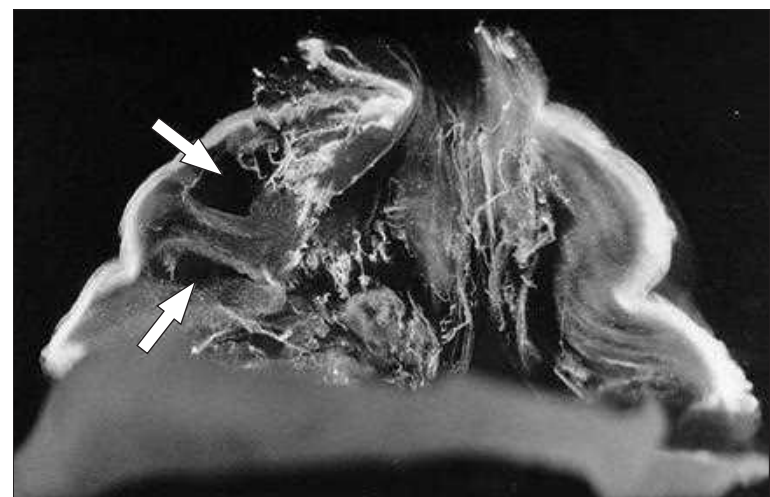
Within the adult human vitreous there are parallel nonbranching fibers that course in an anteroposterior direction (Fig. 6.4.4), arising from the vitreous base, where they insert anterior and posterior to the ora serrata. The connections between the peripheral anterior vitreous fibers and the retina underlie the pathophysiology of retinal tears because of the strong adhesion in this location.<sup>4</sup> The peripheral vitreous fibers are circumferential with the vitreous cortex, whereas the central fibers “undulate” parallel to Cloquet's canal. Ultrastructural studies have demonstrated that collagen, organized in bundles of parallel fibrils, is the only microscopic structure corresponding to these fibers.<sup>3</sup> It is hypothesized that visible vitreous fibers form when hyaluronan molecules no longer separate the microscopic collagen fibrils, which results in the aggregation of collagen fibrils into bundles from which hyaluronan molecules are excluded.<sup>3,4,17</sup> The areas adjacent to these large fibers have a low density of collagen fibrils and a relatively high concentration of hyaluronan molecules. Composed primarily of “liquid vitreous,” these areas scatter very little incident light and, when prominent, constitute the “lacunae” seen with aging (Fig. 6.4.5).



**Fig. 6.4.3** Vitreous anatomy according to classic anatomical and histological studies. (Reprinted with permission from Schepens CL, Neetens A, editors. The vitreous and vitreo-retinal interface. New York: Springer-Verlag; 1987:20.)

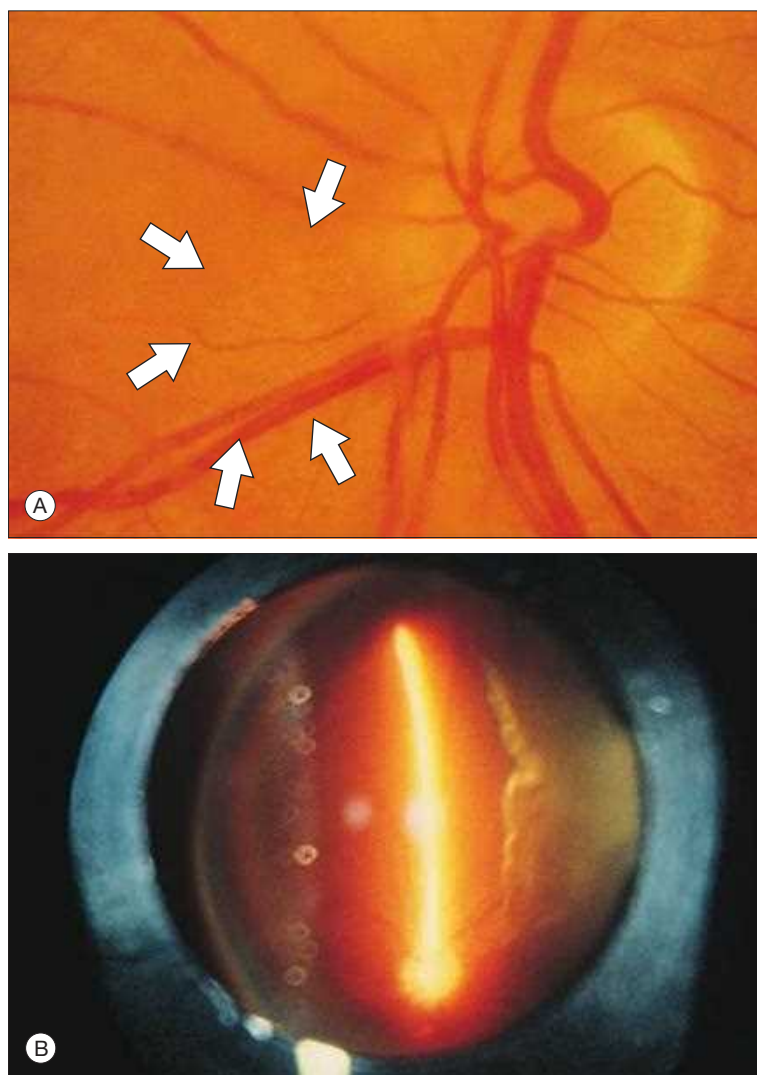


**Fig. 6.4.4** The Eye of a 57-Year-Old Man After Dissection of the Sclera, Choroid, and Retina, With the Vitreous Still Attached to the Anterior Segment. The specimen was illuminated with a slit-lamp beam shone from the side, and the view here is at a 90° angle to this plane to maximize the Tyndall effect. The anterior segment is below and the posterior pole is at the top of the photograph. Bundles of prominent fibers course anteroposteriorly to exit via the premacular dehiscence in the vitreous cortex.



**Fig. 6.4.5** Human Vitreous in Old Age. The central vitreous has thickened, tortuous fibers. The peripheral vitreous has regions devoid of any structure, which contain liquid vitreous. These regions correspond to “lacunae,” as seen clinically using biomicroscopy (arrows).





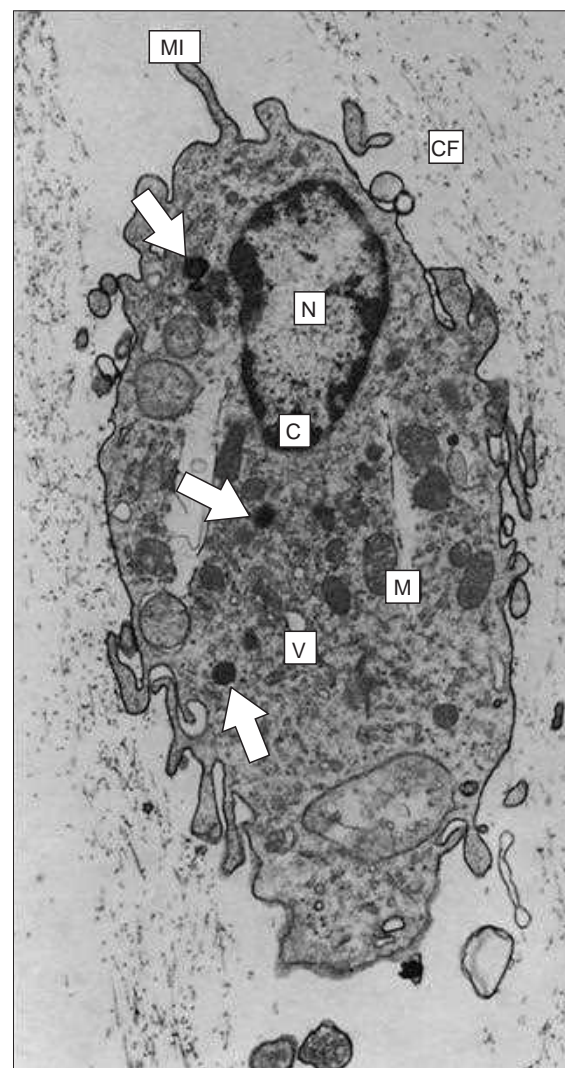
**Fig. 6.4.6 Fundus View of Posterior Vitreous Detachment.** (A) The posterior vitreous in the left eye of this patient is detached, and the prepapillary hole in the posterior vitreous cortex is anterior to the optic disc (*arrows, slightly below and to the left of the optic disc here*). (B) A slit beam illuminates the retina and optic disc (*at bottom*) in the center. To the right is the detached vitreous. The posterior vitreous cortex is the dense, whitish gray, vertically oriented linear structure to the right of the slit beam. (Courtesy C. L. Trempe, MD.)

## Microscopic Morphology

The vitreous cortex is the peripheral “shell” of the vitreous body that courses forward and inward from the anterior vitreous base (anterior vitreous cortex) and posteriorly from the posterior border of the vitreous base, (posterior vitreous cortex). The posterior vitreous cortex is 100–110  $\mu\text{m}$  thick and consists of densely packed collagen fibrils.<sup>4,18</sup> Although no direct connections exist between the posterior vitreous and the retina, the posterior vitreous cortex is adherent to the inner limiting membrane (ILM) of the retina, which is, in part, the basal lamina of retinal Müller cells. Adhesion between the posterior vitreous cortex and the ILM probably results from the action of various extracellular matrix molecules.<sup>19</sup>

A hole in the prepapillary vitreous cortex can sometimes be visualized clinically when the posterior vitreous is detached from the retina (Fig. 6.4.6). If peripapillary tissue is torn away during PVD and remains attached to the vitreous cortex about the prepapillary hole, it is referred to as Weiss’ ring. Vitreous can extrude through the prepapillary hole in the vitreous cortex but does so to a lesser extent than through the premacular vitreous cortex, where, occasionally, vitreomacular adhesion and axial traction can cause vitreomacular traction syndrome.<sup>20</sup> Tangential vitreomacular traction<sup>21</sup> is implicated in the pathogenesis of macular holes and macular pucker,<sup>22</sup> often with vitreoschisis (see below).

Embedded within the posterior vitreous cortex are hyalocytes. These mononuclear phagocytes are spread widely apart in a single layer situated 20–50  $\mu\text{m}$  from the ILM of the retina. The highest density of hyalocytes is in the vitreous base, followed next by the posterior pole, with the lowest density at the equator. Hyalocytes are oval or spindle shaped, 10–15  $\mu\text{m}$  in



**Fig. 6.4.7 Ultrastructure of Human Hyalocyte.** A mononuclear cell is embedded within the dense collagen fibril (CF) network of the vitreous cortex. There is a lobulated nucleus (N) with a dense marginal chromatin (C). In the cytoplasm, there are mitochondria (M), dense granules (*arrows*), vacuoles (V), and microvilli (MI). (Courtesy Joe Craft and D. M. Albert, MD.)

diameter, and contain a lobulated nucleus, a well-developed Golgi complex, smooth and rough endoplasmic reticula, many large lysosomal granules (periodic acid–Schiff positive), and phagosomes (Fig. 6.4.7). Balazs<sup>10</sup> pointed out that hyalocytes are located in the region of highest hyaluronan concentration and suggested that these cells are responsible for hyaluronan synthesis. Hyalocyte capacity to synthesize collagen was first demonstrated by Newsome et al.<sup>23</sup> Similar to chondrocyte metabolism in the joint, hyalocytes may synthesize vitreous collagen at some, but not all, times during life. The phagocytic capacity of hyalocytes is consistent with the presence of pinocytotic vesicles and phagosomes and the presence of surface receptors that bind immunoglobulin G and complement.<sup>18</sup> It is intriguing to consider that hyalocytes are among the first cells to be exposed to any migratory or mitogenic stimuli during various disease states, particularly proliferative vitreoretinopathy. These cells may, therefore, be important in the pathophysiology of proliferative disorders at the vitreous–retinal interface, including macular pucker.<sup>24</sup>

The vitreo–retinal interface is not only important as the site of many tractional and proliferative vitreoretinal disorders<sup>25</sup> but also impacts therapeutics. Pharmacologic vitreolysis of vitreoretinal adhesion<sup>26–28</sup> as well as drug delivery to the macula<sup>29</sup> and transretinal gene therapies via viral vectors that must traverse this interface are influenced by the underlying anatomy and biochemistry of the vitreous–retinal interface.<sup>30</sup> The basal laminae surrounding the vitreous body are composed of type IV collagen closely associated with glycoproteins.<sup>18,30</sup>

At the pars plana, the basal lamina has a true lamina densa. The basal lamina posterior to the ora serrata is the ILM of the retina. The layer immediately adjacent to the Müller cell is a lamina rara, which is 0.03–0.06  $\mu\text{m}$  thick. The lamina densa is thinnest at the fovea (0.01–0.02  $\mu\text{m}$ ) and disc (0.07–0.1  $\mu\text{m}$ ). It is thicker elsewhere in the posterior pole (0.5–3.2  $\mu\text{m}$ )

than at the equator or vitreous base.<sup>4,18</sup> The anterior surface (vitreous side) of the ILM is normally smooth, whereas the posterior aspect is irregular, filling the spaces created by the irregular subjacent nerve fiber layer. This feature is most marked at the posterior pole, whereas in the periphery both the anterior and posterior aspects of the ILM are smooth. The significance of this topographical variation is not known. At the rim of the optic disc the ILM ceases, although the basal lamina continues as the “inner limiting membrane of Elschnig.”<sup>31</sup> This membrane is 50 microns thick and is believed to be the basal lamina of the astroglia in the papilla. At the central-most portion of the optic disc, the membrane thins to 20 microns, follows the irregularities of the underlying cells of the optic nerve head, and is composed only of glycosaminoglycans with no collagen.<sup>31</sup> This structure is known as the *central meniscus of Kuhnt*. The thinness and chemical composition of these membranes may account for, among other phenomena, the frequency with which abnormal cell proliferation arises from or near the optic disc in proliferative diabetic retinopathy and macular pucker.

The vitreous body is most firmly attached at the vitreous base, disc, and macula and over retinal blood vessels. The posterior aspect (retinal side) of the ILM demonstrates irregular thickening farther posteriorly from the ora serrata.<sup>4,18,30</sup> So-called attachment plaques between the Müller cells and the ILM have been described in the basal and equatorial regions of the fundus but not in the posterior pole, except for the fovea.<sup>4,18,30</sup> It has been hypothesized that these develop in response to vitreous traction on the retina. The thick ILM in the posterior pole dampens the effects of this traction, except at the fovea, where the ILM is thin. The thinness of the ILM and the purported presence of attachment plaques at the central macula could explain the predisposition of this region to changes induced by traction. An unusual vitreous–retinal interface overlies retinal blood vessels. Physiologically, this may provide a shock-absorbing function to dampen arteriolar pulsations. However, pathologically, this arrangement could also account for the proliferative and hemorrhagic events that are associated with vitreous traction on retinal blood vessels.

## AGE-RELATED CHANGES

### Embryology and Postnatal Development

Early in embryogenesis, the vitreous is filled with blood vessels, called the *vasa hyaloidea propria*. It is not known what stimulates regression of this hyaloid vascular system, but recent studies have identified significant changes in the proteome of the human embryo that may underlie the process of vascular regression.<sup>31</sup> Teleologically, this seems necessary not only to induce regression of the vascular primary vitreous but also to inhibit subsequent cell migration and proliferation and thereby minimize light scatter and achieve transparency. Identifying the phenomena inherent in this transformation may reveal how to control pathological neovascularization in the eye and elsewhere. Recent studies<sup>32</sup> have characterized the proteomic profile of embryonic human vitreous during hyaloid vessel regression in an attempt to identify the factors that might create and maintain a clear vitreous. These studies found that there is upregulation of certain pathways with concurrent downregulation of others. These findings may, thus, have relevance to developing new therapeutic strategies to induce the regression of pathological neovascularization in ocular and systemic diseases, such as metastatic carcinoma.

### Developmental Anomalies

Persistent fetal vasculature (PFV) syndrome is an uncommon developmental anomaly in which the hyaloid vasculature of the primary vitreous fails to involute. This condition was initially described in detail by Reese<sup>33</sup> in his 1955 Jackson Memorial Lecture, where he named it *persistent hyperplastic primary vitreous*. The subject was revisited by Goldberg<sup>34</sup> in his 1997 Jackson Memorial Lecture, where he coined the term *PFV*.

There is a spectrum of PFV severity, ranging from pupillary strands and a Mittendorf's dot to a dense retrolenticular membrane and/or retinal detachment. Anterior PFV consists of retrolenticular fibrovascular tissue that attaches to the ciliary processes and draws them centrally, inducing cataract formation, shallowing of the anterior chamber, and angle-closure glaucoma. Iris vessel engorgement and recurrent intraocular hemorrhage can result in phthisis bulbi, although the prognosis with surgery is often fair.<sup>35</sup> Posterior PFV consists of a prominent vitreous fibrovascular stalk that emanates from the optic nerve and courses anteriorly. Preretinal membranes at the base of the stalk are common, often with tractional retinal folds and traction retinal detachment. The prognosis for posterior PFV is poor, suggesting that pharmacotherapy may be the only solution for

this form of PFV. In this regard, it has recently been proposed that insufficient levels of vitreous endostatin may be important in the pathogenesis of PFV,<sup>36</sup> consistent with the aforementioned proteomic studies.<sup>32</sup>

Improper vitreous biosynthesis during embryogenesis underlies a variety of developmental abnormalities.<sup>37</sup> Normal vitreous biosynthesis requires normal retinal development because at least some of the vitreous structural components are synthesized by retinal Müller cells.<sup>23</sup> A clear gel, typical of normal “secondary vitreous,” appears only over developed retina. Thus in various developmental anomalies, such as retinopathy of prematurity (ROP), familial exudative vitreoretinopathy, and related entities, vitreous that overlies undeveloped retina in the peripheral fundus is a viscous liquid but not a gel.<sup>37</sup> The extent of this finding depends, at least in ROP, on the gestational age at birth because the younger the individual, the more undeveloped is the peripheral retina, especially temporally. In other truly congenital conditions, there are inborn errors of collagen metabolism that have now been elucidated. In Stickler's syndrome, defects in specific genes have been associated with particular phenotypes, thus enabling the classification of patients with Stickler's syndrome into four subgroups.<sup>38</sup> Patients in the subgroups with vitreous abnormalities are found to have defects in the genes coding for type II procollagen and type V/XI procollagen.

Ongoing synthesis of both collagen and hyaluronan occurs during development to adulthood,<sup>4</sup> and hyaluronan stabilizes the collagen network.<sup>10,11</sup>

### Aging of the Vitreous Body

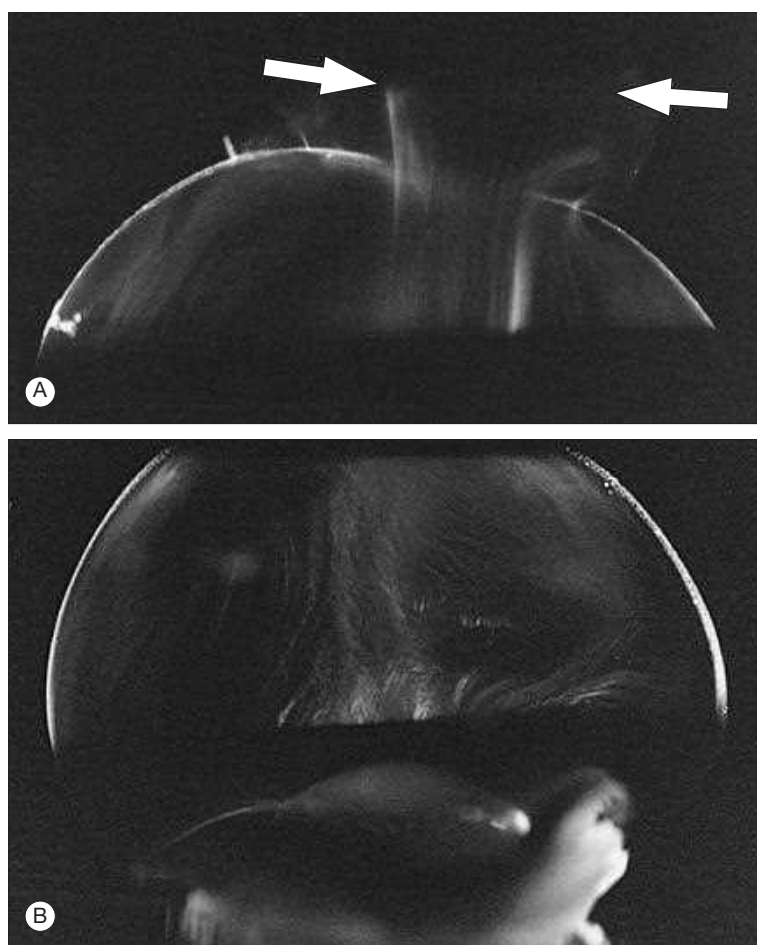
Substantial rheological, biochemical, and structural alterations occur in vitreous during aging.<sup>39–41</sup> After age 45–50 years, there is a significant decrease in the gel volume and an increase in the liquid volume of human vitreous. These findings were confirmed qualitatively in postmortem studies of dissected human vitreous, and liquefaction was observed to begin in the central vitreous.<sup>1,4–6</sup> Vitreous liquefaction actually begins much earlier than detectable by clinical examination or ultrasonography. Postmortem studies have found evidence of liquid vitreous at age 4 years and have observed that by the time the human eye reaches its adult size (ages 16–18 years) approximately 20% of the total vitreous volume consists of liquid vitreous.<sup>40</sup> In these studies of fresh, unfixed postmortem human eyes, it was observed that after age 40 years, there is a steady increase in liquid vitreous, simultaneous with a decrease in gel volume. By age 80–90 years, more than half the vitreous body is liquid. The finding that the central vitreous is where fibers are first observed is consistent with the concept that breakdown of the normal hyaluronan–collagen association results in simultaneous vitreous liquefaction and aggregation of collagen fibrils into bundles of parallel fibrils, seen as large fibers (see Fig. 6.4.4).<sup>1,4–6</sup> In the posterior vitreous, such age-related changes often form large pockets of liquid vitreous, recognized clinically as lacunae, or pockets.<sup>4–6</sup>

The mechanism of vitreous liquefaction is not well understood. Gel vitreous can be liquefied in vivo through the removal of collagen by exogenous enzymatic destruction of the collagen network.<sup>42</sup> It has also been shown that the injection of chondroitinase can induce liquefaction and “disinsertion” of the vitreous.<sup>43</sup> Ocriplasmin is another agent that can induce vitreous liquefaction.<sup>26–28,44</sup> Because of its ability to also induce dehiscence at the vitreous–retinal interface,<sup>45</sup> this agent received approval for pharmacological vitreolysis.<sup>27,28</sup>

Endogenous vitreous liquefaction may be the result of changes in the minor glycosaminoglycans and chondroitin sulfate profile of vitreous.<sup>4,8,10</sup> Another possible mechanism is a change in the conformation of hyaluronan molecules with aggregation or cross-linking of collagen molecules. Singlet oxygen can induce conformational changes in the tertiary structure of hyaluronan molecules. Free radicals generated by metabolic and photosensitized reactions could alter hyaluronan and/or collagen structure and trigger a dissociation of collagen and hyaluronan molecules, which ultimately results in liquefaction.<sup>46</sup> This is plausible because the cumulative effects of a lifetime of daily exposure to light may influence the structure and interaction of collagen and hyaluronan molecules by the proposed free radical mechanism(s).

Biochemical studies support the rheological observations. Total vitreous collagen content does not change after age 20–30 years. However, in studies of a large series of normal human eyes obtained at autopsy, the collagen concentration in the gel vitreous at age 70–90 years (approximately 0.1 mg/mL) was twofold greater than at age 15–20 years (approximately 0.05 mg/mL).<sup>4,40</sup> Because the total collagen content does not change, this finding most likely reflects the decrease in the volume of gel vitreous that occurs with aging and consequent increase in the concentration of the collagen that remains in the gel. The collagen fibrils in aging vitreous gel





**Fig. 6.4.8 Vitreous Structure in Childhood.** (A) The posterior and central vitreous in a 4-year-old child has a dense vitreous cortex with hyalocytes. A substantial amount of vitreous extrudes into the retrocortical (preretinal) space through the premacular vitreous cortex (arrows). However, no fibers are present in the vitreous. (B) Central vitreous structure in an 11-year-old child has hyalocytes in a dense vitreous cortex. No fibers are seen within the vitreous body.

become packed into bundles of parallel fibrils,<sup>3,17</sup> likely with cross-links between them. In patients with diabetes, abnormal collagen cross-links have been identified in the vitreous body, a phenomenon that has been described for other extracellular matrices in patients with diabetes. These findings are consistent with the existence of a diabetic vitreopathy,<sup>47</sup> independent of diabetic retinopathy. The structural effect of these biochemical and rheological changes consists of a transition from a clear vitreous in youth (Fig. 6.4.8), to a fibrous structure in the adult (see Fig. 6.4.4), which results from aggregation of collagen fibrils.<sup>3,4</sup> In patients with diabetes, this occurs earlier in life because of nonenzymatic glycation of vitreous collagen.<sup>47</sup> In old age, advanced liquefaction (synchysis; see Fig. 6.4.5) ultimately leads to collapse (syneresis) of the vitreous and posterior vitreous detachment (PVD).<sup>39</sup>

The vitreous base posterior to the ora increases in size with advancing age to nearly 3 mm, bringing the posterior border of the vitreous base closer to the equator.<sup>48</sup> This widening of the vitreous base was found to be most prominent in the temporal portion of the globe. The posterior migration of the vitreous base probably plays an important role in the pathogenesis of peripheral retinal breaks and rhegmatogenous retinal detachment. Within the vitreous base, a “lateral aggregation” of the collagen fibrils is present in older individuals,<sup>49</sup> similar to aging changes within the central vitreous.<sup>4,17,39,41</sup> Studies<sup>50</sup> have confirmed posterior migration of the posterior border of the vitreous base during aging and also demonstrated intra-retinal synthesis of collagen fibrils that penetrate the ILM of the retina and “splice” with vitreous collagen fibrils. These aging changes at the vitreous base could contribute to increased traction on the peripheral retina promoting retinal tears and detachment.

## Posterior Vitreous Detachment

The most common age-related event in the vitreous body is PVD,<sup>39</sup> defined as separation between the posterior vitreous cortex and the ILM of the

retina. PVD can be localized, partial, or total (up to the posterior border of the vitreous base). Autopsy studies have revealed that the incidence of PVD is 63% by the eighth decade,<sup>51</sup> but more commonly in myopic eyes, where PVD occurs, on average, 10 years earlier than in emmetropic and hyperopic eyes. Cataract extraction in myopic eyes introduces additional effects that promote PVD.<sup>4</sup>

Vitreous liquefaction in conjunction with weakening of vitreoretinal adhesion both result in PVD. It is likely that the dissolution of the posterior vitreous cortex–ILM adhesion at the posterior pole allows liquid vitreous to enter the retrocortical space via the prepapillary hole and perhaps also the premacular vitreous cortex. With rotational eye movements, liquid vitreous can dissect a plane between the vitreous cortex and the ILM, resulting in true PVD. This volume displacement from the central vitreous to the preretinal space causes vitreous syneresis (collapse).

Johnson<sup>39</sup> has proposed that this process of hydrodissection follows a 5-stage (0–4) sequence that is influenced by variations in vitreoretinal adhesion. Stage 0 is complete attachment throughout the fundus. Stage 1 involves detachment of the perifoveal posterior vitreous cortex, probably because this is the area where the liquefied gel first gains access to the retrocortical/preretinal space. There is persistent vitreofoveal adhesion at stage 1. A 500- $\mu$ m diameter area of strong vitreoretinal adhesion in the foveola does not detach until stage 2, at which time there is complete macular separation. In stage 3, there is PVD involving the entire retina except for the vitreopapillary zone, a site of strong vitreoretinal adhesion and thus is the last site of vitreoretinal separation. In stage 4, there is release of the vitreopapillary adhesion and total PVD. It is this last stage that is most often symptomatic.

In 1935, Moore<sup>52</sup> described “light flashes” as a common complaint that results from PVD. Wise<sup>53</sup> noted that light flashes occurred in 50% of cases at the time of PVD; they were usually vertical and temporally located. Voerhoeff<sup>54</sup> suggested that the light flashes result from the impact of the detached posterior vitreous cortex on the retina during eye movement.

“Floaters” are a symptom experienced by patients with PVD. These result from entopic phenomena caused by condensed vitreous fibers, glial tissue of epipapillary origin that adheres to the posterior vitreous cortex, the dense collagen matrix of the posterior vitreous cortex,<sup>4</sup> or less commonly intravitreal blood. Vitreous floaters move with vitreous displacement during eye movement and scatter incident light, which casts a shadow on the retina that is perceived as a gray, “hair-like” or “fly-like” structure. Given time, symptomatic floaters often become less noticeable. Treatment of symptomatic floaters can be performed. YAG laser treatments are performed by some practitioners.<sup>55</sup> There is only evidence for improvement following YAG laser treatments for Weiss’ ring, not other vitreous opacities. Limited vitrectomy can safely and effectively cure the condition (see below).

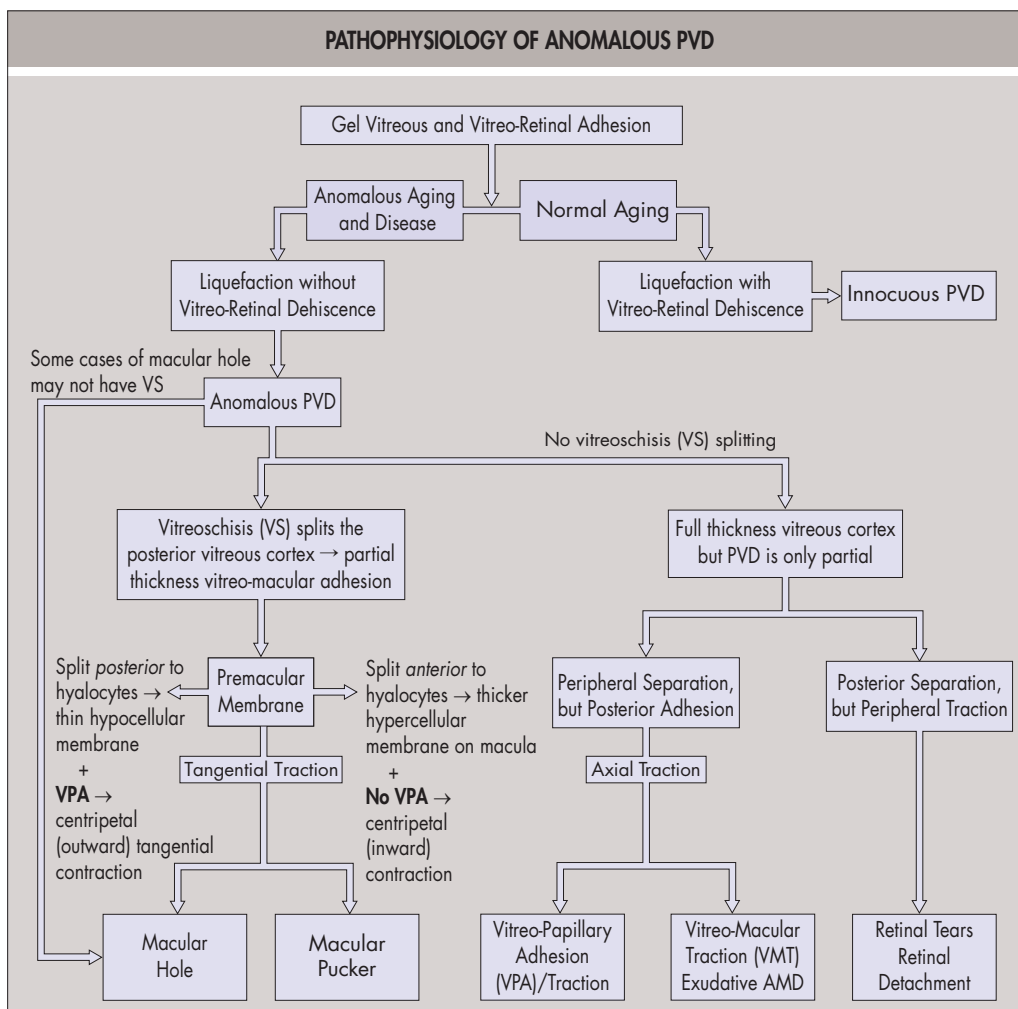
## Anomalous Posterior Vitreous Detachment

Anomalous posterior vitreous detachment<sup>56</sup> occurs when there is extensive vitreous liquefaction without concurrent weakening of vitreoretinal adhesion, resulting in traction at the vitreous–retinal interface. There are various causes for an imbalance between the degree of gel liquefaction and weakening of vitreoretinal adhesion. As described above, inborn errors of collagen metabolism, such as those present in Marfan’s syndrome, Ehlers–Danlos syndrome, and Stickler’s syndrome,<sup>38</sup> result in extensive gel liquefaction at an early age when there is still considerable vitreoretinal adhesion. The result is a high incidence of large posterior retinal tears and detachments. Systemic conditions, such as diabetes induce biochemical<sup>57</sup> and structural<sup>58</sup> alterations in vitreous, known as *diabetic vitreopathy*,<sup>47</sup> which are important in the pathobiology of proliferative diabetic vitreoretinopathy and diabetic macular edema. However, the overwhelming majority of cases are likely caused by an as-yet-unidentified genetic predisposition for firm vitreoretinal adhesion, probably related to the extracellular matrix between vitreous and the retina. Fig. 6.4.9 delineates the various deleterious effects of anomalous PVD.

When the entire (full-thickness) posterior vitreous cortex separates from the macula but is still attached peripherally, there can be vitreoretinal traction causing peripheral retinal tears and detachments. Autopsy studies have found that PVD is associated with retinal breaks in 14.3% of all cases. Patients without diabetes who experience nontraumatic vitreous hemorrhage have retinal tears in up to 67% of cases<sup>59</sup> and retinal detachments in up to 39%<sup>59</sup> of cases.

Posterior full-thickness vitreomacular adhesion with peripheral vitreoretinal separation can pull on the macula and induce vitreomacular traction syndrome. Persistent vitreomacular adhesion may exacerbate age-related





**Fig. 6.4.9 Schematic of Anomalous Posterior Vitreous Detachment.** Vitreous gel liquefaction without concurrent dehiscence at the vitreous–retinal interface causes various anomalies. If separation of vitreous from retina is full-thickness in the axial plane but incomplete in the coronal plane, there can be different forms of partial posterior vitreous detachment (PVD) (right side of diagram). Posterior separation with persistent peripheral attachment can induce retinal breaks and detachments. Peripheral vitreoretinal separation with persistent full-thickness vitreomacular adhesion (VMA) can induce vitreomacular traction syndrome (VMTS). VMA is associated with exudative age-related macular degeneration (Exud AMD) and diabetic macular edema. Persistent attachment to the optic disc can induce vitreopapillopathies and also contribute to neovascularization and vitreous hemorrhage in ischemic retinopathies as well as play a role in macular hole pathophysiology. During PVD, if the posterior vitreous cortex splits (vitreoschisis) anterior to the level of the hyalocytes, a relatively thick, cellular membrane remains attached to the macula. If there is also separation from the optic disc, inward (centripetal) contraction induces macular pucker. If the split is posterior to the hyalocytes, the remaining premacular membrane is relatively thin and hypocellular. Persistent vitreopapillary adhesion (present in 87.5% of cases) results in outward (centrifugal) tangential traction (especially nasally), inducing a macular hole. (From Sebag J. Anomalous PVD—a unifying concept in vitreo-retinal diseases. *Graefes Arch Clin Exp Ophthalmol* 2004;242:690–8; Sebag J. Vitreous and vitreo-retinal interface. In: A. Schachar, editor. *Ryan's Retina*. London: Elsevier; 2018, Ch 23, pp 544–581.)

macular degeneration (AMD). It is not clear by what mechanism this occurs, but patients with dry AMD have a two- to threefold higher prevalence of total PVD, whereas patients with wet AMD have a three- to fourfold higher prevalence of vitreomacular adhesion,<sup>60–62</sup> but these conditions were not influenced by genetic or environmental factors. It is hypothesized that vitreomacular traction could induce low-grade inflammation and/or that the adherent posterior vitreous cortex could alter macular oxygenation from ciliary body and the egress of proangiogenic cytokines from the macula. Similarly, traction on the optic disc can induce vitreopapillary traction syndromes<sup>63</sup> or exacerbate neovascularization with vitreous hemorrhage in proliferative diabetic retinopathy. Moreover, persistent vitreopapillary adhesion may promote macular hole formation as opposed to macular pucker.<sup>64,65</sup>

Anomalous PVD can be associated with splitting of the posterior vitreous cortex, called *vitreoschisis*.<sup>66</sup> This may be the first event in macular pucker and some cases of macular hole pathogenesis.<sup>67,68</sup> Vitreoschisis may also be present in diabetic macular edema.<sup>69</sup> Autopsy studies<sup>70</sup> have reported that PVD was associated with vitreous cortex remnants at the fovea in 26 of 59 (44%) human eyes. Recent studies<sup>67,68</sup> employing combined optical coherence tomography and scanning laser ophthalmoscopy imaging detected vitreoschisis in about half the patients with macular pucker and macular holes.

### Premacular (Epiretinal) Membrane/Macular Pucker

The term *epiretinal membrane* (ERM) is a misnomer. The prefix “epi” means adjacent to, so this could refer to subretinal membranes. The premacular membrane (PMM) that causes macular pucker contains astrocytes and retinal pigment epithelial (RPE) cells<sup>80</sup> as well as hyalocytes. Macular pucker begins when vitreoschisis (Fig. 6.4.9) splits the posterior vitreous cortex anterior to hyalocytes leaving a cellular membrane attached to the macula. Contraction is stimulated by connective tissue growth factor.<sup>24</sup> Recent studies<sup>81</sup> have also identified that nearly half of all eyes with macular pucker have more than one site of retinal contraction associated with a higher incidence of intraretinal cysts and significantly more macular

thickening.<sup>81</sup> Following anomalous PVD with vitreoschisis, the PMM can contract inward toward the fovea (centripetal tangential traction) and cause visual impairment and metamorphopsia, sometimes necessitating surgery (see Chapter 6.33).<sup>71</sup>

### Macular Holes

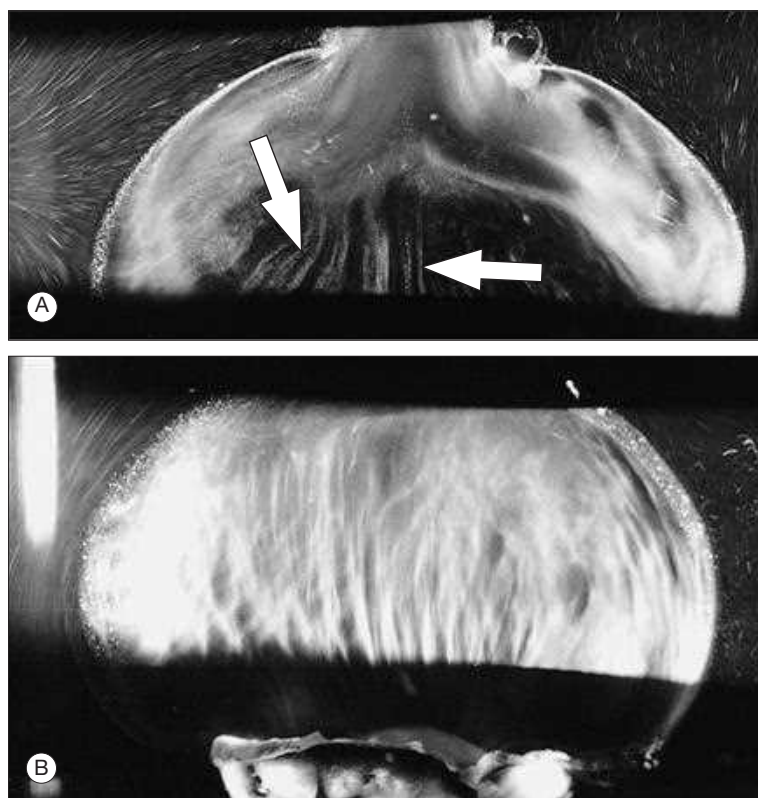
Primary full-thickness macular holes (FTMHs) are caused by anomalous PVD with centrifugal (outward) tangential traction of the PMM accentuated by vitreo-papillary adhesion (Fig. 6.4.9). Secondary macular holes can occur from conditions such as blunt trauma, and lightning strike.

Lamellar macular holes are partial-thickness retinal defects that most commonly occur in association with a thickened posterior premacular membrane (LHEP) in degenerative LMH, or a PMM with pucker in tractional LMH. The prevalence of VPA is greater in the latter than the former (see Chapter 6.32).<sup>82</sup>

### Diabetic Vitreopathy

In diabetes, there is an increase in vitreous glucose levels<sup>72</sup> associated with increased advanced glycation end products.<sup>47,57</sup> In poorly controlled diabetes, fluctuations in systemic glucose levels alter the ionic milieu, influencing vitreous osmolarity and hydration. This could result in swelling and contraction of the entire vitreous body via effects on the very hydrophilic hyaluronan molecules, with consequent traction on structures attached to the posterior vitreous cortex, such as new blood vessels from the optic disc and/or retina.<sup>73</sup> These events could promote the proliferation of neovascular fronds and perhaps even induce rupture of these new vessels with vitreous hemorrhage.

Molecular effects of diabetes result in morphological changes within the vitreous body<sup>47,58</sup> (Fig. 6.4.10). The roles of these and other pathological changes, such as posterior vitreoschisis,<sup>66,69</sup> may lead to therapy designed to inhibit diabetic vitreopathy. Alternatively, the induction of innocuous PVD early in the course of diabetic retinopathy may have long-term salutary effects in patients at great risk.<sup>26–28</sup>



**Fig. 6.4.10 Diabetic Vitreopathy.** (A) Right eye of a 9-year-old girl who has a 5-year history of type 1 diabetes shows extrusion of central vitreous through the posterior vitreous cortex into the retrocortical (preretinal) space. The subcortical vitreous appears very dense and scatters light intensely. Centrally, there are vitreous fibers (arrows) with an anteroposterior orientation and adjacent areas of liquefaction. (B) Central vitreous in the left eye of the same patient shows prominent fibers that resemble those seen in adults without diabetes (see Fig. 6.4.5). (Reprinted with permission from Sebag J. Abnormalities of human vitreous structure in diabetes. *Graefes Arch Clin Exp Ophthalmol* 1993;231:257–60.)

## Asteroid Hyalosis

This generally benign condition is characterized by small, yellow-white, spherical opacities throughout the vitreous body. An autopsy study<sup>74</sup> of 10801 eyes found an incidence of 1.96%; with a male/female ratio of 2:1. Asteroid hyalosis is unilateral in greater than 75% of cases. Asteroid bodies are associated intimately with the vitreous gel and move with vitreous displacement during eye movement, suggesting a relationship with age-related collagen fibril degeneration.<sup>74</sup> However, PVD, either complete or partial, occurs less frequently in individuals with asteroid hyalosis than in age-matched controls,<sup>75</sup> and this finding does not support age-related degeneration as a cause. Histological studies demonstrate a crystalline appearance and a pattern of positive staining to fat and acid mucopolysaccharide stains that is not affected by hyaluronidase pretreatment.<sup>76</sup> Electron diffraction studies have shown the presence of calcium oxalate monohydrate and calcium hydroxyphosphate. Ultrastructural studies have revealed

intertwined ribbons of multilaminar membranes (with a 6-nm periodicity), which are characteristic of complex lipids, especially phospholipids, that lie in a homogeneous background matrix.<sup>77</sup> In these investigations, energy-dispersive X-ray analysis showed calcium and phosphorus to be the main elements in asteroid bodies. Electron diffraction structural analysis demonstrated calcium hydroxyapatite and possibly other forms of calcium phosphate crystals.

Some reports have suggested an association between asteroid hyalosis and diabetes mellitus,<sup>78–81,83</sup> whereas other investigations found no such association.<sup>84</sup> Asteroid hyalosis appears to be associated with certain pigmentary retinal degenerations,<sup>83</sup> although it is not known whether this is related to the presence of diabetes in these patients. Yu and Blumenthal<sup>85</sup> proposed that asteroid hyalosis results from aging collagen, whereas other studies<sup>86</sup> have suggested that asteroid formation is preceded by depolymerization of hyaluronan.

The most interesting aspect of asteroid hyalosis is the marked absence of patient complaints and symptoms. Although it can be difficult, in some cases, to examine and image the fundus, these patients often experience no visual disturbances, whereas patients with PVD can be markedly symptomatic.<sup>87,88</sup> It is hypothesized that the explanation is related to the smooth surfaces of asteroid bodies that may not scatter light in as disturbing a fashion as the irregular surfaces of the collagen matrix in the detached posterior vitreous cortex and/or the collagen fibrils of the vitreous body.<sup>3,4,17,39</sup> The condition of “Vision Degrading Myodesopsia” can be safely cured with limited vitrectomy that normalizes contrast sensitivity function.<sup>89</sup>

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# Contact B-Scan Ultrasonography

Yale L. Fisher, Dov B. Sebrew

# 6.5



**Definition:** Diagnostic technique that is useful in the evaluation of intraocular and orbital contents.

## Key Features

- High-frequency sound waves are emitted and received by a handheld transducer probe.
- Images are processed and displayed on a video monitor.

## Associated Features

- Adequate interpretation for diagnosis of posterior segment disease depends on three concepts:
  - Real time.
  - Gray scale.
  - Three-dimensional analysis.

## INTRODUCTION

Ophthalmic ultrasonography is a useful diagnostic technique for intraocular and orbital evaluation, especially in the setting of opaque media. It involves pulse-echo technology, in which high frequency sound waves are emitted from a handheld transducer probe. Returning echoes are processed and displayed on video monitors or oscilloscopes.

Two modes of display are common:

- A-scan mode (time-amplitude), used predominantly for interpretation of tissue reflectivity—the returning echoes form a graph-like image seen as vertical deflections from a baseline.

- B-scan mode (intensity modulation), used predominantly for anatomical information—it shows cross-sectional images of the globe and orbit.

Both types of sonographic display are complementary. This chapter focuses on B-scan information.

Developed in the mid-1950s with water-immersion techniques, B-scan ultrasonography initially required a laboratory setting. In the early 1970s, contact devices utilizing methylcellulose or a similar sound-coupling agent were introduced, and this rapidly increased the availability and popularity of B-scan ultrasonography. Subsequent improvements in image quality and scanning rates made interpretation easier for the examiner.<sup>1-8</sup>

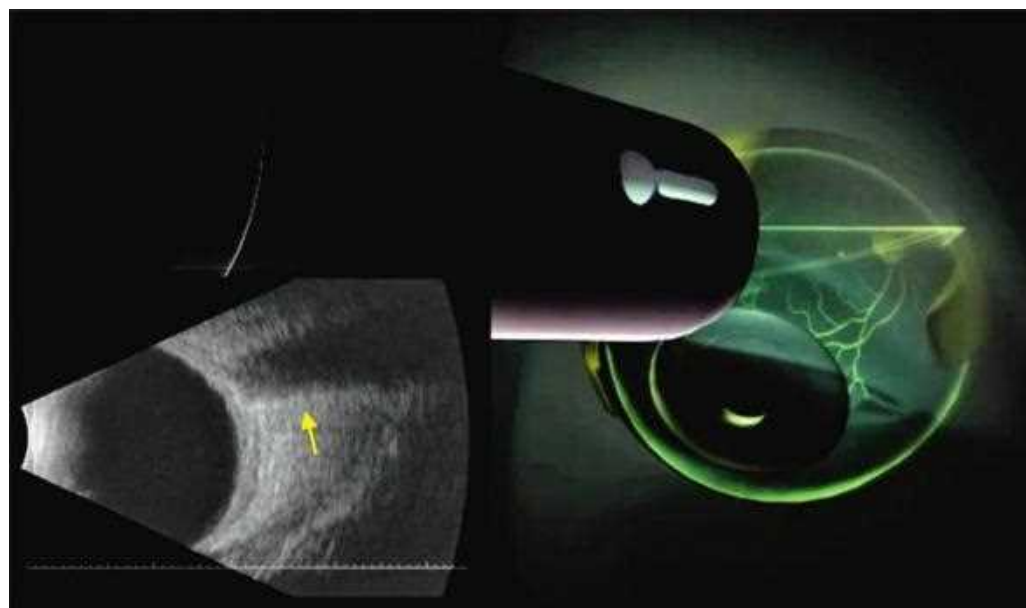
## DEVICES

Commercially available instruments for ocular and orbital contact B-scan ultrasonography usually employ 10-MHz (megahertz; megacycles per second) handheld transducer probes. A motor within the handpiece moves the ultrasonic source in a rapid sector scan to create cross-sectional B-scan images. These devices have resolution capacities of approximately 0.15 mm axially and 0.3 mm laterally. Most contact B-scan machines are freestanding and relatively mobile; they consist of a detachable transducer probe, a signal-processing box, and a display screen. Self-contained processing probes, which are capable of integrating with independent computer laptops or desktop units, are also available. (Video 6.5.1)



## TECHNIQUE OF EXAMINATION

The handheld ultrasonic probe is placed gently against the eyelid or sclera by using a sound-coupling agent, such as methylcellulose or, preferably, heat-sensitive ophthalmic gel. The ultrasonographer can move the probe systematically to scan the globe and orbit. Avoiding the lens system of the globe is important to prevent image artifacts (Fig. 6.5.1).



**Fig. 6.5.1** Illustration demonstrating placement of handheld ultrasonic probe and corresponding B-scan image with optic nerve (arrow) as reference point. (Additional material for ultrasound education available at <http://www.OphthalmicEdge.org>.)

## CONCEPTS OF B-SCAN INTERPRETATION

Interpretation of a B-scan ultrasonogram depends on three concepts:

- Real time.
- Gray scale.
- Three-dimensional analysis.

### Real Time

Ultrasound B-scan images are visualized at approximately 32 frames/sec, allowing motion of the globe and vitreous to be detected. Characteristic real-time movements are useful for identifying tissues. Detached retinal movement, for example, appears as a slow undulation, whereas vitreous movements are usually more rapid. Real-time ultrasonic information is often critical to surgical decisions.

### Gray Scale

A variable gray-scale format displays the returning echoes as intensity-modulated dots. Strong echoes, such as those seen from sclera or detached retina, are displayed brightly at high instrument gain and remain visible even when the gain is reduced. Weaker echoes, such as those from vitreous hemorrhage, are seen as lighter shades of gray that disappear when gain is reduced. Because comparison of echo strengths is critical to tissue analysis, the examiner must ensure that all the returning echoes are captured and displayed. Perpendicularity to the object of regard ensures adequate comparable interpretive signals.

### Three-Dimensional Analysis

Developing a mental three-dimensional image or anatomical map from multiple two-dimensional B-scan images is the most difficult concept to master. The examiner must learn to create a mental topographical map of the eye or orbit from as many imaging views as required. Three-dimensional understanding of ultrasound images is especially critical in the preoperative evaluation of complex retinal detachments and intraocular or orbital tumors.

## DISPLAY PRESENTATION AND DOCUMENTATION

Posterior B-scan images displayed on a screen are presented horizontally. Areas closest to the probe are imaged to the left of the screen, and those farthest away are imaged to the right. The top of the screen correlates with a manufacturer's mark located on the examining probe that represents the initial transducer sweep for each sector scan. Registration of the screen is critical to understanding and interpreting examinations. Movement of the probe from one position to another changes the registration, making instant re-evaluation by the examiner an absolute necessity. Contact B-scan ultrasonography is a dynamic examination. Individual "frozen" cross-sectional images used for documentation should not alone be used for interpretation. (Video 6.5.1)



See clip:  
6.5.1

### Normal Vitreous Cavity

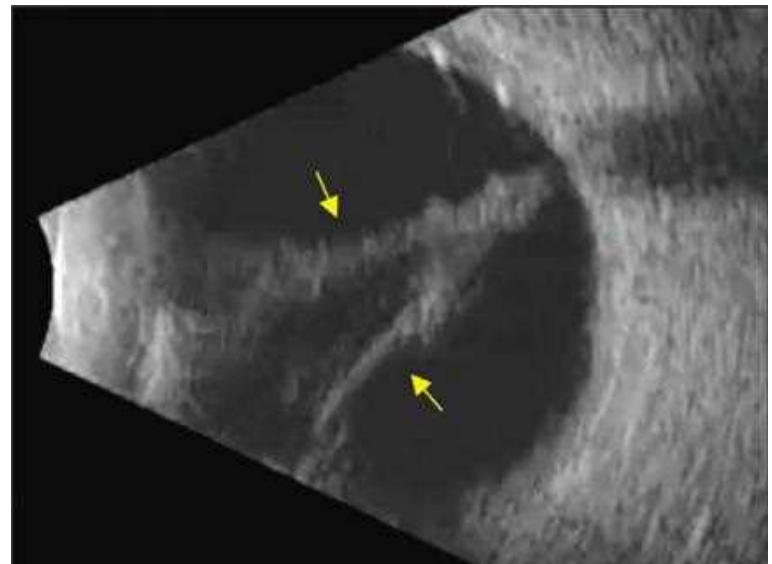
The normal vitreous space is almost clear echogenically. Occasional small dots or linear echoes can be seen at the highest gain settings (90 decibels [dB]), but they fade rapidly as the gain is reduced. Real-time scanning during eye movement usually shows some motion of these fine echoes as well as the position of the vitreous face.

### Vitreous Hemorrhage

Intravitreal hemorrhage produces easily detectable diffuse dots and blob-like vitreous echoes that correlate with the amount of blood present. Reduction of gain to 70 dB results in rapid fading of all but the densest areas of reflectivity. Real-time evaluation usually shows a characteristic rapid motion during command voluntary eye movement.

### Retinal Detachment

Detached retina appears as a highly reflective sheet-like tissue within the vitreous space (Fig. 6.5.2). Small detachments often appear dome-like on



**Fig. 6.5.2 Contact B-Scan Image of a Retinal Detachment.** This axial section of a total retinal detachment reveals a highly reflective sheet-like membrane (arrows) in the vitreous space, detached from the posterior eye wall and attached only to the optic nerve head.

imaging. The appearance of total retinal detachment, which anatomically is cone shaped, varies, depending on the position of the examining probe. Axial images are funnel shaped with attachment to the optic nerve head. Coronal images show a circular cross-section of the cone.

Although recent detachments have a characteristic undulating movement slower than that of the vitreous gel, long-standing detachments appear stiff because of proliferation of scar tissue on the retinal surface.

### Choroidal Detachment

Detached choroid appears smooth and convex on imaging. An elevated dome is usually localized between the pars plana and the posterior equator of the globe. Serous choroidal detachments are echolucent within the suprachoroidal space, whereas hemorrhagic choroidal detachments appear reflective. Clotted blood is highly reflective, whereas liquefied blood is usually less so and more mobile during ocular movement. When severe, the detached choroid can meet at the center of the globe producing retina-to-retina touch, often termed "a kissing choroidal."

A choroidal detachment can be differentiated from a retinal detachment by its location, shape, thickness, and movement.

### Tumors

Evaluation of intraocular tumors requires not only topographical localization but also interpretation of gray-scale characteristics. Malignant choroidal melanomas, for example, have the most characteristic ultrasonic appearance. They are mostly dome shaped or mushroom shaped, and on gray scale, their anterior borders are strongly reflective, whereas the progressively deeper portions of the tumor are less reflective. This is caused by cellular homogeneity that provides a false hollowing appearance. Tissues, such as orbital fat, localized behind these tumors are often shadowed and appear less reflective as a result of absorption of sound by the tumor.

## DIGITAL CONTACT ULTRASONOGRAPHY

Advances in electronic and digital software have made the greatest changes in diagnostic ultrasonography. High-capacity computer memory has revolutionized storage, recall, and transmission of real-time movie segments for documentation and review.

## WHAT'S NEW?

### Anterior Segment High-Frequency Ultrasonography

Although most B-scan focuses on the posterior segment of the globe or the anterior orbit, higher-frequency instruments in the range of 30–100 MHz are available for anterior segment imaging. Penetration of sound at these

frequencies remains limited (approximately 4–5 mm), but resolution is greatly augmented (at 40 MHz: axial 23 microns; lateral 35 microns).

Recent development of digital imaging and specialized software has improved availability of this technology. Furthermore, the examination technique has become less time consuming and more patient friendly, with the introduction of modified, sterile, single-use slip on water condoms covering the exposed and moving transducer.

With a simple adjustment of software, clear images of the anterior segment are now possible. These images can complement posterior segment evaluations, especially in complex scenarios of opaque media and abnormalities behind the iris, within the ciliary body, or involving the pars plana.

Axial, radial, and coronal images in real time are accumulated and stored as easily as posterior segment images.<sup>9</sup>

## SUMMARY

Contact B-scan ultrasonography provides a convenient, noninvasive means for the dynamic examination of the vitreoretinal relationship and the evaluation of intraocular structures in situations where clinical examination is not possible because of opaque media. Three-dimensional and digital technology expands teaching capability and brings the clinical availability of contact ultrasonography to a larger audience. Ultrasound studies should, however, be used in conjunction with detailed clinical examination and other investigational modalities.

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Access the complete reference list online at [ExpertConsult.com](http://www.ExpertConsult.com)



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# Camera-Based Ancillary Retinal Testing: Autofluorescence, Fluorescein, and Indocyanine Green Angiography

6.6

*Eric Feinstein, Jeffrey L. Olson, Naresh Mandava*

**Definition of Fluorescein Angiography:** Fluorescein angiography (FA) is a diagnostic technique that uses intravenous or oral fluorescein dye to allow the sequential visualization of blood flow simultaneously through retinal, choroidal, and iris tissue.<sup>1</sup> Since its introduction, it has been an invaluable aid in the diagnosis, management, and treatment of chorioretinal diseases.<sup>1,2</sup>

## Key Features

- Intravenous or oral dose of fluorescein sodium dye administered.
- Sequential fundus photographs obtained by using a camera equipped with appropriate exciting and absorbing filters or light sources taking advantage of the inherent fluorescent properties of the dye.
- Reflected light captured on either film or as digital images.
- Interpretation of images critically dependent on an understanding of ocular anatomy in both health and disease.
- Indocyanine green dye, administered intravenously, can be an important adjunct to the diagnosis of chorioretinal disease.

**Definition of Indocyanine Green Angiography:** Indocyanine green angiography (ICGA) is a diagnostic technique that exploits indocyanine green (ICG) dye's infrared fluorescence and biochemical properties to adequately portray the characteristics of the choroidal circulation, aiding in the diagnosis of diseases affecting the choroid, such as idiopathic polypoidal choroidal vasculopathy, exudative age-related macular degeneration (AMD), and inflammatory diseases, among others.<sup>3-5</sup>

## Key Features

- Intravenous injection of indocyanine green dye.
- Serial photographs taken with digital imaging system to capture emission for dye.
- Interpretation of resultant images critically dependent on understanding of retinal and choroidal anatomy in health and disease.

**Definition of Fundus Autofluorescence:** Fundus autofluorescence (FAF) is a noninvasive retinal imaging modality used in clinical practice to map out density of lipofuscin within the retinal pigment epithelium (RPE).

## Key Features

- Intrinsic fluorescence emitted by lipofuscin within the RPE after being excited with short to medium wavelength visible light.
- Photographs can be taken with a scanning laser ophthalmoscope (SLO) or standard/wide-field fundus camera.
- Interpretation of resultant images helps to detect and track changes in lipofuscin accumulation, which corresponds to the health and function of the RPE.

## FLUORESCEIN ANGIOGRAPHY

### Introduction

Fluorescein angiography (FA) relies on the special fluorescent property of sodium fluorescein (SF)—defined as the ability of certain molecules to emit light of longer wavelength when stimulated by light of shorter wavelength. After stimulation, electrons return to their base energy level, emitting energy in the form of electromagnetic waves producing visible light.<sup>3-5</sup> The dye has a narrow spectrum of light absorption, with the maximum peak at 490 nm (485–500 nm, blue visible spectrum). Emission (fluorescence) occurs in the yellow-green spectrum with a wavelength of 530 nm (520–535 nm).<sup>3</sup>

A stimulation source transmits light energy to the patient's retina using either a flash/filter or laser in the 485–500 nm range. The energy is then either reflected back by the retina as blue light, or absorbed by the SF and emitted back as green light. A capturing device (camera) uses a green filter (520–535 nm) to selectively save the fluorescent image onto film or a digital surface.

### Purpose of the Test

In normal individuals, the SF molecule freely crosses the wall of highly permeable capillaries (choriocapillaris) but remains within the lumen of retinal and larger choroidal vessels because a good percentage circulates through the blood unbound to plasma proteins. This makes FA the ideal study for evaluating retinal circulation, its vascular architecture, and the status of the inner and outer blood–retinal barrier. Information from the FA can also be used to study the choroidal circulation and retinal pigment epithelial (RPE) cells.<sup>6,7</sup> Vascular diseases, such as diabetic retinopathy, central serous chorioretinopathy, venous occlusive disease, and choroidal neovascularization secondary to age-related macular degeneration (CNV-AMD), can be clearly demonstrated with FA. These images are used to select the appropriate therapeutic approach, guide treatment, and assess therapeutic results.<sup>8</sup>

### Properties of Sodium Fluorescein Dye

SF (sodium resorcinolphathalein) is a yellow-red, synthetic salt dye that is most commonly used to evaluate flow patterns of subterranean waters, as a cosmetic and pharmacological color, and as a labeling agent in protein research.<sup>9</sup> It has a molecular weight of 376.7 kilodaltons (kDa).<sup>10</sup> Once

injected to the bloodstream, approximately 80% of the dye becomes bound to plasma proteins (particularly albumin), and the rest remains unbound.<sup>10</sup> The dye is metabolized by the liver and kidneys and is eliminated in the urine within 24–36 hours of injection. Its most important property for ophthalmological purposes is its fluorescence. It has a narrow spectrum of absorption and excitation that makes the FA technique feasible (see “Introduction”). SF dye is readily available and produced commercially in aliquots of 2–3 mL of 25% or 5 mL of 10% sterile aqueous solution.

## Procedure

A good quality FA is highly dependent on a high-resolution fundus camera, a skilled photographer, and a clear view to the retina.

The spherical refractive error of the patient is corrected by simultaneously focusing the cross-hairs in the eyepieces reticule and the fundus. The focusing wheel is used only for fine focus. Most cameras are equipped with a joystick to help align the camera to the patient's eye. Proper alignment gives even illumination of the fundus, whereas misalignment results in peripheral and central artifacts in the images. This can be ameliorated with careful lateral movements of the joystick. Variable amounts of magnification can usually be selected, depending on the system, and this should be tailored to the pathology being examined.

Pharmacological mydriasis is usually required for most commercially available equipment, but there are a few that do not require it. Before starting the infusion of the dye, a set of baseline red-free images are taken using a green filter. Green light provides excellent contrast and enhances the visibility of the retinal vasculature and vitreous–retinal interface. It is particularly useful in assessing retinal hemorrhages, drusen, epiretinal membranes, and exudates.

The dye is typically injected in the antecubital vein with a 21-gauge butterfly needle in a rapid but controlled infusion ( $\approx 1$  mL/sec) to maximize the contrast of the early filling phase of the angiography.<sup>7,11</sup> Although there is no evidence of increased side effects when using higher concentrations of the dye, many practitioners prefer to use a smaller volume of a more concentrated solution. The two preferred doses are 2.5 mL of a 20% solution and 5 mL of a 10% solution. If the patient is a newborn or premature baby, a 10% solution at a dose of 0.1 mL/kg followed by an isotonic saline flush is recommended.<sup>12</sup> Infusion of the dye can be done from the left or right antecubital vein without changing the times or image qualities. If the patient has undergone mastectomy with lymph node dissection, the dye should probably not be injected in the ipsilateral arm because of the risk of altered lymphatic flow.<sup>9</sup>

Extravasation of the dye should be avoided, as infiltration is painful and may rarely lead to tissue necrosis. A timer is started after injection of the dye, and image acquisition should begin immediately to capture initial choroidal and retinal filling. Photographs are usually taken at 4-second intervals, beginning 15 seconds before injection and continuing with a tapered frequency for 10–20 minutes. However, the timing and the interval between exposures should be adjusted on the basis of the pathology that is being studied. For instance, a choroidal neovascular membrane leaks profusely early in the study; therefore, photographs should be taken with more frequency at the beginning of the study to capture the details of the membrane.

## Complications

FA is an invasive test, and despite being deemed generally safe, it is not free of adverse reactions, ranging from mild to severe. Mild reactions are defined as transient and resolve spontaneously without treatment. Most commonly these are nausea (approximately 3%–15%), vomiting (up to 7%), sneezing, inadvertent arterial injection, and pruritus.<sup>1,13</sup> Moderate adverse reactions resolve with medical intervention. These include urticaria, angioedema, syncope, thrombophlebitis, pyrexia, local tissue necrosis, and nerve palsy.<sup>13</sup> Severe reactions require intensive intervention, and the patients may have poor recovery. These reactions include laryngeal edema, bronchospasm, anaphylaxis, hypotension, shock, myocardial infarction, pulmonary edema, hemolytic anemia, cardiac arrest, tonic-clonic seizures, and death.<sup>1,13</sup> The incidence of adverse reactions has been described in the report on a multicenter, collaborative study (Table 6.6.1).<sup>13</sup> The overall incidence of complications is estimated to be 3%–20%. Although not considered a complication, the yellowing of skin, most commonly in fair-skinned individuals, may lead to photosensitivity, and patients should be cautioned about exposure to ultraviolet rays. Recently, a case of extensive jaundice following fluorescein was reported.<sup>14</sup> Patients should also be advised about possible darkening of urine for 24–48 hours after the study.

**TABLE 6.6.1 Incidence of Adverse Reactions to Intravenous Fluorescein Angiography**

	Reaction	Incidence
Mild	Nausea, vomiting, sneezing	0%–5% (based on 87% of respondents)
	Urticaria	1:82
Moderate	Syncope	1:337
	Other	1:769
	<b>Overall</b>	<b>1:63</b>
	Respiratory	1:3800
	Cardiac	1:5300
Severe	Seizures	1:13900
	Death	1:221781
	<b>Overall</b>	<b>1:1900</b>

From the survey conducted by Yannuzzi LA, Rohler KT, Tindel LJ, et al. Fluorescein angiography complication survey. Ophthalmology 1986;93:611–7.

Previous efforts to relate the procedure technique, dye concentrations, and rate of infusion and volume with the incidence of adverse reactions have been inconclusive.<sup>7</sup> Although in vivo skin tests remains the most reliable diagnostic tool for the diagnosis of immunoglobulin E–mediated allergy to SF (including severe cases of anaphylaxis), it is not particularly effective in predicting mild adverse reactions (ARs) because they are not attributable to immunological mechanisms.<sup>11</sup> Special attention should be paid to patients with reported previous mild or moderate ARs during the study because the rate of recurrence is high (48%–68%), and the study should be avoided, if possible.<sup>1</sup>

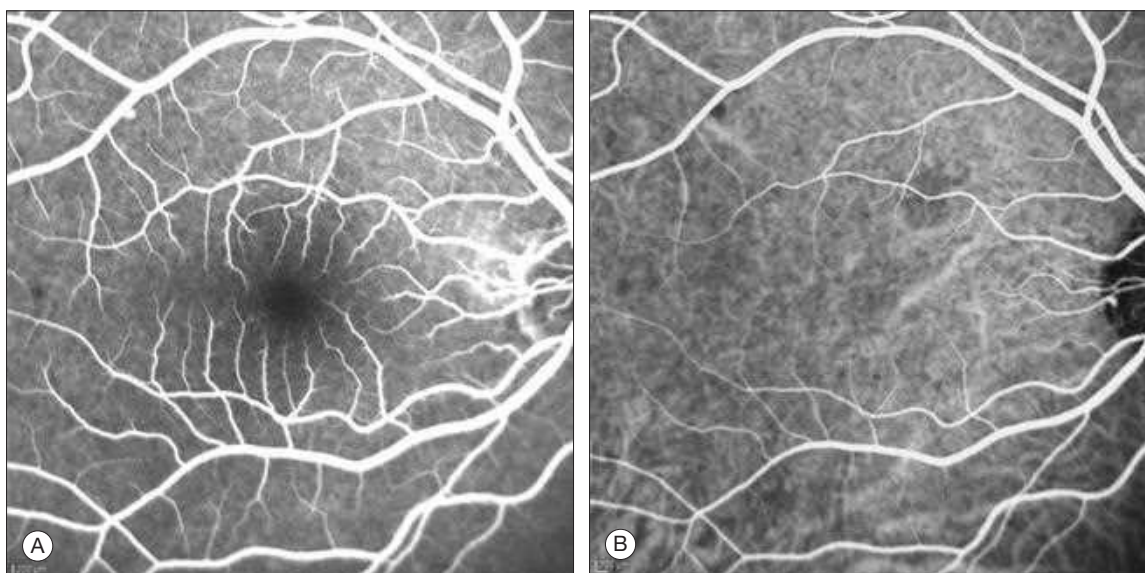
The American Academy of Ophthalmology Preferred Practice Patterns states that each angiographic facility should have in place an emergency protocol to minimize risk and manage complications.<sup>15</sup> Regular stocking and updating of medications is needed, as well as regular training of photographers and supporting staff to recognize signs and symptoms of anaphylaxis. An emergency kit should be available on site and should include an airway bag, intravenous equipment, automated external defibrillator, oral or intramuscular antihistamines, and autoinjectors of epinephrine. The protocol should be posted in a prominent place and be visible to everybody.<sup>15</sup>

Although package inserts from most brands of SF dye state that its use should be avoided during pregnancy, especially during the first trimester, data from several series and animal studies have not been able to identify a higher rate of birth abnormalities or complications (regardless of SF concentration: 10% or 25%).<sup>12,16,17</sup> It is therefore reasonable to perform FA on pregnant patients when vision is threatened by potentially blinding diseases. Nonetheless, most clinicians prefer to wait until after delivery. Nursing mothers are discouraged from breastfeeding for at least 24–48 hours after FA.<sup>18</sup>

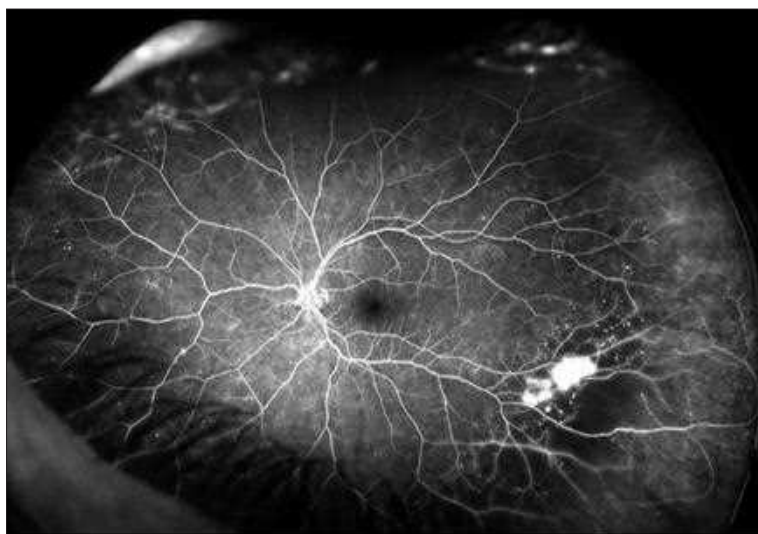
Several technological advances have taken place since the introduction of film angiography:

- *Confocal scanning laser ophthalmoscope (CSLO) as the energy source:* The main benefit of switching to CSLO instead of a traditional cobalt blue flashbulb is that the exact laser wavelength can be selected to generate the peak emission of light of the SF dye.<sup>2,9</sup> This means a significant increase of the signal-to-noise ratio in each examination. Despite the fact that the retina receives a higher emission of light energy with this modality, the toxic threshold is not exceeded because the energy is emitted only for 0.1–0.7 microseconds.<sup>19</sup> This enables high-speed acquisition of images and short movies, allowing a dynamic evaluation of the blood flow through the retinal and choroidal vessels. The wavelength of the laser can be tuned or combined to acquire images with different dyes simultaneously (SF and indocyanine green). The procedure is more comfortable for the patient because there is no bright flash (Fig. 6.6.1).<sup>9,19</sup>
- *The change of film to digital images:* The development of high-resolution (high-definition [HD]) cameras along with computers with higher storage capacity has allowed digital equipment to mostly supplant traditional film equipment.<sup>3,4,6</sup> Digital images can have a similar or greater resolution than that of a traditional film-based one (4096 × 2736 pixels).<sup>6</sup> The coupling of CSLO with pinhole cameras effectively blocks scattered light as well as details outside the optical focus. As a result, greater detail in the capillary network becomes visible. And, finally, a digital image enables real-time correction of gain, exposure, and focus, as well as instant visualization, which means better image quality.<sup>4</sup> It also makes the examination and manipulation of the images easier, allows

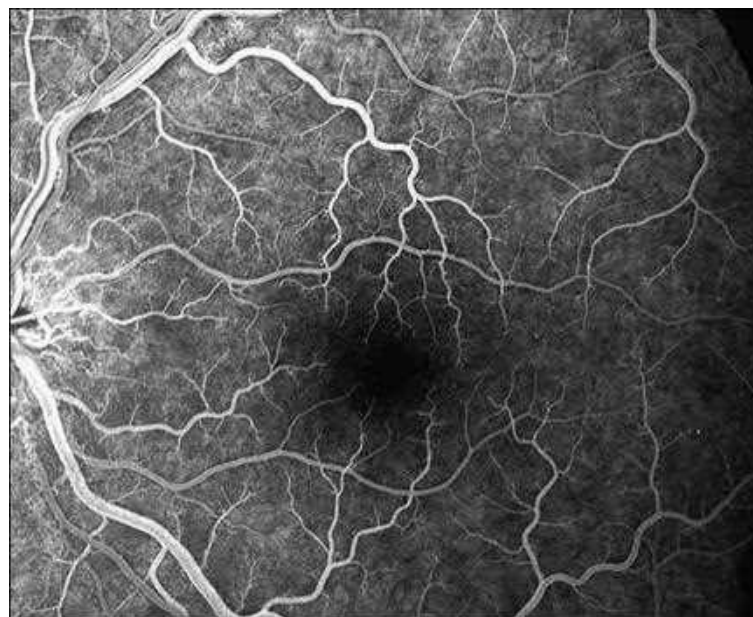




**Fig. 6.6.1 Fluorescein Angiography (FA) and Indocyanine Green Angiography (ICGA) Images Taken Simultaneously in the Same Patient.** (A) FA image. (B) ICGA image, in which, in addition to the normal fluorescence of the retinal vessels, the deep choroidal vessels are visualized. (Courtesy Jans Fromow-Guerra, MD: Associate Professor. Asociación para Evitar la Ceguera en México, IAP. México DF.)



**Fig. 6.6.2 Example of Ultra-Wide Field Fluorescein Angiography (FA) Images (200° Angle View).** Mid-phase angiogram in a patient with proliferative diabetic retinopathy. Note the neovascularization elsewhere (NVE) along the distance inferotemporal arcades with surrounding areas of nonperfusion and mild leakage from the large vessels. Small areas of punctate hyperfluorescence represent multiple microaneurysms in all quadrants.



**Fig. 6.6.3 Peak Phase Angiogram.** Approximately 25 seconds after injection, maximal fluorescence of the retinal circulation is evident. Note the intricate detail of the perifoveal capillary network.

for the rapid transmission of data by electronic means, and eliminates the need for physical storage space.<sup>4</sup>

- **Wide and ultra-wide angle of view:** Traditionally, the standard angle of view was 30–50° with a 2.5 magnification,<sup>3</sup> making the evaluation of peripheral retinal pathology difficult. Contact lens systems increased the angle of view to up to 160°. A new ultra-wide field system that uses a rotating ellipsoidal mirror with two conjugate focus points combined with a scanning laser ophthalmoscope creates an ellipsoidal surface capable of focusing light rays emanating from the peripheral retina, (up to 200°) (Fig. 6.6.2).<sup>2,20,21</sup> Ultra-wide field angiography has shown to be useful for identification and management of peripheral pathology in various diseases, including diabetes, sickle cell anemia, posterior/panuveitis, and pediatric retinal disease, among others.<sup>21–24</sup>

## Interpretation of Results

### Normal Fluorescein Angiogram

The dye first enters the eye in the short posterior ciliary arteries 10–15 seconds after injection in patients with normal circulation. The dye is then visualized in the choroid and optic nerve head. This initial filling is dependent on the cardiovascular condition and age of the patient as well as the speed of injection. The choroidal circulation is seen initially as the choroidal flush—a mottled and patchy fluorescence created as dye fills the choriocapillaris. The patchy appearance is created as separate lobules of the choriocapillaris fill sequentially. As dye leaks from the choriocapillaris

during the early phases of the angiogram, Bruch's membrane is stained, and choroidal vasculature detail is obscured. A cilioretinal artery is seen simultaneously with the fluorescence of the choroidal circulation in 10%–15% of patients.

One to three seconds after choroidal filling, the retinal circulation begins to fluoresce (at 11–18 seconds). The retinal arterial system should fill completely in about 1 second. The early arteriovenous phase is characterized by the passage of fluorescein dye through the central retinal arteries, the precapillary arterioles, and the capillaries, and the late arteriovenous phase is characterized by the passage of dye through the veins in a laminar pattern. During the late arteriovenous phase, maximal fluorescence of the arteries occurs, with early laminar filling of the veins. Laminar filling of veins is caused by the preferential concentration of unbound fluorescein along the vessel walls. Several factors are responsible for the laminar pattern of venous filling; these include the more rapid flow of plasma along the vessel wall as well as the higher concentration of erythrocytes in the central vascular lumen.

Maximal fluorescence is achieved in the juxtafoveal or perifoveal capillary network after 20–25 seconds. The normal capillary-free zone, or foveal avascular zone, is approximately 300–500 μm in diameter. A dark background to this capillary-free zone in the macula is created by blockage of choroidal fluorescence by both xanthophyll pigment and a high-density of RPE cells in the central macula. This phase of angiography has been termed the *peak phase* because maximal fluorescence of the capillaries and enhanced resolution of capillary detail occurs (Fig. 6.6.3). The management

**BOX 6.6.1 Causes of Hypofluorescence****Blocked Retinal Fluorescence**

- Media opacity
- Vitreous opacification (hemorrhage, asteroid hyalosis, vitritis)
- Subhyaloid hemorrhage.
- Intraretinal pathology (hemorrhage [vein occlusion], edema)

**Blocked Choroidal Fluorescence**

- All entities that cause blockade retinal fluorescence.
- Outer retinal pathology (lipid, hemorrhage, xanthophyll)
- Subretinal pathology (hemorrhage, lipid, melanin, lipofuscin, fibrin, inflammatory material)
- Subretinal pigment epithelium pathology (hemorrhage)
- Choroidal pathology (nevus, melanoma)

**Vascular Filling Defects****Retina**

- Occlusion or delayed perfusion
- Central or branch artery occlusion
- Capillary nonperfusion (diabetes, vein occlusion, radiation, etc.)
- Atrophy or absence of retinal vessels

**Choroid**

- Occlusion of large choroidal vessels or choriocapillaris (sectoral infarct, malignant hypertension, toxemia, lupus, choroidopathy, renal disease)
- Atrophy or absence of choroidal vessels or choriocapillaris (choroideremia, acute multifocal placoid pigment epitheliopathy)

**Optic Nerve**

- Occlusion (ischemic optic neuropathy)
- Atrophy or absence of tissue (coloboma, optic nerve pit, optic nerve hypoplasia, optic atrophy)

of microvascular diseases of the retinal capillaries, such as diabetic macular edema, requires excellent peak phase imaging.

The first pass of fluorescein through the retinal and choroidal vasculature is complete after 30 seconds. The recirculation phases, characterized by intermittent mild fluorescence, follow. After approximately 10 minutes, both the retinal and choroidal circulations generally are devoid of fluorescein. Many normal anatomical structures continue to fluoresce during late angiography, such as the disc margin and optic nerve head. The staining of Bruch's membrane, choroid, and sclera is more visible in patients who have lightly pigmented RPE.

**Abnormal Fluorescein Angiography**

The terms *hypofluorescence* and *hyperfluorescence* are used in the interpretation of fluorescein angiograms. Hypofluorescence is a reduction or absence of normal fluorescence (Box 6.6.1), whereas hyperfluorescence is increased or abnormal fluorescence (Box 6.6.2).

- **Hypofluorescence:** Hypofluorescence can be categorized into *blockage* (masking of fluorescence) or *vascular filling defects*. Blocked fluorescence can provide clues as to the level of the blocking material, such as vitreal, retinal, or subretinal. Only structures or material anterior to the area of fluorescence can block fluorescence. Blocked retinal fluorescence may be caused by any element that diminishes the visualization of the retina and its circulation (Fig. 6.6.4). Blockage of retinal fluorescence also may localize the pathology to the inner retina. The retinal circulation is unique in that the large retinal vessels and precapillary first-order arterioles lie in the nerve fiber layer, whereas the capillaries and post-capillary venules are located in the inner nuclear layer. Flame-shaped hemorrhages are superficial and block all retinal vascular fluorescence, whereas deeper dot or blot hemorrhages (or intraretinal lipid) block capillary fluorescence but do not block larger superficial vessels. Fluorescence may also be blocked by melanin (scars, melanoma, nevus), lipofuscin deposits (Stargardt disease and Best disease), hemorrhage (diabetic retinopathy), and serosanguinous fluid beneath the RPE (CNV-AMD). Vascular filling defects produce hypofluorescence because of the reduced or absent perfusion of tissues. Retinal vascular filling defects can involve large-, medium-, or small-caliber vessels. Capillary nonperfusion manifests as vascular filling defects and is typically seen in common ischemic disease processes, such as diabetic retinopathy and venous occlusive disease (Fig. 6.6.5). Choroidal vascular filling

**BOX 6.6.2 Causes of Hyperfluorescence****Pseudo-fluorescence****Autofluorescence****Transmitted Fluorescence**

- Geographic atrophy
- "Bull's eye" maculopathy
- Macular hole
- Atrophic chorioretinal scar
- Drusen

**Abnormal vessels****RETINA**

- Angioma; Wyburn–Mason syndrome
- Cavernous hemangioma
- Vascular tumor
- Retinoblastoma

**CHOROID**

- Melanoma
- Choroidal neovascularization
- Choroidal hemangioma

**OPTIC NERVE**

- Peripapillary vascular loops

**Leakage****RETINAL VESSELS**

- Venous occlusive disease
- Frosted angiitis
- Phlebitis

**NEOVASCULARIZATION**

- Diabetes retinopathy
- Radiation retinopathy
- Sickle cell retinopathy

**Pooling:****Neurosensory detachment**

- Central serous chorioretinopathy
- Optic nerve pit
- Best disease

**Subretinal neovascularization****Retinal pigment epithelium detachment**

- Serous
- Fibrovascular

**Staining**

- Staphyloma
- Disc
- Sclera
- Chorioretinal scar

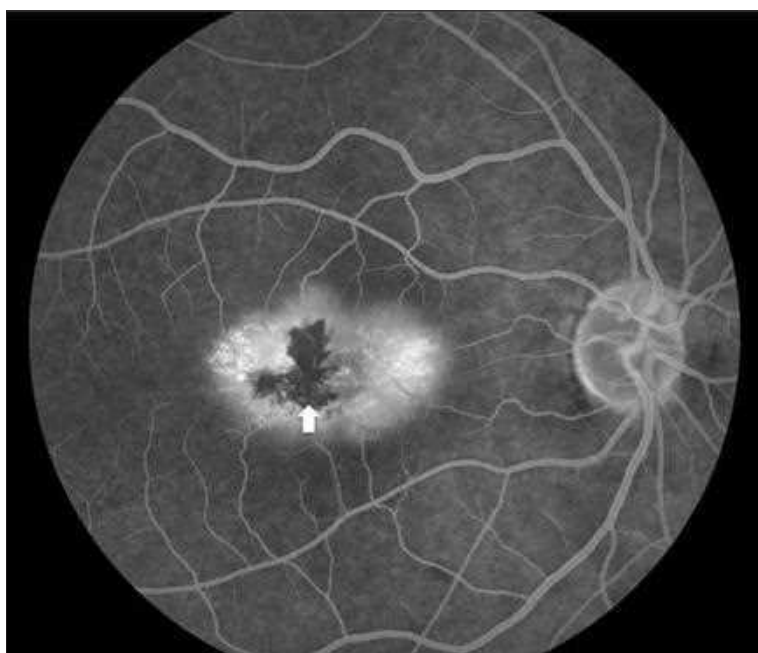
defects are more difficult to visualize because the native RPE prevents adequate visualization of the choroidal circulation. In general, occlusive diseases that involve isolated, larger choroidal vessels manifest as sectoral, wedge-shaped areas of hypofluorescence. Systemic diseases, including malignant hypertension, toxemia of pregnancy, giant cell arteritis, and lupus choroidopathy, produce zones of hypofluorescence secondary to focal choroidal nonperfusion. Vascular filling defects of the optic nerve head may be noted by fluorescein angiography. Ischemic optic neuropathy manifests as sectoral or complete optic disc hypofluorescence, whereas other atrophic or hereditary anomalies of the optic nerve head have diffuse hypofluorescence.

- **Hyperfluorescence:** Hyperfluorescence is defined as an abnormal presence of fluorescence or an increase in normal fluorescence in the FA. It can be secondary to increased transmission of choroidal fluorescence caused by a window defect created by an area with a decreased or absent RPE that allows a clear view of the underlying choroidal fluorescence (Fig. 6.6.6). The most frequent cause of hyperfluorescence is *leakage* of dye from the intravascular space into the extravascular space. In this case a localized, diffuse hyperfluorescent spot increases in both size and intensity as the study progresses (Fig. 6.6.7). When the dye leaks into an anatomical space (cysts, subretinal space, sub-RPE space) it is called *pooling*. In this case, the boundaries of the hyperfluorescence are more defined, and the speed of appearance depends mostly on the cause (Fig. 6.6.8). Finally, *staining* refers to the deposition of dye within involved tissue and occurs in both normal (optic nerve and sclera) and pathological states (drusen, disciform scars).

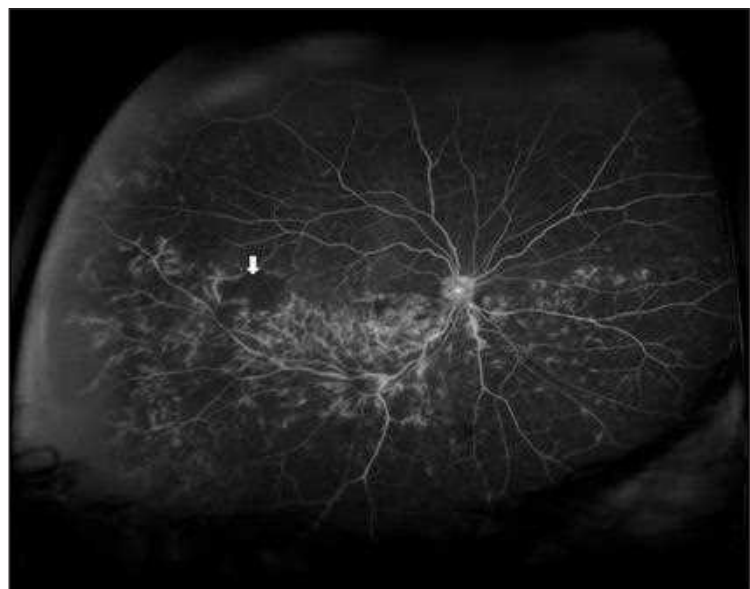
**INDOCYANINE GREEN ANGIOGRAPHY****Introduction**

Currently there are two commercially available types of imaging systems for indocyanine green angiography (ICGA): modified fundus cameras (which utilize continuous illumination from a halogen bulb and periodic xenon lamp flashes), and scanning laser ophthalmoscope (SLO)-based systems, which use a focused laser beam to sweep the retina, allowing continuous image acquisition (20–30 images per second).<sup>25</sup>



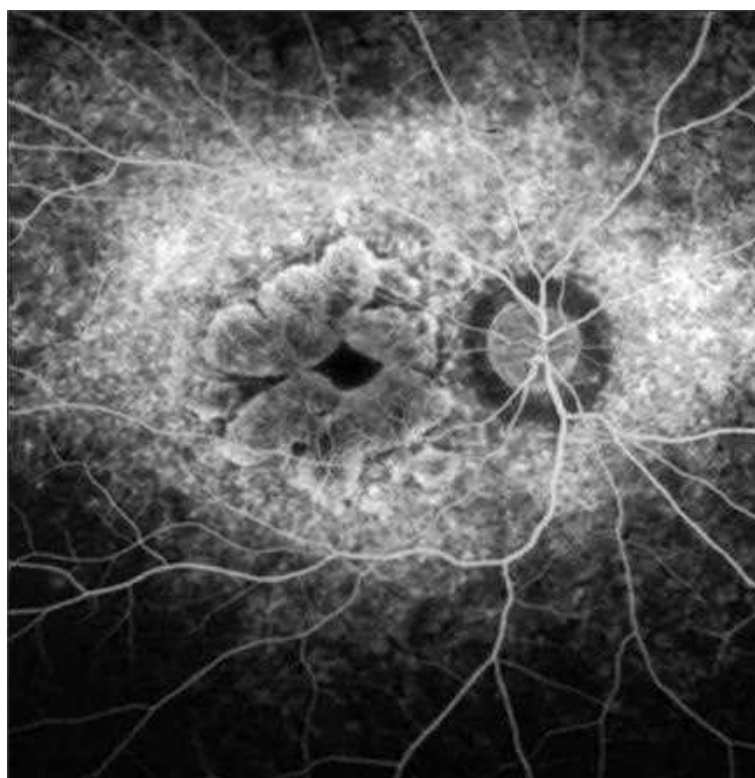


**Fig. 6.6.4 Blockage.** Fluorescein angiography (FA) image from a patient with idiopathic macular telangiectasia. In this late-phase angiogram, intraretinal pigment plaques are blocking (arrow) the background choroidal fluorescence. Note the significant leakage from the telangiectatic vessels worse temporally as well as staining of the scleral crescent around the optic nerve. (Courtesy Michael Bono, CRA, COT Rocky Mountains Lions Eye Institute, Denver, CO.)



**Fig. 6.6.5 Vascular Filling Defect.** Ultra-wide field fluorescein angiography (FA) image of an inferior hemiretinal vein occlusion in the late phase. There are areas of significant nonperfusion with a large area noted temporal macula (arrow). Note the blockage from heme, leakage from large and small vessels in the macula and periphery. (Courtesy Hoang Nguyen, COT Rocky Mountains Lions Eye Institute, Denver, CO.)

Although the ICG dye gives off 4% of the fluorescence of SF, its maximal peak of absorption is at 790–805 nm and has a peak emission of 835 nm.<sup>18,19</sup> Both exciting and emitted lights are in the near-infrared spectrum, and this allows deeper penetration through the retina, and the emitted light passes more easily through the RPE, blood, lipids deposits, pigment, and mild opacities (cataracts) to form images.<sup>25</sup> Moreover, because the dye has a significantly greater molecular weight, and a greater proportion of molecules remain bound to proteins in the bloodstream, the ICG dye normally remains within the fenestrated walls of the choriocapillaris, unlike SF which leaks freely from these vessels. This property makes ICGA an ideal technique for portraying the anatomy and hemodynamics of the choroid (Fig. 6.6.9).<sup>3</sup>



**Fig. 6.6.6 Window Defect.** Fluorescein angiography (FA) image from a patient with an advanced case of Stargardt disease. The picture shows increasing fluorescence caused by atrophy, noted since the early phases of the angiogram. (Courtesy Valentina Franco-Cardenas, MD: International Retina Fellow, University of California Los Angeles (UCLA).)

## Properties of Indocyanine Green

ICG (benzoindotricarbocyanin) is an amphiphilic tricarbocyanine dye with a molecular weight of 775 kDa.<sup>26</sup> Because of its ability to form aggregates, the ICG lyophilisate has to be dissolved in water for injection. In the bloodstream, the dye is rapidly bound to proteins (98%), especially to albumin, globulins, and lipoproteins, thus remaining longer in large blood vessels and having a lesser tendency to diffuse into the interstitial space.<sup>10</sup> The dye has been approved by the U.S. Food and Drug Administration for use in cardiac, hepatic, and ophthalmic studies.<sup>9</sup> ICG is solely metabolized by the liver through a specific carrier-mediated transport system and excreted in the biliary system. This explains the rapid elimination of the dye from the circulation after an intravenous injection.<sup>26</sup> The dye has a plasma half-life of 2–4 minutes.

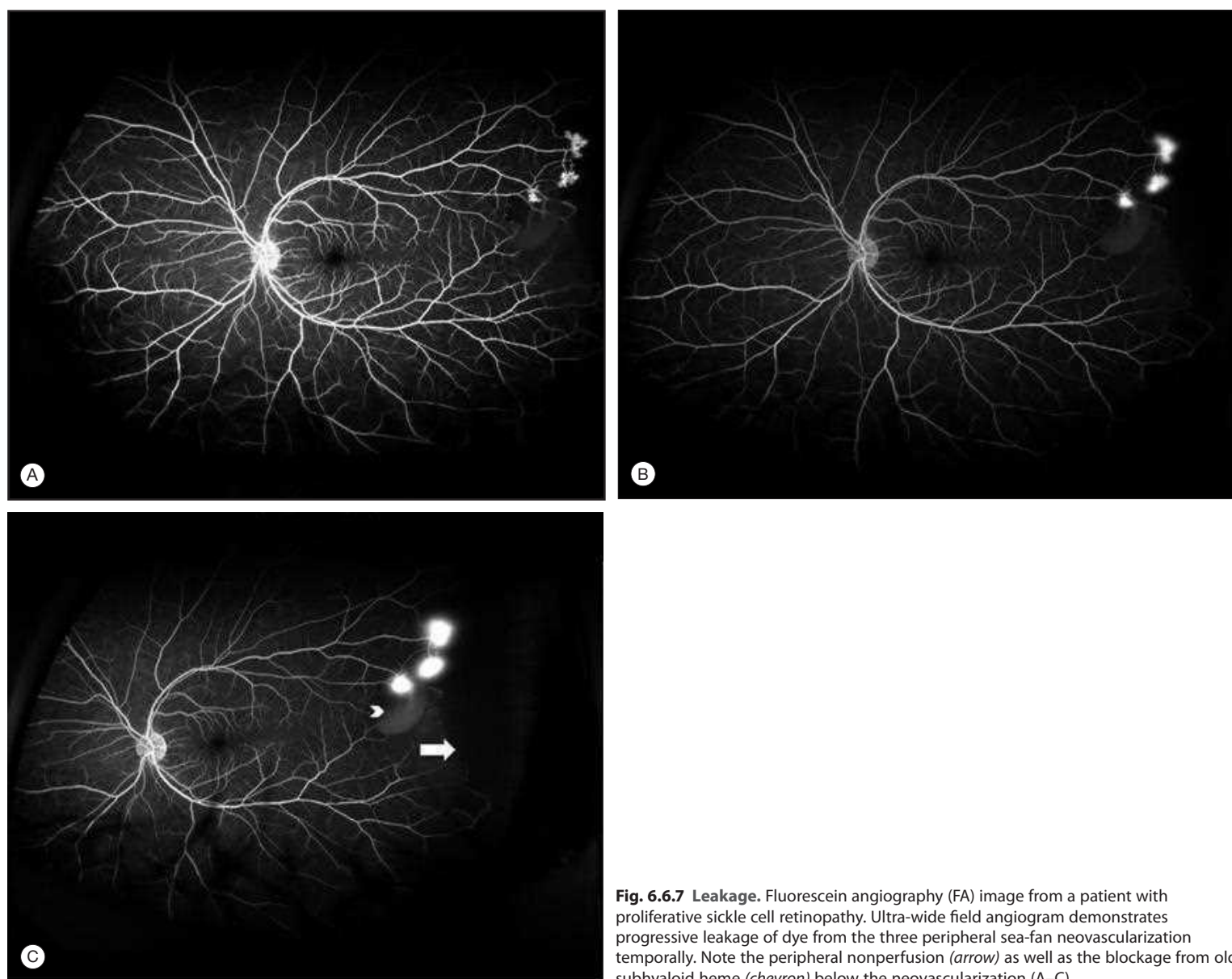
## Procedure

Pharmacological mydriasis is usually required with most systems. The infusion technique is similar to FA, as described above.

The dosage of ICG can vary from 20–50 mg of dye dissolved in 2–4 mL of aqueous solvent. The preferred technique is to slowly inject 25 mg of ICG dye in 5 mL of water. A higher dosage typically results in a larger degree of hyperfluorescence and thereby changes excitation. If both FA and ICGA are performed sequentially, an intravenous catheter may be placed to avoid multiple needlesticks.<sup>18</sup>

Excitation illumination should be at a maximum, with a video gain of +6 dB. Approximately 10 images are acquired over the initial 30 seconds, starting immediately after injection. The video gain and excitation illumination levels should not be changed during the transit phase unless image bloom occurs (an increased fluorescence that obscures images). If this happens, the excitation level is reduced. The best images are retained, and ideally, the transit of ICG through the choroidal vasculature is captured again every 15 seconds. Late images at 5, 10, 15, 20, and 40 minutes after injection also are obtained. Alteration of the excitation level can be increased during the late phase of ICGA if signal intensity is reduced. During the very late stages, both excitation and video gain can be increased; however, a concomitant reduction in detail results.





**Fig. 6.6.7 Leakage.** Fluorescein angiography (FA) image from a patient with proliferative sickle cell retinopathy. Ultra-wide field angiogram demonstrates progressive leakage of dye from the three peripheral sea-fan neovascularization temporally. Note the peripheral nonperfusion (*arrow*) as well as the blockage from old subhyaloid heme (*chevron*) below the neovascularization (A–C).

## Complications

Mild adverse reactions, such as nausea, vomiting, sneezing, and transient itching, occur in 0.15% of cases.<sup>5</sup> Moderate adverse reactions, such as urticarial, syncope, fainting, and pyrexia, may also occur. Severe adverse reactions, such as hypotension, shock, anaphylaxis, and death, have also been reported and occur in equal incidence following ICG and FA (1:1900).<sup>5</sup>

ICG is currently available in several pharmaceutical preparations. Because some of the manufacturing process adds iodine to allow crystallization of the molecule ( $\approx 5\%$  of commercial ICG dyes), crossover allergy to iodine can occur in patients with seafood allergies (shellfish).<sup>9,26</sup> Current contraindications to ICGA include prior anaphylactic reaction to ICG dye or contrast agents that contain iodine, hepatic insufficiency, uremia, and pregnancy. Patients undergoing hemodialysis are also at increased risk of complications from ICG.<sup>9,18</sup>

When local extravasation of the ICG occurs, minimal damage is observed, in contrast to SF, which may cause severe tissue necrosis.

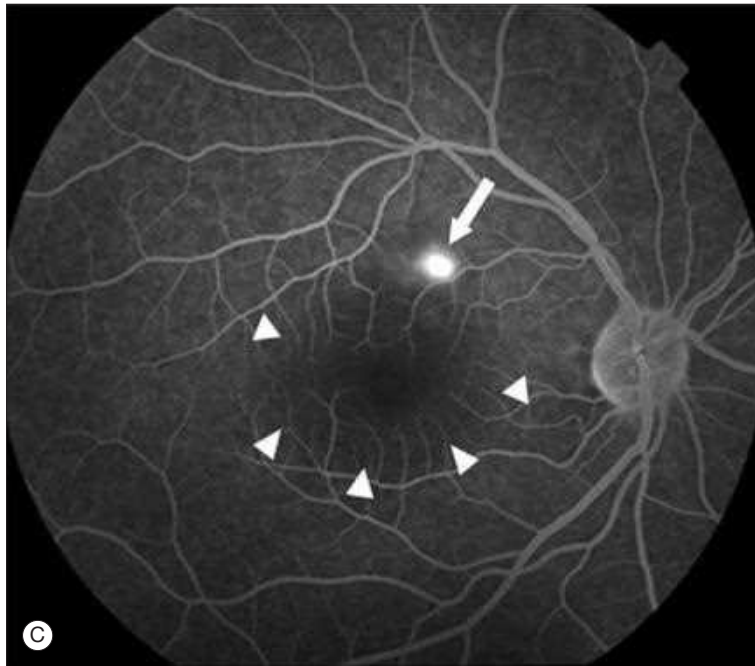
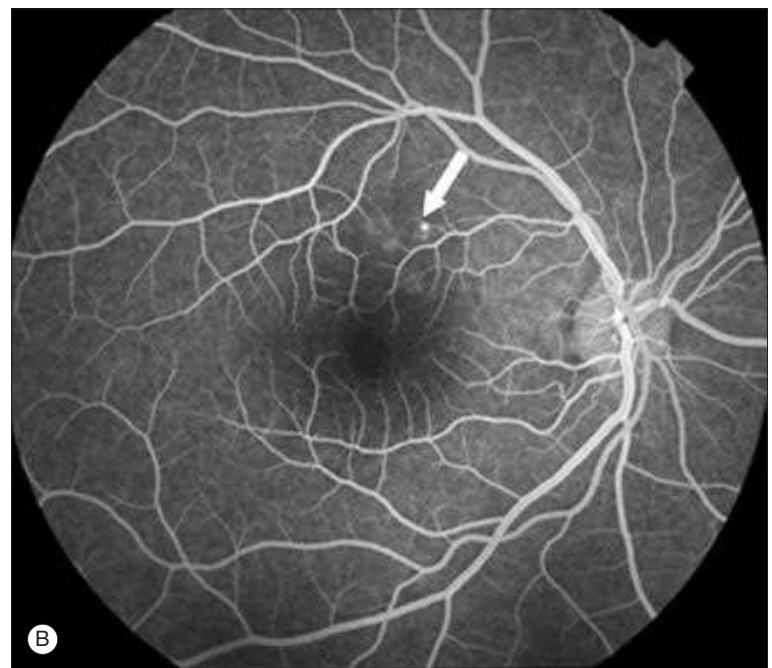
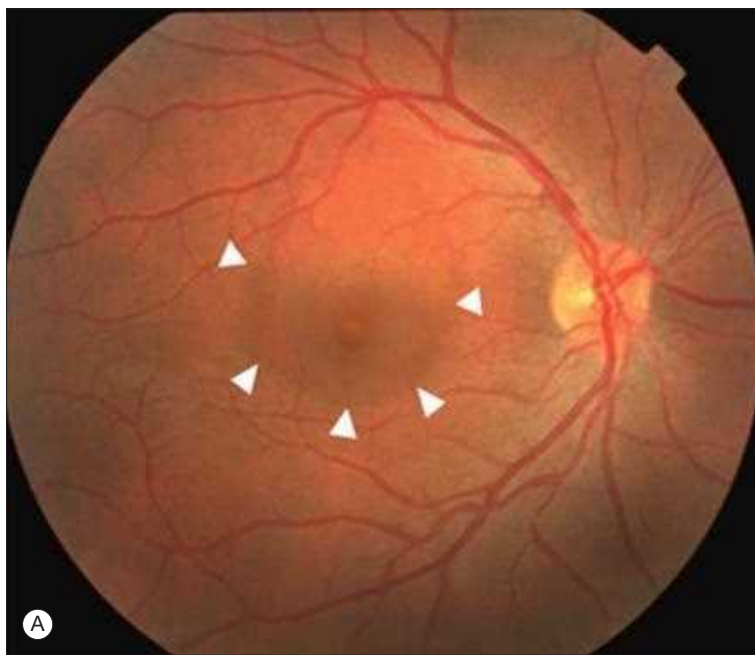
## Interpretation of Results

In the *early phase* of the test, 2 seconds after ICG injection, filling of both the choroidal arteries and choriocapillaris, with early filling of the choroidal veins, occurs. The retinal blood vessels are still dark along with the choroidal “watershed zone” around the optic nerve head. Then, 3–5 seconds after ICG injection, the larger choroidal veins begin to fill and fluoresce along with the retinal arteries as the dye flows. Later, at 6 seconds to 3 minutes, the outer-shed zone is now filled, but the choroidal arteries and large choroidal veins begin to fade (Fig. 6.6.10).<sup>18</sup>

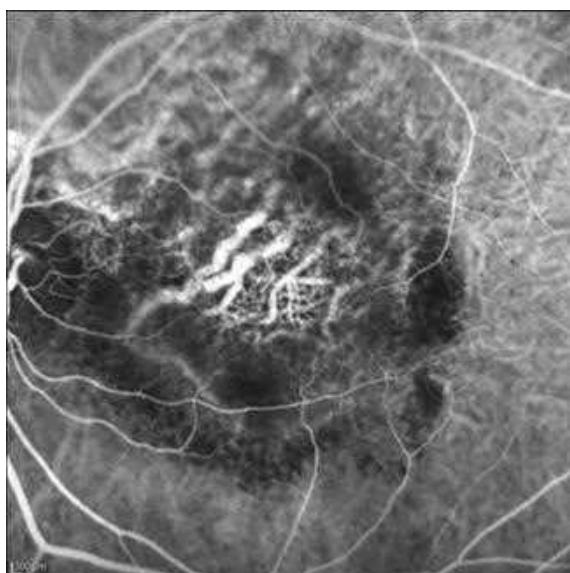
The *middle phase* occurs 3–15 minutes after ICG injection. It is marked by continuous fading of the choroidal and retinal vessels. The *late phase* occurs 15–60 minutes after ICG injections. It demonstrates staining of the extrachoroidal tissue, giving the choroidal vasculature the illusion of hypocyanescence, compared with the background tissue. No retinal vessels are seen during this phase.<sup>18</sup>

Abnormal areas on an ICGA are interpreted as in FA. There can be either *hypo-* or *hypercyanescence*. Hypocyanescence can be attributed to blockage (by blood, serous fluid, pigment, or exudates); impaired choroidal perfusion, either by blocked blood flows on a given area or by loss of choroidal vasculature tissue (acute posterior multifocal placoid pigment epitheliopathy). Hypercyanescence can be caused by a lack of overlying tissue (RPE dropout, lacquer cracks), leakage from retinal or choroidal blood vessels (producing subsequent staining of surrounding tissue), or leakage from abnormal blood vessels (CNV, polypoidal vasculopathy). The terms *hot spots* and *plaques* are used to define areas of intense hypercyanescence during the middle to late phases of the ICGA. *Hot spots* are defined as  $<1$  disc diameter (DD) in size. Hot spots have been attributed to one of three etiologies: polypoidal choroidal neovascularization, retinal angiomatous proliferation, or occult choroidal neovascularization (Fig. 6.6.11). *Plaques*, which are more common, are larger ( $>1$  DD), more amorphous, and reveal less obvious leakage. Combined lesions, which have characteristics of both hot spots and plaques, can also occur.<sup>18,27,28</sup>

*Wide and ultra-wide angle of view:* Wide-field ICGA allows for up to  $160^\circ$  field of view and ultra-wide angiography reaches  $200^\circ$  field of view.<sup>29,30</sup> Peripheral changes are common on ultra-wide field ICGA in many ophthalmic conditions, including, but not limited to, central serous chorioretinopathy, AMD, polypoidal choroidopathy, and myopic degeneration.



**Fig. 6.6.8 Pooling.** Color picture and fluorescein angiography (FA) sequence from a patient with central serous chorioretinopathy. (A) & (C), Small arrowheads delineate an area of neurosensory detachment of the macula with pooling of the dye in the late phase of the study. (B) & (C), Large white arrows indicate areas of retinal pigment epithelium leakage of fluorescein. (Courtesy Valentina Franco-Cardenas, MD: International Retina Fellow, University of California Los Angeles [UCLA].)

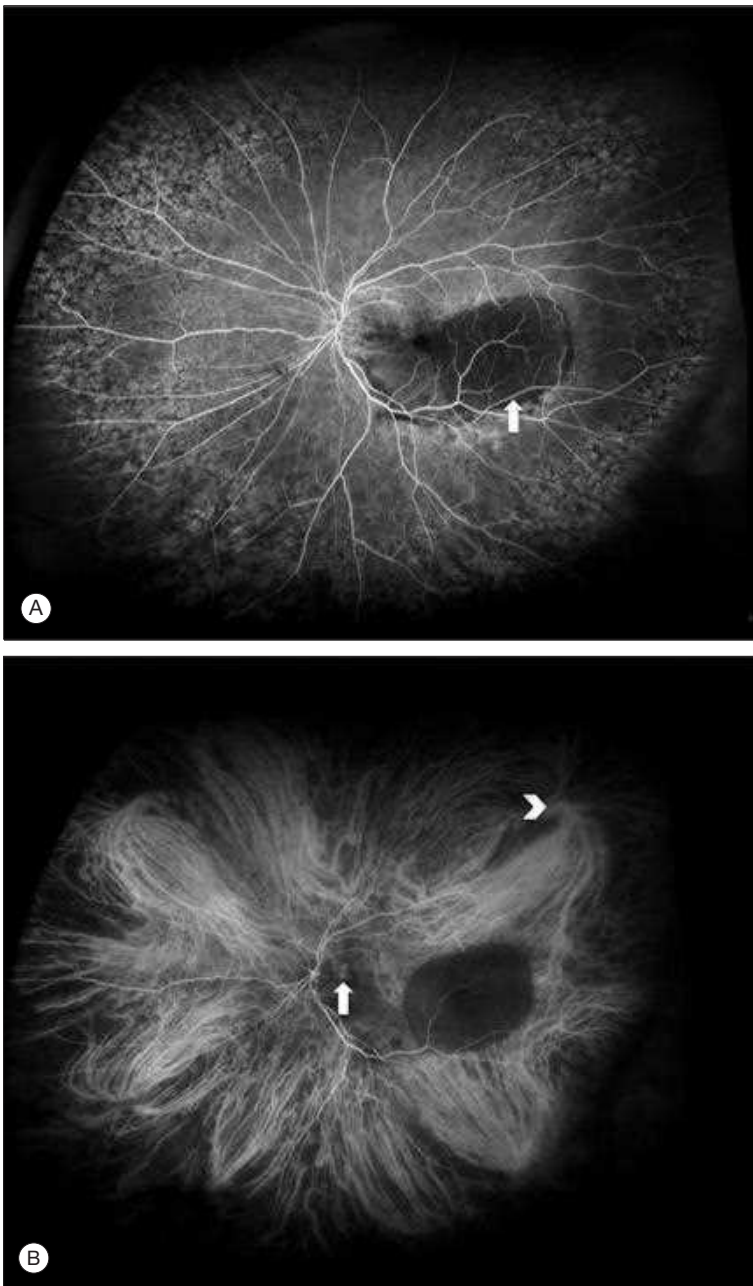


**Fig. 6.6.9** Indocyanine green angiography (ICGA) image from a patient with severe atrophy of the retinal pigment epithelium (RPE), in which the choriocapillaris, as well as medium and large choroidal vessels, can be observed. (Courtesy Jans Fromow-Guerra, MD: Associate Professor. Asociación para Evitar la Ceguera en México, IAP. México DF.)



**Fig. 6.6.10** Final stage of the early phase of a normal indocyanine green angiography (ICGA) (at 90 seconds of the study), where the retinal and large choroidal vessels are clearly visible. (Courtesy Jans Fromow-Guerra, MD: Associate Professor. Asociación para Evitar la Ceguera en México, IAP. México DF.)



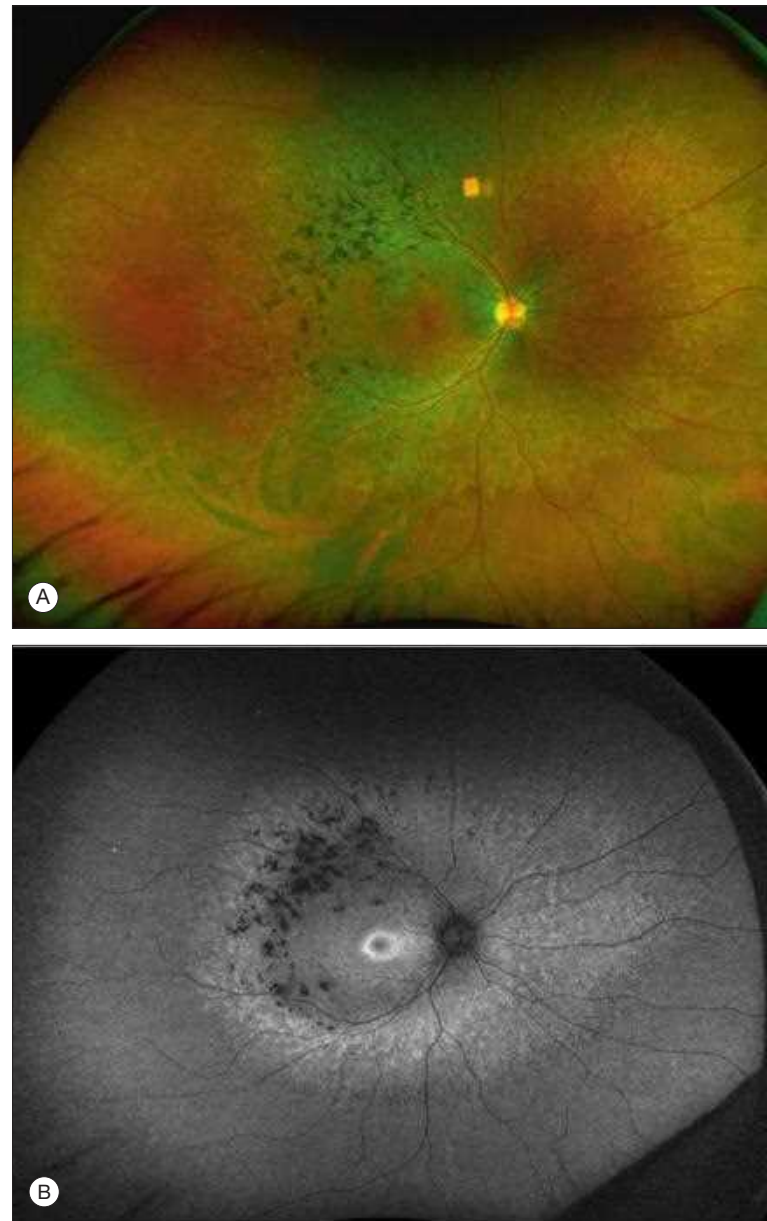


**Fig. 6.6.11** Fluorescein angiography (FA) and indocyanine green angiography (ICGA) images from a patient with idiopathic polypoidal choroidal vasculopathy and hemorrhagic pigment epithelial detachment. (A) FA with a large hemorrhagic pigment epithelial detachment in the temporal macula (*arrow*) showing blockage and RPE mottling in the periphery. (B) ICGA demonstrates characteristic saccular dilations of the choroidal vasculature just temporal to the disc (*arrow*). The vortex ampullae are also highlighted (*chevron*).

Uveitic (infectious and noninfectious) peripheral changes, including, but not limited to, posterior uveitis, birdshot chorioretinopathy, acute zonal occult outer retinopathy, systemic lupus erythematosus, and sarcoidosis, were also identified.<sup>31,32</sup>

## FUNDUS AUTOFLUORESCENCE

Fundus autofluorescence (FAF) is a noninvasive imaging modality that works by using autofluorescent molecules called *fluorophores* (found in lipofuscin in RPE cells) to provide diagnostic and prognostic information for retinal diseases (Fig. 6.6.12).<sup>33</sup> Camera systems include fundus camera, fundus spectrophotometry, CSLO, and ultra-wide field. FAF is now used widely for various pathologies, including, but not limited to, evaluating AMD, macular dystrophies, retinitis pigmentosa, white dot syndromes, retinal drug toxicities.<sup>34</sup> FAF provides accurate clinical correlation, which has been confirmed by microperimetry and visual field testing. Areas of decreased FAF demonstrates absolute scotomas, whereas increased FAF shows no visible correlate but may be a sign of future cell loss.<sup>34</sup>



**Fig. 6.6.12** Widefield Optos photo (A) and corresponding fundus autofluorescence (B) from a patient with paracentral retinitis pigmentosa. Note the “bull’s eye” maculopathy centrally, hypoautofluorescence in areas of pigment clumping, and mottled hyperautofluorescence seen in a ring around the macula and optic nerve, corresponding to RPE changes noted on the Optos fundus photo.

## ACKNOWLEDGMENTS

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# Optical Coherence Tomography in Retinal Imaging

## 6.7

Arthi Venkat, Miriam Englander, David Xu, Peter K. Kaiser

**Definition:** Optical coherence tomography (OCT) is a noninvasive imaging technique based on the principle of optical reflectometry light, which enables precise anatomical examination of ocular structures.

### Key Features

- High-resolution evaluation of tissue pathology at the cellular level, achieving axial resolution of up to 2–3  $\mu\text{m}$  in tissue.
- Direct correspondence to the histological appearance of the retina, cornea, and optic nerve in health and disease.
- Critical tool in the diagnosis and monitoring of ocular disease involving the retina, choroid, optic nerve, and anterior segment.

### Associated Features

- Easy to use, noninvasive, reproducible, safe.
- Obtainable through most media opacities, including vitreous hemorrhage, cataract, and silicone oil.
- Recent advances allow for a dramatic improvement in the cross-sectional image resolution with improved acquisition speed.
- Helpful in the interpretation of pathologies in all layers of the retina as well as the vitreous–retinal interface.
- Also used for the detection and monitoring of optic nerve, glaucoma, and anterior chamber pathology.

## INTRODUCTION

Optical coherence tomography (OCT) is a noninvasive imaging technique that allows for the examination of ocular structures. This technique utilizes light waves to create the image in a manner similar to ultrasonography, except that reflected light, rather than sound, is used to create the image. Low-coherence light is scanned across the tissue and focused with an internal lens on the ocular structure of interest. A second beam internal to the OCT unit is used as a reference, and a signal is formed by measuring the alteration of the reference beam and comparing this with the reflected beam. The interface between different ocular tissues can be determined by changes in reflective properties between the tissues. Detection of these beams is based on time-domain or spectral-domain protocols.<sup>1</sup>

The use of light allows for high resolution and evaluation of tissue pathology at the cellular level, achieving resolution of 2–3  $\mu\text{m}$ . Other advantages include ease of use, reproducibility, noninvasiveness, safety, and repeatability. In addition, OCT can image through most media opacities, including vitreous hemorrhage, cataract, and silicone oil.

## OCT TECHNOLOGY PLATFORMS

### Time-Domain OCT

In time-domain (TD)-OCT, an individual A-scan is acquired by varying the length of the reference arm in an interferometer such that the scanned length of the reference arm corresponds to the A-scan length. The image is then constructed by using a false color scale that represents the quantified amount of backscattered light, with brighter colors representing high reflectivity and darker colors representing little or no reflectivity. The main

limitations in the clinical use of TD-OCT are the limited resolution and slow acquisition.<sup>2</sup>

### Spectral-Domain OCT

In spectral-domain (SD) or Fourier-domain OCT, the light composing the interference spectrum of echo time delays is measured simultaneously by a spectrometer and a high-speed, charge-coupled device, which allows information of the full-depth scan to be acquired within a single exposure. The interference spectrum is made up of oscillations with frequencies that are proportional to the echo time delay. By calculating the Fourier transform, the machine calculates the axial scan measurements without adjusting the reference mirror. This results in improved sensitivity and image acquisition speed compared with TD-OCT. As a result, SD-OCT is several orders of magnitude more sensitive than TD-OCT.<sup>2</sup> SD-OCT's higher acquisition speeds allow for a shift from two-dimensional to three-dimensional images of ocular anatomy.

### Multifunctional OCT

Functional extensions to OCT add to the clinical potential of this technology. Polarization-sensitive OCT (PS-OCT) provides intrinsic, tissue-specific contrast of birefringent (e.g., retinal nerve fiber layer [RNFL]) and depolarizing (e.g., retinal pigment epithelium [RPE]) tissue with the use of circular or otherwise polarized light. This allows PS-OCT to be useful in glaucoma diagnosis and for the diagnosis of RPE disturbances associated with some diseases, such as age-related macular degeneration (AMD).<sup>3,4</sup>

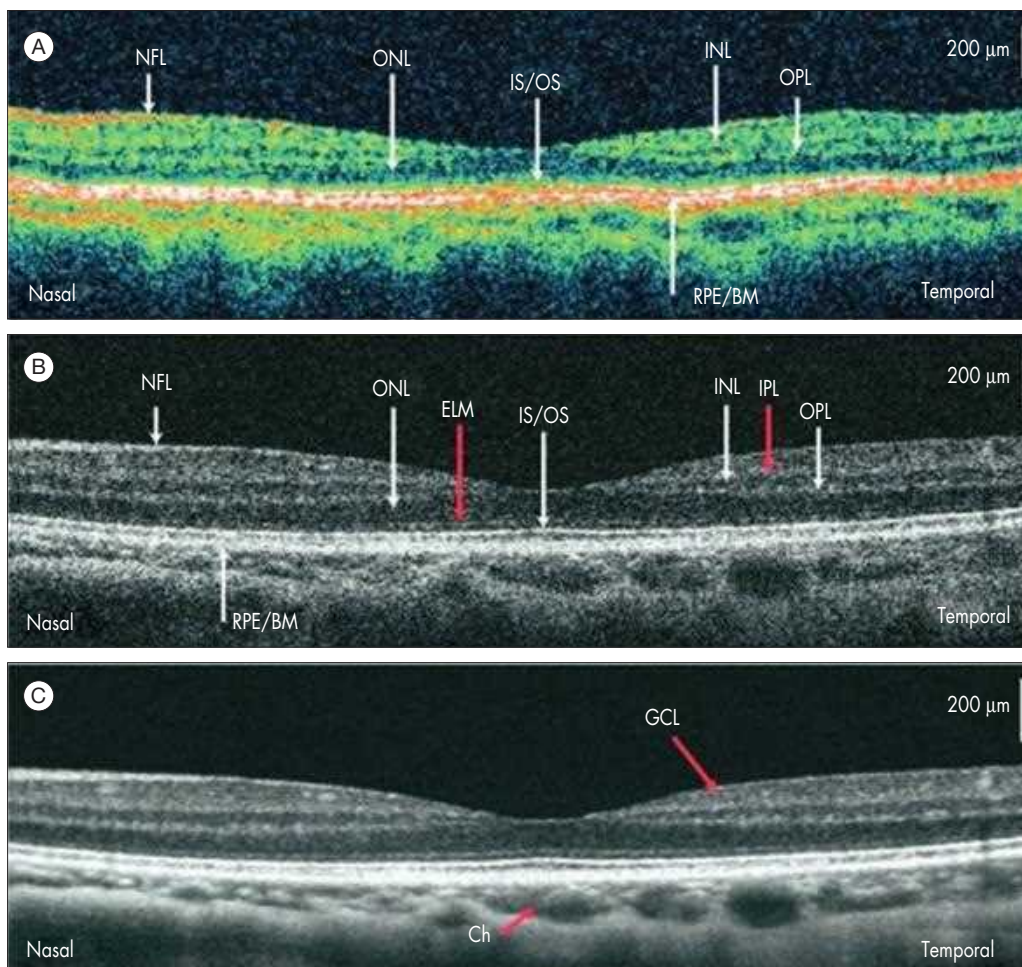
Doppler tomography enables depth-resolved imaging of flow by observing differences in phase between successive depth scans. This technology provides valuable information about blood flow patterns in the retina and choroid, allowing absolute quantification of flow within retinal vessels. Ultimately, this adjunct of OCT could potentially reduce the need for fluorescein angiography.<sup>5</sup>

### Time-Encoded Frequency-Domain OCT (Swept-Source OCT)

Swept-source OCT, a variation on Fourier-domain OCT, sweeps the frequency of a narrow band continuous wave light source and collects the time-dependent interference signal. Here, the advantage lies in high signal to noise ratio detection technology, achieving very small instantaneous bandwidths at high frequencies (20–200 kHz). This dramatically increases acquisition speed and scan depth. Drawbacks include nonlinearities in the wavelength, especially at high scanning frequencies, and high sensitivity to movements of the scanning target.<sup>2</sup>

### High-Speed, Ultra-High-Resolution OCT

Another variation on Fourier-domain OCT, high-speed, ultra-high-resolution OCT (hsUHR-OCT) allows for a dramatic improvement in cross-sectional image resolution and acquisition speed. The axial resolution of hsUHR-OCT is approximately 3.5  $\mu\text{m}$ , compared with the 10  $\mu\text{m}$  resolution in standard OCT. Imaging speeds are approximately 75 times faster than that with standard SD-OCT. The ultra-high resolution enables superior visualization of retinal morphology in a number of retinal abnormalities. hsUHR-OCT further improves visualization by acquiring high-transverse-pixel density, high-definition images.<sup>6–8</sup>



**Fig. 6.7.1 Optical Coherence Tomography (OCT) Images of a Normal Retina.** (A) Conventional OCT. (B) Spectral-domain (SD) OCT. (C) Average of 12 SD-OCT images (SD-OCT with multiple B-scan averaging). Retinal structures visible include the hyperreflective retinal nerve fiber layer (NFL), hyporeflexive inner nuclear layer (INL), hyperreflective outer plexiform layer (OPL), hyporeflexive outer nuclear layer (ONL), hyperreflective lines that correspond to the junction of the inner and outer photoreceptor segment layers (IS/OS), retinal pigment epithelium (RPE)/Bruch's membrane (BM) complex (RPE/BM), external limiting membrane (ELM), inner plexiform layer (IPL), ganglion cell layer (GCL), and choroidal vessels (Ch). Red arrows indicate structures delineated only by single-scan SD-OCT or SD-OCT with multiple B-scan averaging. (From Sakamoto A, Hangai M, Yoshimura N. Spectral-domain optical coherence tomography with multiple B-scan averaging for enhanced imaging of retinal diseases. *Ophthalmology* 2008;115(6):1071–1078.)

**TABLE 6.7.1 Commercially Available OCT Systems**

System (Company)	Axial Resolution ( $\mu\text{m}$ )	A-Scans per Second	Advanced Features
Cirrus HD-OCT5000 (Carl Zeiss Meditec)	5	68 000	Fixation-independent scan adjustment; multilayer en face C-scan visualization; high-resolution anterior segment imaging; drusen and GA mapping; OCT angiography (AngioPlex)
Spectralis HRAOCT (Heidelberg Engineering)	7 (digital 3.5)	42 000	Point-to-point registration with eye tracking; up to six diagnostic methods in one platform with pinpoint registration between imaging devices; wide-field imaging module for OCT and FA/ICGA; OCT angiography
Avanti RTVue XR (Optovue)	5	70 000	14-mm wide-field macular scans with wide-field analysis; drusen and GA mapping; OCT angiography (Angiovue); software for quantitative analysis of OCTA images
3D-OCT 2000 (Topcon)			Capable of exportation to common multimedia devices; able to import time-domain Stratus OCT images
OCT-HS100 (Canon)	3	70 000	10-mm scan length; 10-layer segmentation analysis; multilingual interface; Doppler retinal blood flow analysis capable
SDOCT (Bioptigen)	4	20 000	Handheld head for pediatric patients or animal research; portability facilitates use in an operating room; Doppler retinal blood flow analysis capable
RS-3000 Advance (Nidek)	3	53 000	12-mm scan length option; segmentation analysis of six distinct retinal layers; OCT angiography capable (Angioscan)
DRI-OCT-Triton (Topcon)	5	100,000	Swept Source device; deeper penetration and 12-mm scan length; OCT angiography capable

FA, Fluorescein angiography; GA, geographic atrophy; ICGA, indocyanine green angiography; OCT, optical coherence tomography; SOCT, spectral OCT; SDOCT, spectral-domain OCT.

## Adaptive Optics OCT

The resolution of OCT systems in the axial dimension is set by the coherence properties of the light source. Current light sources can provide axial resolution below 3  $\mu\text{m}$ , which is more than sufficient to resolve the axial dimensions of most retinal cells. However, the lateral resolution is substantially degraded from the diffraction limit by optical aberrations present in the eye. Consequently, most ophthalmic OCT systems are designed to be operated with a lateral resolution in the range of 15–20  $\mu\text{m}$ . Adaptive optics OCT (AO-OCT) measures aberrations by using a wavefront sensor and uses a wavefront corrector to compensate for the measured aberrations. The ability to correct for diffraction from ocular imperfections allows for very high resolution (2–3  $\mu\text{m}$ ), sufficient for resolution of individual cells<sup>6</sup> (Table 6.7.1).

## ANATOMICAL RESULTS

OCT images correspond to the histological appearance of the retina. The highly reflective nerve fiber layer (NFL) is represented by a red signal.

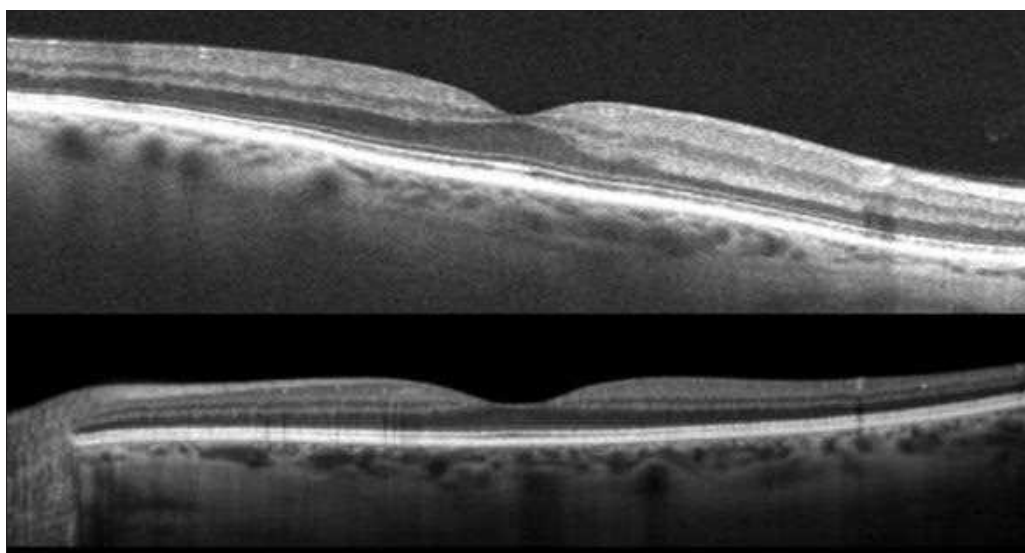
Similarly, the RPE layer, Bruch's membrane, and choriocapillaris are represented by a red signal because of their higher reflectivity. A third red line represents the junction of the inner and outer segments (called *outer segment ellipsoid zone*). Inner cellular layers have lower reflectivity and are represented by yellow, green, and blue colors. The nonreflective vitreous cavity has a black signal, but the posterior hyaloid face can occasionally be seen as an additional reflective layer anterior to the NFL (Fig. 6.7.1).

The choroid is a highly vascular structure with blood flow and thickness varying in relation to the intraocular pressure, perfusion pressure, refractive error, disease state, and age. It is possible to image the choroid with conventional OCT imaging (Fig. 6.7.2).

## IMAGE OPTIMIZATION

OCT measures the intensity of a backscattered optical signal, which represents the optical properties or reflectivity of the target tissue. The tissue reflectivity varies among different structures, allowing for measurements that can be displayed as false or pseudo-color or gray-scale images. The gray scale runs continuously from high signal (white) to no signal (black),





**Fig. 6.7.2 Comparative Choroidal Imaging With Optical Coherence Tomography (OCT) Sections Through the Fovea Obtained With Various OCT Instruments.** (Top) Heidelberg Spectralis spectral-domain (SD)-OCT using enhanced depth imaging to obtain more choroidal details, including better visualization of the hyporeflective line indicating the edge of the choroid. (Bottom) Cirrus SD-OCT image in which choroidal details are visible with oversampling.

and images can contain up to 256 shades of gray corresponding to the optical reflectivity of the various tissue interfaces. The standard color scale uses a modified continuous rainbow spectrum in which darker colors, such as blue and black, represent regions of minimal or no optical reflectivity and lighter colors, such as red and white, represent a relatively high reflectivity, as described in the Anatomical Results section above.<sup>9</sup>

Studies have shown that compared with the color images, the gray-scale images are easier to interpret and are more informative because of their improved ability to visualize subtle retinal structures, such as photoreceptor inner and outer segment junction (IS/OS), and subtle pathologies, such as thin epiretinal membranes (ERMs).<sup>10</sup>

Another method to improve image quality is to average multiple OCT scans. Frames with the least amount of motion artifacts are chosen. These frames are then averaged. Each pixel value is calculated as an average intensity from all frames, to create one frame. On average, 50 frames are used to create one image.<sup>11</sup>

## OCT IMAGE INTERPRETATION

### Preretinal

The use of OCT has facilitated the diagnosis and description of diseases involving the vitreoretinal interface, including vitreomacular traction syndrome, ERMs, macular holes, and schisis.

#### Posterior Vitreous Detachment

The vitreous in a healthy eye is optically clear. When the vitreous is completely attached, the vitreoretinal interfaces can be detected by the marked change in reflectivity between the vitreous and the internal limiting membrane (Fig. 6.7.3).

#### Vitreomacular Traction

Vitreomacular traction (VMT) is a complication of anomalous partial posterior vitreous detachment (PVD), where the vitreous is separated from the retina throughout the peripheral fundus but remains adherent in a broad region encompassing the macula and/or the optic nerve. A subtle variant demonstrates a localized perifoveal vitreous detachment with a small, focal vitreofoveolar adhesion resulting in an anterior–posterior tractional force that may lead to retinal distortion, cystoid macular edema (CME), or even a macular hole. Several OCT studies have documented that surgical or pharmacological separation of the vitreofoveal adhesion promotes the resolution of macular thickening, usually with improvement in visual acuity in patients with vision loss caused by vitreomacular traction<sup>12</sup> (Fig. 6.7.4).

#### Epiretinal Membrane

An ERM is a result of proliferation of abnormal tissue on the surface of the retina. It is semitranslucent and proliferates on the surface of the internal limiting membrane. ERM has been found to consist of glial cells, RPE cells, macrophages, fibrocytes, and collagen fibers.<sup>13</sup>

On OCT, the ERM appears as a highly reflective thick membrane on the surface of the retina. The strength of the reflection can differentiate it from the posterior hyaloid, which appears as a minimally reflective signal<sup>12</sup> (Fig. 6.7.5).

### Macular Holes

OCT has become the gold standard in diagnosing and monitoring macular holes. OCT technology has been instrumental in the classification of macular hole development, following the sequence of events from anteroposterior vitreofoveal traction to full-thickness macular hole (FTMH)<sup>14–16</sup> (Fig. 6.7.6).

### Lamellar Holes

Lamellar holes are believed to be in the spectrum of macular hole disease but, at least in some eyes, represent an aborted process. In these eyes, OCT imaging shows an irregular, thinned foveal floor with split foveal edges and near-normal thickness of the perifoveal retina (Fig. 6.7.7). OCT images show intact photoreceptors posterior to the area of dehiscence, in contrast to a full macular hole.

### Pseudo-Hole

A macular pseudo-hole is a clinical diagnosis given to an eye with the appearance of a full-thickness defect, but an OCT image that proves an alternative diagnosis. OCT images can readily distinguish between macular pseudo-hole and an FTMH.<sup>17</sup> As with lamellar holes, OCT shows an intact photoreceptor layer. Foveal pseudocyst has also been described as an early stage in the development of macular holes. In these cases, the posterior hyaloid is partially detached over the posterior pole but is still adherent to the fovea, causing a biconvex appearance.<sup>18</sup>

### Intraretinal

#### Macular Edema

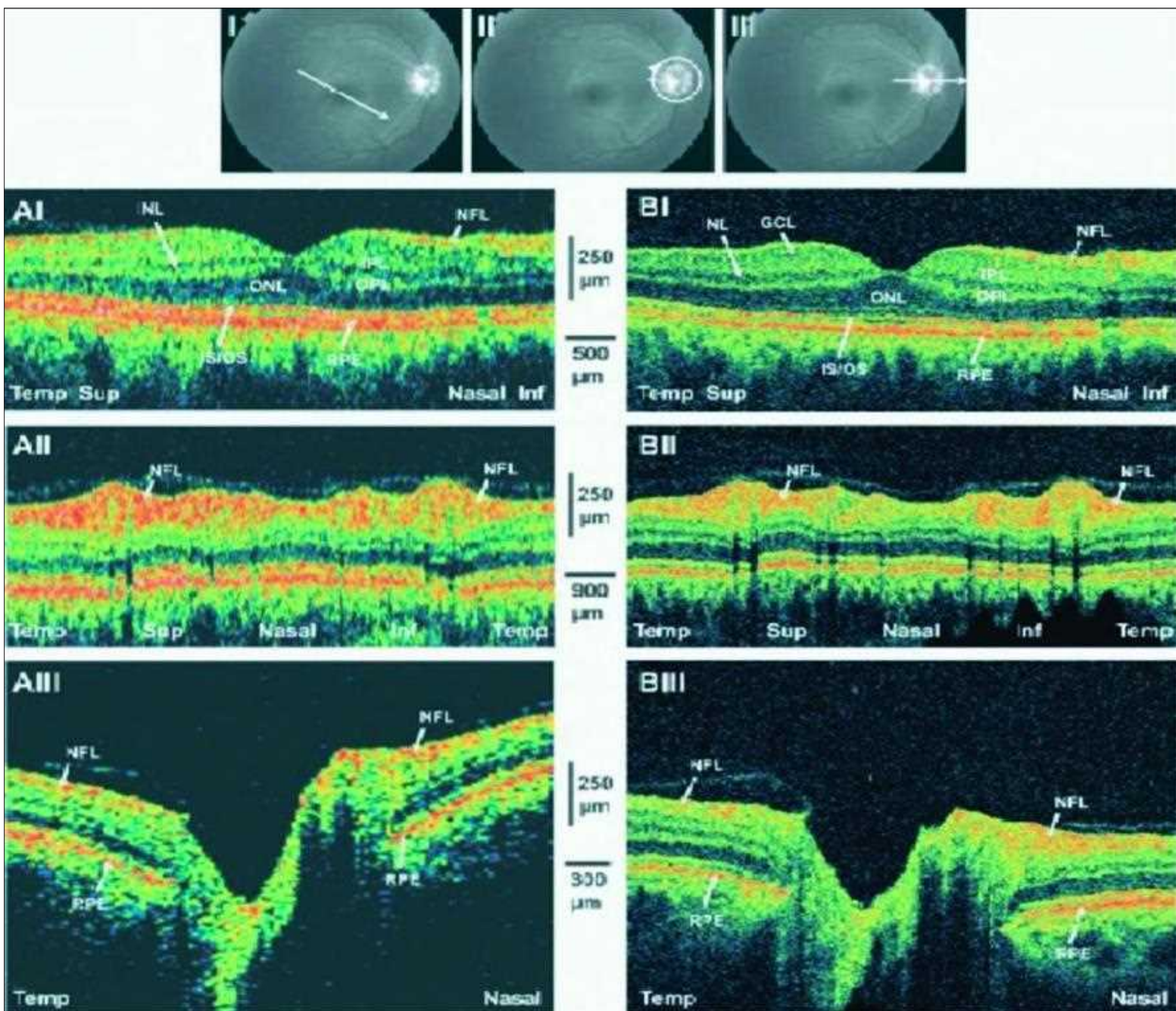
OCT has been shown to be able to detect subtle irregularities and has become essential for monitoring the pre- and postoperative courses of macular edema. Moreover, OCT can aid in differentiating the cause of the edema by identifying cystic spaces in CME or by visualizing the posterior hyaloid in cases of VMT. The advantage of OCT for the assessment of macular edema is its accuracy and reproducibility. In addition, retinal thickness more accurately correlates with visual acuity compared with the degree of fluorescein leakage on fluorescein angiography (FA).<sup>19</sup>

#### Irvine–Gass Syndrome: Cystoid Macular Edema After Cataract Surgery

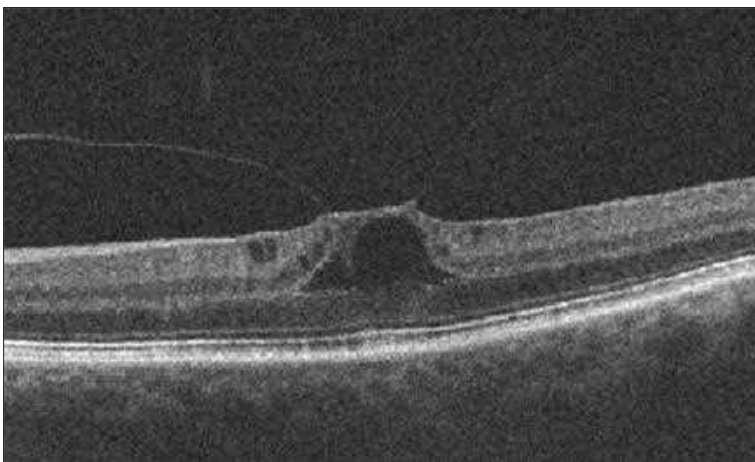
Approximately 20% of the patients who undergo uncomplicated phacoemulsification or extracapsular extraction develop CME, which can be detected on FA. Macular edema after cataract surgery begins in the inner nuclear layer in the perifoveal area. The central cysts tend to expand to the entire thickness of the retina to the IS/OS junction (Fig. 6.7.8).

### Retinal Exudates

Exudates in the retina are the result of leakage of fluid and lipoproteins as a result of increased vascular permeability. Resorption of the fluid results in the precipitation of lipids, most commonly in the outer plexiform layer of the retina but can also be seen in the subretinal space.<sup>20</sup> These exudates can be seen in any condition that causes chronic vascular leakage, including, but not limited to, diabetes, hypertension, Coats' disease, choroidal neovascularization, retinal macroaneurysm, and capillary hemangioma.



**Fig. 6.7.3** Stratus time-domain (TD)-OCT (A) and prototype, ultra-high-resolution optical coherence tomography (UHR-OCT) (B) scans of a normal subject. I, Macular linear scans, whose orientations are depicted in the upper image. II, Peripapillary circular scans. III, Optic nerve head (ONH) linear scans. Inf, inferior; INL, internal nuclear layer; IS/OS, inner segment/outer segment; NFL, nerve fiber layer; ONL, outer nuclear layer; OPL, outer plexiform layer; RPE, retinal pigment epithelium; Sup, superior; Temp, temporal. (From Wollstein G, Paunescu LA, Ko TH, et al. Ultrahigh-resolution optical coherence tomography in glaucoma. *Ophthalmology* 2005;112(2):229–37.)



**Fig. 6.7.4** Vitreomacular Traction (VMT). Vitreofoveolar traction resulting in an anterior–posterior tractional force leading to cystic macular edema.

On OCT, these exudative lesions appear as highly reflective areas that cause a shadowing effect of the underlying retinal layers (Fig. 6.7.9).

## Subretinal

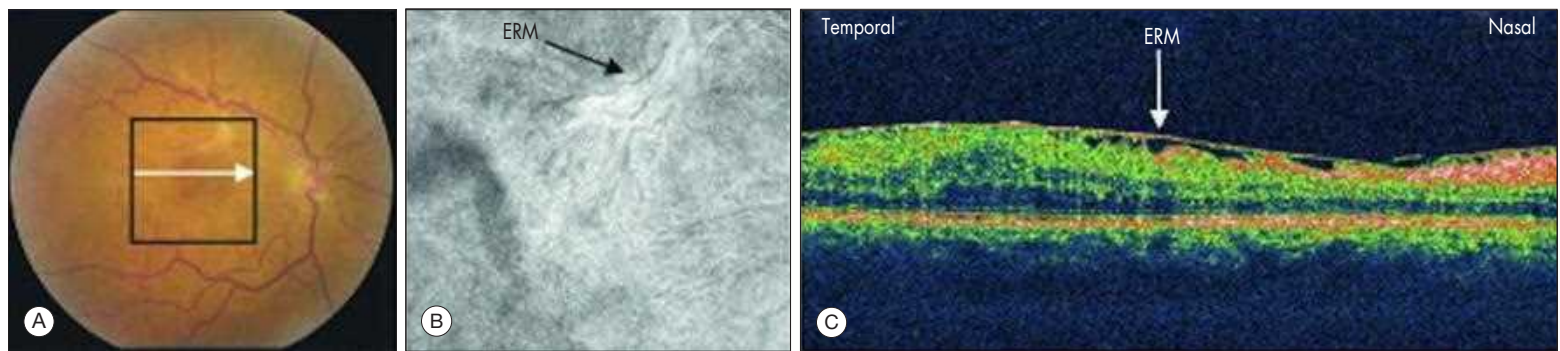
### Subretinal Fluid

Subretinal fluid causes a separation of the neurosensory retina from the underlying RPE. On OCT, an optically empty space can be seen between the detached retina and the RPE. This cavity is filled with serous fluid. Causes of subretinal fluid include retinal detachment, central serous chorioretinopathy, and choroidal neovascular membrane.

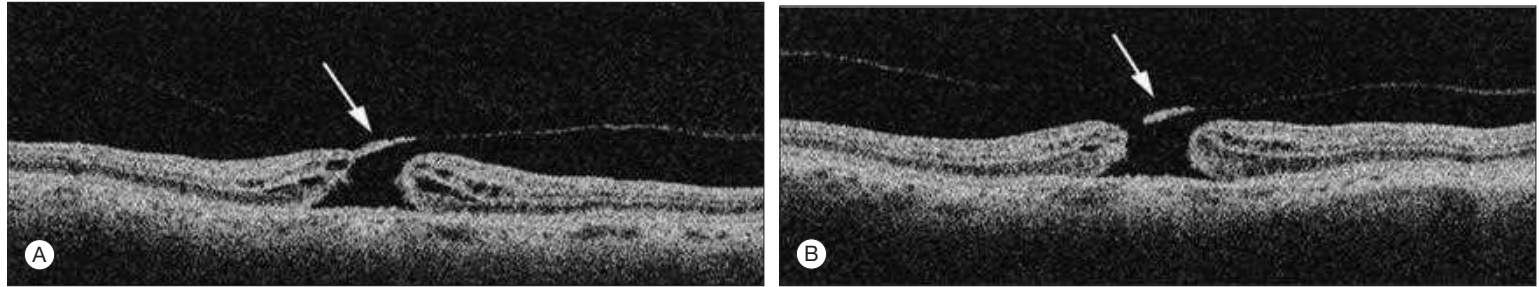
### Pigment Epithelial Detachment

A retinal pigment epithelial detachment (PED) is formed by the separation of the RPE from Bruch's membrane because of the presence of sub-RPE fluid, blood, fibrovascular membrane, or drusenoid material (Fig. 6.7.10). The various forms of PEDs differ in their underlying pathogenesis, OCT appearance, and response to therapy.

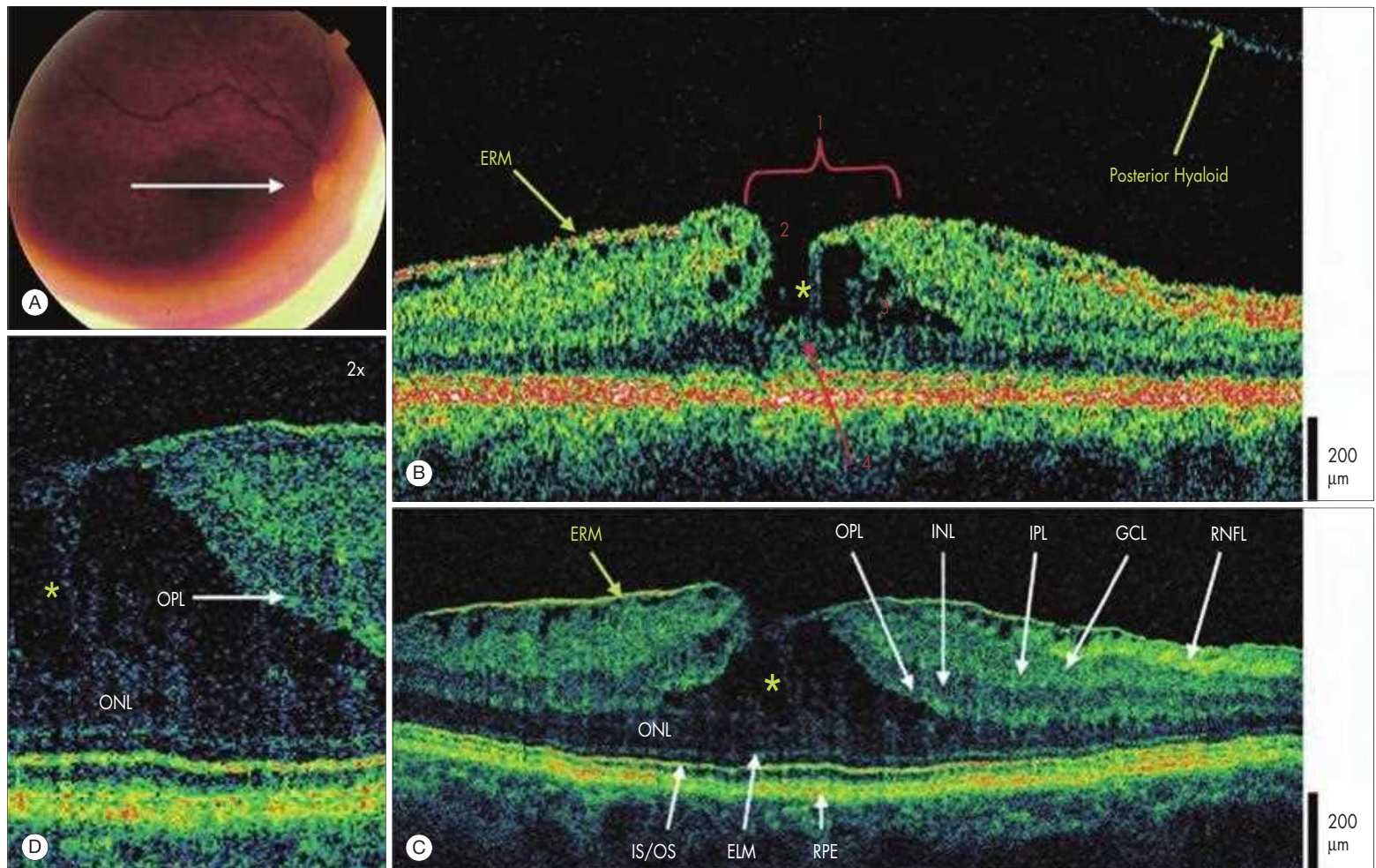




**Fig. 6.7.5** (A) Fundus photograph showing an epiretinal membrane (ERM) on the macula. (B) Reconstructed fundus image corresponding to black box on fundus photograph. (C) Spectral-domain optical coherence tomography image showing the ERM. (From Legarreta JE, Gregori G, Knighton RW, Punjabi OS, Lalwani GA, Puliafito CA. Three-dimensional spectral-domain optical coherence tomography images of the retina in the presence of epiretinal membranes. *Am J Ophthalmol* 2008;145(6):1023–30.)

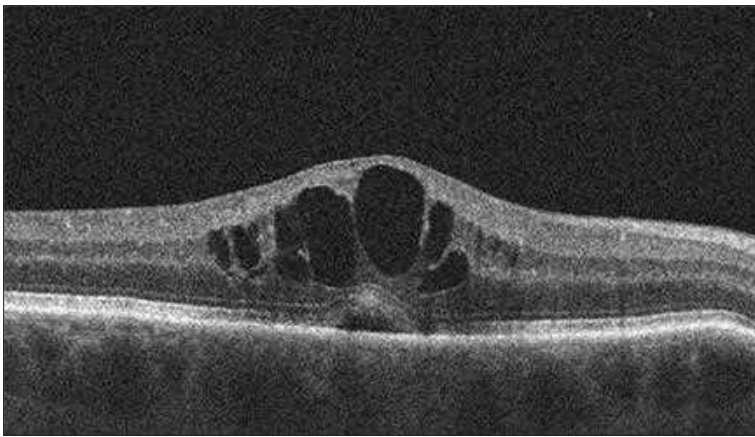


**Fig. 6.7.6** (A) Optical coherence tomography (OCT) scan shows a stage 2 hole. (B) OCT shows a stage 3 hole. (From Smiddy WE, Flynn HW, Jr. Pathogenesis of macular holes and therapeutic implications. *Am J Ophthalmol* 2004;137(3):525–37.)

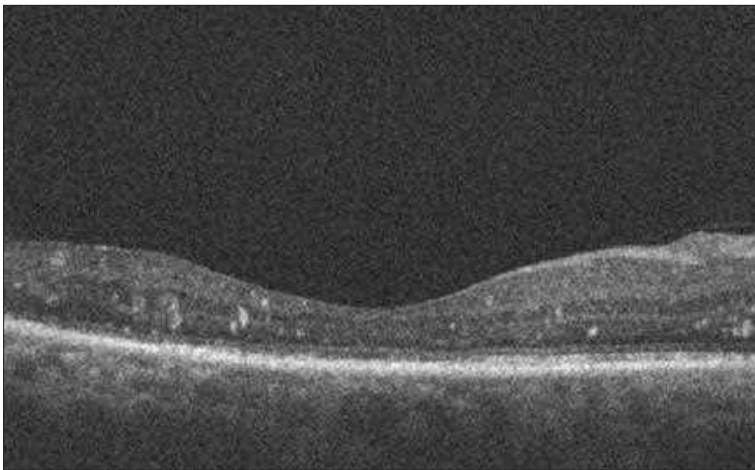


**Fig. 6.7.7** (A) Fundus photograph depicting lamellar hole and the direction of optical coherence tomography (OCT) scans. (B) Stratus OCT image demonstrates a lamellar hole. (C) Ultra-high-resolution optical coherence tomographic (UHR-OCT) image, which also shows intraretinal separation occurring between the outer plexiform layer (OPL) and the outer nuclear layer (ONL). The foveal photoreceptor layers are intact below the area of foveal dehiscence. (D) Magnification (x2) of UHR-OCT image shows strands of tissue spanning between the separated ONL and OPL (yellow asterisks), and the intraretinal split. (From Witkin AJ, Ko TH, Fujimoto JG, et al. Redefining lamellar holes and the vitreomacular interface: an ultrahigh-resolution optical coherence tomography study. *Ophthalmology* 2006;113(3):388–97.)

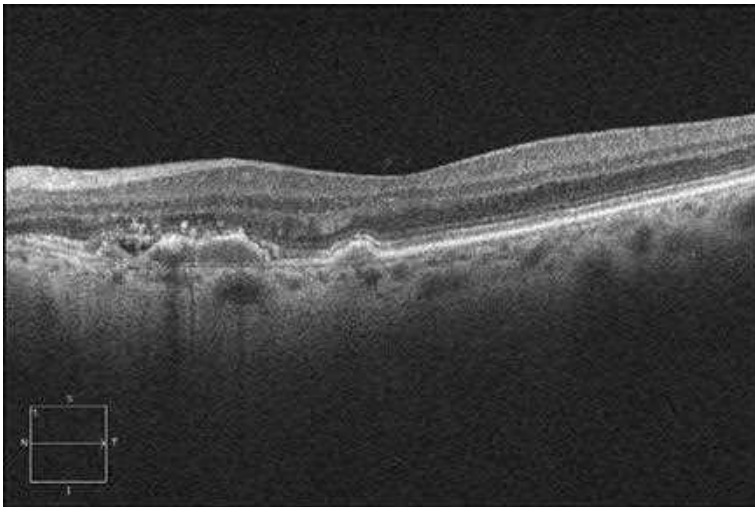




**Fig. 6.7.8** Pseudo-phakic cystoid macular edema (CME) 4 weeks following phacoemulsification cataract surgery.



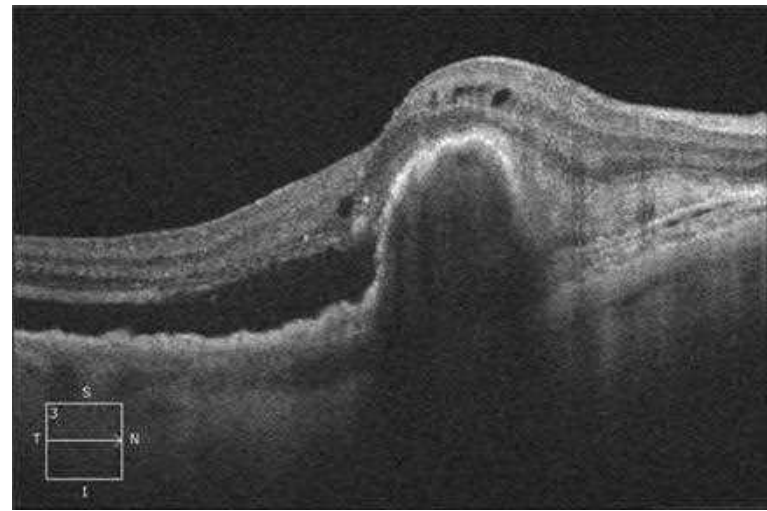
**Fig. 6.7.9** Highly reflective hard exudates accumulated in the inner portion of the neurosensory retina. A faint shadow of low reflectivity is behind the hard exudates in the outer retinal layers and retinal pigment epithelium.



**Fig. 6.7.10** Optical coherence tomography (OCT) image through drusenoid pigment epithelial detachment (PED).

### RPE Tear

RPE tear is a potentially visually devastating complication of PED. The tear is caused by contraction and retraction of the elevated PED, leading to absence of RPE underneath the neurosensory retina. Tears can be seen after treatments, including laser photocoagulation, photodynamic therapy, and anti-vascular endothelial growth factor therapy. Characteristic findings on OCT include focal interruption of the RPE signal, hyperreflectivity of the retracted and rolled RPE, and increased reflectivity of the bare choroid as a result of increased signal penetration in the absence of overlying RPE<sup>21,22</sup> (Fig. 6.7.11).



**Fig. 6.7.11** Optical coherence tomography (OCT) image of a retinal pigment epithelium (RPE) tear.

## Choroidal Pathology

Cross-sectional imaging of the choroid is challenging because of light scattering and absorption. One method using SD-OCT is enhanced depth imaging (EDI). In EDI, the OCT machine is moved closer to the eye, thereby placing the peak sensitivity curve closer to the region of the choroid. Averaging approximately 100 images together improves the image resolution. The image is then reinverted to correlate to the anatomical orientation of the tissue. Averaging images is possible with instruments that are capable of eye tracking.<sup>23</sup>

### Choroidal Neovascularization

Choroidal neovascularization (CNV) can complicate many ocular conditions, including AMD, uveitis, myopia, presumed ocular histoplasmosis, angioid streaks, and choroidal rupture. CNV is subdivided into different subtypes: type 1 (below the RPE), type 2 (above RPE below retina), and type 3 (retinal angiomatous proliferation [RAP]). Choroidal blood vessels invade the sub-RPE (type 1) or subretinal space (type 2) via a break in Bruch's membrane or from an anastomosis with the retinal circulation (type 3). Histologically, these blood vessels lack endothelial tight junctions, which leads to serous fluid leakage.

Advancements in high-resolution three-dimensional OCT suggest that retinal neovascularization alone or concomitant CNV can be present in early RAP. Early lesions present with extensive macular edema and cyst formation as the lesion progresses, the neovascularization extends beneath the retina, and subretinal fluid accumulates. In later stages, serous PED occurs, and CNV becomes evident. At this stage, it is difficult to differentiate between CNV subtypes. Therefore, OCT is useful in the initial stage of type 3 neovascularization to image the vessels and the cystic spaces within the retina. However, once a PED occurs, it is very challenging to assess the sub-RPE changes.<sup>24</sup>

NOTE: Applications of OCT in the fields of glaucoma, cornea, and neuro-ophthalmology are discussed in the other chapters in this text.

## OCT Artifacts

### Time-Domain OCT

Artifacts are commonly encountered with the use of TD-OCT, often related to errors in acquisition or interpretation. Acquisition errors are caused by the speed of obtaining the image and the presence of media opacities or optical aberrations. Because of the relatively long acquisition time, excessive eye movements or poor fixation will degrade the image.

### Spectral-Domain OCT

Compared with TD-OCT, acquisition speed is about 50 times faster with SD-OCT, minimizing motion artifacts. In spite of this, acquisition artifacts can still occur as a result of poor centration of the image or presence of media opacities. In addition, the capability of generating a three-dimensional image of the macula reduces the chances of missing focal lesions. SD-OCT also facilitates acquisition of significantly larger numbers of scans, allowing for higher resolution.

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# Optical Coherence Tomography Angiography

6.8

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**Definition:** Optical coherence tomography angiography (OCTA) is an imaging modality that uses variation (or decorrelation) in the optical coherence tomography (OCT) signal to detect motion in biological tissues.

### Key Features

- OCTA can noninvasively detect the movement of red blood cells at capillary-level resolution.
- OCTA is particularly useful for detecting regions of impaired perfusion and neovascularization.
- OCTA has been used to evaluate many of the pathological macular changes in retinal vascular diseases, including diabetic retinopathy, retinal vein occlusion, macular telangiectasia, and neovascular age-related macular degeneration.

### INTRODUCTION

Optical coherence tomography (OCT) is a noninvasive imaging method that has been used extensively in the field of ophthalmology since 2002. OCT generates high-resolution cross-sectional images of the retina based on the interference of back-scattered coherent light.<sup>1</sup> Progress in OCT technology has facilitated new OCT-based imaging methods, such as polarization-sensitive OCT,<sup>2</sup> spectroscopic OCT,<sup>3</sup> phase-sensitive OCT,<sup>4-6</sup> and spectral-domain (SD) OCT angiography (OCTA).<sup>7</sup> OCTA is a functional extension of OCT and is being used increasingly to detect microvascular changes in many retinal diseases since approval by the U.S. Food and Drug Administration in 2016. We will briefly review the biological basis of OCTA imaging, highlight the various methods of generating OCTA images, and discuss the strengths and limitations of this novel method.

### BIOLOGICAL BASIS OF OCTA

OCTA is based on the variation in OCT signal caused by moving particles, such as red blood cells (RBCs), in contrast to stationary surrounding neurosensory tissue. This variability is relatively analogous to the Doppler shift that moving particles impose on reflected light. Although there are several different methods of performing OCTA imaging (Table 6.8.1), all of these methods differentiate moving particles from static retinal tissue by comparing multiple (two or more) OCT B-scans performed at the same location.<sup>8</sup> This is in contrast to standard OCT, which performs a single B-scan at each location. Because RBCs are constantly moving, they generate

a unique variation in the intensity and phase of the backscattered OCT signal compared with the nonmoving retinal tissue within each repeated B-scan at the same location. Several methods of analyzing this variance have been developed and can be divided into those that use the phase variance of light, the intensity variance of light, or both phase and intensity (see Table 6.8.1).

OCTA images provide a map of retinal vessels with blood flow detectable on SD-OCTA devices, but do not provide the rate of blood flow at any locations (Fig. 6.8.1). In vitro studies and some in vivo studies suggest that current SD-OCTA devices can detect blood flow in the range of 0.3–3.3 mm/sec.<sup>8</sup> This is approximately the range that has been demonstrated by confocal scanning laser ophthalmoscopy.<sup>9</sup> Flow rates above or below this range may artifactually appear as regions of “nonperfusion.” Also of note, although RBCs are the most mobile component of retinal tissue, any particulate motion can theoretically generate similar motion contrast signal. For example, lipid particulates in solution generate OCTA signals as a result of Brownian motion.<sup>10</sup> Therefore, the possibility of artifactual signal should be considered when interpreting OCTA images.

### OCTA VERSUS DYE-BASED ANGIOGRAPHY METHODS

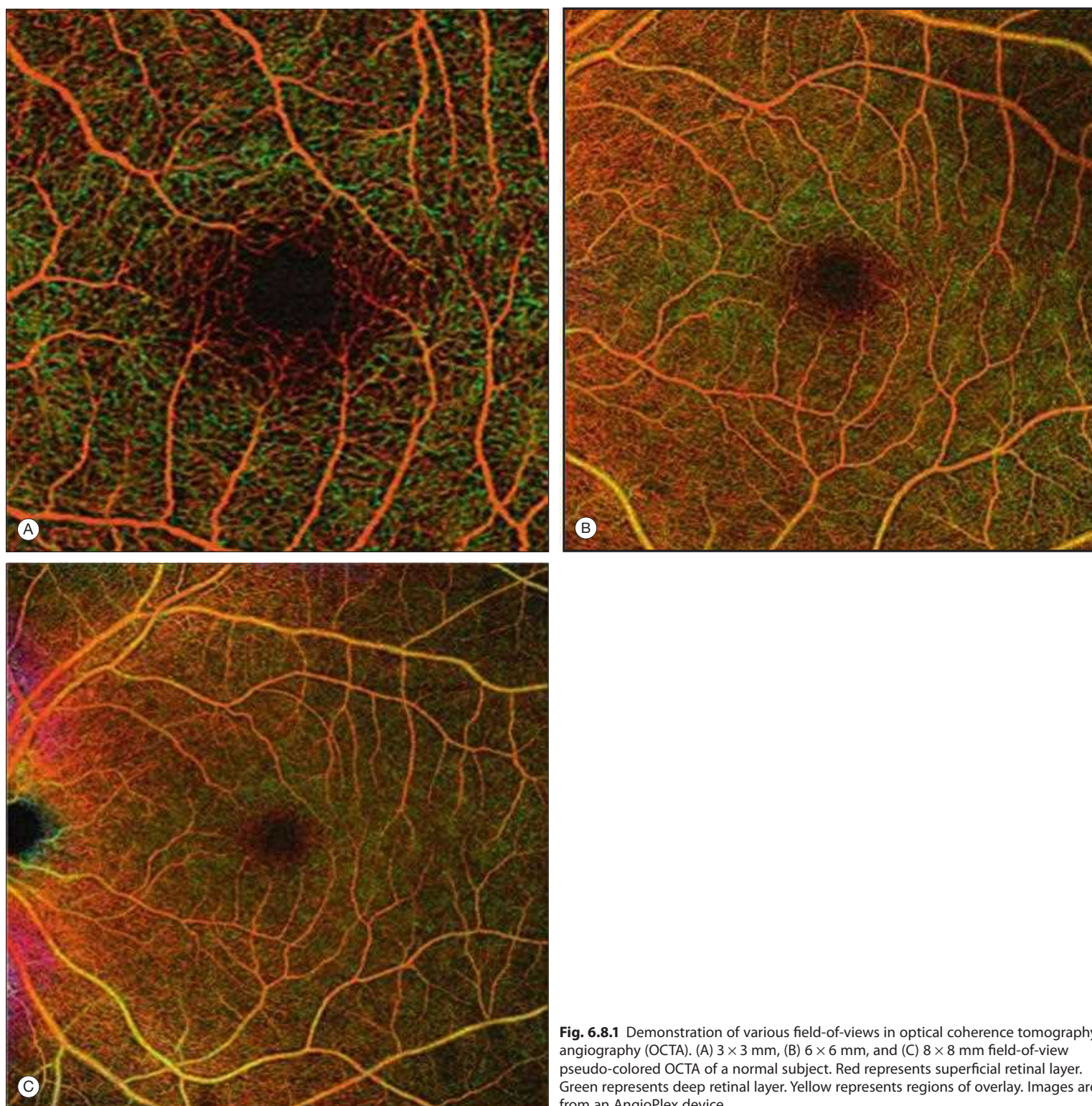
With the rapid adoption of OCTA, it becomes necessary to determine the appropriate roles of OCTA versus those of fluorescein angiography (FA) and indocyanine green angiography (ICGA). Table 6.8.2 summarizes many of the strengths, limitations, and practical applications of these methods. It is important to recognize that although OCTA and dye-based angiography methods provide somewhat similar en face images, they measure different biological phenomena. Specifically, OCTA is based on light scattering from RBCs and particulate debris, so there is no diffusion of dye on OCTA images. This fundamental difference is illustrated by the absence of “leakage” on OCTA images in subjects who have macular edema on FA. Another illustration of this difference is the variable rate of microaneurysm detection on OCTA in comparison with FA.

Many studies have demonstrated that OCTA does not directly detect hyporeflective pockets of intraretinal fluid as observed on OCT. Nor does OCTA demonstrate the hyperfluorescence that is observed in late phase FA in subjects with diabetic macular edema or cystoid macular edema.<sup>11-14</sup> This is attributed to the notion that fluid within most cystoid spaces does not contain large particles that can backscatter light.<sup>10</sup> In contrast, FA is based on the tissue distribution and fluorescence of dye molecules that leak into cystoid spaces. Although dye leakage highlights cystoid spaces as well as abnormal vessels, such as neovascularization (Fig. 6.8.2), it also tends to obscure potentially relevant details both in pathological cases as well as normal cases. This is because there is still modest dye leakage from normal vessels which increases the background noise in FA and ICGA.<sup>15-17</sup> For example, high background fluorescence can make it appear as though the macula is completely ischemic by obscuring fine capillaries in proliferative diabetic retinopathy, whereas OCTA can clearly demonstrate the persistence of capillaries and visual potential.

Some recent studies have highlighted the significant difference in appearance of microaneurysms on OCTA versus FA,<sup>12</sup> whereas others have shown significant similarities.<sup>13</sup> In some cases, the excellent depth resolution of OCTA images has revealed that lesions consistent with the appearance of microaneurysms on FA are actually small tufts of neovascularization.<sup>14</sup> It has also been demonstrated that, at least in some cases, microaneurysms are not detected as frequently on OCTA as on FA.<sup>12</sup> Even

TABLE 6.8.1 Summary of Optical Coherence Tomography Angiography (OCTA) Methods

Phase-Based OCTA	Intensity-Based OCTA	Phase + Intensity (Complex) OCTA
<ul style="list-style-type: none"><li>• Doppler OCTA</li><li>• Phase variance</li></ul>	<ul style="list-style-type: none"><li>• Speckle variance</li><li>• Correlation mapping</li><li>• Split-spectrum amplitude decorrelation (SSADA)</li></ul>	<ul style="list-style-type: none"><li>• Optical microangiography (OMAG)</li><li>• Multiple signal classification OMAG</li><li>• Imaginary part-based correlation mapping</li><li>• Split spectrum-phase gradient</li></ul>



**Fig. 6.8.1** Demonstration of various field-of-views in optical coherence tomography angiography (OCTA). (A)  $3 \times 3$  mm, (B)  $6 \times 6$  mm, and (C)  $8 \times 8$  mm field-of-view pseudo-colored OCTA of a normal subject. Red represents superficial retinal layer. Green represents deep retinal layer. Yellow represents regions of overlay. Images are from an AngioPlex device.

when microaneurysms are detected on OCTA, they are usually of different sizes and shapes compared with those on FA. It is likely that the reason for this and the discrepancy among studies is that some microaneurysms are sclerosed or clotted and without blood flow, whereas others are patent or partially patent.<sup>18</sup> Because OCTA only detects the movement of RBCs, sclerosed or clotted microaneurysms will not appear at all on OCTA. In addition, the flow rate of blood within microaneurysms may be outside the detection speed of SD-OCTA devices.<sup>19</sup> Microaneurysms that are partially sclerosed or partially recanalized will also appear much smaller on OCTA than on FA because only the region with RBC flow will be visualized on the former, whereas the whole lesion will stain with dye on FA.

Other considerations for the use of dye-based angiography versus OCTA are their practical limitations and strengths (see Table 6.8.2). These considerations include how each method is performed and the resolution of the images. The most important drawback of any dye-based method is

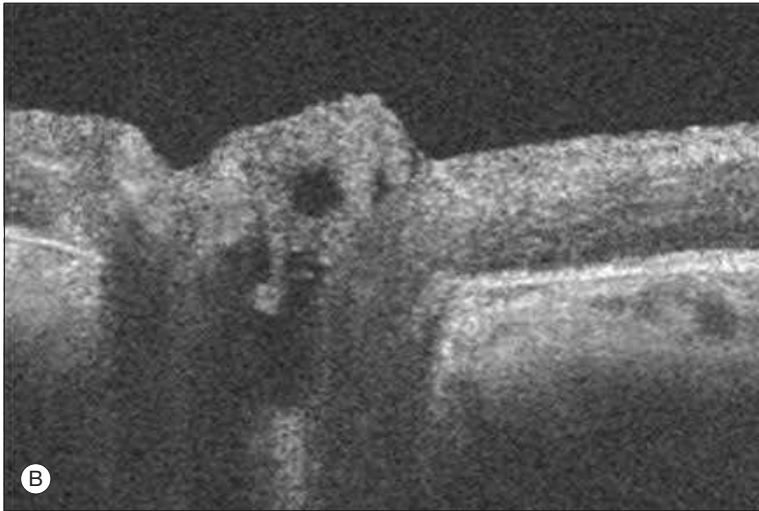
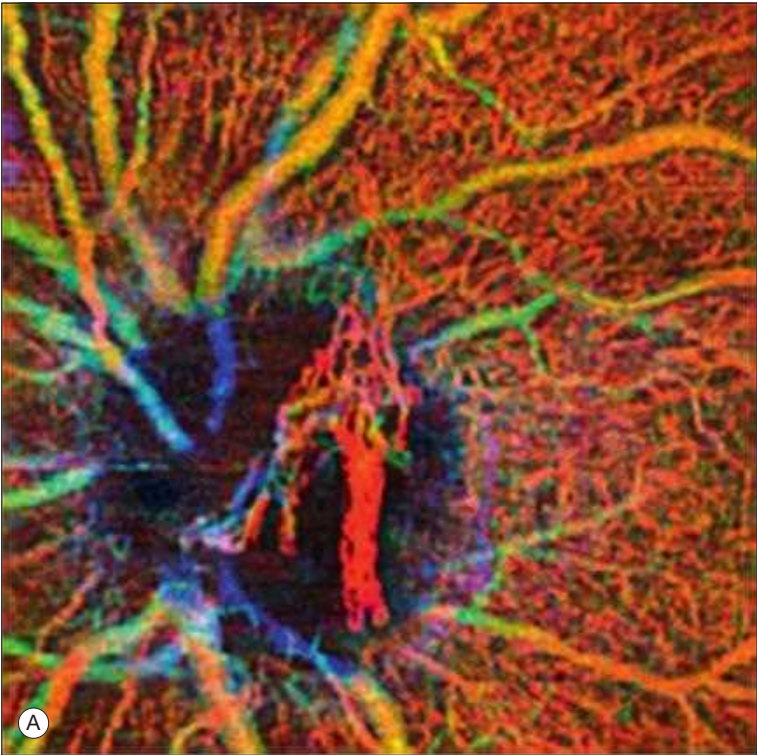
the possibility of adverse reactions ranging from mild reactions to severe and possibly life-threatening reactions.<sup>16,20,21</sup> An important strength of dye-based imaging methods is that current wide-field systems provide an almost comprehensive assessment of the central and peripheral retina. In addition, ICGA is generally superior in detection of choroidal neovascularization (CNV) compared with current OCTA systems because of the limited penetration of the OCTA signal through the retinal pigment epithelium (RPE). Lastly, compared with OCTA, dye-based angiography has relatively limited resolution. For example, although FA can delineate the foveal avascular zone very well in primates, <40% of the capillaries outside the foveal center are visualized on FA as compared with histology.<sup>22</sup> Mendis et al. showed that FA assessment of capillary density is  $\approx 50\%$  less than histology-based assessments.<sup>15</sup> Specifically, FA cannot resolve the radial peripapillary plexus or the capillaries in the deep retinal layers.<sup>23</sup> In contrast, OCTA clearly and reliably resolves these capillaries in human subjects.<sup>23,24</sup>



TABLE 6.8.2 Strengths and Limitations of Optical Coherence Tomography Angiography (OCTA) Versus Dye-Based Imaging Methods

Imaging Method	Strengths	Limitations <sup>a</sup>	Optimal Applications
Fluorescein angiography (FA)	<ul style="list-style-type: none"><li>• Wide-field imaging</li><li>• Leakage demonstrates compromised vessels and vascular permeability</li><li>• Retinal neovascularization</li></ul>	<ul style="list-style-type: none"><li>• Mild and severe adverse reactions</li><li>• Time intensive (15–20 minutes)</li><li>• Labor intensive (requires nurse or trained photographer)</li></ul>	<ul style="list-style-type: none"><li>• Baseline evaluation of any retinal vascular disease</li><li>• Evaluation of peripheral retina</li><li>• Detection of neovascularization</li></ul>
Indocyanine green angiography (ICGA)	<ul style="list-style-type: none"><li>• Wide-field imaging</li><li>• Leakage demonstrates compromised vessels and vascular permeability</li><li>• Choroidal neovascularization and sub-RPE lesions</li><li>• Noninvasive</li><li>• Minimal risk</li><li>• Fast (3–4 minutes)</li><li>• Not labor intensive</li></ul>	<ul style="list-style-type: none"><li>• Requires ancillary supplies</li><li>• Requires invasive dye injection</li><li>• Limited time to acquire transit images</li><li>• Leakage from normal vessels increases background noise</li><li>• Relatively low resolution compared to histology</li></ul>	<ul style="list-style-type: none"><li>• Baseline evaluation of any choroidal vascular disease</li><li>• Evaluation of peripheral retina</li><li>• Detection of choroidal neovascularization</li><li>• Patients with known dye allergy or sensitivity</li></ul>
OCTA	<ul style="list-style-type: none"><li>• High resolution (analogous to histology)</li><li>• Depth resolved images illustrates peripapillary plexus and deep retinal capillaries</li><li>• Repeatable on monthly basis or more often, as needed</li></ul>	<ul style="list-style-type: none"><li>• Limited resolution of sub-RPE pathology such as CNV</li><li>• Limited resolution of choriocapillaris changes</li><li>• Limited field-of-view</li><li>• Projection artifacts</li><li>• Movement artifacts</li><li>• No specific billing code</li></ul>	<ul style="list-style-type: none"><li>• Follow-up evaluation of any retinal vascular disease with macular findings</li><li>• Detection of mild perfusion defects</li><li>• Detection of layer specific perfusion changes</li><li>• Patients who are pregnant, are breast-feeding, have severe renal disease, are transplant recipients, or have poor IV access</li></ul>

<sup>a</sup>Limitations column applies to both ICGA and FA.  
CNV, Choroidal neovascularization; IV, intravenous; RPE, retinal pigment epithelium.



**Fig. 6.8.2** Illustration of neovascularization of the disc in a subject with proliferative diabetic retinopathy. (A) Depth-encoded optical coherence tomography angiography (OCTA) image of optic disc with overlying neovascularization in red. In this case, the neovascularization appears red because it is within the same plane or above the plane of the superficial retinal layer. (B) B-scan illustrates the location of the neovascularization above the optic disc. Red = superficial retinal layer; green = deep retinal layer; yellow = overlap. Images are from an AngioPlex device.

One final caveat with regard to OCTA is the potential to misinterpret images because of artifacts.<sup>25</sup> In many cases, the artifacts on OCTA are similar to and derived from artifacts that are observed on standard OCT images. The most common in OCTA images is called a “projection artifact,” where vessels in the superficial retinal layers cast shadows or “projections” on deeper retinal layers, which results in the artifactual appearance of vessels where none exists. This is most clinically relevant in the interpretation of choroidal pathology and CNV. An excellent review of the subject is available,<sup>26</sup> and several methods of removing these artifacts have been developed.<sup>26,27</sup>

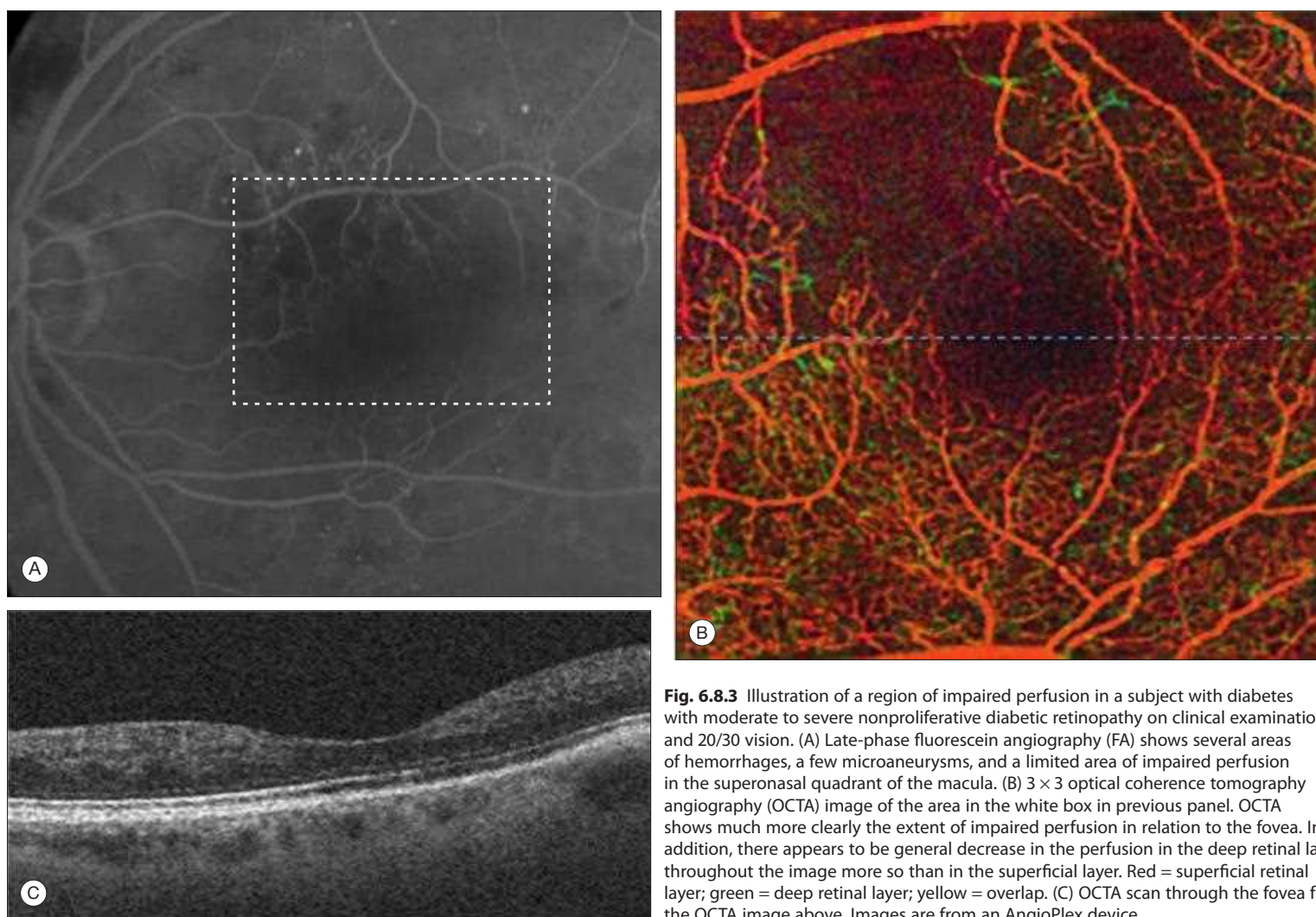
KEY APPLICATIONS OF SD-OCTA

Detection of Impaired Perfusion (or “Nonperfusion”)

In this chapter, we refer to “nonperfusion” as “impaired perfusion.” Because it is very hard to absolutely demonstrate lack of blood flow with

any current imaging method, the term “nonperfusion” is misleading and likely inaccurate in many cases. For both dye-based imaging studies as well as OCTA, there can be very slow blood flow rates that are either obscured by background noise or undetectable. Because of the relatively low resolution of FA, impaired perfusion is likely very severe by the time it is detectable on FA. In contrast, OCTA can reliably resolve individual capillaries with unprecedented depth-resolution in humans.<sup>23,24,26,28</sup> OCTA images demonstrate capillary detail approaching the resolution of histology.<sup>15,23,24,29</sup> This makes OCTA an ideal method for detecting and monitoring regions of impaired perfusion in subjects with retinal vascular disease (Fig. 6.8.3). In addition, OCTA can be repeated many times to obtain the ideal image with essentially no risk to subjects, which is not possible with FA. Therefore, OCTA provides a whole new dimension of depth information regarding the severity of impaired perfusion that is not possible with FA. For example, studies have suggested that impairment of perfusion in the deep retinal layers is more severe in certain diseases, such as paracentral acute maculopathy,<sup>30</sup> diabetic retinopathy,<sup>31</sup> and retinal venous occlusion.<sup>11,32,33</sup> In addition, detection of capillary loss in the macula of patients with diabetes<sup>28,34</sup> and peripapillary capillary plexus of patients with glaucoma<sup>35,36</sup>





**Fig. 6.8.3** Illustration of a region of impaired perfusion in a subject with diabetes with moderate to severe nonproliferative diabetic retinopathy on clinical examination and 20/30 vision. (A) Late-phase fluorescein angiography (FA) shows several areas of hemorrhages, a few microaneurysms, and a limited area of impaired perfusion in the superonasal quadrant of the macula. (B) 3 × 3 optical coherence tomography angiography (OCTA) image of the area in the white box in previous panel. OCTA shows much more clearly the extent of impaired perfusion in relation to the fovea. In addition, there appears to be general decrease in the perfusion in the deep retinal layer throughout the image more so than in the superficial layer. Red = superficial retinal layer; green = deep retinal layer; yellow = overlap. (C) OCTA scan through the fovea from the OCTA image above. Images are from an AngioPlex device.

is now possible before clinical lesions are evident. The clinical relevance of this additional information remains to be determined, but at the least OCTA will allow for detection of impairment in blood flow (ischemia) much earlier than before and help assess the severity of the impairment with far more precision.

### Detection of Choroidal Neovascularization

Many studies have demonstrated that OCTA is useful for detecting and assessing the severity of CNV in several diseases, including neovascular age-related macular degeneration (AMD),<sup>37–39</sup> macular telangiectasia,<sup>40</sup> uveitis,<sup>41</sup> and central serous retinopathy,<sup>42</sup> among others (Fig. 6.8.4). Because OCTA is completely noninvasive and easy to perform in the clinic, it provides an unprecedented opportunity for real-time evaluation of retinal vascular changes. For example, the real-time regression of CNV during antivascular endothelial growth factor therapy has been demonstrated by using OCTA.<sup>43</sup> Although OCTA can detect the presence and extent of CNV above the RPE (type 2), CNV detection for lesions below the RPE may be more challenging because the RPE is highly reflective and can severely attenuate the OCTA signal.<sup>38,44–46</sup> Nevertheless, OCTA imaging of CNV lesions can be useful because it can be performed with higher frequency compared with FA or ICGA. The clinical significance of this has yet to be determined, but it is promising that OCTA is allowing earlier detection of lesions that could progress and cause vision loss.

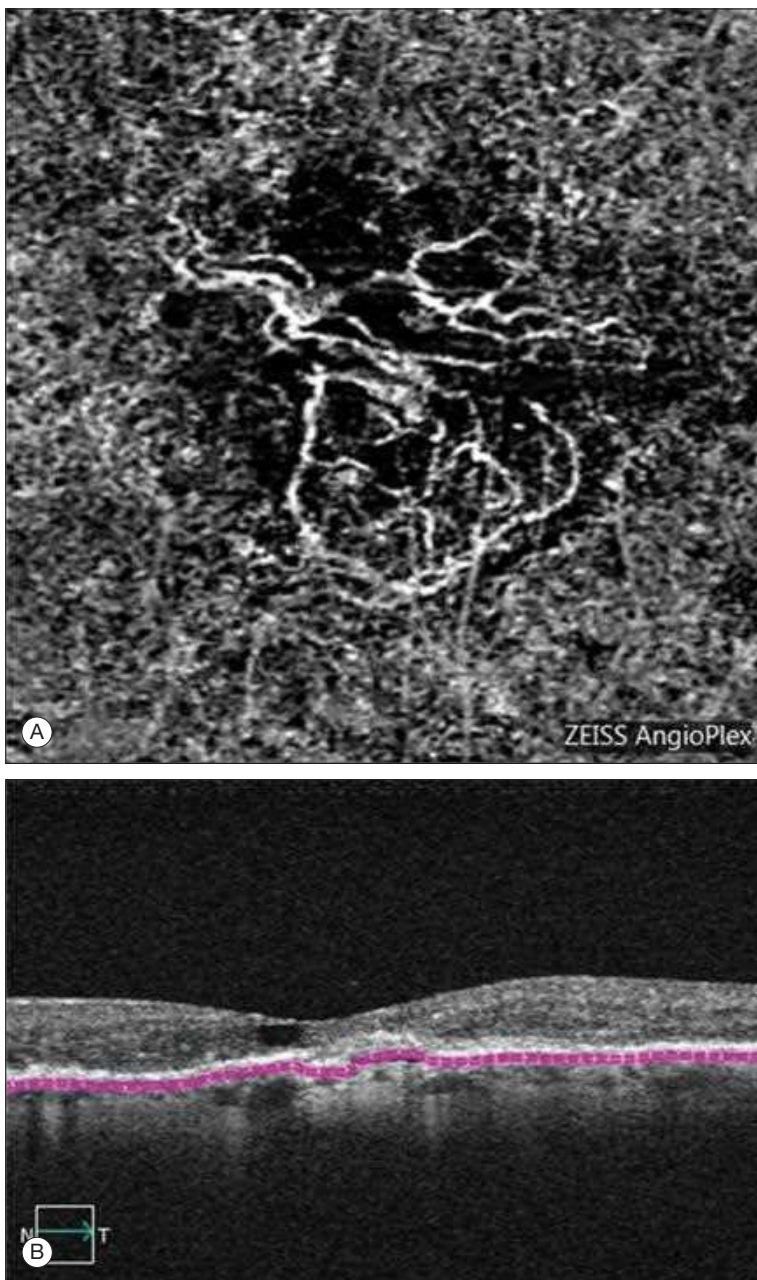
### Quantification of Vascular Changes

One of the most promising applications of OCTA is objective and quantifiable assessment of capillary level changes in the retina. The fact that OCTA has excellent spatial resolution, poses minimal risk, and is very fast makes it amenable for real-time assessment of capillary level changes in several

retinal diseases. For example, in diabetic retinopathy, several studies have demonstrated that OCTA-based metrics, such as capillary density, correlate with the clinical severity of the disease.<sup>31,47–49</sup> Similar metrics have been demonstrated to correlate with clinical severity of disease in subjects with retinal venous occlusion,<sup>50–53</sup> history of uveitis,<sup>54</sup> and glaucoma.<sup>36,55</sup>

### CONCLUSIONS

In summary, OCTA is rapidly becoming an important tool for the diagnosis and management of retinal vascular diseases. It is clear that OCTA is at least as good as invasive dye studies for assessing the macular complications of retinal diseases, such as diabetic retinopathy, retinal venous occlusion, and some forms of macular degeneration. It is also clear that the excellent depth and lateral resolution of OCTA in general makes it superior to FA, allowing for detection of much milder vascular changes. The main limitation of OCTA in clinical applications is the field of view, but this is rapidly improving as commercial systems adopt larger scan patterns. Therefore dye-based angiography is still necessary for assessment of the peripheral retina. Another major limitation of OCTA is the suboptimal detection of choroidal neovascularization and other pathology found beneath the RPE. It is very likely that emerging swept-source systems with longer wavelengths of coherent light will overcome both of these limitations. For the spectrum of retinal vascular disease that has been managed with invasive dye studies in the past, it is very likely that OCTA will gradually become the dominant modality for both diagnosis and management of macular complications. For diseases in which dye-based angiography had no role, such as glaucoma, OCTA provides a novel tool to assess the peripapillary capillary plexus. Given the speed with which clinical interest around OCTA is evolving, it will not be long before all of these limitations are overcome. OCTA stands to change the practice of ophthalmology in the next decade as profoundly as it has changed it in the last.



**Fig. 6.8.4** Illustration of choroidal neovascularization (CNV) in a subject with neovascular age-related macular degeneration (AMD). (A) OCTA image of choriocapillaris slab demonstrates large caliber and irregularly organized vessels in the CNV complex. (B) B-scan illustrates the boundaries of the OCTA slab shown in the above panel and location of the CNV within the retinal profile. Images are from an AngioPlex device.

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# Retinal Electrophysiology

Elias Reichel, Kendra Klein

## 6.9

**Definition:** Objective functional ancillary testing of the retina and/or retinal pigment epithelium (RPE) that records electrical responses based on various stimuli and assists in the diagnosis and management of various retinal diseases, especially inherited retinal dystrophies, autoimmune disorders, inflammations, and medication toxicities.

### Key Features

- Electroretinography (ERG) records the electrical response evoked from the entire retina by a brief flash of light and consists of an *a*-wave, which represents the photoreceptor response, and a *b*-wave, which represents the combined response of the Müller and bipolar cells.
- The multifocal ERG (mfERG) is a record of multiple local ERG responses elicited from the central 40° of the retina.
- Electrooculography (EOG) records the standing electrical potential generated by the RPE.
- The International Society for Clinical Electrophysiology of Vision (ISCEV) provides worldwide standardized clinical protocols for electrophysiological testing, including guidelines for ERG, mfERG, and EOG testing.

### INTRODUCTION

Electrophysiology encompasses several objective examination techniques that measure the function of the retina by measuring action potentials caused by particular patterns of light stimulation within the retina. Clinical electroretinography (ERG) is useful to determine the existence of retinal degenerative conditions caused by hereditary, toxic, metabolic, retinal vascular, or inflammatory etiologies, being particularly valuable in determining the abnormal nature of what clinically appears to be a normal retina. Full-field ERG represents a mass-evoked response of the outer retinal layers, which reflects total retinal function. The multifocal (mf)-ERG represents a cone-generated response of localized retinal function in the central macula, which is useful in establishing the presence of macular dysfunction. Electro-oculography (EOG) represents the standing electrical potential of the entire eye, which reflects the pigment epithelium. These electrophysiological results should be considered in conjunction with those of complete medical and ophthalmic evaluations, including a careful history and laboratory testing, when indicated.<sup>1,2</sup>

### FULL-FIELD ERG

The full-field, or Ganzfeld, ERG measures a mass response generated by cells from the entire retina. Photoreceptors generate the initial negative component, or *a*-wave, whereas Müller cells and bipolar cells are responsible for the later, positive, *b*-wave. Both *a*-wave and *b*-wave are best illustrated in the maximal combined rod-cone response. The ganglion cell layer does not contribute to the ERG. The full-field ERG is useful for establishing generalized loss of rod or cone function, or both. Patients who have focal macular disorders do not have abnormalities of full-field ERG amplitude, nor do patients who have diseases of the inner retina, optic nerve, or cortical conditions.<sup>1,2</sup>

Starting in 1989, the International Society for Clinical Electrophysiology of Vision (ISCEV) has put forth standardized basic ERG protocols to allow comparison across laboratories, and these protocols are periodically updated. The most recent ISCEV standard for full-field clinical ERG includes six protocols, which are named according to the stimulus (flash

strength in candela-seconds per meter squared [ $\text{cd/s/m}^2$ ]) and the adaptation state<sup>3</sup> (Fig. 6.9.1). In preparation, the pupils should be maximally dilated, and the pupil size should be noted before and after the responses are recorded. Prior to recording scotopic electroretinograms, the patient should have 20 minutes of dark adaptation, and prior to recording scotopic electroretinograms, the patient should have 10 minutes of light adaptation. Following dark adaptation, weaker flashes of light stimuli should be presented prior to stronger flashes. Likewise, fluorescein angiography (FA) and fundus photography should be avoided directly prior to testing. Contact electrodes (connected to the positive input) are utilized and include corneal contact lenses, conjunctival conductive fibers, and lower eyelid skin electrodes. The cornea is protected with nonirritating conductive solution, and topical anesthesia is employed, as necessary. Reference electrodes (connected to the negative input) are incorporated either as a contact lens–speculum assembly or as skin electrodes placed near each orbital rim. A separate electrode is used as the common electrode and is attached to the earlobe, mastoid, or forehead. Full-field (Ganzfeld) stimulation is used for uniform retinal illumination with a fixation spot. The maximum flash duration is 5 milliseconds (ms). The flash strength for ERG testing is described in units of  $\text{cd/s/m}^2$ , with a weak flash stimulus strength of 0.010 photopic  $\text{cd/s/m}^2$ , a standard flash stimulus of 3  $\text{cd/s/m}^2$ , and a strong flash stimulus of 10 photopic  $\text{cd/s/m}^2$ . Light adaptation and background luminance are set at 30  $\text{cd/s/m}^2$ . Stimulus and response names are described by the state of light adaptation and the flash strength in photopic  $\text{cd/s/m}^2$ .<sup>3</sup>

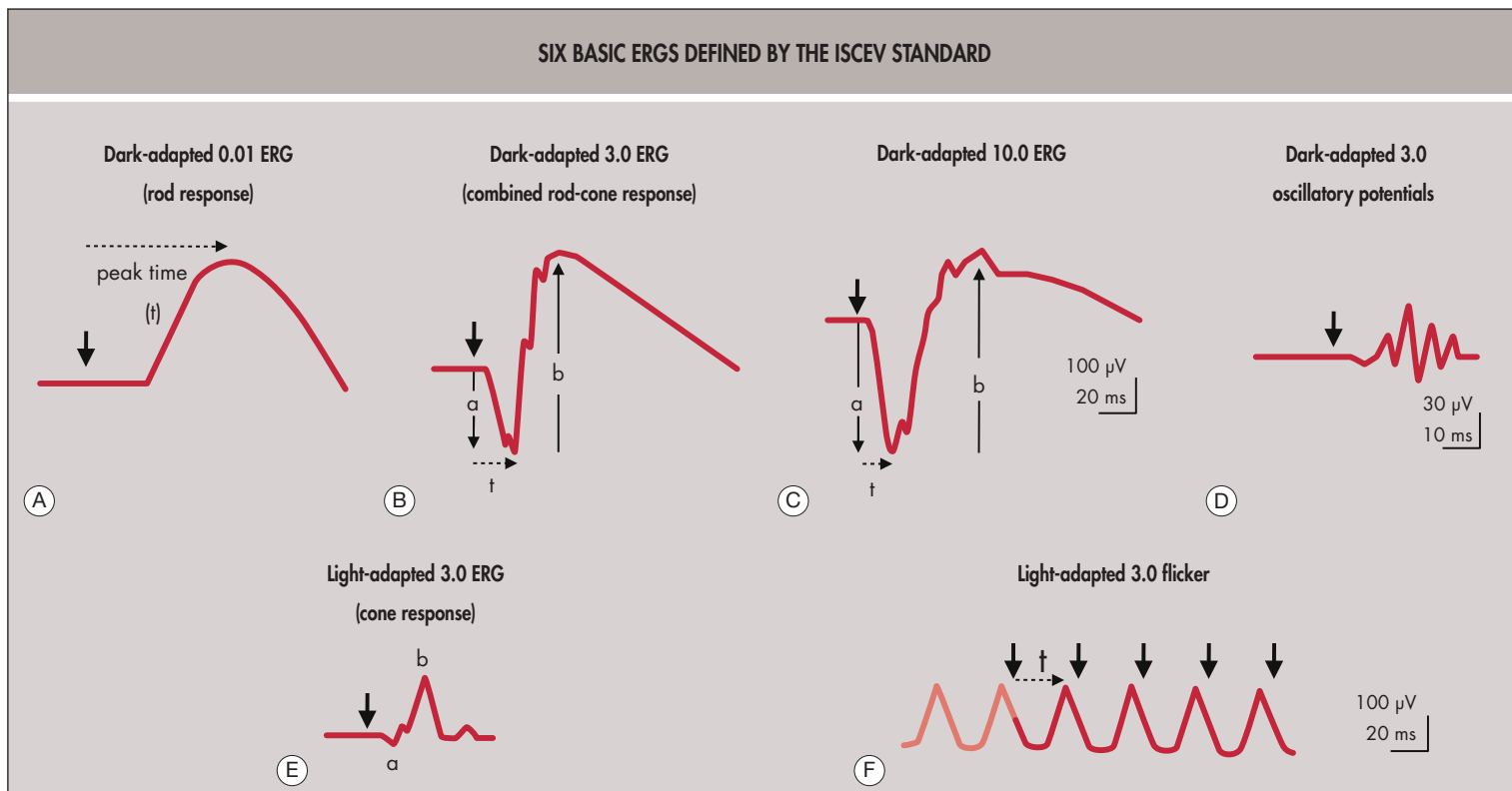
Normal values for full-field ERG vary by laboratory, so normal intralaboratory value ranges should be given with every ERG report, and reference values should be adjusted for age. Ocular pigmentation, high refractive errors, and time of recording should be noted.<sup>3</sup>

An electrophysiological response may be affected in both amplitude and/or timing (Fig. 6.9.2). The *a*-wave amplitude is measured from the prestimulus baseline to the *a*-wave trough, and the *b*-wave amplitude is measured from the *a*-wave trough to the *b*-wave peak. Timing includes the peak time (also called *implicit time*, *t*) and is measured from the time of the flash to the peak of the wave of interest (see Fig. 6.9.2, arrows). The amplitude of a flicker ERG is measured from the trough to the peak of a typical wave, and the implicit time is measured from the midpoint of the stimulus to the following peak. With regard to measuring oscillatory potentials, most clinical applications are noting the presence and waveform of the peaks in comparison with reference data.<sup>3</sup>

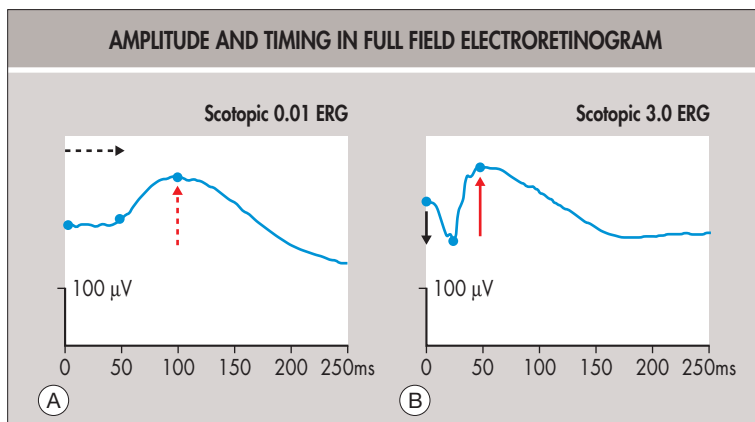
Full-field ERG can establish loss of retinal function in pathological states, exhibited as alterations in amplitude and timing of the recorded retinal responses when compared with normative responses and assists in diagnosis in clinical scenarios that include unexplained loss of peripheral vision, loss of central vision, and nyctalopia.

When retinal degeneration is suspected, full-field ERG can differentiate between an isolated cone abnormality and a condition that involves both the rods and cones. In addition, full-field ERG can differentiate between stationary forms of night blindness and progressive degenerations. In cone-rod dystrophy, photopic (cone) responses are affected more compared with scotopic (rod) responses; the reverse is true in rod-cone dystrophy. However, as each of these dystrophies progresses, both rods and cones can become affected.<sup>4</sup> In retinitis pigmentosa, for example, the earliest sign of retinal damage is a delayed cone implicit time. As the disease progresses, however, the ERG demonstrates both markedly reduced rod and cone responses to bright flash and a markedly reduced cone response to a 30-hertz (Hz) flicker. Late in the disease course, responses are often non-recordable<sup>5</sup> (Fig. 6.9.3).

Full-field ERG testing can be helpful in diagnosing various systemic conditions that result in loss of retinal function, such as autoimmune retinopathy, vitamin A deficiency, and various drug toxicities.<sup>6</sup> Full-field



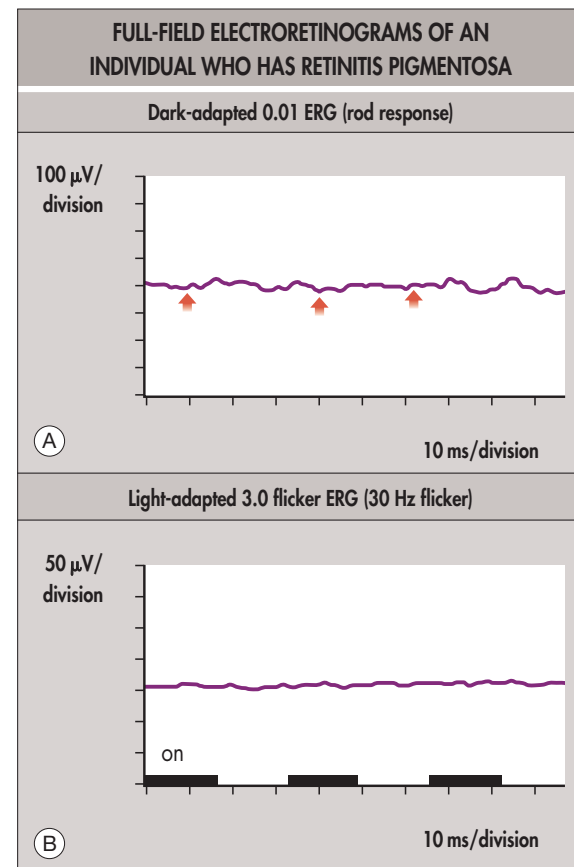
**Fig. 6.9.1 Normal Full-Field Electroretinography (ERG) Responses.** The six basic ERG responses are depicted for a normal individual. After a minimum dark adaptation time of 20 minutes, the dark-adapted or scotopic responses (top four diagrams, A–D) are obtained. (A) The dark-adapted 0.01 ERG (rod response) is obtained using a dim white flash stimulus of 0.01 cd/s/m<sup>2</sup> with a minimum interval of 2 seconds between flashes. (B) The dark-adapted 3.0 ERG (maximal combined rod-cone response) is obtained with a white flash stimulus of 3.0 cd/s/m<sup>2</sup> with a minimum interval of 10 seconds between flashes. (C) The dark-adapted 10.0 ERG is obtained with a white flash stimulus of 10.0 cd/s/m<sup>2</sup> with a minimal interval of 20 seconds between flashes. (D) The dark-adapted 3.0 oscillatory potentials are obtained with a white flash stimulus of 3.0 cd/s/m<sup>2</sup> using high- and low-pass filters. (E–F) After a minimum light adaptation time of 10 minutes, the light-adapted or photopic responses are obtained with a background luminance of 30 cd/s/m<sup>2</sup>. (E) The light-adapted 3.0 ERG (single flash cone response) is obtained with a white flash stimulus of 3.0 cd/s/m<sup>2</sup> with a minimum interval of 0.5 seconds between flashes. (F) The light-adapted 3.0 flicker ERG (30-Hz flicker) is obtained with a white flash stimulus of 3.0 cd/s/m<sup>2</sup> with a flash rate of 30 stimuli per second. (From McCulloch DL, Marmor MF, Brigell MG, Hamilton R, Holder GE, Tzekov R. ISCEV standard for full-field clinical electroretinography [2015 update]. Doc Ophthalmol 2015;130:1–12. Figure 1.)



**Fig. 6.9.2 Illustration of Amplitude and Timing on Full-Field Electroretinogram.** (A) Dark-adapted 0.01 ERG or rod response illustrates latency (dashed black line) and implicit time,  $\tau$  (dashed red line). (B) Dark-adapted 3.0 ERG or maximal combined rod-cone response illustrates both a-wave (solid black line) and b-wave (solid red line) amplitudes.

ERG likewise is useful in evaluating activity in certain uveitic conditions, such as birdshot chorioretinopathy, multiple evanescent white dot syndrome (MEWDS), and acute posterior multiple placoid pigment epitheliopathy (APMPPE).<sup>7</sup> Additionally, full-field ERG testing has a role in ocular trauma in establishing a diagnosis of siderosis when an iron-containing small metallic intraocular foreign body is suspected, and serial ERGs can be helpful in monitoring the health of the retina in these cases.<sup>6</sup>

In a number of retinal conditions, inner retinal dysfunction is a predominant feature. In these cases, many of which lack defining fundus features, ERG can be crucial for accurate diagnosis. Particular inherited conditions, such as congenital stationary night blindness and X-linked retinoschisis, have “electronegative” ERG, in which the waveform to a high-intensity flash under scotopic conditions has a preserved a-wave with a selectively



**Fig. 6.9.3 Full-Field Electroretinogram in Retinitis Pigmentosa.** (A) Dark-adapted 0.01 ERG or rod response to a single flash of bright white light is diminished markedly, consistent with the diagnosis of a retinal degeneration. (B) The light-adapted 3.0 flicker ERG (30 Hz flicker) is completely extinguished.

reduced *b*-wave. Likewise, several acquired conditions, such as central retinal artery occlusion, ischemic central retinal vein occlusion, diffuse unilateral subacute neuroretinitis, and melanoma-associated retinopathy can demonstrate this distinct ERG phenotype along with retinotoxicities from vigabatrin, methanol, and quinine. In these disorders, the selective *b*-wave reduction highlights the predominance of post-photoreceptor inner retinal dysfunction.<sup>6</sup>

Although an ERG phenotype may often be nonspecific, there are a few instances in which electrophysiological responses are pathognomonic for a particular disease. One such disease is cone dystrophy with supernormal rod ERG, a recessively inherited disorder with an underlying genetic defect in *KCNV2*. The electroretinogram is characterized by reduced and delayed photopic responses, reduced and delayed dim flash scotopic responses, and a disproportionate increase in *b*-wave amplitude with relatively small increases in stimulus intensity. The dark-adapted 11.0 ERG has a normal *a*-wave slope with a broadened and squared shape with a late negative *a*-wave peak. In enhanced S-cone syndrome, a recessively inherited disorder associated with a mutation in *NR2E3*, the scotopic 3.0 ERG, although reduced, has a waveform similar to that of the photopic 3.0 ERG, both of which are dominated by S-cone responses. Further, the S-cone ERG is markedly increased compared with normal.<sup>8</sup>

Last, in certain clinical scenarios, a normal ERG can provide reassurance to both the patient and the physician.

## MULTIFOCAL ERG

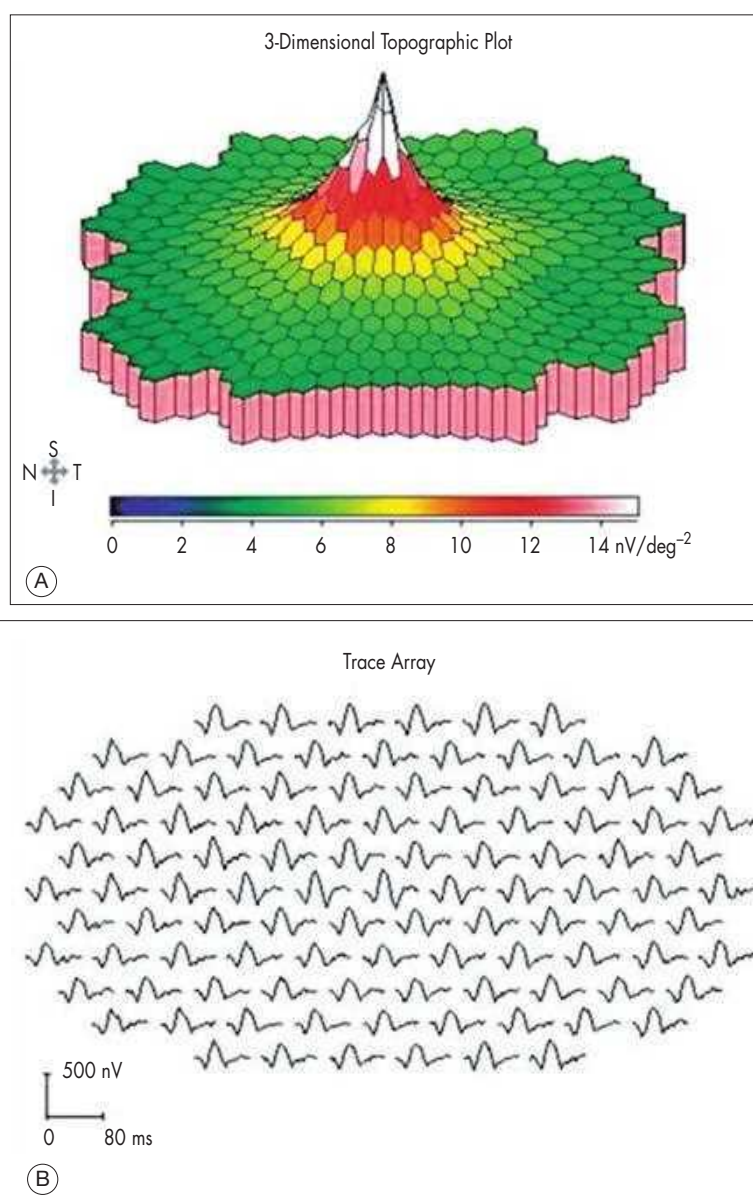
Multifocal ERG (mfERG) has supplanted focal ERG testing and records multiple (61 or 103 hexagons) local ERG responses elicited from the central 40–50° of the retina under light-adapted conditions. These responses are then displayed individually so that abnormal spatial variations can be localized to their corresponding areas in the macula, perimacula, or remaining posterior pole. Worldwide standardized protocols for mfERG testing have been set forth by the ISCEV. mfERG typically displays both an array of individual mfERG traces and a three-dimensional topographic plot<sup>9</sup> (Fig. 6.9.4).

Clinically, mfERG is most useful to assess macular function in patients with unexplained or central loss of vision who may have normal results on full-field ERG. mfERG can aid in the diagnosis of macular diseases, including Stargardt dystrophy, cone dystrophy, and occult macular dystrophy.<sup>9,10</sup>

Multifocal ERG plays an important role in the assessment of drug-induced retinopathy, particularly chloroquine and hydroxychloroquine toxicity. The 2011 American Academy of Ophthalmology revised screening recommendations for chloroquine and hydroxychloroquine toxicity recommended addition of at least one objective test, such as mfERG, spectral-domain optical coherence tomography, or fundus autofluorescence to be used with 10-2 automated visual fields. Further, recommendations specified that mfERG could be used in place of visual fields. Most commonly, mfERG demonstrates a paracentral ring depression of signals around the fovea. This can be followed by central amplitude reduction and widespread depression in advanced retinopathy. In patients taking the medications mentioned above, mfERG can be a quantitative measure of retinal function, potentially providing a more sensitive objective test compared with other modalities, allowing earlier recognition of dysfunction.<sup>11,12</sup>

## ELECTRO-OCULOGRAPHY

EOG measures the difference in electrical potential between the front and the back of the eye, which is mostly a function of the retinal pigment epithelium (RPE) and regulated, in part, by the bestrophin gene. EOG is performed by placing electrodes on the skin of the medial and lateral canthal angles of each eye, in addition to placing a ground electrode on the forehead. The electric potential across the eye is recorded as the patient's eyes move back and forth horizontally under both dark (scotopic) and light (photopic) conditions. Clinical EOG is represented as an Arden ratio (light/dark ratio), which is the ratio of the highest amplitude in light to the lowest amplitude in dark. Normal values should exceed 1.5. Clinically, EOG is most useful in aiding the diagnosis of Best disease and differentiating this entity from adult-onset vitelliform macular dystrophy and pattern dystrophy. Worldwide standardized protocols for EOG testing have been set forth by the ISCEV.<sup>13,14</sup>



**Fig. 6.9.4 Normal Multifocal Electroretinogram.** (A) Three-dimensional topographic plot. (B) Trace array.

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# Light and Laser Injury

Caroline R. Bauman

6.10

**Definition:** Structural damage to the retina produced by a light source.

### Key Features

- Mechanism of damage is often photochemical.
- Thermal enhancement of retinal damage is possible.
- Sources include solar eclipse, welding arc, operating microscope, and handheld laser pointer.

### Associated Features

- Delayed appearance of the lesion after the injury by hours to days.
- Variable recovery of vision.
- Severity of damage proportional to duration and intensity of exposure.

## INTRODUCTION

The potentially damaging effects of light on the retina have been recognized since the time of Plato, who described eclipse blindness. Breakdown of the intrinsic ocular protective mechanisms and/or exposure to external high-risk conditions can produce light or photic damage to the retina. The development and severity of light-induced damage depends on a number of factors, including ocular anatomical protective mechanisms, area of tissue involved, and the parameters of the light source, such as the wavelength, duration of exposure, and the total energy exposure.

## LIGHT INTERACTION WITH THE RETINA

The eye primarily perceives radiation in the optical spectrum, comprising the visible (400–760 nm), ultraviolet (UV; 200–400 nm), and infrared (IR; >760 nm) wavelengths. Radiation in this region can be produced by the sun, ophthalmic instruments, and lasers.

Tissue effects produced by light are classified as mechanical, thermal, or photochemical and determined by irradiance (watt per square centimeter [W/cm<sup>2</sup>]), wavelength, duration of light exposure and the absorption of target tissue.<sup>1</sup> Table 6.10.1 outlines tissue effects induced by commercial ophthalmic lasers. Mechanical injury results from high irradiance, short-duration exposure in the nanosecond (10<sup>-9</sup>) to picosecond (10<sup>-12</sup>) range, and the energy strip electrons from molecules and disintegrates target tissue into *plasma*. This is the mechanism of *photodisruption*. At moderate irradiance and exposure greater than 1 microsecond (μsec), thermal effects result from a critical temperature rise in tissue. Elevation of retinal temperature by 10–20°C produces protein denaturation and enzyme inactivation, which results in *photocoagulation*, cellular necrosis, and hemostasis.<sup>2,3</sup> Long visible and infrared (IR) wavelengths produce thermal injury

to the retina and choroid during laser photocoagulation. *Photochemical* or phototoxic effects occur with low-to-moderate irradiances that are below coagulation thresholds and with shorter wavelengths, in particular UV and visible blue wavelengths. Damage to cellular components occurs at temperatures too low to cause thermal destruction, which may account for a delay of 24–48 hours before the appearance of a lesion. Absorption of a photon by the outer electrons of a molecule produces an excited molecular state, which can drive a chemical reaction. Because the energy per photon is inversely proportional to its wavelength, short-wavelength photons have more energy with which to induce a photochemical reaction. Long-wavelength visible light also can induce photochemical changes when tissues are sensitized by an exogenous photosensitizer, as with photodynamic therapy. At intermediate values of irradiance and exposure, more than one of the above mechanisms may be in effect.

The ocular media transmit 75%–90% of electromagnetic radiation in the range of 400–1064 nm.<sup>4</sup> Several mechanisms exist to reduce retinal light exposure. The cornea absorbs most UVB (280–315 nm) and UVC (<280 nm), as well as some IR radiation, and reflects up to 60% of incident light that is not perpendicular to its surface.<sup>4</sup> The lens absorbs most UVA (315–400 nm) and visible blue wavelengths. Intrinsic ocular defenses against retinal light damage include xanthophyll absorption of near-UV and blue light to protect photoreceptors, temperature control by the choroidal circulation, intracellular molecular detoxification of free radicals, and retinal pigment epithelium (RPE)–mediated photoreceptor renewal.<sup>5</sup> Physiological protective mechanisms include squint and blink reflexes, eyebrow ridge, aversion response, and pupillary miosis. Light damage to the retina may occur when protective mechanisms are impaired or as a result of deliberate gazing at a light source. Young patients may be at increased risk because of efficient light transmission through clear ocular media.

## PHOTIC RETINOPATHY

*Photic retinopathy* is a general term for light-induced retinal damage. It is most often caused by inadvertent exposure. The mechanism is typically photochemical, with potential enhancement by elevated tissue temperature and increased blood oxygen tension.<sup>6</sup> Increased chorioretinal pigmentation facilitates light absorption in the RPE and may elevate the background retinal temperature and thermally enhance photochemical damage. It has been hypothesized that retinal defenses against toxic free radicals from light and oxygen are overwhelmed by supranormal light exposure. Damage manifests as a disorder of RPE and photoreceptor outer segments.<sup>7</sup> Retinal phototoxic injury was originally considered permanent; however, visual recovery has been noted in solar retinopathy, laser pointer, welding arc, and operating microscope phototoxicity. Mild photochemical damage may not be symptomatic or visible ophthalmoscopically, and case reports represent the more severe injuries. The extent of retinal injury and the likelihood of visual recovery depend on multiple factors, including the location and area of exposed retina, duration, intensity, spectrum of the light source, and host susceptibility factors, including age, nutritional status, ocular pigmentation, core temperature, clarity of ocular media, and pre-existing retinal disease. Individuals with emmetropia and hyperopia may be at increased risk caused by effective light focusing on the retina.<sup>5</sup> Systemic photosensitizing agents, such as tetracycline and psoralen, may predispose to photochemical damage.

## Solar Retinopathy

Solar retinopathy, which describes retinal injury induced by direct or indirect solar viewing, is also referred to as *foveomacular retinitis*, *photoretinitis*, and *eclipse retinopathy*. The harmful effects of solar viewing have been recognized for centuries. Foveomacular retinitis was initially described

TABLE 6.10.1 Tissue Effects Induced by Commercial Ophthalmic Lasers

Laser Modality	Mechanism of Damage
Argon laser	Photocoagulation
Transpupillary therapy (TTT)	Photocoagulation
Photodynamic therapy (PDT)	Photochemical injury
Neodymium:yttrium–aluminum–garnet (Nd:YAG) laser	Photodisruption

as bilateral decreased vision and foveal lesions in military persons after solar viewing.<sup>8</sup> Solar retinopathy has been associated with religious sun gazing, solar eclipse observing, telescopic solar viewing, sunbathing, psychiatric disorders, and psychotropic drug use.<sup>9</sup> Solar radiation induces photochemical retina damage, which may be enhanced by elevated tissue temperature. Direct solar observation through a 3-mm pupil produces a 4°C temperature rise, which is below thermal damage thresholds.<sup>3</sup> Sustained solar viewing for more than 90 seconds through a constricted pupil exceeds the threshold for photochemical retinal damage.<sup>10</sup> Solar observation through a dilated 7-mm pupil produces a 22°C increase in retinal temperature, which is above photocoagulation thresholds.<sup>3</sup>

Symptoms usually develop 1–4 hours after solar exposure and may include unilateral or bilateral decreased vision, metamorphopsia, scotomata, chromatopsia, photophobia, afterimage, and periorbital ache. Acuity ranges from 20/40–20/200 acutely. A small yellow spot with a gray margin measuring up to 200 µm may develop in the parafoveal area corresponding to the image of the sun (Fig. 6.10.1A).<sup>3,9</sup> A lesion may not be visible in mild cases. Histopathology of acute solar retinopathy demonstrates RPE injury with necrosis, detachment, irregular pigmentation, and minimal photoreceptor damage.<sup>11</sup> Fluorescein angiography (FA) may be normal or reveal RPE transmission defects (see Fig. 6.10.1B). The yellow lesion is replaced by focal depression with RPE mottling or lamellar hole and vision usually improves to 20/20–20/40 within 6 months, although scotomata or metamorphopsia can persist. Optical coherence tomography (OCT; see Fig. 6.10.1C) demonstrates disrupted reflectivity in the outer retina and ellipsoid layer.<sup>12</sup> Ultrastructural findings in experimentally induced solar retinopathy have demonstrated parafoveal cone and

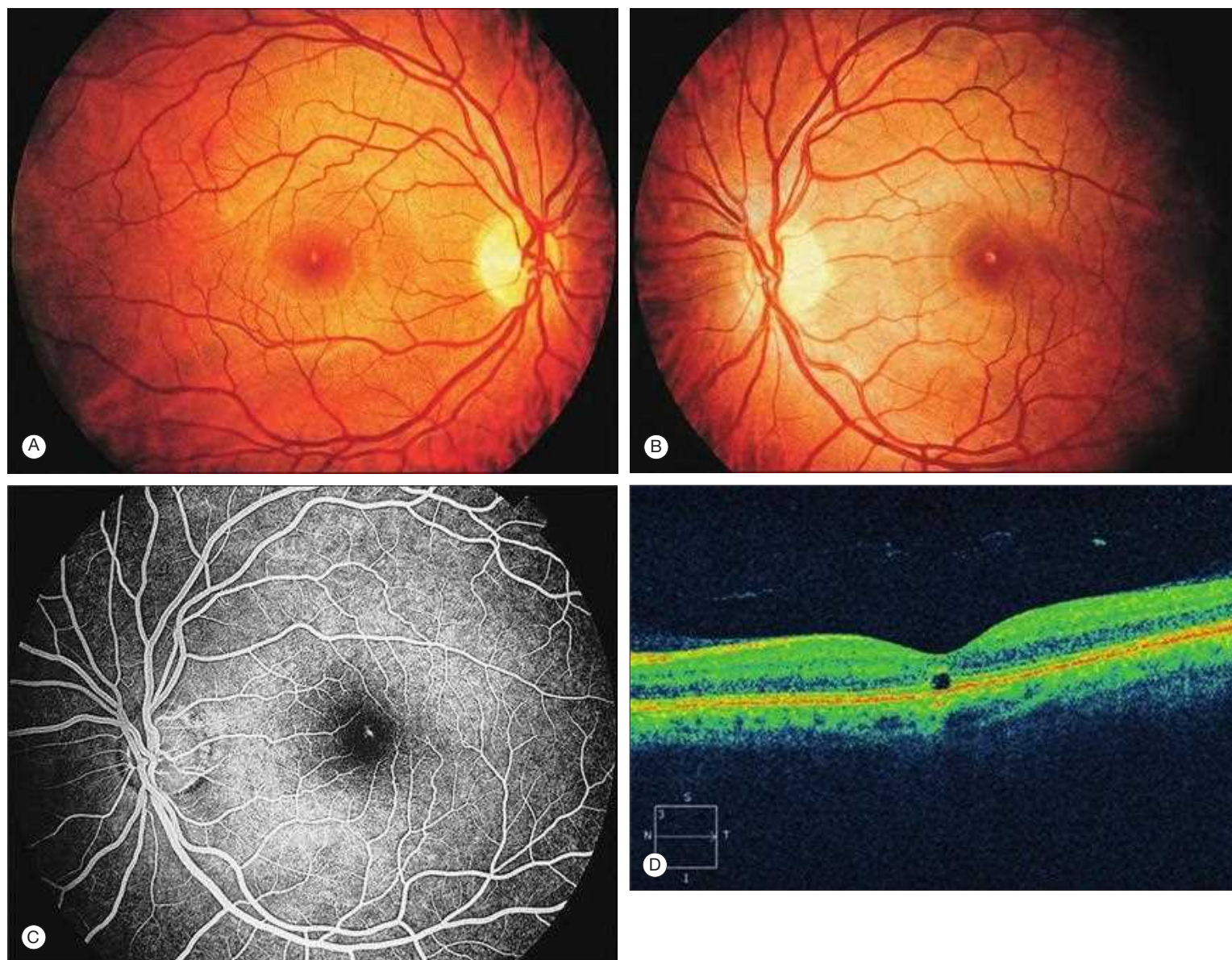
rod outer segment changes and scattered RPE degeneration. The good visual prognosis has been attributed to the resistance of the foveal cones to photochemical damage.<sup>13</sup>

*Eclipse retinopathy* describes similar macular damage after solar eclipse viewing. Evaluation of visual morbidity associated with the full solar eclipse on August 11, 1999, demonstrated abnormal macular appearance in 84% of symptomatic patients with rare cases of persistent symptoms.<sup>14,15</sup> Excessive light exposure in rats has been shown to induce irreversible neuronal apoptosis of retinal cells, which may account for permanent visual impairment as well as gliovascular responses, which may be responsible for the transient clinical symptoms.<sup>16</sup>

No specific therapy exists for solar retinopathy. Further episodes of solar viewing should be discouraged. Eclipse viewing without proper protective eyewear with tested solar filters should be discouraged. Oral corticosteroids have been used to treat acute lesions, but their beneficial effect has not been demonstrated conclusively because vision often improves spontaneously.

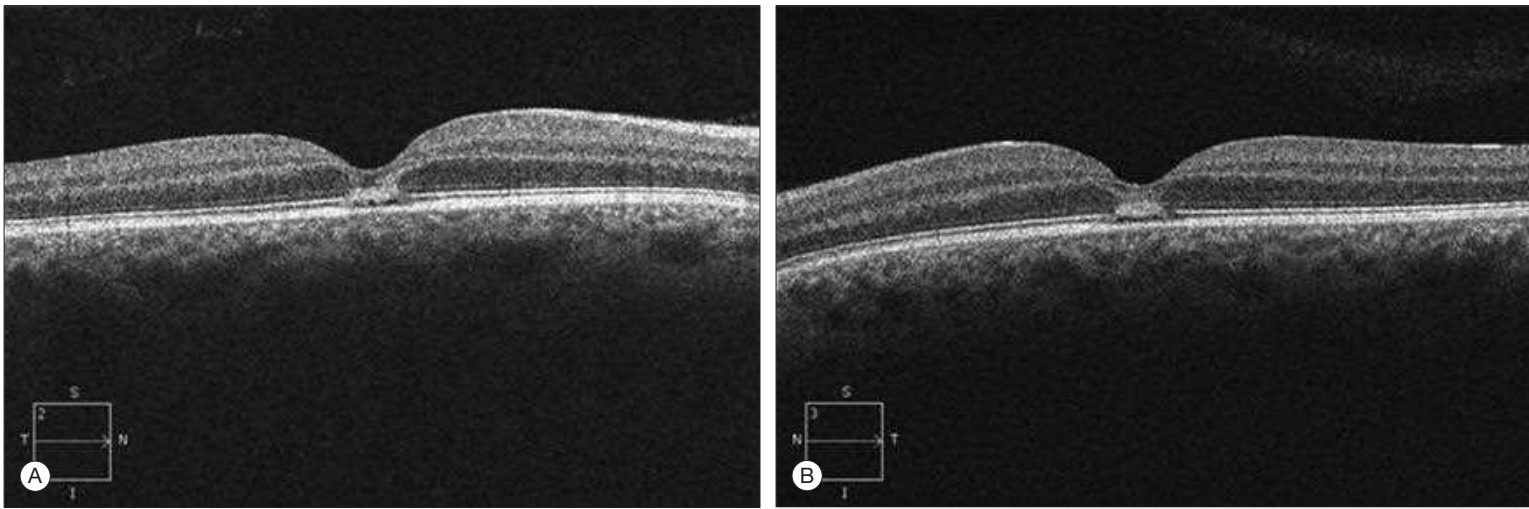
## Welding Arc Exposure

Welding arcs emit radiation, and the most common injury is keratitis caused by corneal absorption of UV rays. Retinal injury is rare but can occur after a welding arc viewing without proper ocular protection.<sup>17</sup> The retinal temperature increase is below photocoagulation thresholds, and injury is produced by photochemical effects from UV and short blue wavelength exposure. The symptoms and clinical course are similar to solar retinopathy. A yellow edematous foveal lesion develops acutely (Fig. 6.10.2),

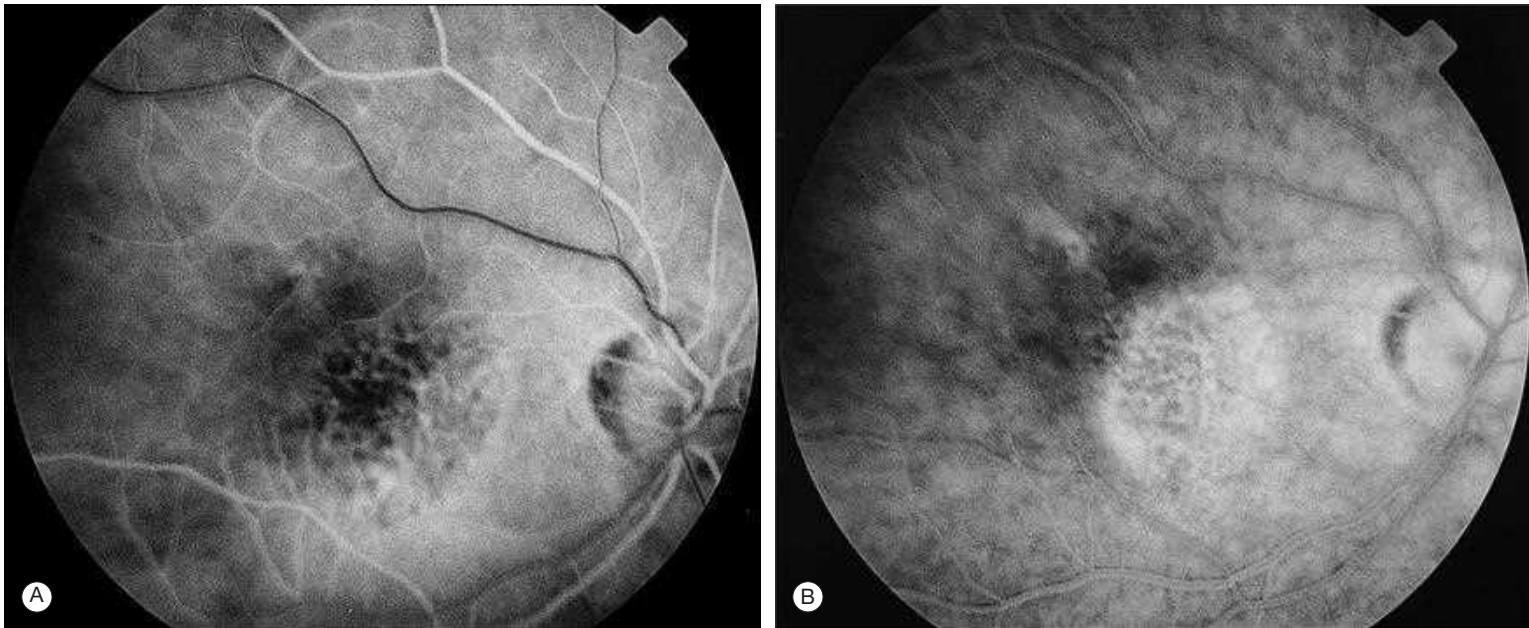


**Fig. 6.10.1 Solar Retinopathy.** In the right eye (A) and left eye (B), of the same patient. (C) Fluorescein angiography of solar retinopathy in the left eye. Transmission hyperfluorescence corresponds to the retinal pigment epithelium defect. (D) Optical coherence tomography of solar retinopathy, left eye.





**Fig. 6.10.2 Optical Coherence Tomography of Welding Arc Retinopathy That Occurred After Shield Failure.** (A) Right eye. (B) Left eye.



**Fig. 6.10.3 Acute Retinal Phototoxicity, 2 Weeks After Cataract Surgery.** (A) Perifoveal fluorescein mottling in the early-stage angiogram. (B) Modest fluorescein leakage and retinal pigment mottling in the late phase. Visual acuity is 20/60. (Courtesy Gordon A. Byrnes, MD.)

which is replaced over time by RPE irregularity or lamellar hole. No effective therapy exists, and vision usually improves with time, with permanent vision effects being rare.

Phototoxicity has also been described following brief incidental light exposure from camera flashes or welding arcs in four patients who were taking photosensitizing drugs (hydrochlorothiazide, furosemide, allopurinol, and benzodiazepines).<sup>18</sup>

### Lightning Maculopathy

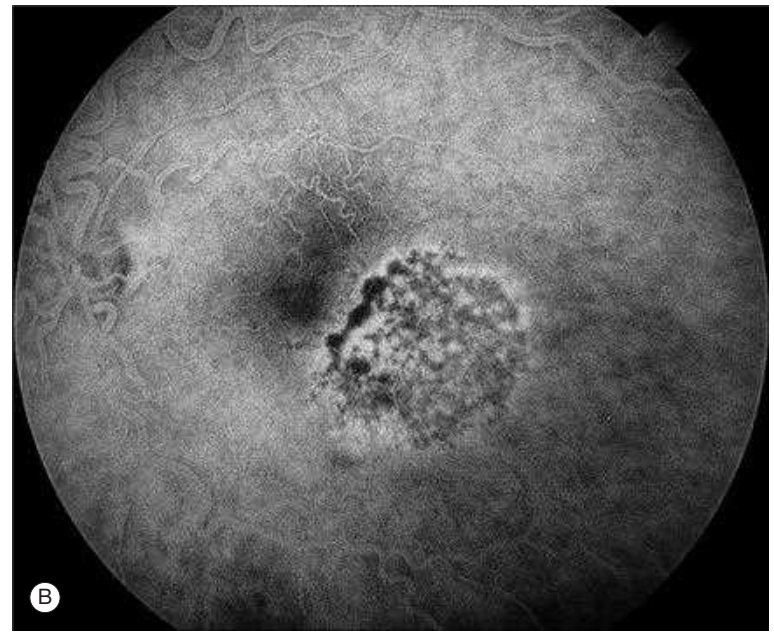
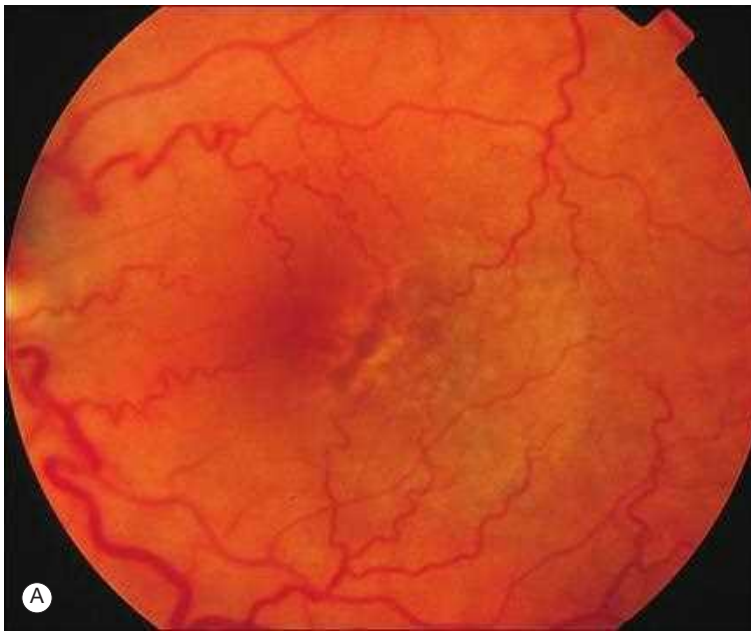
Lightning maculopathy describes acute visual loss and macular changes after lightning injury. Vision loss may be severe to light perception and lesions may include macular edema, macular hole, cyst, or a solar retinopathy-like picture, cataract, retinal detachment, retinal artery occlusion, and relative afferent pupillary defect.<sup>19</sup> Visual recovery often occurs over time, even with severe maculopathy. High-dose intravenous methylprednisolone treatment may play a role in vision recovery, and its use was associated with reversal of lightning-induced blindness in two cases.<sup>20</sup>

### Retinal Phototoxicity From Ophthalmic Instruments

Ophthalmologists use a variety of powerful light sources. Retinal injury caused by light exposure from the operating microscope and endoillumination has been described. Iatrogenic phototoxicity has been reported after cataract extraction, combined anterior segment procedures, and

vitreous surgery.<sup>7</sup> The most frequent cause is the operating microscope as initially described after uncomplicated extracapsular cataract extraction, with reported incidence ranging from 0% to 7%.<sup>21–23</sup> The mechanism of intraoperative phototoxicity is photochemical, with potential thermal enhancement. Because operating microscopes generate little UV radiation, photochemical damage probably is caused by short-wavelength visible blue and green light. The incorporation of UV and IR filters in the intraocular lens (IOL) and microscope may reduce, but do not completely eliminate, the risk of photic and thermal effects, respectively, as demonstrated by experimentally induced human photic retinal injury in a blind phakic eye after 60 minutes of operating microscope exposure with UV and IR filtered light.<sup>24</sup>

Few patients show symptoms immediately after exposure, and the level of vision depends on lesion size and location. A foveal lesion can produce severe permanent vision loss, whereas an eccentric lesion is compatible with good acuity and pericentral scotoma. The lesion shape matches the surgical illuminating source. Immediately after exposure, there is little evidence of macular pathology but within 24–48 hours, a yellow lesion, measuring 0.5–2.0 disc diameter at the level of the RPE, with retinal edema develops. FA acutely reveals dye leakage (Fig. 6.10.3), which may simulate choroidal neovascularization (CNV). Over weeks, the yellow lesion is replaced by RPE clumping and atrophy (Fig. 6.10.4A), which correspond angiographically to blocking and transmission defects, respectively (see Fig. 6.10.4B). Other long-term sequelae include postoperative erythropsia, retinal surface wrinkling, and choroidal neovascularization.<sup>25,26</sup> Mild light-induced retinal injuries may be overlooked clinically because subtle postoperative pigmentary changes may be attributable to other causes.



**Fig. 6.10.4 Chronic Retinal Phototoxicity in the Left Eye.** (A) Visual acuity is 20/50 (6/15). A well-defined area of retinal pigment epithelium mottling is present. The patient also has congenital retinal venous tortuosity. (B) Fluorescein angiography reveals blocking and transmission defects without late fluorescein leakage. (Courtesy Gordon A. Byrnes, MD.)

Histopathology of acute operating microscope-induced injury has revealed RPE and photoreceptor damage.<sup>27</sup> In primates, early photic lesions have demonstrated photoreceptor damage and disruption of RPE tight junctions, with regeneration of photoreceptor outer segments 3–5 months after injury.<sup>26</sup> This may correspond to recovery of vision after injury noted in some human eyes. Operating microscope phototoxicity has been associated with surgical factors, including microscope brightness, wavelength of light exposure, surgical duration, and technique. Retinal phototoxic lesions may occur after short-duration (under 30 minutes) phacoemulsification and were associated with near emmetropia and diabetic retinopathy.<sup>28</sup> The risk of photic damage may increase after IOL insertion, which can focus incoming light on the retina. Patient susceptibility factors include increased body temperature and blood oxygenation, chorioretinal pigmentation, pre-existing maculopathy, pupillary dilatation, diabetes mellitus, retinal vascular disease, deficiencies of either ascorbic acid or vitamin A, and photosensitizer use. Photic damage secondary to endoillumination during vitrectomy is uncommon and can be avoided by minimizing length of surgery and light output, filters, maximizing light pipe distance from the retina and using eccentric endoillumination techniques.<sup>29</sup>

There is no specific treatment for acute lesions, and spontaneous visual improvement usually occurs within months, even when lesions involve the macula. Methods to reduce the risk include reduction of coaxial illumination and operative time, use of IR and UV filters in the microscope and IOL, placement of an air bubble in the anterior chamber to defocus incident light, and use of a corneal cover.

The irradiance produced by the indirect ophthalmoscope and the fundus camera is lower than experimentally determined retinal injury thresholds. Furthermore, the total energy delivered to the eye is less under nonoperative conditions than in operative conditions. These instruments have not been shown to produce acute retinal injury in humans; however, prolonged exposure to the indirect ophthalmoscope has been shown to produce lesions in primates. The cumulative effect of repeated examination is unknown, and it is recommended that retinal examinations be performed with the minimal illumination required.

## LIGHT EXPOSURE AND AGE-RELATED MACULAR DEGENERATION

An association between long-term solar exposure and age-related macular degeneration (AMD) was considered when AMD was found to be less common in patients with nuclear cataract.<sup>30</sup> Histopathology of acute photic injury reveals damage to the macular RPE and photoreceptors, which is the same tissue depth and geographical location as changes observed in AMD.<sup>23</sup> Solar viewing acutely damages the RPE and produces RPE pigmentary irregularities, which are similar in appearance to those in AMD, although the diffuse thickening of Bruch's membrane noted in AMD does

not occur with damage caused by solar viewing.<sup>11</sup> The relationship between light and AMD has been evaluated with epidemiological studies. In the Chesapeake Bay watermen study, no association was found between cumulative UVA or UVB exposure and mild or advanced AMD.<sup>31</sup> An association was noted between blue or visible light exposure during the preceding 20 years and the risk of developing advanced AMD.<sup>32</sup> In the Beaver Dam Eye Study, no association was found between estimated ambient UVB exposure and AMD.<sup>33</sup> The amount of outdoor leisure time in summer was associated with increased retinal pigmentation in men and late AMD in both men and women. To date, no study has yet conclusively defined the relationship between long-term UV light exposure and AMD. Until this is clarified, sunglasses to filter UV and blue light may be considered for individuals at risk, such as those with pseudo-phakia and those with aphakia who do not wear UV-protective intraocular lenses and individuals with decreased ocular pigmentation or at risk of AMD.<sup>5</sup>

## LASER INJURY

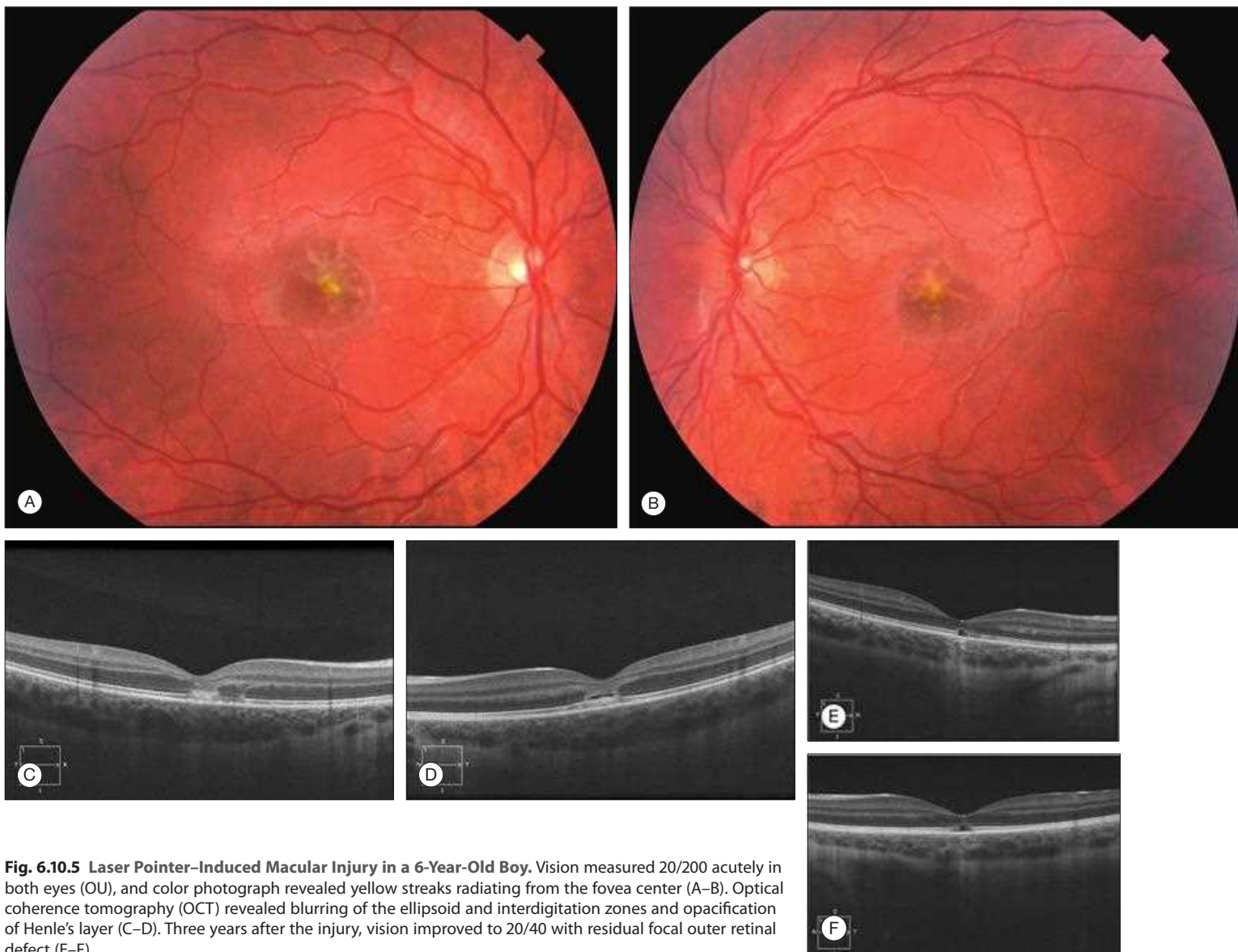
Laser applications in industrial, military, and laboratory situations account for many cases of accidental retinal injury, resulting from either direct laser exposure or its reflections. It usually occurs when the laser is fired inadvertently around an individual without ocular protection. The retinal tissue damage depends on the laser parameters and ranges from a small, subtle lesion to macular hole formation and extensive hemorrhage and disruption of the retina and choroid. Accidental foveal photocoagulation can produce immediate loss of vision up to 20/200, with a foveal cyst or yellow discoloration of the RPE (Fig. 6.10.5). Long-term evaluation may reveal RPE irregularities, epiretinal membrane, macular hole, and gliosis. Recovery of vision is variable and is related to the extent and location of the initial injury.<sup>34</sup> On the basis of findings from animal models, corticosteroids have been variably used to treat laser-induced retinal injuries.

Laser operators and persons in the laser vicinity are at risk from laser light scattered from optical interfaces, such as contact lenses and mirrors; therefore protective goggles should be worn by these individuals. Lasers for retinal photocoagulation contain filters to protect the operator. Decreased color discrimination in a tritan color-confusion axis had been noted in ophthalmologists who used argon blue-green laser.<sup>35</sup> This may have been caused by chronic exposure to reflections from the argon blue aiming beam, so currently lasers use either red or green aiming beam to minimize operator risk.

## LASER POINTERS

Laser pointers are portable low-energy devices that emit a narrow, coherent, low-powered laser beam. In the United States, lasers are classified by American National Standards Institute and the U.S. Food and Drug Administration (FDA) specifications that a handheld laser for use as





**Fig. 6.10.5 Laser Pointer-Induced Macular Injury in a 6-Year-Old Boy.** Vision measured 20/200 acutely in both eyes (OU), and color photograph revealed yellow streaks radiating from the fovea center (A–B). Optical coherence tomography (OCT) revealed blurring of the ellipsoid and interdigitation zones and opacification of Henle's layer (C–D). Three years after the injury, vision improved to 20/40 with residual focal outer retinal defect (E–F).

a pointer must be a class 1, 2 (<1 milliwatt [mW]), 2A, or 3A (1–5 mW) device. In contrast, class 3B lasers generate 5–500 mW, and class 4 lasers generate over 500 mW.

Laser pointers are common and have the potential for misuse that could lead to inadvertent ocular exposure and secondary retinal damage.<sup>36–40</sup> It is difficult to produce ocular injury with a low-energy class 3A laser pointer unless with inappropriate, prolonged, foveal exposure. Certain individual factors, such as age, pre-existing maculopathy, and clarity of the ocular media, play a role in determining susceptibility. The mechanism depends on the wavelength but appears to be thermal chorioretinal damage or phototoxicity. Handheld lasers are readily available on the Internet from dubious sources that may not comply with FDA standards, with power outputs exceeding class 3A, or may have inaccurate device labeling. Handheld devices that exceed recommended standards can produce permanent retinal injury and visual impairment with resultant photoreceptor damage as shown by optical coherence tomography (OCT).<sup>40–42</sup>

Damage manifests as unilateral or bilateral transient visual abnormalities, scotoma, and perimacular RPE disturbances.<sup>36</sup> OCT reveals acute photoreceptor damage and opacification of Henle's layer, with some recovery of vision over time (see Fig. 6.10.5).<sup>41,42</sup> Systemic corticosteroids have been shown to improve lesions in primate models of laser injury.

## COMPLICATIONS OF THERAPEUTIC RETINAL LASER PHOTOCOAGULATION

With proper laser use, complications are rare, but risks and informed consent should be discussed with patients when laser is used clinically. Inadvertent photocoagulation of the fovea, cornea, iris, or lens can be minimized with careful technique and appropriate laser settings. The risk

of choroidal effusion after extensive panretinal photocoagulation can be reduced by spreading treatment over multiple sessions. Secondary CNV and hemorrhage caused by damage to Bruch's membrane can be minimized by reducing laser intensity and duration and by avoiding small spot sizes (50  $\mu$ m).

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# Scleral Buckling Surgery

Bozho Todorich, Lisa J. Faia, George A. Williams

# 6.11



**IN THIS CHAPTER**  
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**Definition:** Closure of retinal breaks by scleral indentation.

## Key Features

- Identification, localization, and treatment of retinal breaks.
- Scleral imbrication.

## Associated Features

- Anatomical success rate high—generally 80%–90%.
- External drainage of subretinal fluid sometimes performed.
- Can be combined with vitrectomy surgery.

## INTRODUCTION

Although primary vitrectomy is being increasingly utilized, an essential surgical procedure for the repair of certain rhegmatogenous retinal detachments is scleral buckling. The goal of scleral buckling is to close retinal breaks by indenting the eye wall, thus preventing the passage of liquefied vitreous into the subretinal space. This flexible approach incorporates the benefits and advantages of different techniques and materials, maximizing the rate of anatomical and visual success while minimizing potential complications.

## HISTORICAL REVIEW

Recognition of vitreoretinal traction and retinal breaks in the pathogenesis of retinal detachment by Gonin in 1919 ushered in the era of repair, in which drainage of subretinal fluid and treatment of retinal breaks were employed. Custodis, 30 years later, introduced the concept of scleral buckling. The introduction of the binocular indirect ophthalmoscope and scleral depression by Schepens in 1951 revolutionized the localization of peripheral retinal pathology. Advancements were made when Schepens combined scleral dissection, diathermy, and intrascleral implantation of silicone buckles for scleral buckling. Lincoff et al. refined Custodis' procedure by using silicone sponge explants and cryotherapy.<sup>1,2</sup>

## PREOPERATIVE EVALUATION AND DIAGNOSTIC APPROACH

The diagnosis of rhegmatogenous retinal detachment is suggested by symptoms of floaters, photopsia, peripheral vision loss, and decreased central vision in cases of macular involvement. In patients with clear media, the diagnosis is confirmed by indirect ophthalmoscopy with scleral depression. Slit-lamp biomicroscopy with a three-mirror contact lens may also be helpful in identification of retinal pathology and localization of retinal breaks. The location and type of retinal breaks, as well as the size and duration of retinal detachment, are factors that help determine the timing and type of scleral buckling procedure performed.

Optical coherence tomography (OCT) is useful in documenting subretinal fluid, especially in the macula, and the extent of any accompanying

intraretinal edema or epiretinal proliferation. In patients with opaque media, the retinal status may not be visualized. Diagnostic ultrasonography is critical in establishing retinal detachment.

## DIFFERENTIAL DIAGNOSIS

Not all retinal detachments are rhegmatogenous. Other causes include tractional retinal detachments (as in advanced diabetic retinopathy), exudative retinal detachments (as in uveitic conditions, tumors, or uveal effusion syndrome), and combined detachments.

## ALTERNATIVES TO SCLERAL BUCKLING

Rhegmatogenous retinal detachments can be repaired by other surgical techniques. Pneumatic retinopexy involves injection of an expansible gas bubble into the vitreous and postoperative positioning so that the gas bubble closes the retinal break.<sup>3</sup> The break is treated with either cryopexy or laser photocoagulation. Pneumatic retinopexy is generally reserved for detachments in the superior hemiretina with a single break or several closely spaced breaks with clinical posterior vitreous detachment and no inferior retinal pathology.

Vitrectomy techniques, described in Chapter 6.12, also can be used to repair rhegmatogenous retinal detachments. The indications for scleral buckling versus pneumatic retinopexy or vitrectomy remain controversial.

## ANESTHESIA

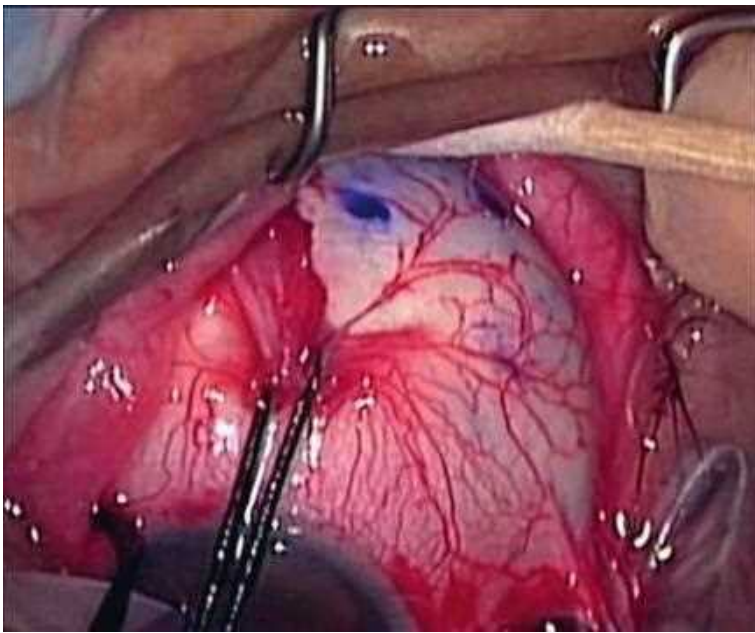
Scleral buckling can be performed with the patient placed under local or general anesthesia. The anesthetic technique that is used is a matter of surgeon and patient preference. The advantages of local anesthesia include shorter operating time, quicker postoperative recovery, and possibly decreased morbidity and mortality. However, retrobulbar placement of local anesthetic is not without risk. Perforation of the globe, particularly in patients with myopia, and damage to the optic nerve may result in permanent visual loss. Respiratory arrest and grand mal seizures also have been reported with inadvertent intrathecal administration of retrobulbar anesthetic. These complications can be minimized with a subconjunctival or a peribulbar technique.<sup>4,5</sup>

## GENERAL TECHNIQUES

A peritomy (conjunctival opening) is performed either at the limbus or several millimeters posterior to it. Because of considerable conjunctival manipulation, radial relaxation incisions are recommended to prevent tearing. In patients who have filtering blebs or recent limbal wounds, the peritomy can be extended posteriorly to avoid those areas. If only one or two quadrants are to be buckled, conjunctiva and Tenon's capsule can be reflected in the required quadrants only (Video 6.11.1).

After the peritomy, the space between Tenon's capsule and sclera is entered, the muscle insertion is engaged with a muscle hook, and the connections to Tenon's capsule are identified and separated from the muscle. A traction suture is placed around each of the four rectus muscles. After all recti have been isolated, the surface of the sclera is inspected for evidence of thinning (most common superotemporally), staphyloma, and anomalous vortex veins. Traction on the extraocular muscle insertions may

See clip:  
6.11.1



**Fig. 6.11.1** Felt-tip pen purple mark on sclera denoting posterior margin of small flap tear.

produce a bardycardic oculocardiac reflex, so it is important to carefully monitor patient's heart rate during this step.

No aspect of scleral buckling is more critical than accurate placement of the buckle, requiring precise localization of retinal breaks on the scleral surface. For small flap tears or holes, a single mark on the posterior edge of the break is sufficient. Larger flap tears and nonradial tears require localization of both the anterior and posterior extents of the break (Fig. 6.11.1) (Video 6.11.2).



See clip:  
6.11.2

## Treatment of Retinal Breaks

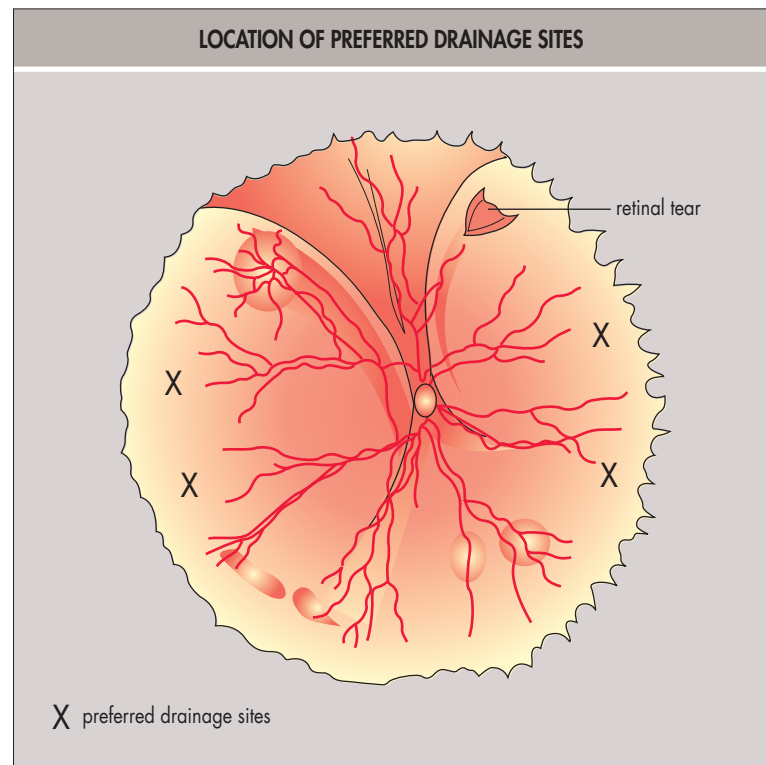
The rationale for the treatment of retinal breaks is to create an adhesion between the retinal pigment epithelium (RPE) and the retina. This is accomplished by inducing a thermal injury by using one of three energy sources: diathermy, cryotherapy, or laser. The morphological and cellular response of the retina and RPE to each of these energy sources is essentially similar. After 2 weeks, all three modalities show comparable effects on the retinal adhesive force.<sup>6</sup>

## Explant Scleral Buckling Techniques

Explant techniques allow the placement of buckling elements to support retinal pathology.<sup>7</sup> Explants are made of either solid silicone rubber or silicone sponges and come in a variety of sizes and shapes. They are secured to the sclera with partial-thickness scleral sutures (Video 6.11.2). For most detachments, the selected element is not as important as the accurate localization and placement of it. Proper placement requires an effective suturing technique, involving the use of a spatula needle with a 5-0 nonabsorbable suture, such as polyester, nylon, or polypropylene. The suture is placed either snug with the band (buckle height achieved by circumferential tightening of the band) or 1 mm or more on each side (buckle height achieved by suture imbrication. To ensure that the most posterior edge of the break is supported, the posterior suture is placed a minimum of 2–3 mm posterior to the scleral localization mark.

Element placement can be either segmental or encircling. Segmental buckles usually are reserved for detachments with single or closely spaced retinal breaks, <1 clock hour in extent. Although segmental buckles close isolated tears effectively, they are less useful in preventing new breaks because they provide no support elsewhere. Encircling procedures are particularly indicated in patients with the following conditions:

- Multiple breaks in different quadrants.
- Aphakia.
- Pseudo-phakia.
- Myopia.
- Diffuse vitreoretinal pathology, such as extensive lattice degeneration or vitreoretinal degeneration.
- Proliferative vitreoretinopathy (PVR).



**Fig. 6.11.2** Location of preferred drainage sites.

The anteroposterior position of the encircling element depends on the location of the pathology to be supported. When retinal breaks in the detached retina are associated with traction, the buckle should be positioned such that the posterior edge of the break lies on the posterior crest of the buckle. The buckling effect should extend for 30° on either side of the tear and extend anteriorly to the ora serrata. When the encircling element supports pathology in the attached retina, such as a retinal break, it should be positioned to support the most posterior aspect of the pathology. If no specific pathology is to be supported, the encircling element should support the posterior margin of the vitreous base.

The height of the encircling element (imbrication) can be obtained in two ways. For thin encircling elements, such as solid silicone bands, the explant can be shortened in relation to the circumference of the globe. The second method is via suture placement. This technique is used with wider and thicker explants and does not require the element to be shortened in relation to the ocular circumference. The farther apart the bites of the mattress suture are placed, the greater the height when the sutures are tightened<sup>7</sup> (Video 6.11.1).



See clip:  
6.11.1

## Drainage of Subretinal Fluid

Indications for drainage of subretinal fluid during scleral buckling remain controversial. Some authors believe that most cases can be managed without drainage, whereas others believe that drainage is a crucial aspect of the procedure.<sup>7,8</sup> The rationale for drainage is twofold:

- To diminish intraocular volume, allowing elevation of the buckle without elevating intraocular pressure (IOP).
- To allow the retina to settle on the elevated buckle by removing fluid from the subretinal space.

Effective drainage places the retinal breaks in juxtaposition to the choroid overlying the buckle, thus facilitating closure.

The selection of an external drainage site is affected by several factors (Fig. 6.11.2). Although the location of subretinal fluid is a primary concern, it is not necessary to drain where the amount of fluid is greatest but, rather, where there is adequate fluid to safely enter the subretinal space. Whenever possible, it is preferable to drain just above or below the horizontal meridian, either temporally or nasally (see Fig. 6.11.2), avoiding the major choroidal vessels and vortex veins.

Drainage in the posterior third of the bed of the buckle is preferred. This provides adequate support of the drainage site in the event of a complication, such as retinal incarceration or choroidal hemorrhage, and immediate closure when the buckle is tightened. If, because of the configuration





See clip:  
6.11.3

of the detachment or the position of the buckle, it is not possible to drain in the bed of the buckle, closure of the site with a suture should be considered. Drainage outside the bed of the buckle allows the buckle to be pulled up as drainage proceeds. Entry through the choroid and into the subretinal space is performed with a needle (27–30 gauge), with the presence of fluid signifying entry into the subretinal space. As the fluid drains, it is important to maintain a relatively normal and constant IOP to prevent retinal incarceration and choroidal hemorrhage (Video 6.11.3).

After successful drainage and closure of the site, the buckle is positioned with the appropriate preplaced scleral sutures. Any suture that overlies a retinal break is tightened first. The encircling band, if present, is then adjusted with a silicone sleeve. As the sutures are tightened, they are secured with temporary ties, as this allows easy adjustment of buckle height and position, and the optic nerve is inspected for perfusion. Once the buckle is positioned and the band adjusted, the fundus is inspected again to determine the status of the breaks and perfusion of the optic nerve.

Nondrainage procedures can be used to reattach the retina, with success rates comparable with those of drainage procedures. The primary advantage of a nondrainage procedure is that it avoids the potential complications associated with drainage. In eyes with relatively shallow detachments, the eye may soften enough after scleral depression and cryopexy to allow placement of the buckle without IOP problems. Waiting several minutes between tightening of the scleral sutures also may soften the eye. However, nondrainage techniques often require the IOP to be lowered by additional medical or surgical means. An injection of a small volume of air or gas (0.2–0.4 cc of 100% SF<sub>6</sub> or C<sub>3</sub>F<sub>8</sub>) is often used as an adjunct in drainage or nondrainage buckles, to promote closure of the retinal break.

## Chandelier-Assisted Scleral Buckling

Chandelier-assisted scleral buckling is a relatively novel technique in which traditional scleral buckle placement and maneuvers (e.g., marking of retinal breaks, cryopexy, and external drainage) are performed under wide-angle visualization through the operating microscope. The visualization is enabled by endoillumination provided by a small-gauge fiberoptic chandelier placed near the beginning of the case. The advantage of this procedure is that it allows for identification of all retinal breaks even in the far periphery, which is very helpful to less experienced surgeons. It is also a great tool for teaching as it allows simultaneous viewing by the surgeon and vitreoretinal fellow. The chief disadvantage of the chandelier during primary scleral buckle is that it requires entry into the vitreous cavity and carries a small risk of vitreous incarceration at the sclerotomy site.

## Closure

After final adjustments, the sutures are tied and the knots rotated posteriorly. Tenon's capsule and the globe can then be irrigated with an antibiotic solution. Retrobulbar irrigation with 0.75% bupivacaine significantly decreases postoperative pain after general or local anesthesia.

Tenon's capsule is then identified in all quadrants. A layered closure, initially closing Tenon's capsule to the muscle insertions, ensures that the explant and the nonabsorbable sutures are covered by Tenon's capsule and removes the tension on the conjunctival closure, minimizing the possibility of buckle erosion. During conjunctival closure, the relaxation incisions are typically closed with 6-0 plain gut suture or 7-0 vicryl. The conjunctiva is secured at the limbus with one or more sutures.

Long-term, a fibrous capsule forms overlying the scleral buckle, which maintains the scleral buckle position and indentation effect (Figs. 6.11.3 and 6.11.4).

## COMPLICATIONS

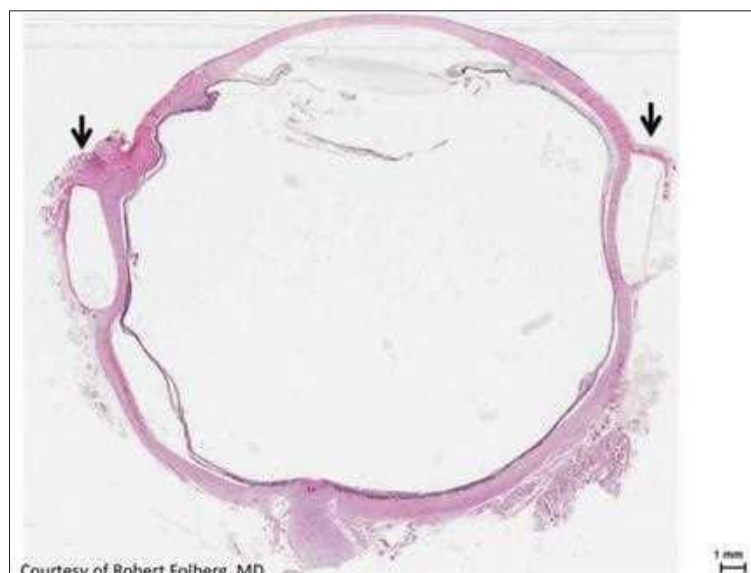
### Intraoperative Complications

#### Scleral Perforation

Scleral perforation during suture placement is a potentially devastating complication. Perforation usually is noticed at the time of suture placement and is heralded by the presentation of blood, pigment, or subretinal fluid through the suture tract.

#### Drainage Complications

The most common drainage complications are retinal incarceration and choroidal or subretinal hemorrhage.<sup>8</sup> Retinal incarceration may occur



**Figure 6.11.3** Cross-sectional hematoxylin and eosin–stained section of an eye with history of scleral buckling procedure. Fibrous capsule outlining the prior location of buckling element is observed (black arrows).



**Figure 6.11.4** Intraoperative image of an eye undergoing scleral buckle removal demonstrates the fibrous capsule being cut and reflected by the blade longitudinally along the axis of the buckling element (yellow arrow).

despite attempts to avoid large fluctuations in IOP during drainage, and is identified by the characteristic dimpled appearance of the retina over the site. Minimal degrees of incarceration rarely result in retinal breaks, but large amounts of incarceration require support with a buckle.

Choroidal or subretinal hemorrhage is perhaps the most feared complication of subretinal fluid drainage. This usually occurs at the time of choroidal perforation and is marked by the appearance of blood at the site. If this occurs, the drainage site should be closed as quickly as possible with either the buckle or a suture and the IOP elevated above the systolic perfusion pressure. If the drainage site is temporal, the eye should be positioned to place the located site as inferiorly as possible to prevent gravitation of the blood to the fovea.

### Postoperative Complications

#### Glaucoma

A variety of secondary glaucomas may develop after scleral buckling. Angle closure after scleral buckling may take place with or without pupillary block. One presumed mechanism of closure is shallow detachment of the ciliary body, which results in anterior displacement of the ciliary body and occlusion of the angle. Anterior segment ischemia also may cause glaucoma.

### Infection and Extrusion

Scleral buckling materials constitute foreign bodies and therefore carry the risk of infection and extrusion. The incidence of explant infection and extrusion is about 1%. Effective management of infected scleral buckling material usually requires removal. Topical and systemic antibiotics occasionally result in symptomatic improvement, but they are rarely curative. Removal of the scleral buckling material carries a redetachment risk of 4%–33%.

### Choroidal Effusion

Accumulation of serous or serosanguinous fluid in the suprachoroidal space is relatively common after scleral buckling, referred to as a choroidal (or ciliary body) effusion. Choroidal effusion is related to the size and extent of the scleral buckle.<sup>9</sup>

### Cystoid Macular Edema and Residual Subretinal Fluid

Using cryotherapy and explant techniques, the incidence of angiographic cystoid macular edema (CME) 4–6 weeks after surgery in phakic eyes is 25%–28%, and typically resolves spontaneously.<sup>10</sup> Additional therapies, such as corticosteroids, may be needed for resolution.<sup>11</sup>

### Macular Pucker

Macular pucker is a major cause of decreased vision after scleral buckling, with the incidence in the range of 3%–17%.<sup>12</sup> Risk factors identified include preoperative PVR of grade B or greater, age, total retinal detachment, and vitreous loss during drainage.<sup>10</sup>

### Diplopia

The incidence of postoperative diplopia is low. In a series of 750 patients who underwent scleral buckling for retinal reattachment, 3.3% complained of diplopia postoperatively.<sup>13</sup> The incidence of diplopia is greater after reoperations involving buckle revision and with larger buckles.

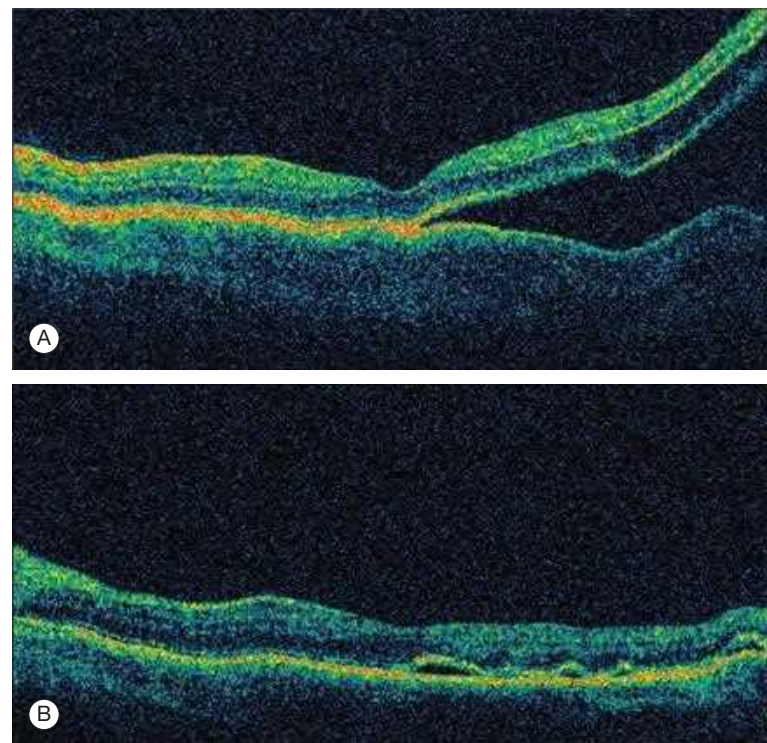
### Changes in Refractive Error

The extent of change in refractive error after scleral buckling depends on the surgical technique employed. Segmental buckles have little effect on refractive error. However, large radial elements, such as full-thickness sponges that extend anteriorly beyond the ora serrata, may induce an irregular astigmatism. Encircling procedures induce the greatest change in refractive error, greater for phakic than for aphakic eyes, because of the anterior displacement of the lens, resulting in an increased myopic shift.<sup>14</sup>

## OUTCOME

The anatomical results following scleral buckling are impressive, with an overall reattachment rate of around 90%. Unfortunately, the visual results after scleral buckling do not parallel the anatomical results. Multiple factors correlate with visual and anatomical prognosis. Detachments with the macula attached (macula-on detachments) at the time of surgery have a significantly better prognosis compared with detachments in which the macula is involved. Some series demonstrate successful anatomical reattachment in 99% of cases of macula-on retinal detachments.<sup>15,16</sup> However, decreased visual acuity can occur, usually caused by postoperative macular changes, such as CME or macular pucker. Approximately 10% of patients who have macula-on detachments suffer a visual loss of two Snellen lines or greater with respect to their preoperative vision.

Detachment of the macula results in a variable degree of permanent photoreceptor damage that correlates with the duration of the detachment.<sup>17</sup> Macula-off detachments are usually larger and of greater duration compared with macula-on detachments; therefore, it is not surprising that macula-off retinal detachments have a lower rate of success. Although the overall anatomical success rate for macula-off detachments is at least 90%,



**Fig. 6.11.5** (A) Optical coherence tomography of acute retinal detachment of 3 days' duration. Note the retinal edema. (B) Optical coherence tomography of same eye 6 weeks after scleral buckling. Note the persistent subfoveal fluid despite resolution of retinal edema and retinal attachment.

only 40%–60% of patients have a final visual acuity of 20/50 or better.<sup>18–20</sup> Preoperatively, OCT documents the status of the macula and the presence of retinal edema (Fig. 6.11.5). Postoperatively, OCT may demonstrate the presence of CME or residual subretinal fluid.<sup>21</sup>

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# Vitrectomy

Michael Engelbert, Stanley Chang

# 6.12



**IN THIS CHAPTER**  
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**Definition:** Vitrectomy is an intraocular surgery during which the vitreous is removed to allow for adjunctive procedures to repair retinal and/or macular pathology or to remove foreign, abnormal, or dislocated tissue or material from the posterior segment or to place therapeutic medications, devices, or tamponades into the eye.

## Key Features

Three ports in pars plana to accommodate:

- Infusion to replace intraocular volume and maintain IOP and to infuse vitreous tamponade.
- Endoillumination cutter, forceps, scissors, endodiatheirmy, endolaser.
- Visualization with contact or noncontact viewing system.

## INTRODUCTION

Since its genesis, remarkable advances in vitreous surgery have established this microsurgical procedure as the second-most common intraocular operation after cataract extraction. Progress in two major areas has fueled the extraordinarily rapid growth in vitreous surgical techniques:

- Understanding of the pathoanatomical changes that affect the retina and vitreous.
- Introduction of new technology and instrumentation.

In the early years, vitrectomy was used to restore ambulatory vision in eyes that were otherwise destined to become blind. Both removal of opacified vitreous and removal of fibrovascular tissue in diabetic retinopathy often resulted in restoration of functional vision. Eyes that had complicated retinal detachments, such as those associated with proliferative vitreoretinopathy or that resulted from severe penetrating injury, were regarded as inoperable previously. As advances in technology continued and the safety of the vitrectomy procedure was established, the focus shifted to newer applications (e.g., macular surgery). The goals of this surgery are to improve and restore central visual acuity in such conditions as macular pucker, macular hole, and retinal detachment.

## HISTORICAL REVIEW

In 1970, Machemer and Parel introduced the first instrument to cut and remove vitreous, and the first vitrectomy procedure was in a patient with diabetes who had a long-standing vitreous hemorrhage (Video 6.12.1).



See clip:  
6.12.1

## PREOPERATIVE EVALUATION AND DIAGNOSTIC APPROACH

The preoperative evaluation of patients who are to undergo vitrectomy includes a careful examination of the eye and assessment of the patient's medical status and risk of anesthesia-related complications. The surgeon reviews the planned procedure with the patient to explain expected outcomes and potential benefits and risks.

Slit-lamp examination is used to evaluate the anterior segment structures, whereas indirect biomicroscopy allows for assessment of vitreoretinal anatomy. When a gas bubble tamponade is planned, the depth of the anterior chamber is assessed because a large bubble may result in shallowing and angle-closure glaucoma. The cornea, size of the dilated pupil, and clarity of the lens are noted to ensure that, intraoperatively, the retina can be visualized adequately. In pseudo-phakic eyes, the type of intraocular lens (IOL) and its composition are studied. Because of its hydrophobic properties, a silicone IOL may develop condensation on its surface during fluid–air exchange, and the placement of silicone oil intravitreally may result in adhesion of oil droplets to the implant surface, which reduces the clarity of the optical zone. Gonioscopic evaluation is carried out in patients with diabetes and those who have inflammatory conditions.

The status of the vitreous is best studied using indirect biomicroscopy—either a noncontact +78.00 diopters (D) or +90.00 D lens or a contact lens may be used. The absence or presence of separation of the posterior hyaloid surface is determined first, as this finding is critical to the surgical approach in macular conditions. These findings are supplemented by those of careful indirect ophthalmoscopy, which provides information about the severity of epiretinal membrane (ERM) proliferation, the location of retinal breaks, and anatomical changes in the vitreous base and peripheral retinal structures. Optical coherence tomography (OCT) as an adjunctive diagnostic tool has revolutionized the assessment of the vitreous–retinal interface as well as the retina, retinal pigment epithelium (RPE), and subretinal space at a close to ultrastructural level in a noninvasive fashion. This has greatly facilitated the distinction between “true” macular holes, pseudo- and lamellar holes, as well as cystic macular edema. Sensitivity, specificity, and reproducibility exceed that of a contact lens examination. It is also increasingly being used to help prognosticate surgical outcomes for macular hole and macula-off detachment surgery.

In cases of media opacity, ultrasonographic evaluation provides an accurate map of the vitreoretinal relationships. In particular, the mobility of retinal detachment, delineation of tractional regions, and localization of vitreous or subretinal hemorrhage may be depicted. The location and dimensions of prior scleral buckling elements may be determined. In trauma situations, ancillary tests using computed tomography or orbital radiographic analysis may be necessary to aid in the localization of foreign bodies and damage to periocular structures.

## INDICATIONS AND ALTERNATIVES TO SURGERY

The surgical indications for vitrectomy are given in [Box 6.12.1](#). These include a wide range of conditions, some of which involve the vitreous or retina focally, whereas others represent more diffuse processes. Other chapters in this book describe the alternative medical approaches for many of the listed conditions.

## ANESTHESIA

The majority of vitrectomies are carried out under local anesthesia (retrobulbar block, peribulbar block, or subconjunctival irrigation) with monitored anesthesia care. In instances of extreme patient apprehension or an inability to cooperate, general anesthesia is required. When using general anesthesia and intraoperative gas administration, it is important to discontinue inhalation of nitrous oxide at least 20 minutes prior to the final

### BOX 6.12.1 Indications for Vitrectomy

#### Diabetic Retinopathy

- Nonclearing or repeated vitreous hemorrhage
- Traction retinal detachment
- Combined traction and rhegmatogenous retinal detachment
- Progressive fibrovascular proliferation
- Macular distortion by fibrovascular proliferation
- Macular edema that results from a taut posterior hyaloid

#### Retinal Detachment

- Retinal detachment with proliferative vitreoretinopathy
- Giant retinal tears
- Retinal detachment with posterior retinal breaks
- Some primary retinal detachments

#### Complications of Anterior Segment Surgery

- Dislocated lens fragments
- Dislocated intraocular lens
- Aphakic or pseudo-phakic cystoid macular edema
- Endophthalmitis
- Choroidal hemorrhage
- Epithelial downgrowth
- Anesthetic needle perforation

#### Trauma

- Hyphema evacuation
- Traumatic cataract or dislocated lens
- Posterior penetration injuries with vitreous hemorrhage and/or retinal detachment
- Reactive intraocular foreign body
- Subretinal membranes or hemorrhage
- Traumatic macular holes

#### Macular Surgery

- Macular pucker
- Macular hole
- Massive subretinal hemorrhage
- Vitreomacular traction syndrome
- Myopic traction maculopathy
- Retinal detachment secondary to optic pit, and other optic nerve anomalies
- Transplantation of retinal photoreceptors or retinal pigment epithelium

#### Pediatric Retinal Disorders

- Retinopathy of prematurity
- Persistent hyperplastic primary vitreous
- Familial exudative vitreoretinopathy
- Giant retinal tears/dialysis
- Juvenile retinoschisis
- Juvenile rheumatoid arthritis
- Retinal detachment secondary to choroidal coloboma
- Retinal detachment in “morning glory” syndrome or optic nerve colobomas
- Gene therapy for treatment of retinal degenerations

#### Tumors

- Choroidal melanoma
- Complications of retinal angiomas
- Combined hamartoma of the retina and retinal pigment epithelium
- Intraocular lymphoma
- Diagnostic vitrectomy, fine needle aspiration

#### Uveitis

- Viral retinitis—cytomegalovirus infection, acute retinal necrosis
- Intraocular infections—bacterial, viral, fungal, parasitic
- Ophthalmomyiasis
- Inflammatory conditions—sarcoidosis, Behçet’s syndrome, uveal effusion
- Pars planitis
- Whipple’s disease
- Familial amyloidosis
- Hypotony



**Fig. 6.12.1** Typical small gauge vitrectomy cutters of 23-, 25-, and 27-gauge cutters showing the relative sizes of the cutting tips.



**Fig. 6.12.2** Small-Gauge Instruments Also Include Forceps and Scissors. Tips of the forceps have been designed to provide more delicate grasping of tissue (top), whereas scissors can be straight or curved to conform to the shape of the eye (bottom).

injection of gas. Otherwise, elevated intraocular pressure or an inadequate gas fill may result.

## GENERAL TECHNIQUES

Microincision vitrectomy uses instruments of 23-gauge,<sup>1</sup> 25-gauge,<sup>2</sup> or 27-gauge<sup>3</sup> caliber (Fig. 6.12.1) and has replaced standard 20-gauge vitrectomy for most cases in the hands of most surgeons. Microincision vitrectomy employs self-retaining microcannula ports, which are inserted transconjunctivally by using trocar needles. During insertion, the needles are directed at such an angle that a beveled self-sealing incision results. The cannulas are placed 3.5–4.0 mm posterior to the corneal limbus, depending on the phakic status of the eye. Usually the inferior cannula is connected to an infusion line to replace the vitreous removed with balanced saline. A vitreous cutter probe, and a fiberoptic light probe are inserted through the superior sclerotomy openings. “Valved” cannulas, which have a thin membrane covering the entrance of the cannula, are increasingly utilized so that fluid egress from the eye is limited during the procedure and turbulent flow and pressure oscillation in the eye are minimized. Additional light fibers of 2-gauge or 27-gauge (“chandelier” lighting) can be inserted through the pars plana to supplement the light from the fiberoptic probe or allow two instruments to be placed into the eye for bimanual dissection. An assortment of additional instruments, such as forceps, scissors, and laser probes, is also available for membrane manipulation (Fig. 6.12.2). Even the most complex vitrectomies can be done with smaller gauges, with 20-gauge instruments still required to remove dense lens fragments or foreign bodies. Most of the small-gauge incisions are



**Fig. 6.12.3** Wide-angle indirect contact lenses afford a view of much of the retina, here during air–fluid exchange. Inferiorly, a buckle anterior to the equator is visible.

self-sealing, but occasionally, a single transconjunctival suture is necessary to close a leaky opening.

A high-resolution surgical microscope is used to view the fundus during surgery. A plano-concave contact lens is used most commonly, but additional surgical viewing lenses (e.g., prism lenses, lenses of higher refractive index) have been developed to improve intraoperative visualization. Of increasing acceptance is the use of contact or noncontact wide-field or panoramic viewing systems based on the principles of binocular indirect ophthalmoscopic visualization (Fig. 6.12.3). Such systems offer an expanded visualization area and increased depth of focus but require that an image inverter be mounted on the microscope. Recently, systems using binocular video cameras placed onto the body of a surgical microscope have been developed for vitrectomy. The surgeon views a large surgical monitor with three-dimensional glasses and is able to perform the delicate surgical maneuvers required. Advantages for such an approach are that lower illumination is required, and ergonomically, the surgeon's neck and back are less prone to stress.

## SPECIFIC TECHNIQUES

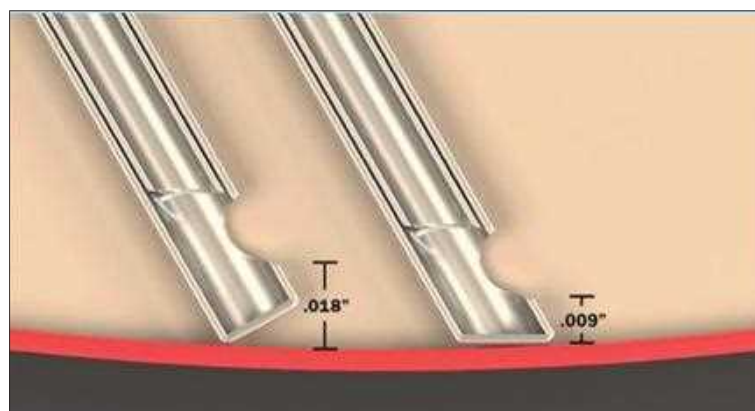
### Lensectomy

Lensectomy is indicated when cataract prevents visualization of the fundus or when the lens is subluxated. Furthermore, the lens is removed if vitreoretinal traction located at or anterior to the vitreous base must be dissected, which is most frequently seen in proliferative vitreoretinopathy (PVR) and trauma. Ultrasonic fragmentation of the lens is usually approached from the pars plana with the lens equator entered by the fragmentation probe. If no IOL is to be placed, the capsule is excised completely by using the vitreous cutter or removed en bloc with forceps.

It has become increasingly common to combine standard phacoemulsification, using an acrylic foldable IOL, with vitrectomy.<sup>4</sup> This combined approach speeds the recovery time for stabilization of visual acuity.

### Vitreous Cutters

The vitreous cutting technology used is the guillotine cutter. This instrument, which comes in 20, 23, 25, and 27 gauges, consists of a round needle-like shaft with a small opening near the tip. Tissue is aspirated into the port and cut by an inner hollow sleeve that moves back and forth along the long axis of the probe. Currently, cutting speeds of up to 10000 cuts/min are attainable. Higher cutting speeds result in less traction on the tissue, and theoretically, fewer iatrogenic tears would occur when the probe is working near the surface of the retina. Higher cutting rates have also been introduced by modifying the inner cutting sleeve to have two openings so that with each stroke, the tissue is cut twice with one cycle. Enhancements, such as placing the port closer to the end of the probe or beveling the end of the probe, also allow the port to be placed closely to the tissue that is being cut (Fig. 6.12.4).



**Fig. 6.12.4** A vitreous cutter with a beveled tip can allow the port to be closer to the retinal surface. This is particularly useful in cases of proliferative diabetic retinopathy.

## Epiretinal Membrane Dissection

Two types of epiretinal proliferation are encountered:

- Fibrovascular proliferation, which contains neovascularization, most commonly seen in proliferative diabetic retinopathy (PDR).
- Nonvascular membranes, found in PVR and macular pucker.

In cases of PDR, the surgical goals are to separate the posterior hyaloid from the retinal surface peripherally and to remove the epiretinal proliferative tissue or release its tractional effects centrally and/or peripherally. Surgical techniques employed to remove the proliferative tissue are:

- Segmentation.
- Delamination.
- En bloc dissection.

The dissections are achieved by using microsurgical instruments. The smaller-gauge cutters are able to access small openings in the tissue planes and can be quite effective in removing layers of fibrovascular proliferation. Scissors that cut perpendicularly across fibrovascular tissue or scissors that have curved blades to cut between the retinal attachments of the proliferative tissue are available. The use of lit, multifunction instruments allows for bimanual delamination of tissue, which can be carried out more safely and with less bleeding. Attainment of the surgical objectives results in a stabilization of the retinopathy and vision.

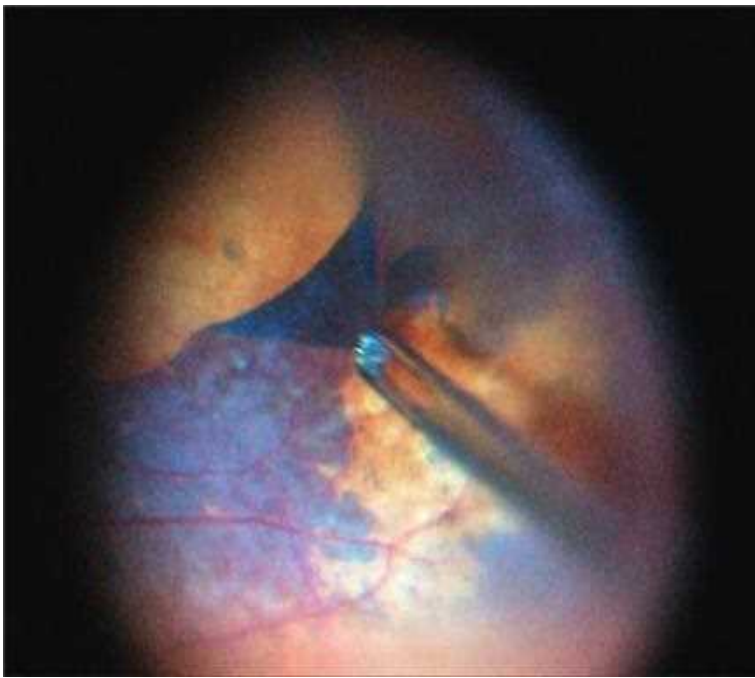
Nonvascular ERMs are found in PVR and, in a less severe form, macular pucker. Such membranes may adhere strongly to the surface of the retina and are best removed by using end-gripping membrane forceps; a bimanual approach with the use of an illuminated membrane pick and forceps reduces the possibility of the formation of iatrogenic retinal tears.

It is recognized now that mechanical effects of the posterior hyaloid at the vitreous–retinal interface may result in macular hole formation and central visual loss. The actual structural changes within this layer of cortical vitreous that cause retinal pathology are unclear. A critical step in the surgical management is separation of the posterior hyaloid from the retina. After a central vitrectomy has been performed, the adherent layer of cortical vitreous at the vitreous–retinal interface is engaged and elevated by using the vitreous cutter. The posterior hyaloid is most adherent at the optic disc and at the macular region. After separation of the hyaloid, noted by observation of Weiss' ring, the vitreous layer can be excised out to the periphery.

## Intraoperative Tissue Staining

Because many preretinal tissues, such as the cortical vitreous, ERM, and internal limiting membrane, are transparent by nature, several chemicals can aid in their visualization during vitrectomy. Intravitreal indocyanine green (ICG) dye was first employed to stain the internal limiting membrane in order to facilitate peeling and complete removal. ICG is widely employed, especially for macular hole surgery. However, photosensitivity and the creation of deeper cleavage planes when peeling the internal limiting membrane have been observed. This has prompted the use of alternative stains, such as trypan blue for staining of ERM; brilliant blue for staining of the internal limiting membrane (Fig. 6.12.5); and triamcinolone, which appears to be particularly useful in highlighting cortical vitreous (Fig. 6.12.6).





**Fig. 6.12.5** Staining of internal limiting and epiretinal membranes, in this case with brilliant blue, can be particularly helpful in cases where poor and irregular pigmentation of the fundus make visualization challenging, in this case in a high myopic eye with tractional foveoschisis.



**Fig. 6.12.6** Cortical vitreous stains particularly well with triamcinolone, and this can aid in its complete and safe removal, as in this case of myopic foveoschisis.

## Perfluorocarbon Liquids

Perfluorocarbon liquids are useful as an intraoperative mechanical tool. The various perfluorocarbon liquids currently used in vitreous surgery have different physical and optical properties. Perfluoro-*n*-octane, because of the better visibility it allows, low viscosity, and high vapor pressure, is the most commonly used of these. Giant retinal tears with large, inverted posterior flaps can be repositioned easily into their normal anatomical position, which allows for the successful management of this condition without the use of special equipment to rotate the patient intraoperatively.<sup>5</sup>

In PVR, as perfluorocarbon liquid flattens the posterior retina, retinal folds are opened and allow for traction and visualization of additional membranes. A posterior retinotomy for internal drainage of subretinal fluid is no longer necessary. The retina is stabilized as membrane dissection proceeds, and large retinotomies, when necessary, can be carried out more safely.

Other applications of perfluorocarbon liquids are to float dislocated lens fragments or dislocated IOLs anteriorly, to provide intraocular hemostasis by localization of bleeding, and to express liquefied subretinal blood from under the retina.

## Endophotocoagulation

Laser photocoagulation is applied around retinal breaks and circumferential retinotomies; in general, 2–3 rows of treatment are adequate. In more advanced cases of retinal detachment, such as PVR, laser spots may be placed contiguously in two or three rows on the anterior slope of the scleral buckle. In PDR, scatter photocoagulation is applied to areas of peripheral ischemia, thus reducing the risk of neovascular glaucoma.

## Gas and Silicone Oil Tamponade

The final step in vitreous surgery is to decide whether it is necessary to fill the vitreous space by using a tamponade agent. An automated air-infusion pump is used to perform the fluid–air exchange. A flute needle is used actively or passively to aspirate the intraocular fluid as air is infused through the infusion line.

In cases where no retinal detachment exists, a bubble tamponade may be unnecessary; but in some cases, air is used to smooth out retinal folds or to allow visualization through a hemorrhagic medium postoperatively. In macular hole surgery, a longer-lasting gas bubble is useful as its buoyant force may help to close the hole. When retinal detachment is present, the subretinal fluid must be evacuated to achieve a complete fill with gas and ensure that the retina flattens without posterior folds. Perfluorocarbon liquid may be injected to flatten the retina up to the level of peripheral retinal breaks—the posterior subretinal fluid is expressed anteriorly. Internal drainage of the remaining subretinal fluid is accomplished by placement of the aspirating needle through the retinal break as air enters the eye. The descending air bubble flattens the anterior retinal detachment and forces the anterior subretinal fluid through the retinal break. When the subretinal fluid has been aspirated completely or nearly completely, the perfluorocarbon liquid may be removed.

The type of gas used is dependent on the individual clinical situation.<sup>6</sup> In eyes with simple retinal detachment, the role of the gas bubble is to allow adequate time for the chorioretinal adhesion from laser treatment to form. Usually, air or sulfur hexafluoride, which persists for 10–14 days, may be used. For more complex retinal detachments, such as PVR, trauma, and giant retinal tears, a longer-lasting gas bubble is usually required. Perfluorohexane or perfluoropropane gases are chosen frequently in these situations.

Silicone oil tamponade may also be used as a long-term tamponade agent. This clear viscous liquid, which is immiscible with water, replaces the vitreous. Its surface tension and mild buoyant force mechanically hold the retina against the choroid. The advantage of silicone oil is that the patient has vision through the oil bubble and that extensive prone-head positioning (required with gas bubbles) is unnecessary. However, silicone oil may require surgical removal months after the retina has been reattached. The results of a multicenter, randomized clinical trial, in which the use of perfluoropropane gas was compared with the use of silicone oil for the treatment of severe PVR, found no statistically significant difference in the final retinal reattachment rate between the two modalities.<sup>7</sup>

## COMPLICATIONS

Many of the potential complications of vitreous surgery may be realized during the later postoperative period. The rate of complications has decreased gradually as improvements in technology have been introduced. However, experience, surgical skill, and training are also significant factors that can reduce the rate of complications. The more widely described intraoperative and postoperative complications encountered with vitreous surgery are given in [Box 6.12.2](#).

## OUTCOMES

The introduction of new surgical techniques and instrumentation and improved knowledge of the pathophysiology of abnormal vitreoretinal structural changes have resulted in a steady improvement in the anatomical and visual results of vitreous surgery. Some of the results reported for the most common indications of vitrectomy are given in [Table 6.12.1](#) and represent significant advances in the surgical treatment of retinal disorders.

TABLE 6.12.1 Surgical Outcomes in Vitreous Surgery

Vitreoretinal Disorder	Outcome
Diabetic vitreous hemorrhage	89% improvement with clear vitreous <sup>8</sup>
Diabetic traction retinal detachment	66%–95% retinal reattachment rate <sup>9</sup>
Proliferative vitreoretinopathy	94% final retinal reattachment rate <sup>10</sup>
Giant retinal tears	96% final retinal reattachment rate <sup>5</sup>
Macular pucker	80%–90% visual improvement by two or more Snellen lines <sup>11</sup>
Idiopathic macular hole	85% visual improvement by two or more lines <sup>12</sup>
Dislocated lens fragments	68% final visual acuity 20/40 (6/12) or better <sup>13</sup>
Retinal detachment	70%–90% primary reattachment rate <sup>14</sup>

BOX 6.12.2 Potential Complications of Vitreous Surgery

Intraoperatively

- Corneal epithelial defect
- Posterior retinal breaks
- Peripheral retinal breaks
- Choroidal hemorrhage (rare)

Postoperatively

- Retinal breaks
- Rhegmatogenous retinal detachment
- Elevated intraocular pressure (multiple potential causes)
- Neovascular glaucoma
- Angle-closure glaucoma
- Inflammatory debris
- Corticosteroid response
- Overfilling with gas
- Anterior hyaloidal fibrovascular proliferation
- Fibrin deposition in the anterior chamber (not rare, especially in individuals with diabetes)
- Progressive nuclear sclerosis (almost universal in phakic eyes)
- Corneal decompensation
- Hypotony
- Endophthalmitis (incidence 1 in 2500)

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# Intravitreal Injections and Medication Implants

6.13

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**Definition:** Intravitreal injections and implants, most often administered as an office procedure, are a safe, effective, and common method of delivering medication locally to the eye.

## Key Features

- Topical anesthesia is usually sufficient.
- Sterile technique is used.
- Small-gauge needles (30-gauge or smaller) can be used for intravitreal injections.
- Effective method to deliver antivascular endothelial growth factor medications, corticosteroids, antibacterial and antiviral agents, air, and gas.

## Associated Features

Complications include:

- Infectious endophthalmitis.
- Sterile inflammation.
- Retinal tears.
- Vitreous hemorrhage.
- Cataract.
- Intraocular pressure elevation; intraocular pressure should be monitored when injecting larger volumes of medication and in patients with glaucoma.
- Different techniques of insertion for multiple platforms of sustained-release implants.

## INTRODUCTION

The office delivery of medication directly into the vitreous cavity via injection or implant has become commonplace in ophthalmology. This method allows for higher concentrations of medication in the eye with less systemic absorption compared with other methods of administration. In 1911, the injection of air into the vitreous cavity for retinal detachment (RD) repair was initially reported, followed by reports of the injection of penicillin for endophthalmitis in 1947.<sup>1</sup> Fomivirsen (Vitravene; Isis Pharmaceuticals) was the first medication approved by the U.S. Food and Drug Administration (FDA) for intravitreal use in 1998 for the treatment of cytomegalovirus (CMV) retinitis. Pegaptanib (Macugen; OSI Pharmaceuticals), ranibizumab (Lucentis; Genentech), and aflibercept (Eylea; Regeneron Pharmaceuticals) have all since been FDA approved for use in exudative age-related macular degeneration (AMD),<sup>2</sup> and bevacizumab (Avastin; Genentech) is commonly used off-label to treat many forms of choroidal neovascularization and macular edema. The introduction of these vascular endothelial growth factor (VEGF) inhibitors for the treatment of common ocular conditions, such as diabetic retinopathy and exudative AMD, has resulted in a critical need for the ophthalmologist to fully understand the process of performing intravitreal injections.

## PREINJECTION PREPARATION

Patients for whom intravitreal injection is recommended should be evaluated prior to injection for any signs of ocular infection (Box 6.13.1). Overt, active blepharitis should be treated before injection to decrease the bacterial

## BOX 6.13.1 Intravitreal Injection Technique Recommendations

### Preinjection

- External ocular examination, visual acuity, and intraocular pressure check
- Informed consent form
- Anesthesia (topical or subconjunctival)
- Topical povidone-iodine (5% for the ocular surface, 10% for the lids and lashes)

### Injection

- Surgical pause confirming the correct patient, laterality, and medication
- Surgical gloves (sterile or nonsterile)
- Placement of sterile lid speculum or manual lid retraction
- Caliper to measure 3.5–4.0 mm posterior to limbus in preferred quadrant
- 5% povidone-iodine to injection site
- Penetration with small gauge needle through conjunctiva and sclera (perpendicular to surface or “tunneled”)
- Slow, steady injection of medication
- Sterile cotton tip applicator at injection site to prevent reflux as needle is removed
- Removal of speculum (if used)
- Maintain sterility of instrument surfaces that contact the eye, prior to injection

### Postinjection

- Irrigation of ocular and periocular surfaces with balanced salt solution
- Confirmation of central retinal artery perfusion (visual acuity or direct visualization)
- Intraocular pressure (IOP) check with administration of IOP-lowering medication, if indicated
- Lubricating drops or ointment at end of procedure
- Instruction sheet with information on injection procedure as well as emergency contact number

load, which may increase the risk of infection.<sup>3</sup> Patients with bacterial or viral conjunctivitis should be treated appropriately to manage infection and should have their injection rescheduled. Prophylactic preinjection antibiotics have not been shown to decrease the conjunctival bacterial load compared with application of 5% povidone-iodine prior to injection.<sup>4</sup> There is also concern that routine use of prophylactic antibiotics will increase resistant strains of bacteria on the conjunctival surface without decreasing rates of endophthalmitis.<sup>5</sup> As with any surgical procedure, all patients should sign an informed consent form after being explained the risks, benefits, and alternatives to injection.

## Pupillary Dilation

Evaluation of central retinal artery perfusion following an intravitreal injection may be required in patients with a history of elevated intraocular pressure (IOP). This may also be beneficial in patients who are receiving larger doses of medication or multiple medications.<sup>6</sup> Dilation may not be required in patients presenting only for injection and who have stable visual acuity and unchanged visual symptoms.

## Anesthesia

Topical, subconjunctival, and peribulbar routes of local anesthesia have all been employed for intravitreal injections with similar levels of pain control.<sup>7</sup> Use of topical 0.5% proparacaine or 0.5% tetracaine drops provide adequate analgesia with minimal side effects.<sup>8,9</sup> A cotton pledget soaked with 4% lidocaine can also be applied to the conjunctival surface. Injection of subconjunctival 2% lidocaine is effective as well but may be associated with subconjunctival hemorrhage, which could be of cosmetic concern to the patient.<sup>6</sup> Topical lidocaine gel is another alternative,<sup>10</sup> but theoretical concerns that the gel may prevent the bactericidal effect of the povidone-iodine have been raised.<sup>11</sup> These are several available options, and different patients may respond more favorably to different forms of anesthesia.

The majority of patients receive their injections in the clinic, with very low complication rates and appropriate analgesia.<sup>7,12</sup> Furthermore, patients being treated for endophthalmitis may have different anesthesia requirements because of their significant inflammatory response.

## Antisepsis

Povidone-iodine is recommended for preinjection antisepsis and has been shown to decrease the rate of endophthalmitis in cataract surgery.<sup>3,13</sup> It is bactericidal and has rapid cytotoxicity.<sup>14</sup> The periocular lids and lashes can be cleaned with 10% povidone-iodine. Cleaning should begin at the lashes and move peripherally so as not to introduce bacteria to the ocular surface. Gentle cleaning of the lid margin is recommended to prevent discharge of bacteria from the meibomian glands onto the ocular surface, which may otherwise result from vigorous cleaning.<sup>3</sup> The ocular surface is treated with 5% povidone-iodine, which reduces ocular irritation but still has a bactericidal effect.<sup>15,16</sup> There have been no reported cases of anaphylaxis to povidone-iodine related to ophthalmic use.<sup>17</sup> One may consider referral for skin testing by an allergy specialist for patients reporting any allergies. Allergic contact dermatitis and surface irritation are side effects of povidone-iodine that may result in postinjection discomfort.<sup>18</sup> An endophthalmitis rate of 9.4% has been associated with the failure to use povidone-iodine for injections in patients with self-reported allergies.<sup>19</sup> Chlorhexidine is effective at reducing surgical site infections, and the aqueous form can be used to prepare the ocular surface.<sup>19,20</sup>

Use of a sterile lid speculum or manual lid retraction is recommended to prevent contact between the tip of the needle and the patient's lids or lashes. However, this may compress the meibomian glands, resulting in discharge of their contents onto the ocular surface, so an additional application of 5% povidone-iodine may be given prior to injection. The use of gloves (sterile or nonsterile) is considered essential; however, the use of drapes or gowns is not.<sup>3</sup>

Minimal talking or the use of masks after the preparation of the ocular surface is encouraged to prevent airborne contamination by *Streptococcus*.<sup>3</sup> There is theoretical concern that airborne droplets may settle on the exposed needle prior to injection.<sup>21</sup> Maintaining silence may be difficult, however, in cases where patients require further instruction after sterile preparation.

## INJECTION

The needle used for injection need be no larger than 30-gauge for a routine injection of medication or gas. Use of a smaller-gauge needle may reduce procedural discomfort in patients.<sup>22</sup> The force required to penetrate the sclera is almost doubled when using a 27-gauge needle compared with a 30- or 31-gauge needle.<sup>23</sup> Needle length should be 5/8 of an inch or shorter to prevent globe trauma.<sup>3</sup> The majority of retinal specialists surveyed in 2010 reported using a 30-gauge needle for injections of bevacizumab and ranibizumab, and a 27-gauge needle for triamcinolone.<sup>24</sup> Triamcinolone can precipitate within the syringe and clog a needle smaller than 30-gauge. Separate needles should be used to remove the medication from the vial (usually a filter needle) and to perform the actual injection (30–32 gauge). This helps prevent both contamination and dulling of the needle.

The injection is given through the pars plana approximately 3.5–4.0 mm posterior to the limbus.<sup>3</sup> Injections are commonly performed in the inferotemporal and superotemporal quadrants. The quadrant of injection may be influenced by the indication for injection or other factors. For example, injecting an opaque corticosteroid superiorly may initially obscure the visual axis more compared with an inferiorly administered injection. Similarly, a patient with a large inferotemporal retinoschisis cavity may benefit from having the injection given in another quadrant.

The traditional injection method involves inserting the needle perpendicular to the sclera in a single plane to penetrate the globe, although tunneling methods have also been described.<sup>25</sup> The final needle direction should always be toward the center of the eye to prevent damage to other intraocular contents.<sup>3</sup>

The medication should be injected in a slow, steady manner to prevent a sudden flux through the vitreous cavity because this may disrupt vitreoretinal adhesions. A sterile cotton tip applicator may be used to prevent reflux after needle removal.<sup>26</sup> Injection of larger volumes of medication (e.g., for endophthalmitis) may require removal of aqueous or vitreous humor to prevent IOP elevation.

## POSTINJECTION

The use of topical antibiotics following intravitreal injections had previously been a common practice but is no longer recommended.<sup>3</sup> Recent clinical trials have demonstrated that postinjection topical antibiotics may not be required for patients undergoing routine intravitreal injections of anti-VEGF or corticosteroid medications.<sup>27</sup> Routine use of topical fluoroquinolones after injections has been shown to increase rates of antibiotic resistance of conjunctival flora.<sup>28</sup>

The ocular and periocular surfaces should be irrigated to remove the povidone-iodine. Lubricating drops or ointment may be placed on the eye to alleviate ocular discomfort associated with the povidone-iodine preparation.

IOP elevation is common after intravitreal injection but remains below 35 mm Hg in the majority of patients. Patients with glaucoma may be more susceptible to IOP elevation. IOP can be monitored following injection and topical medications given, if needed.<sup>3,6</sup> Anterior chamber paracentesis should not be performed routinely after each injection to lower IOP.<sup>3</sup> However, injection of larger volumes or multiple medications may require paracentesis. The presence of at least light perception vision suggests that the central retinal artery is perfused, but the most reliable method to confirm perfusion is direct visualization with the indirect ophthalmoscope.<sup>29</sup>

Prior to leaving the office after the injection, the patient should be counseled regarding ocular care at home and about symptoms that would require evaluation prior to the next scheduled visit. Appropriate education regarding expected side effects from the povidone-iodine preparation and intravitreal injection, versus symptoms of injection complications, may help avoid unnecessary concern or additional visits (Table 6.13.1). Providing an instruction sheet in large print with the above information, as well as a 24-hour contact number, is beneficial.

## COMPLICATIONS

### Endophthalmitis

Endophthalmitis is a potentially devastating complication that may result in poor visual outcomes. A systematic review of data from approximately 40 years and including >14,000 intravitreal injections reported that the prevalence of endophthalmitis was 0.2% per injection. This review included injections for a wide range of diagnoses, and there was a higher prevalence (0.6% per injection) of endophthalmitis after injection of triamcinolone acetonide. All other therapeutics had a risk of 0.1% per injection.<sup>30</sup> A more recent review of pooled data from 20 case series, including 510 396 anti-VEGF injections, indicated that the prevalence of endophthalmitis was 0.028%, or approximately 1 of every 3544 injections. One case series included in the review reported no cases of endophthalmitis after 15,444 injections.<sup>31</sup> *Staphylococcus* is the most common organism associated with endophthalmitis, and *Streptococcus* is a known cause of endophthalmitis that has been suggested to originate from nasopharyngeal droplets.<sup>12</sup> Vitreous wick syndrome is a theory that suggests vitreous incarceration into a scleral wound may act as a conduit for bacteria. A tunneled injection,<sup>25</sup> smaller-gauge needle,<sup>32</sup> and placement of a sterile cotton tip applicator over the injection site may prevent this from occurring.<sup>33</sup>

TABLE 6.13.1 Intravitreal Injection Complications

Endophthalmitis	Retinal pigment epithelium tear
Retinal vascular occlusion	Retinal tear or detachment
Elevated intraocular pressure	Subconjunctival hemorrhage
Corneal abrasion	Vitreous hemorrhage
Cataract progression	Inflammation

## Hemorrhage

Ocular hemorrhage is another possible complication of intravitreal injections. Subconjunctival hemorrhage may occur as a result of laceration of subconjunctival or episcleral vessels. Vitreous hemorrhage may occur if the needle contacts the ciliary body or the retina or in patients with abnormal neovascularization, such as in those with proliferative diabetic retinopathy. Patients on warfarin in the MARINA study did not have significant ocular hemorrhagic complications, and discontinuation of systemic anticoagulation is not recommended.<sup>3,34</sup> Discontinuation of antithrombotic or anticoagulation medications may increase the risks of thromboembolic or cerebrovascular events and should only be done in coordination with a patient's primary care physician.<sup>35</sup>

## Intraocular Pressure Changes

Immediate, transient elevations in IOP following intravitreal injections are a known side effect,<sup>6</sup> but sustained elevation in IOP has also been reported. Patients receiving repeated injections of anti-VEGF medications have been shown to have elevated IOP readings over several visits.<sup>36–39</sup> Ocular hypertension is a known side effect of corticosteroids, but this mechanism of sustained IOP elevation is related to the corticosteroid rather than to the injection itself.<sup>40</sup> Hypotony has been reported after uncomplicated intravitreal injections but was believed to be secondary to ciliary body toxicity from the injected medication.<sup>30</sup>

## Retinal Pigment Epithelium Tears

Retinal pigment epithelium (RPE) tears have been reported following intravitreal injections of anti-VEGF medications.<sup>41–44</sup> However, patients receiving injections for exudative AMD in the ANCHOR, MARINA, and PIER studies of ranibizumab did not have an increased prevalence of RPE detachments compared with controls.<sup>45</sup>

## Retinal Tears and Detachments

Retinal tears or detachments may be associated with intravitreal injections. The incidence of RD was 1 per 7188 injections in nearly 36000 patients receiving anti-VEGF medications.<sup>46</sup> A large review reported the incidence of RD to be 0.9% per injection. However, this included patients with ocular conditions that predispose to RD, such as CMV retinitis and diabetic retinopathy.<sup>30</sup>

## Other Complications

Uveitis has been reported following intravitreal injections, but it is believed that the inflammatory reaction is secondary to the injected medication rather than to the injection itself. Progression of cataract in patients with phakia has been reported, in addition to rare instances of trauma to the lens or lens capsule, which may also result in cataract formation.<sup>30</sup> Tiny silicone oil droplets following intravitreal injections have been reported in the vitreous cavity. They are believed to be from the silicone lubricant in the needles or syringes and have no adverse side effects.<sup>47</sup> Corneal abrasions may occur with removal of the lid speculum or as a result of the toxic effects of the anesthetic and povidone-iodine on the ocular surface. Retinal vascular occlusions have also been reported following intravitreal injections.<sup>30</sup> When complications do occur, the physician should try to determine whether it was from the injection procedure or the injected medication.

## OTHER CONSIDERATIONS

Patients with bilateral ocular disease requiring intravitreal injections may have them performed on the same day<sup>48</sup> or on separate days. Same-day bilateral injections may be especially beneficial for patients in whom transportation to office visits is difficult and long-term bilateral injections are anticipated. Nearly 57% of retina specialists in the United States reported giving same-day bilateral intravitreal injections for exudative AMD in 2016.<sup>49</sup> These patients should be counseled on the possible risk of bilateral ocular complications after the injections. Endophthalmitis has been associated with contaminated batches of bevacizumab from compounding pharmacies.<sup>50</sup> To reduce the risk of medication contamination when injecting a compounded off-label medication, ideally, each eye should be treated from a different batch of compounded medication from the same compounding

pharmacy, or medications obtained from different compounding pharmacies should be used.

## IMPLANTS

Intravitreal implants that allow for long-term release of medication are also being used in the management of retinal diseases and uveitis. The search for delivery systems and medications with longer durations of efficacy may result in intravitreal implants becoming a more common treatment modality.

A sustained-release 0.7 mg dexamethasone implant (Ozurdex; Allergan) has been FDA approved for use in macular edema secondary to retinal vein occlusions, diabetic retinopathy, and noninfectious posterior uveitis.<sup>2</sup> The implant comes loaded in a disposable injector with a 22-gauge needle. It is injected through the pars plana, similar to an intravitreal injection.<sup>51</sup> Because of the larger-gauge needle, patients may have increased requirements for anesthesia (e.g., subconjunctival anesthetic injection) compared with a standard intravitreal injection with a smaller-gauge needle (which may be done under cover of topical anesthesia). This implant, which is biodegradable, has been shown to have clinical efficacy for several months.<sup>51</sup> Sustained-release 0.2 µg/day fluocinolone acetonide implant (Iluvien; Alimera Sciences) is FDA approved for the treatment of chronic diabetic macular edema. It was shown to have visual benefit for up to 3 years, with primary adverse events, including IOP elevation and cataract formation.<sup>52</sup> This nonbiodegradable implant is inserted through a 25-gauge needle.<sup>53,54</sup> Another corticosteroid implant, 0.59 mg fluocinolone acetonide (Retisert; Bausch and Lomb), is also approved for use in noninfectious posterior uveitis. This fluocinolone acetonide implant has clinical efficacy for up to 3 years and is also associated with elevated IOP and cataract formation.<sup>55</sup>

A ganciclovir implant (Vitrasert; Bausch & Lomb) is available and has been shown to decrease progression of CMV retinitis.<sup>56</sup> Placement of both 0.59 mg fluocinolone acetonide and ganciclovir implants is performed in the operating room under cover of local (peribulbar or retrobulbar) or general anesthesia. After creating a small opening in the conjunctiva, the implant is placed into the vitreous cavity through a sclerotomy wide enough to allow insertion of the implant into that area. The implant is then sutured in place at the sclerotomy, and the wounds are closed. Any prolapsed vitreous is removed.<sup>57</sup> These implants are not biodegradable and remain in the eye.

## CONCLUSIONS

As new developments in medications and medication delivery become available, the ophthalmologist will have to continue to evaluate the safest and most efficacious method of performing intravitreal injections to treat ocular disease.

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# Progressive and “Stationary” Inherited Retinal Degenerations

6.14

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## Definition of Progressive Inherited Retinal Degenerations:

Retinitis pigmentosa and the related rod-cone and cone-rod dystrophies constitute a broad set of disorders that generally result in progressive visual dysfunction secondary to loss of photoreceptors.

## Key Features

- Night blindness.
- Visual field constriction.
- Progressive photoreceptor dysfunction and death.
- Loss of rod and cone electroretinography (ERG) responses.
- Clinical degeneration of the outer retina.
- Intraneural retinal “bone-spicule” pigment.

## Associated Features

- Poor correlation between acuity and extent of “tunnel vision”.
- Retinal arteriolar narrowing.
- “Waxy nerve pallor” from reactive gliosis.
- Posterior subcapsular cataracts in middle age.
- Progressive chorioretinal atrophy.
- Frequently, but not always, a family history.
- Associated systemic abnormalities uncommon but important.

## Definition of “Stationary” Inherited Retinal Degenerations:

“Stationary” retinal degenerations are stable in comparison with, and less progressive than, most forms of retinitis pigmentosa (RP), even though there is often some change over time.

## Key Features

- Poor night vision present since birth.
- Fundus appearance may be normal or abnormal.

## Associated Features

- The pathology has an anatomical locus, as revealed by visual function tests.
- Molecular genetic studies suggest pathogenetic mechanisms in certain types.

## PROGRESSIVE DIFFUSE/PANRETINAL DEGENERATIONS

### Introduction

The term *retinitis pigmentosa* (RP) encompasses a set of diverse hereditary disorders that affect the photoreceptors and retinal pigment epithelium (RPE) diffusely across the entire fundus but begin with initial geographical involvement in either the periphery or the macula. These conditions typically, but not always, progress over many years to an advanced stage

and result in global reduction or loss of vision. As a group, the majority of forms of RP lead initially to death of the rod photoreceptors, which impairs vision in dim light and causes loss of peripheral vision, and later involves cones as the symptoms progress leading to “tunnel vision.” However, some of the allied forms primarily cause cone photoreceptor loss and initially manifest with a reduction in central visual acuity.

Such conditions are determined genetically, and all genetic patterns of inheritance are represented. In many cases, a patient represents an isolated case with no known affected relatives, which makes a genetic etiology less obvious and must be differentiated from acquired etiologies, such as inflammatory or infectious retinal insults. The possibility and availability of genetic diagnosis is much higher than ever before, and identification of the various defects within the abnormal genes that result in these conditions is possible. New treatment options are being tested, and others are anticipated in the years ahead because of a new understanding of the pathophysiology of the disease.

The approach to the patient involves initial categorization of the degeneration into either a rod-cone disease or cone-rod disease, two conditions that carry different prognoses. Further subtyping of the disease provides even better information about prognosis. Rod-cone degeneration is typically more severe—the long-term prognosis is loss of most or all vision by later years. Cone-rod degeneration affects central vision quite early and peripheral vision only later. Because the human retina has 120 million rods and only 6 million cones, it may function well without cones, as exemplified by achromatopsia. The prognosis in cone-rod dystrophy is good for at least some future vision, even though central vision is jeopardized. A review of the patient’s symptoms and retinal function studies, particularly visual field testing and electroretinography (ERG), are required to differentiate rod-cone from cone-rod degenerations.

## Epidemiology and Pathogenesis

Familial retinal degeneration with intraneural retinal pigmentation was described as early as 1855 by Donders.<sup>1</sup> It is now understood that most cases have a genetic basis<sup>2</sup> and involve photoreceptor cell death through apoptosis. No racial or ethnic predisposition exists. Men may be affected slightly more than women because of X-linked conditions.

The term *retinitis pigmentosa* refers to a broad category of genetically heterogeneous diseases, which includes many different forms of primary photoreceptor abnormalities—some affect rods first and cones later (termed *rod-cone dystrophy*) or the reverse (termed *cone-rod dystrophy*). The prevalence of primary photoreceptor degeneration is in the range 1:3000–1:5000.<sup>3</sup> The carrier state for recessive retinitis pigmentosa is approximately 1:100, based on the prevalence of recessive retinitis pigmentosa.<sup>4</sup> These numbers are approximate because of the complexity of the many different forms of RP now identified by gene cloning. In most cases, these diseases are thought to be simple Mendelian traits that result from DNA alteration in single genes.

### Rod-Cone Dystrophy

Rod-cone dystrophy manifests clinically with typical RP and affects the rod photoreceptors earlier and more severely than it does the cone photoreceptors. Severe cone involvement occurs in the end stage of the disease, when total vision loss ensues. The key features of the rod-cone type of disease are progressive night blindness and visual field constriction, which become more severe as more rods die, leading to cone loss. The appearance of midperipheral ring scotomas during progressive stages of visual field loss is not uncommon. Typically, both eyes are affected similarly.

Visual acuity is initially affected minimally and typically remains near to 20/20 (6/6) for many years despite progressive field loss to severe tunnel vision. Careful history taking frequently reveals some night blindness, even in early-stage rod-cone disease. Symptoms of typical RP include prolonged dark adaptation. However, many patients with RP are able to drive at night on well-lit streets. Patients complain of problems in dimly lit restaurants and theaters and are symptomatic when they come indoors from bright sunlight. By the midstage of the disease, visual field constriction occurs. Patients may appear clumsy because they collide with a door frame or a friend who walks alongside because of unrecognized tunnel vision. End-stage rod-cone disease results in loss of both peripheral vision and central vision. Many patients have only barely functional central vision by late middle age and lose all vision later. However, the changes occur slowly, and the young patient may be reassured that some vision is most likely to remain for many years or decades, even though the long-term prognosis is grim. Glare sensitivity to bright light occurs in end-stage rod-cone dystrophy, when the diseased cones saturate in bright light.

The functional profile of early-stage rod-cone dystrophy is shown in Fig. 6.14.1. The rod ERG amplitude loss is worse than that for cones (light-adapted: single flash and 30 Hz flicker). Goldmann visual fields are still relatively large with the large V4e target but considerably constricted to the small I4e target—such disparity between the ratio of field area with the V4e versus I4e targets is typical for rod-cone dystrophy. Tests of dark-adapted thresholds show 1–3 log units of rod sensitivity loss, which equates with 10–1000 times more light required to see at night. The disease does not act uniformly across the retina, and rod threshold should be tested at multiple points of vision to give a sensitivity profile across the central and peripheral vision.

As visual fields constrict further, even to the large V4e target, dark-adapted thresholds become worse because only cones remain to mediate vision, even in dim light. At this stage, the patient suffers from

severe night blindness. With time, the cone ERG responses deteriorate further until eventually both the rod and cone responses are reduced profoundly, and all ERG responses are termed “nonrecordable.” By this time, visual acuity is typically less than 20/40 (6/12), color discrimination is impaired, and fields are greatly constricted.

Cone-Rod Dystrophy

Patients with cone-rod dystrophy complain of poor acuity, reduced color vision, and glare sensitivity to bright sunlight.

Particularly in the early stages, the fundus may appear normal, with minimal diffuse retinopathy and normal vessels and disc. Visual fields initially remain full with the Goldmann V4e target but may be constricted slightly with the I4e target. It is more likely that at least some peripheral vision is retained in patients who have cone-rod dystrophy as opposed to those who have rod-cone dystrophy. ERG shows that cone-mediated responses (30 Hz flicker and photopic single flash responses) are reduced proportionally more than the dark-adapted rod b-wave (see Fig. 6.14.1). Although the rod b-wave amplitudes may be subnormal technically, rod dark-adapted threshold sensitivity remains nearly normal when tested using a Goldmann-Weekers dark adaptometer after 45 minutes in the dark. The combination of ERG and psychophysical rod threshold tests is the best way to diagnose cone-rod dystrophy. Patients who have the least rod involvement carry the best prognosis for intermediate-term vision. At the other end of the prognosis spectrum are rare patients who develop a central scotoma early in life; the field defect enlarges gradually but relentlessly toward the periphery, with practically total visual loss by late middle age. These patients usually receive the diagnosis of “macular degeneration” in childhood; the condition has been termed “inverse retinitis pigmentosa” because pigment spicules are more abundant in the central retina than in the midperiphery. Infrequently, a patient with cone-rod dystrophy has an essentially normal rod but a very reduced cone on ERG and is considered to have “cone dystrophy.” Such patients have a good prognosis for vision into later age. Some patients with cone-rod dystrophy are first symptomatic after age ≥50 years and may progress quickly to considerable vision loss.<sup>5</sup> Such patients are a diagnostic challenge because of the later age at presentation; initially, ERG results may be marginally normal, but the results of repeat ERGs after 6–12 months progress to subnormal.

Diagnosis and Ancillary Testing

For diagnosis, visual function tests are an important adjunct to retinal examination. Tests may also help identify correctly the clinical subtype of the disease. Accurate subtyping provides the basis for counseling about expectations for school and career choices, for the provision of genetic information to the extended family, and for potential treatment.

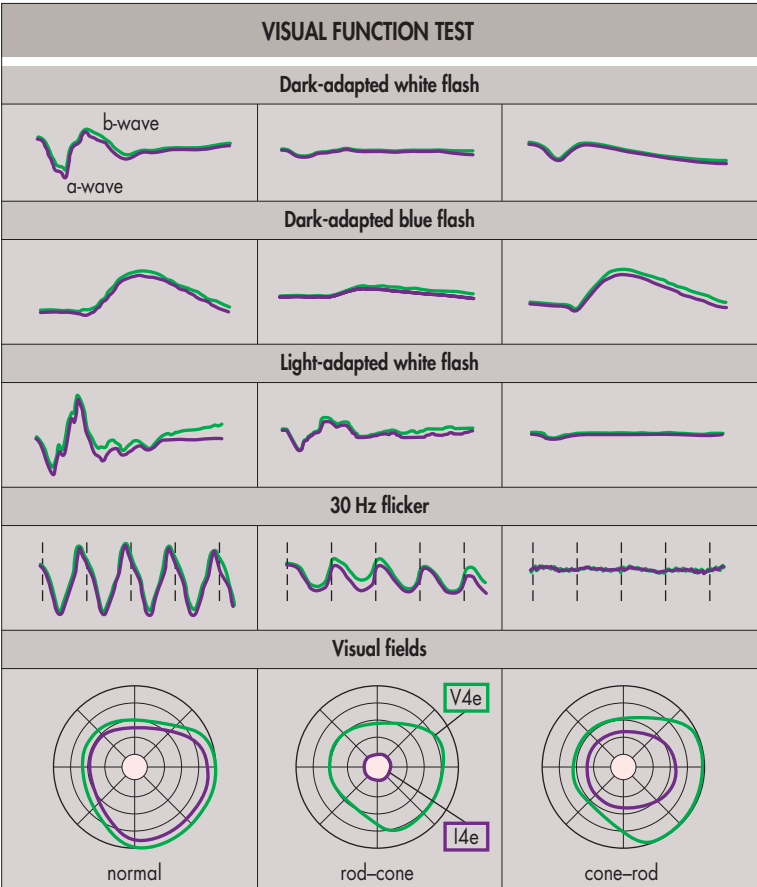
The history can be helpful. Complaints of “night blindness” may indicate total lack of vision in very dim light or diminished acuity as ambient light dims. Tunnel vision may be suggested by recent automobile accidents or clumsiness in the narrow spaces of elevators or doorways. Any family history of slowly progressive unexplained vision loss must be sought.

Electroretinography

Full-field (Ganzfeld) electroretinography (ERG) is quite sensitive to even mild photoreceptor impairment. Rod b-wave amplitudes are reduced in the earliest stages of disease when the retina may appear clinically normal and vision complaints are minimal. For the diagnosis of genetically at-risk younger patients who have otherwise minimal retinal findings, ERG is essential. ERG helps in the diagnosis of the disease in relatives when a retinitis pigmentosa pedigree is established.

Initially, ERG is used to test the rod system by testing with a dim flash after 30 or more minutes in the dark (“scotopic ERG”). The cone system is tested by using single, bright flashes superimposed on a bright background that suppresses activity of rods (“photopic ERG”) and also using a 30-Hz flicker to which cones respond but rods do not. Many complex and analytical schemes of ERG analysis are employed in special circumstances, but the most useful initial measures of ERG abnormality will be discussed below.<sup>6</sup> Scotopic (dark-adapted condition, rod-driven) and photopic (light-adapted, cone-driven) b-wave amplitudes are key in that they provide the first index of disease severity and help differentiate rod-cone from cone-rod disease.

- Scotopic b-waves reduced by 50% or more—this indicates progressive disease rather than a variant of “stationary” disease.
- Early cone system disease—this frequently reduces the amplitudes of 30-Hz flicker before photopic b-wave responses to single flashes.



**Fig. 6.14.1 Visual Function Tests.** For normal subjects, dark-adapted rod a- and b-waves result from bright, white flashes and, primarily, b-waves from dimmer blue flashes; cone responses are elicited by a single, light-adapted, white flash (a- and b-waves) and by 30-Hz flicker. For patients with rod-cone dystrophy, rod responses are reduced proportionally more than cone responses. For patients with cone-rod dystrophy, major losses in light-adapted and 30-Hz responses occur, with relative preservation particularly of the rod b-wave, to dim, dark-adapted, blue flash. Goldmann visual field tests using the small I4e target show major tunnel vision in patients with rod-cone dystrophy.



- Delayed flicker implicit time (from flash to response peak)—this is a highly sensitive measure of abnormality,<sup>7</sup> and implicit times may be prolonged even with normal flicker amplitude; implicit times are very robust and relatively immune to artifacts caused when the patient squeezes on the ERG contact lens electrode (which reduces flicker amplitude but does not change timing).
- Photopic oscillatory potentials (high-frequency wavelets of small amplitude that originate in the proximal retina)—these are generally reduced earlier or to a greater degree than the photopic, single-flash b-wave, and oscillatory potentials may be reduced in retinal vascular diseases.
- Relative preservation of the scotopic a-wave amplitude (from rod photoreceptors) but reduced scotopic b-wave (from signaling by second-order bipolar cells)—this is called an “electronegative” ERG wave-form and is highly suggestive of congenital stationary night blindness (CSNB) or X-linked juvenile retinoschisis.<sup>8,9</sup> In these cases, the ERG change indicates faulty synaptic signaling from rods to bipolar cells, deficient bipolar responsivity, or Müller cell disease.
- Broad and flat bottom trough to the photopic a-wave—this is highly suggestive of CSNB.
- The full-field ERG reflects global retinal activity and is insensitive to macular scars; thus, it does not correlate with visual acuity determined solely by foveal function.

### Monitoring Disease Progression

After some time, the ERG is repeated for the following reasons:

- Confirmation of the diagnosis.
- Determination of the rate of progression.
- Monitoring of the effects of therapy, such as vitamin A administration or other.
- Provision of objective information about progression, to help the patient cope with a disease that causes vision loss.

ERG may be repeated 1–2 years after the first test just to confirm the findings, or serial yearly tests may be used to estimate progression. Exceptionally rapid cone ERG loss in a child may raise suspicion of atypical forms of RP, which include neuronal ceroid lipofuscinosis and indicate the need for a neurological evaluation, particularly if seizure activity is reported.

### Visual Field Testing

Goldmann perimetry is preferable for initial RP visual field testing out to 90° in the far temporal periphery because the midperipheral retina is involved first in the rod-cone type of disease. The recent introduction of semi-automated kinetic perimetry might prove a valuable alternative. Even moderate stages of rod disease typically show extensive peripheral field loss to the small, I4e Goldmann target, whereas cone-rod disease leaves peripheral fields more intact. Subjects with RP may respond poorly to automated perimeters—careful studies using a Goldmann perimeter are more successful for obtaining representative fields. Macular dysfunction may be well followed by testing the central field by using automated static perimeters (e.g., Humphrey Visual Field Analyzer 24–2 or 10–2 programs). Many patients with RP are unaware of lost peripheral vision or a ring scotoma even after several suggestive events (i.e., recent automobile accidents). The patient will appreciate the physician who simply takes the time to explain visual field test results and may immediately recall instances of previous problems with everyday activities.

### Dark Adaptation Testing

Night vision symptoms occur early in the course of RP disease and must be evaluated by using dark adaptation studies. One of the instruments to do this is the Goldmann-Weekers dark adaptometer. The patient is placed in darkness and asked to detect the dimmest possible (threshold) light, which becomes progressively dimmer as time proceeds. Final absolute threshold sensitivity is normally reached after 30–40 minutes in the dark. An alternative test strategy is to determine only the final thresholds after 45–60 minutes in the dark. Thresholds are tested in several different retinal locations to sample the distribution of disease. Some patients who complain of difficulty seeing at night are found to have normal dark-adapted thresholds. Such patients may have under corrected myopia, and the complaint is really of blurred vision in dimmer light. Other patients may have maculopathy and notice worse acuity in dimmer light, even though normal rod-mediated, absolute dark sensitivity is maintained.

### Color Vision Tests

In degenerative retinopathy, color testing is a useful adjunct to visual acuity tests because it provides additional information about the condition of the

macular cones. Patients with RP rarely volunteer information about problems with color vision because nearly all can readily differentiate the major colors of red, green, and blue. However, in rod-cone dystrophies, tritan (“blue-yellow”) color discrimination loss on the Farnsworth D-15 panel is a sensitive index of early foveal cone involvement and may presage acuity loss within the next few years. In cone dystrophies, loss of color discrimination normally parallels visual acuity loss. The D-15 test, which consists of 15 color chips that must be arranged in color sequence, is simple, is rapid, does not tire the patient, and is easy to score. In the D-15 test, >2 minor neighbor errors indicate pathology. The Farnsworth 100 Hue test is more elaborate but seems to be no more sensitive for detecting maculopathy. The Ishihara and American Optical color plates were designed specifically to identify individuals with congenital red–green abnormality and are less useful than the D-15 test for the evaluation of early macular dysfunction that results from a retinal dystrophy.

### Fluorescein Angiography

Fluorescein angiography (FA) is sometimes used for hereditary maculopathies, such as Stargardt disease and Best disease, or in suspected toxic maculopathy from hydroxychloroquine, chloroquine, or psychotropic agents, but in many cases, the information can be gained from less invasive modalities, such as fundus autofluorescence.

### Fundus Autofluorescence

Fundus autofluorescence with excitation at 488 nm is increasingly recognized to demonstrate characteristic, and in some cases pathognomonic, changes in many retinal diseases especially inherited retinal degenerations.<sup>10</sup> It is thought to elicit the autofluorescence of lipofuscin primarily and, as such, demonstrates distinctive patterns in Stargardt, Best, and bull’s-eye maculopathies. Even in RP, characteristic autofluorescence patterns of a hyperautofluorescence ring have been observed to correlate with retinal sensitivity and optical coherence tomography (OCT) and may reflect progression of RP.<sup>11</sup>

### Optical Coherence Tomography

In vivo high-resolution cross-sectional images of the central retina can be obtained using OCT. In RP, OCT abnormalities range from reduction in retinal thickness caused by photoreceptor loss, to increase in retinal thickness caused by macular edema. Structural changes measured by OCT correlate with functional changes, as measured by visual fields and multifocal ERG, and can also be used to monitor disease progression in RP.<sup>12–14</sup>

### Electro-oculography

Electro-oculography (EOG) result is abnormal whenever the ERG result is abnormal, and thus it provides useful information only when the ERG result is normal. Therefore, EOG is not performed automatically with every ERG examination. One of the very few current uses for EOG is to track the genetic pattern in Best vitelliform macular dystrophy, in which the expressivity is highly variable.

### Multifocal Electoretinography

In contrast to full-field (Ganzfeld) ERG, in which a global response is elicited by stimulation of all the retina by a single light stimulus, in multifocal ERG (mfERG) a localized response is elicited by simultaneous stimulation of multiple discrete areas of the central retina. The local responses may be extracted by correlating the recorded response with the stimulus sequence. In a diffuse retinal disease, such as RP, Ganzfeld ERG is a more useful overall estimator of retinal function. However, mfERG can be used to explore the local aspects of cone function.<sup>15</sup> Diagnostically, it is perhaps most useful in the determination of chloroquine and hydroxychloroquine toxic maculopathies,<sup>16</sup> as well as occult maculopathy and for the differentiation of macular versus optic nerve related central scotomas.

### Visual Evoked Cortical Potential

Visual evoked cortical potential (VECP) monitors visual signals that reach the cortex and is dominated heavily by macular function, with a far smaller contribution from the peripheral retina. Any disturbance of retinal function, altered optic nerve conduction, or visual cortex processing alters the VECP. Retinal, and particularly macular, dystrophies affect the VECP, but these conditions are nearly always identified and monitored better by using other visual function tests.

Retinal function tests have value beyond simple diagnosis because they give insight into the nature of the disease, inform about the severity or stage, and provide information for genetic counseling. Results of the examination must be communicated to the patient because subtyping and

staging the disease provide information about expectations for the course of future vision and the genetic implications for the patient’s family.

### Genetic Testing

As clinical examination and testing lead physicians to a clinical diagnosis, new advances in understanding the genetic basis for disease now support genetic testing to confirm clinical diagnoses and provide additional information about familial risk. In conjunction with genetic counseling, genetic information can be informative for prognosis, as well as providing risk information to family members. From a research perspective, genetic testing improves the understanding of the pathophysiology of the disease and is also a prerequisite before contemplating any gene-based therapies. The speed of identification of genes involved in various retinal degenerations far outpaces the rate of publications produced, and any attempt to enumerate them would be obsolete far before this ever gets to print. The RetNet retinal information network database (<http://www.sph.uth.tmc.edu/Retnet>) provides an updated catalog of genes associated with RP and other inherited retinal diseases. Many of these genes are available for sequencing through commercial enterprises as well as through research institutions. As the number of genes identified as being associated with RP and other retinal degenerations increases, the development of screening systems, such as high-throughput arrays, has made genetic testing feasible in these genetically heterogeneous diseases.<sup>17</sup> Efforts using whole exome sequencing or even whole genome sequencing have also led to the identification of genes involved in retinal degenerations.

The National Eye Institute at the National Institutes of Health is working with the vision community in creating the eyeGENE (National Ophthalmic Disease Genotyping and Phenotyping) Network. This genetic repository allows patients to harness an organization of existing research laboratories within the vision community that have been certified by the Clinical Laboratory Improvement Amendments, and to develop a database of genotypes and phenotypes. The Network will assist in developing public and professional awareness of genotype/phenotype resources that are available to people with various ocular genetic diseases, their clinicians, and scientists studying these diseases. Ultimately, the eyeGENE Network will enhance our understanding of genotype–phenotype correlations and aid in the recruitment of patients interested in participating in future clinical trials related to genetic eye diseases.

## Ocular Findings/Manifestations

### Typical Retinitis Pigmentosa

The key features of typical RP normally found are as follows:

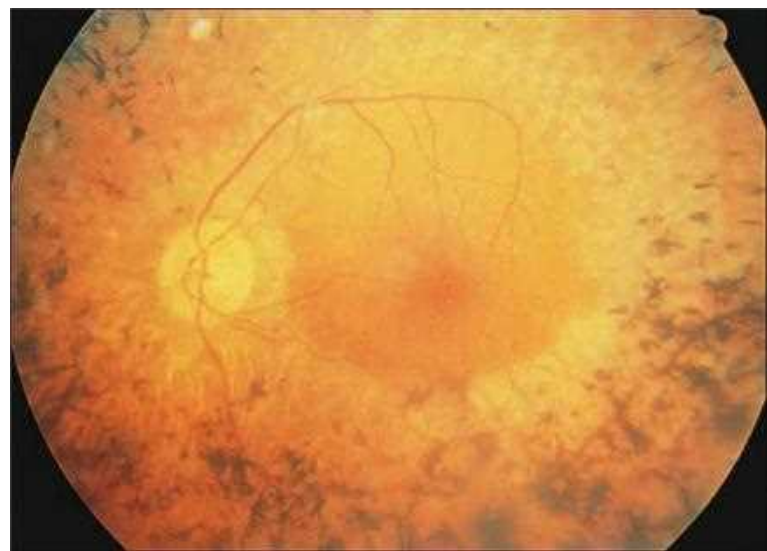
- “Bone-spicule” intraneural retinal pigment.
- Thinning and atrophy of the RPE in the mid- and far-peripheral retina.
- Relative preservation of the RPE in the macula.
- Gliotic “waxy pallor” of the optic nerve head.
- Attenuation of retinal arterioles.

The extent of bone-spicule pigmentation is quite variable—many involved retinas have some, even if very little, of this pigment. This is particularly true in children in whom more subtle abnormalities of RPE pigmentation are more common than are typical spicules. The severity of the features increases with age, such as the amount of pigment, the extent of disc gliosis, and the degree of arteriolar narrowing. Major deviations from this clinical picture suggest atypical RP. In particular, several of the X-chromosome retinal dystrophies (described subsequently) deviate widely from this standard picture. The identification of typical RP is particularly important for clinical trials because diagnosis implies the exclusion of other RP subtypes that may have unusual rates of progression.

Typically, both eyes are affected to a comparable extent,<sup>18</sup> although some degree of difference between each eye is expected normally. Highly asymmetric differences are described as “unilateral retinitis pigmentosa,” in which one eye lags in degeneration by the equivalent of many years, although both eyes invariably show involvement on careful testing.<sup>19</sup> Such apparent unilateral retinitis pigmentosa cases may also result from post infectious causes or blunt trauma to one eye.<sup>20</sup>

Other manifestations of the disease include cataracts, especially of the posterior subcapsular variety, and cystoid macular edema (CME). Both of these complications may reduce the central acuity, even when the underlying disease process affects the peripheral retina only.

Careful clinical examination, careful taking of family history, and diagnostic testing may lead the clinician to suspicion of a certain genetic involvement. Molecular identification of the causative gene is possible in some cases (e.g., pro-23-his rhodopsin mutation) (Fig. 6.14.2). A



**Fig. 6.14.2 “Typical” Retinitis Pigmentosa Changes in a 73-Year-Old Woman Who Had a Pro-23-His Rhodopsin Autosomal Dominant Mutation.** Visible are extensive, intraneural retinal, bone-spicule pigmentation, severely constricted retinal arterioles, waxy pallor of the disc, and extensive retinal pigment epithelium atrophy in the macula and midperiphery (which reveals underlying choroidal vessels). Her visual acuity was 20/50 (6/15), but she made no errors on Ishihara color testing; her fields were severely constricted to 17° tunnel vision with the Goldmann V4e target.

long-sought goal is to correlate a specific gene with a specific phenotype, but this is accomplished rarely because most retinitis pigmentosa mutations result in a similar phenotype. Some unique conditions exist, such as the mutations in RDS/peripherin gene, which may cause a peculiar maculopathy in addition to peripheral retinal degeneration.<sup>21</sup> In general, however, it is not yet possible to predict the specific causative gene from the clinical presentation.

Further, even within the RP cases attributed to a particular gene, such as that which codes for rhodopsin, major variations in the clinical features and disease severity are caused by mutations at different positions within the gene. In rhodopsin RP, the pro-23-his mutation causes fairly typical retinitis pigmentosa<sup>21</sup>; the cys-187-tyr mutation results in a rapid course of degeneration<sup>22</sup>; and the thr-58-arg mutation results in sectoral involvement.<sup>23</sup> The clinical course may vary even within a single family with a single genotype. Consequently, it is impossible to summarize retinitis pigmentosa as a single definition or clinical picture. In general, however, typical RP progresses slowly, such that a period of 1–3 years is needed to document changes.<sup>22</sup>

### X-Linked Retinitis Pigmentosa

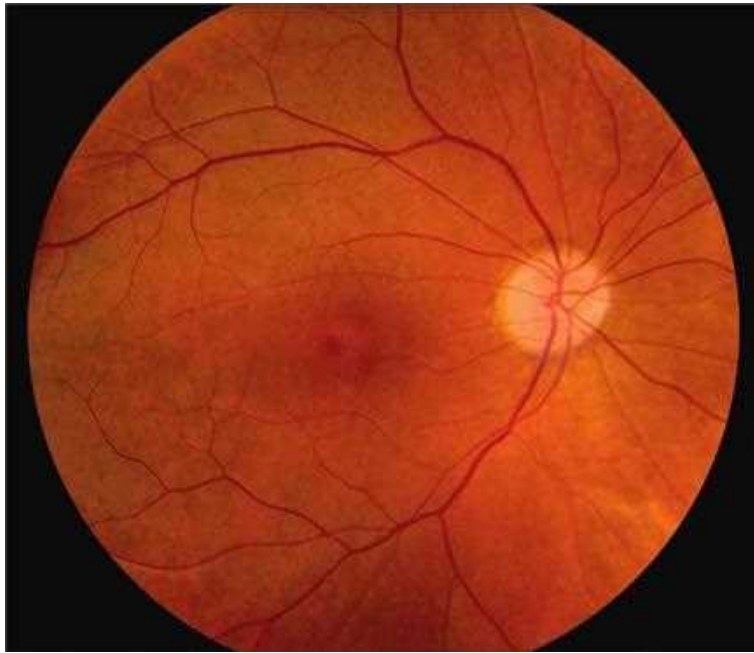
X-linked retinitis pigmentosa (XLRP) has features of typical retinitis pigmentosa, although prominent parafoveal atrophy may be present. Affected boys show subtle or modest RPE granularity, but frank, intraneural retinal bone-spicule pigment typically does not appear until the teenage years. Acuity is good during childhood, but by age 20 years, acuity loss and field constriction rule out the acquisition of a driver’s license, and dark-adapted thresholds are elevated by as much as 3 log units (1000-fold sensitivity loss). Night blindness is severe by the mid-teenage years. Rate of vision decline is rapid, and major functional loss is expected by age 30 years; blindness by age 40 years is common.

The clinical features of two different forms of XLRP (RP2 and RP3, the latter caused by mutations in the *RPGR* gene)<sup>24</sup> overlap extensively, and both progress to severe vision disability by young adulthood. All those affected show typical characteristics of RP, although cone vision is affected to a greater degree than in many autosomal forms of RP, particularly in those who have RP3. ERG reveals a major reduction of both the rod and cone responses even in young boys and is essential to stage the disease.

### Leber’s Congenital Amaurosis

The term *Leber’s congenital amaurosis* (LCA) describes a group of retinal dystrophies characterized by very early onset of severe disease. The first sign noticed by the child’s parents is usually nystagmus, a common finding in children who have never developed good central vision. The severity of visual loss can range from moderate to very marked (light perception) and is usually progressive. Children with severe visual loss may self-elicited phosphenes by rubbing their eyes through their eyelids (the oculodigital





**Fig. 6.14.3 Cone Dystrophy in a 37-Year-Old Man.** The bull's-eye maculopathy in this case is not found in all cases of this entity.

sign). Fundus findings are variable. They can be limited to moderate pigmentation abnormalities, but frank atrophic retinal changes are common; marked attenuation of retinal vessel diameter is the norm. The amplitude of all ERG responses is markedly reduced; this test is therefore essential for the differential diagnosis with other ophthalmic diseases associated with congenital visual loss and nystagmus. LCA is usually inherited as an autosomal recessive trait. Mutations of more than a dozen genes can cause LCA; about half of them are also implicated in adult-onset retinitis pigmentosa.<sup>25</sup>

### Cone Dystrophy

Fundus changes are quite variable, with the classic fundus finding being described as a “bull’s-eye” maculopathy (Fig. 6.14.3). Particularly in the early stages, the fundus may appear benign, with minimal diffuse retinopathy and normal vessels and disc. At the other end of the prognosis spectrum are rare patients who develop a central scotoma early in life; the field defect enlarges gradually but relentlessly toward the periphery, with practically total visual loss by late middle age. These patients usually receive the diagnosis of “macular degeneration” in childhood; the condition has been termed “inverse retinitis pigmentosa” because pigment spicules are more abundant in the central retina than in the midperiphery. Typically, ERG findings indicate that cone function (photopic responses) is more affected than rod function (scotopic responses), but both are abnormal.<sup>26</sup> Infrequently, a patient with cone-rod dystrophy has an essentially normal rod but a very reduced cone on ERG and is considered to have “cone dystrophy.”

### Genetics and Pathology

RP can be inherited in an autosomal dominant, autosomal recessive, or X-linked fashion. Frequently, no other family members are known to be affected, a condition known as “sporadic,” “isolated,” or “simplex” RP. According to different surveys, up to 50% of patients with RP are in this category. Many, but not all, of these patients have autosomal recessive RP, and others may be caused by new mutations. Pedigree analysis shows evidence of autosomal dominant inheritance in about 25%, of autosomal recessive inheritance in about 25%, and of X-linked inheritance in about 10% of patients.

RP can be caused by mutations in multiple genes, many of which encode proteins essential for photoreceptor structure and function. To date, the field has identified more than 20 genes which cause autosomal dominant RP, more than 30 genes which cause autosomal recessive RP, and more than 2 genes which cause X-linked RP. More have been located but not identified, and these numbers are expected to increase in the future (Table 6.14.1). The RetNet retinal information network database (<http://www.sph.uth.tmc.edu/Retnet>) provides an updated catalog of genes associated with RP and other inherited retinal diseases.

The identified RP-associated genes may be grouped into mainly five categories:

- Phototransduction.
- Retinal metabolism.
- Tissue development and maintenance.
- Cellular structure.
- Splicing.<sup>27</sup>

Rhodopsin was the first major retinitis pigmentosa gene to be identified.<sup>28</sup> As with rhodopsin, the majority of the RP genes identified thus far involve components of the phototransduction cascade within the rod photoreceptor, which include transducin, phosphodiesterase ( $\alpha$ - and  $\beta$ -subunits of PDE), arrestin, recoverin, and the G protein-coupled Na<sup>+</sup>/K<sup>+</sup> light-activated channel on the rod membrane. Another set of genes code for structural proteins in rod cells and include RDS/peripherin<sup>29</sup> and ROM1.<sup>30</sup> Developmental genes, such as the homeobox gene CRX, are also implicated in the development of cone-rod degeneration.<sup>31</sup> More recently, genes involved in the spliceosomal protein complex, which catalyzes the removal of intronic sequences, such as PRPF3, PRPF8, and PRPF31, have been identified and found to comprise  $\approx 10\%$  of the RP-associated genes.<sup>27</sup>

The molecular mechanisms by which these genetic mutations eventually cause rod-cell death are unclear, although ample evidence indicates that apoptosis is involved in the final pathway of cell death.<sup>32</sup>

That the cone photoreceptors ultimately die from a disease that begins with rod-cell disease remains a puzzle. One hypothesis invokes common elements of the RPE that are involved intimately in the diurnal cycle of phagocytosis of the outer-segment discs shed daily by both rods and cones. In the case of rhodopsin mutation RP, rhodopsin is the major protein in the rod outer segments and the diurnal process of phagocytosis of the shed rod-disc membrane by the RPE may eventually result in secondary RPE pathology. With time, the RPE cannot properly service the cone photoreceptors, which subsequently die as “innocent bystanders.” Alternative explanations are that cone viability depends on the existence of a rod-derived factor<sup>33</sup> and that the mechanical scaffold provided by rods is required for cone survival.

Clinical examination of the retina from a 73-year-old woman who had autosomal dominant RP from a pro-23-his rhodopsin mutation revealed that she had 20/50 (6/15) visual acuity several months before her death, and her fields were only 17°. Her fundus had typical RP changes of heavy bone-spicule pigmentation across the entire 360° periphery, and the underlying RPE was atrophic (see Fig. 6.14.2). After her death, histological examination of her eye showed major loss of the photoreceptors (Fig. 6.14.4). Tissue from the parafoveal region of the left eye in the region of relative preserved retina showed the following:

- Photoreceptor outer segments shortened greatly, such that they are nearly absent, and the inner segments shortened.
- Number of photoreceptor nuclei (outer nuclear layer) decreased greatly, the majority of those left being cone nuclei—virtually no rod photoreceptors remain in this end-stage RP.
- RPE swollen grossly by intraretinal debris, with loss of melanosomes and dispersion of pigment granules.

### Systemic Associations and Differential Diagnosis of Pigmentary Retinopathy

RP is associated with many systemic conditions, of which the following warrant particular attention either because of their incidence (e.g., Usher syndromes, in which early-onset hearing loss is associated with RP) or because the diagnosis, which may be recognized by the ophthalmologist first, has major medical implications. At other times, diagnosis can be important for early treatment with subsequent long-term positive health and vision effects (e.g., Refsum’s disease, abetalipoproteinemia). Secondary causes of RP-like disease should be entertained in the absence of family history of the disease; the differential diagnosis of pigmentary retinopathy includes multiple nonhereditary conditions. Table 6.14.1 lists the main features of many retinal degenerations and associated systemic conditions, with a brief updated list of associated genes as well as acquired conditions that are part of the differential diagnosis.

### Course and Outcomes

Projections about future vision are always difficult in degenerative disease, particularly because the RP subtypes do not have a single clinical course. XLRP typically affects visual acuity by young adulthood, and visual acuity



TABLE 6.14.1 Retinal Degeneration/Retinitis Pigmentosa: Differential Diagnosis

Autosomal Dominant (AD) Conditions	Autosomal Recessive (AR) Conditions	X-linked (XL) Conditions	Systemic Diseases with Retinal Degeneration Component	Acquired Conditions
AD retinitis pigmentosa (RP) <ul style="list-style-type: none"> <li>Rod-cone dystrophy</li> <li>Causative genes: 23 identified genes; most common are <i>RHO</i>, <i>RDS</i>, <i>PRPF31</i>, <i>RP1</i>, <i>PRPF8</i>, <i>IMPDH1</i></li> </ul>	AR RP <ul style="list-style-type: none"> <li>Rod-cone dystrophy</li> <li>Causative genes: 36 known genes</li> </ul>	XL RP <ul style="list-style-type: none"> <li>Rod-cone dystrophy (usually early onset and severe disease)</li> <li>Causative genes: <i>RPGR</i> and <i>RP2</i> cause the majority of cases</li> </ul>	Usher’s syndrome <ul style="list-style-type: none"> <li>AR inheritance</li> <li>RP-like retinal degeneration in association with: sensorineural hearing loss, <math>\pm</math> hearing loss</li> <li>Causative genes: 5 genes known to cause type I (best known <i>MYO7A</i>), 3 genes known to cause type II (best known <i>USH2A</i>), one gene known to cause type III (<i>CLRN1</i>)</li> </ul>	Toxic retinopathy <ul style="list-style-type: none"> <li>Pigmentary retinopathy can be secondary to a variety of medications (thioridazine, clofazimine, hydroxychloroquine (Fig. 6.14.9), chloroquine) or toxic agents</li> </ul>
AD cone-rod dystrophy <ul style="list-style-type: none"> <li>Cone or cone-rod dystrophy</li> <li>Causative genes: at least 10 identified genes, including <i>CRX</i>, <i>GUCY2D</i>, <i>PROM1</i>, and <i>PRPH2</i></li> </ul>	AR cone-rod dystrophy <ul style="list-style-type: none"> <li>Cone or cone-rod dystrophy</li> <li>Causative genes: at least 13 identified genes, including <i>ABCA4</i>, <i>CERKL</i>, <i>KCNV2</i>, <i>RDH5</i>, and <i>RPGRIP1</i></li> </ul>	XL cone-rod dystrophy <ul style="list-style-type: none"> <li>Cone or cone-rod dystrophy</li> <li>Causative genes: <i>RPGR</i>, <i>CACNA1F</i></li> </ul>	Bardet–Biedl syndrome <ul style="list-style-type: none"> <li>AR inheritance</li> <li>RP-like retinal degeneration (Fig. 6.14.10) in association with: polydactyly, obesity, mental retardation, and hypogenitalism</li> <li>17 identified genes, including <i>BBS1</i>, 2, 6, 9, 10, and <i>MKS1</i>, <i>CEP290</i></li> </ul>	Postinfectious retinopathy <ul style="list-style-type: none"> <li>Pigmentary retinopathy can be secondary to a number of infectious agents (syphilis, rubella, parasitic agents)</li> </ul>
AD Leber’s congenital amaurosis <ul style="list-style-type: none"> <li>Causative genes: <i>CRX</i>, <i>IMPDH1</i>, <i>OTX2</i></li> </ul>	AR Leber’s congenital amaurosis <ul style="list-style-type: none"> <li>Early-onset rod-cone dystrophy, nystagmus, flat electroretinography responses</li> <li>At least 16 genes identified, including <i>CEP290</i>, <i>CRB1</i>, <i>AIPL1</i>, <i>CRX</i>, <i>RPE65</i>, <i>LRAT</i>, <i>RDH12</i>, <i>RPGRIP1</i></li> </ul>	Choroideremia <ul style="list-style-type: none"> <li>Early-onset night vision difficulties, progressive visual field defects, central vision maintained till later in disease</li> <li>Carriers usually show fundus changes</li> <li>Causative gene: <i>CHM</i></li> </ul>	Refsum’s disease <ul style="list-style-type: none"> <li>AR inheritance</li> <li>RP-like retinal degeneration in association with: hearing loss, anosmia, ataxia, ichthyosis, peripheral neuropathy, cataract</li> <li>Elevated serum phytanic acid</li> <li>Improved prognosis with early dietary intervention</li> <li>Causative gene: <i>PEX7</i></li> </ul>	Pigmentary retinopathy secondary to trauma
AD congenital stationary night blindness <ul style="list-style-type: none"> <li>Nyctalopia and nonprogressive retinal dysfunction</li> <li>Causative genes: <i>GNAT1</i>, <i>PDE6B</i>, <i>RHO</i></li> </ul>	Achromatopsia <ul style="list-style-type: none"> <li>Reduced central vision, light aversion, nystagmus, color vision defects, severely reduced cone electroretinography responses</li> <li>Causative genes: <i>CNGB3</i>, <i>CNGA3</i>, <i>GNAT2</i>, <i>PDE6C</i></li> </ul>	Juvenile retinoschisis <ul style="list-style-type: none"> <li>Characteristic spoke-wheel pattern, foveal and/or peripheral schisis, electronegative electroretinography pattern</li> <li>Causative genes: <i>RS1</i> / <i>XLRS1</i></li> </ul>	Kearns–Sayre syndrome <ul style="list-style-type: none"> <li>Mitochondrial disease</li> <li>RP-like retinal degeneration in association with: progressive external ophthalmoplegia and complete heart block</li> <li>Causative genes: <i>KSS</i></li> </ul>	Melanoma-associated retinopathy <ul style="list-style-type: none"> <li>Symptoms include photopsias and flickering lights, reduced acuity, and visual field defects</li> <li>Electroretinography typically shows electronegative response</li> </ul>
Best disease <ul style="list-style-type: none"> <li>Reduction of central vision with typical fundus changes (differ according to stage of disease), vitelliform lesions, abnormal electrooculography with reduced Arden ratio</li> <li>Causative gene: <i>Best1</i> (also known as <i>VMD2</i> / <i>RP50</i>)</li> </ul>	AR congenital stationary night blindness <ul style="list-style-type: none"> <li>Nyctalopia and nonprogressive retinal dysfunction</li> <li>Electronegative electroretinography responses</li> <li>Causative genes: 9 genes, including <i>GNAT1</i>, <i>TRPM1</i>, <i>RDH5</i></li> </ul>	XL congenital stationary night blindness <ul style="list-style-type: none"> <li>Nyctalopia and nonprogressive retinal dysfunction</li> <li>Electronegative electroretinography responses</li> <li>causative genes: <i>CACNA1F</i>, <i>NYX</i></li> </ul>	Joubert’s / Senior–Loken syndrome <ul style="list-style-type: none"> <li>AR inheritance</li> <li>RP-like retinal degeneration in association with: nephronophthisis (Senior–Loken)</li> <li>Multisystem findings sometimes including retinal degeneration (Joubert’s)</li> <li>Causative genes: more than 15 identified genes, including <i>AHI1</i>, <i>NPHP1</i> and <i>NPHP2</i>, <i>CEP290</i>, <i>RPGRIP1L</i>, and <i>KIF7</i></li> </ul>	Cancer-associated retinopathy <ul style="list-style-type: none"> <li>Symptoms include photopsias and flickering lights, reduced acuity, and visual field defects</li> <li>Electroretinography typically shows electronegative response</li> </ul>
		XL blue cone monochromatism <ul style="list-style-type: none"> <li>Reduced central vision, light aversion, nystagmus, color vision defects, severely reduced cone electroretinography responses</li> <li>Causative genes: <i>OPN1LW</i>, <i>OPN1MW</i></li> </ul>		

of some XLRP female carriers also becomes severely impaired. Thus a simple summary of vision loss in the various forms of retinal degeneration is not possible, particularly for visual acuity. In all cases, functional tests using ERG and visual thresholds best establish the current stage of retinal cell function in aggregate and thus provide an initial basis for any prognostic statement. Prognostic statements depend on careful disease subtyping. When subtyping is elusive, analysis of whether the patient has rod-cone disease or cone-rod disease provides vision estimates that may be used for general prognosis.

## “STATIONARY” RETINAL DISORDERS

The generalized main feature of rod-cone or cone-rod degenerations described above, is their progressive nature. In contrast, some inherited retinal disorders are less progressive, and, even though there is often some change over the lifetime, are relatively stable by comparison to most forms of RP.<sup>34</sup> Historically they have carried the descriptor “stationary.”

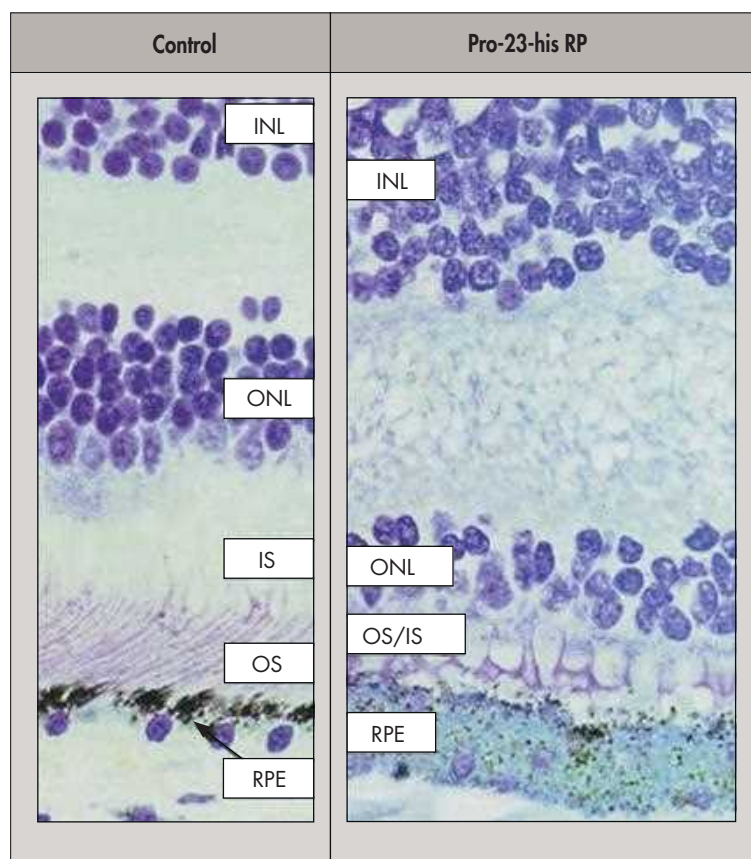
## Congenital Stationary Night Blindness

CSNB comprises a heterogeneous group of disorders that have a common history but differ considerably in terms of clinical pictures and visual

function studies. The main symptom of patients with CSNB is one of night blindness, which is often severe from birth, but color discrimination is unaffected, and visual acuity is usually mildly affected. Refractive changes vary, but high myopia and nystagmus may be present. There are many forms of CSNB that have been classified based on inheritance pattern (all types seen), ERG findings (electronegative most common), and fundus appearance (normal most common).<sup>35</sup> X-linked CSNB is most common and may be confused with XLRP at first presentation, as both occur in young boys and cause complaints of difficult vision at night and show alterations in the fundus pigmentation. Differentiation between these two forms is critical because in CSNB vision remains “stationary” in contrast to the progressive nature of XLRP.<sup>36</sup>

## Congenital Stationary Night Blindness With Normal Fundus

Both ERG and visual field tests are critical in the diagnosis of CSNB. The scotopic ERG is the most significant finding and most commonly demonstrates an electronegative ERG in which the dark-adapted response b-wave amplitude is considerably more reduced than the a-wave amplitude. The photopic ERG is also abnormal with a characteristically wide cone a-wave



**Fig. 6.14.4** Histology of the parafoveal retina of a 73-year-old woman who had a pro-23-his rhodopsin mutation (same patient and eye as in Fig. 6.14.2). Only the macula retained any photoreceptors. The eyes were fixed about 1 hour postmortem. INL, inner nuclear layer; IS, inner segments; ONL, outer nuclear layer; OS, outer segments; RPE, retinal pigment epithelium.

trough. Visual fields are full for CSNB, whereas they are constricted to the Goldmann I4e target even in early XLRP and choroideremia.

A classification of “complete” and “incomplete” CSNB is suggested on the basis of visual function studies performed on patients with autosomal recessive and X-linked recessive CSNB manifesting the most commonly seen Schubert–Bornschein electronegative ERG findings.<sup>37</sup> The complete type of CSNB (also known as type 1, CSNB1) manifests no detectable rod function, with only a slight reduction in cone function in association with diminished vision and myopia. The incomplete type of disease manifests some remaining rod function, more severe cone dysfunction, visual acuity loss, and no specific refractive error. There are now identified genetic bases for these differences.

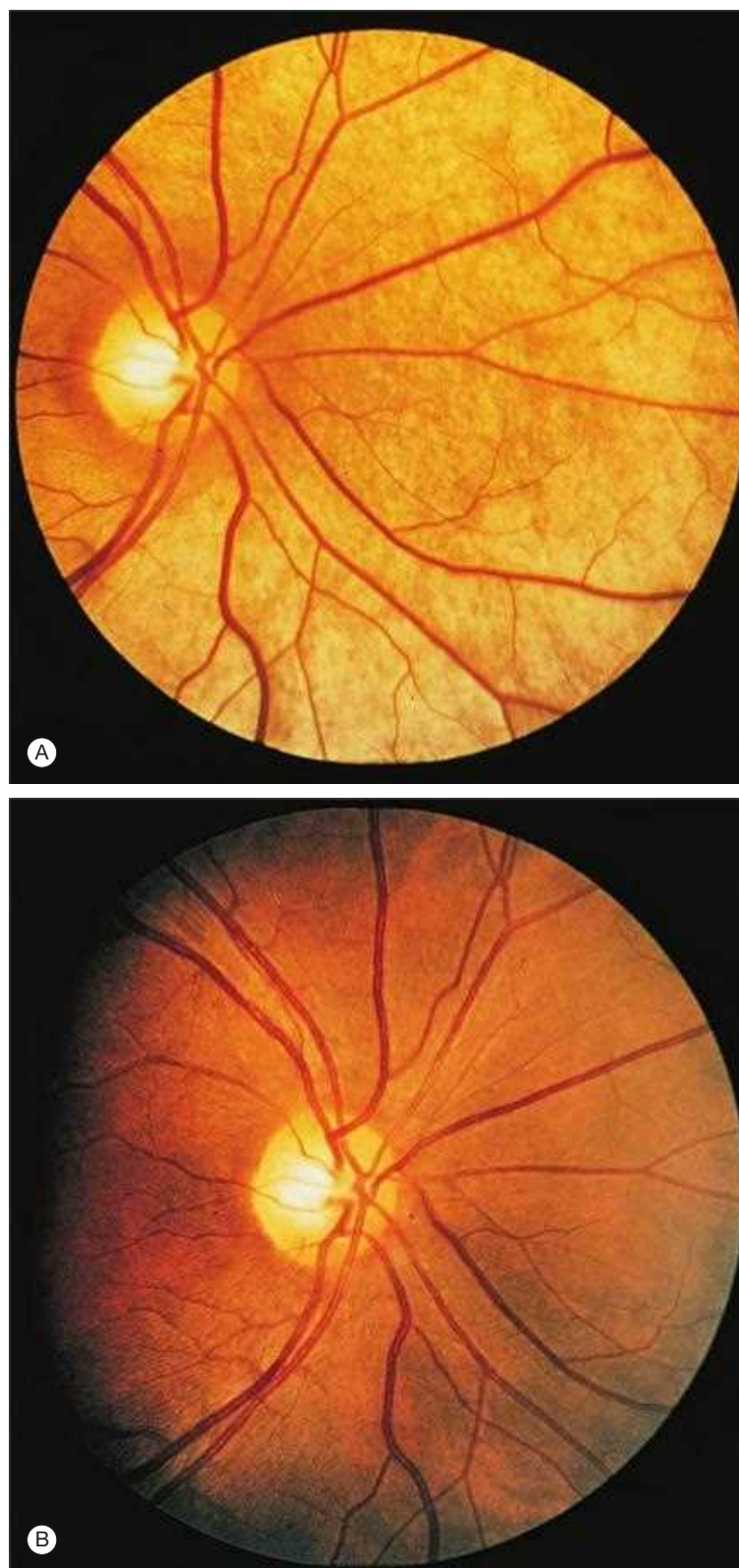
Mutations in genes involved in the phototransduction cascade (*GNAT1*, *PDE6B*, *RHO*, *RHOK*, and *SAG*) underlie autosomal dominant CSNB. Complete CSNB has been found to be associated with defects in the ON bipolar pathway (*GRM6* and *NYX*).<sup>38</sup> Incomplete CSNB (also known as type 2, CSNB2) is associated with defects in the ON/OFF pathway (*CACNA1F*, *CABP4*, and *CACNA2D4*). Ultimately, it has been found that mutations in *CACNA1F* and *NYX* account for 80% of all mutations in CSNB.<sup>38</sup>

CSNB most often has a normal fundus; however, other less common diseases have an abnormal fundus. A fundus of abnormal appearance in association with CSNB includes Oguchi’s disease and fundus albipunctatus. These two diseases have very little in common, except early-onset non-progressive night blindness.

## Oguchi’s Disease

Named by the Japanese ophthalmologist Oguchi, the characteristic fundus findings in this disease is the yellowish metallic sheen of the posterior pole makes for a clinical diagnosis<sup>39</sup> (Fig. 6.14.5A). After prolonged dark adaptation, the yellowish fundus appearance reverts to normal, a phenomenon described by and named after Mizuo<sup>40</sup> (see Fig. 6.14.5B). Re-exposure to light results in the return of the metallic sheen.

Cone function appears normal. Rod function is abnormal, with normal rod thresholds reached only after 4 hours or longer (30 minutes is normal) and scotopic ERG showing only a small electronegative response, even when the rod thresholds have reached normal values. Oguchi’s disease is



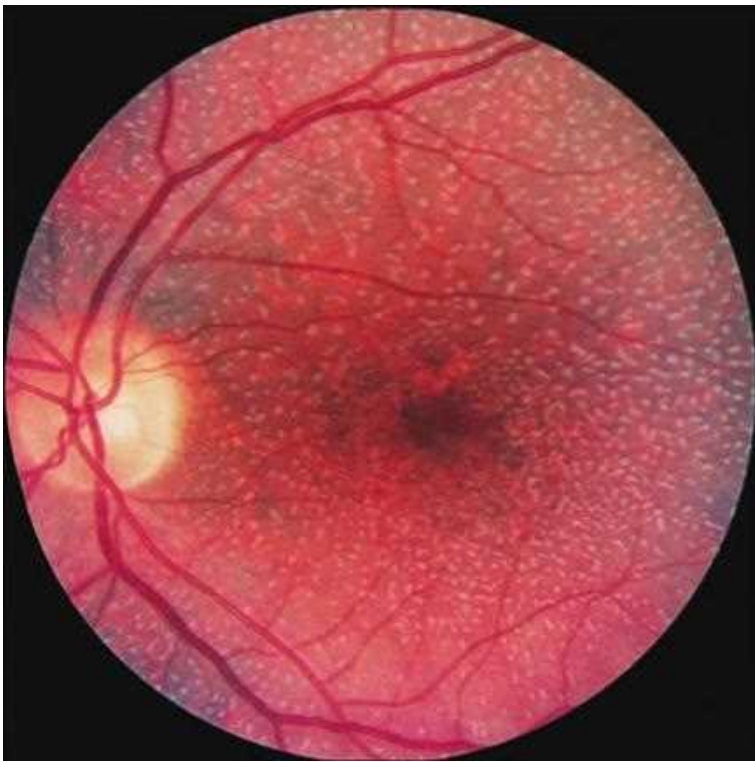
**Fig. 6.14.5** Oguchi’s Disease. (A) The yellowish metallic sheen is apparent nasal to the optic disc. (B) After 3 hours of dark adaptation the fundus reverts to the normal coloration (Mizuo phenomenon).

inherited in an autosomal recessive pattern. Mutations in *RHOK* (rhodopsin kinase) and *SAG* (arrestin), which are involved in terminating the phototransduction cascade, lead to the disease.<sup>39,41,42</sup>

## Fundus Albipunctatus

Like Oguchi’s disease, fundus albipunctatus has a distinctive fundus appearance, which, again, leads to a clinical diagnosis. There are multiple tiny white dots that are very regularly spaced, involve the posterior pole, spare the macula, and extend into the midperiphery (Fig. 6.14.6). Fundus albipunctatus is inherited in an autosomal recessive manner, and the main symptoms are delayed dark adaptation and night blindness. This should be





**Fig. 6.14.6 Fundus Albipunctatus.** Numerous small round yellow-white lesions throughout the retina but excluding the central macula where atrophy and hyperpigmentation is observed.

distinguished from retinitis punctata albescens, which can also have the appearance of a flecked retina but, unlike fundus albipunctatus, behaves clinically like RP. However, although amplitudes of the ERG a-wave and b-wave of the photopic and scotopic responses are diminished under normal test conditions, the scotopic response slowly returns to normal after a few hours in the dark, distinguishing this entity from retinitis punctata albescens. Mutations in retinol dehydrogenase (RDH5) are associated with this disease.<sup>43</sup>

## Congenital Red–Green Color Deficiency

The genes encoding the three main photopigments give rise to the three classes of cone photoreceptors that underlie normal color vision. The genes encoding the red or long-wave-sensitive (L) photopigment and the green or middle-wave-sensitive (M) photopigment are arranged in a head-to-tail tandem array on the X-chromosome (Xq28).<sup>44</sup> Their close proximity and high sequence homology makes this area prone to recombinations during gamete formation in females, giving rise to X-linked color deficiencies. Total “red–green” color vision deficiency caused by lack of red-sensitive cones (protanopia) or green-sensitive cones (deutanopia) affects 2%–3% of men. Partial forms are termed *anomalous color perception* (e.g., protanomaly or deuteranomaly). Tritanopia (total blue blindness) is exceedingly rare. For all forms together, 4%–7% of men manifest some type of congenital color deficiency. Given this frequency, some men who are affected by other retinal degenerations are also “color blind,” and the congenital condition must be differentiated from the acquired disease. Progressive cone dystrophy also impairs color discrimination but is differentiated by abnormal visual acuity and/or peripheral fields, both of which are usually normal in the congenital color deficiencies. Female carriers manifest no clinical signs.

## Blue Cone Monochromatism

Blue cone monochromatism (BCM) is a rare (<1 in 100 000) X-linked disorder. Different mutational pathways have been proposed leading to BCM, both resulting in a loss of functional L- and M-cones, but preserved S-cones and rods.<sup>45</sup> Boys and men affected by BCM have normal nighttime rod vision but poor day vision as a result of the loss of both red- and green-sensitive cone function.<sup>21</sup> Color vision is severely limited, but differences in bluish hues are detectable. Furthermore, BCM causes small-amplitude nystagmus, reduced acuity (between 20/80 [6/24] and 20/200 [6/60]), and glare sensitivity. The fundus may show minimal RPE pigmentary mottling.

All other aspects of vision remain stable in BCM, and acuity may even improve slightly and reach 20/70 by age 20 years, by which time the nystagmus is barely detectable. Some older men with BCM have progressive macular atrophy. The dark-adapted ERG b-wave amplitude is normal or slightly subnormal for patients with BCM, but rod psychophysical threshold sensitivity remains normal, which differentiates BCM from degenerative rod disease cases. The light-adapted cone ERG single-flash and flicker responses are reduced by >80%–95%. Only 1% of cones are blue-sensitive cones, and no blue-sensitive cones are found within the human fovea, which accounts for the poor acuity in patients with CM. Female carriers show no changes. An X-linked family history helps differentiate BCM from autosomal dominant or autosomal recessive, early age, progressive cone dystrophy.

## Achromatopsia

Achromatopsia, or “total color blindness,” is monogenic congenital retinal dystrophy that causes reduced visual acuity, extremely limited color vision discrimination, nystagmus, and photophobia. It is inherited as an autosomal recessive trait, and thus both sexes are affected.

Patients with BCM as well as those with achromatopsia fail the Ishihara and American Optical Hardy-Rand-Rittler color plate tests and the Farnsworth D-15 and 100 Hue tests. Differentiation between those with achromatopsia and patients with BCM is aided by specially designed “blue arrow” color plate tests, which boys and men affected by BCM pass but those with achromatopsia fail.<sup>46</sup> Achromatopsia was traditionally regarded as a “stationary” disease, but more recent evidence points to slow progression over time.<sup>47</sup>

## Ocular Albinism

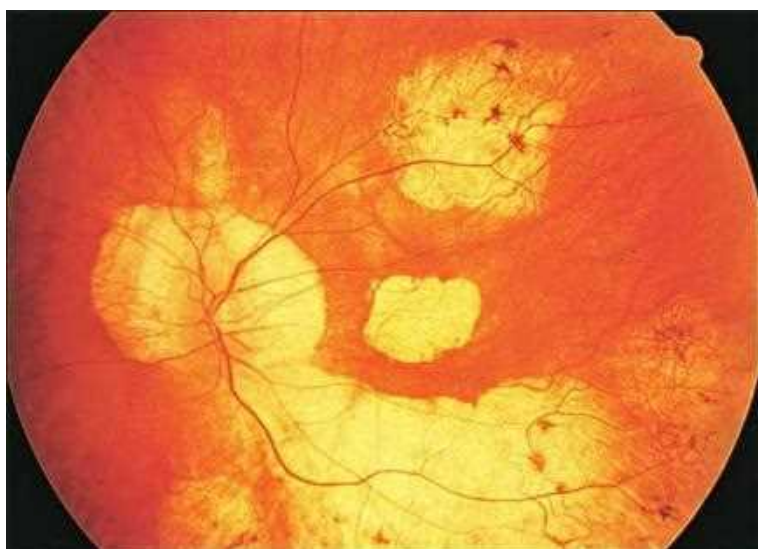
Ocular albinism occurs in several forms and follows all the inheritance patterns. When restricted to the eyes (“ocular albinism” [OA]) is inherited most frequently as an X-linked recessive trait. When the skin is also involved (“oculocutaneous albinism” [OCA]) inheritance is usually autosomal recessive. All forms are evident from birth and cause moderate-amplitude nystagmus, which the parents notice quite early. The fundus is hypopigmented, and the iris may transilluminate. Acuity is between 20/70 and 20/200 but is difficult to test precisely during infancy. Color vision remains normal, and nyctalopia does not occur. The foveal reflex may be muted, and the fovea may be hypoplastic. The ERG result is normal or even supranormal because of enhanced intraocular light reflection. OCA results with systemic manifestations include Hermansky–Pudlak syndrome (platelet dysfunction) and Chediak–Higashi syndrome (white blood cell lysosomal dysfunction). Diagnosis is made through clinical examination. Vision remains stable. Confusion arises in the differentiation of ocular albinism from the “blond fundus” of patients who have pale skin and hair tones but normal acuity. The pattern-onset visual evoked potential is useful for this differential diagnosis.<sup>48</sup>

## FEMALE CARRIERS OF X-LINKED RETINAL DEGENERATIONS

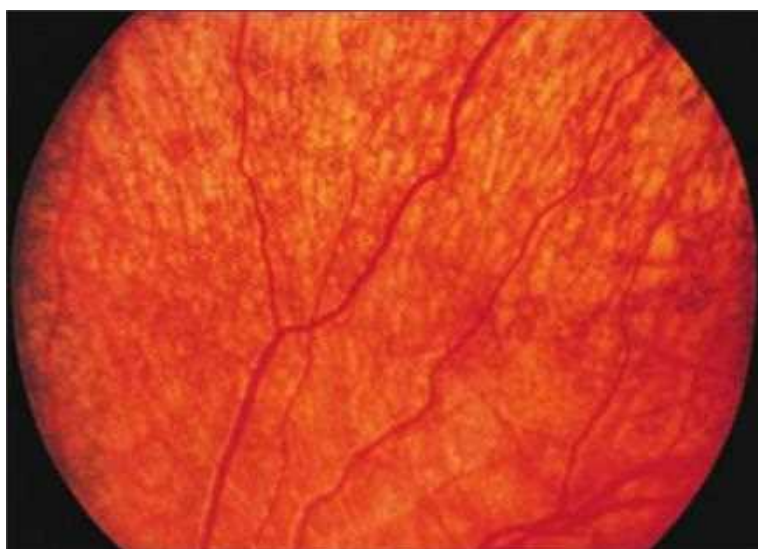
Female carriers of X-chromosomal retinal dystrophies may manifest retinal pigmentary changes and have functional vision impairment that present special difficulty in diagnosis. Recognition of the carrier state is important to establish the correct inheritance pattern for family genetic counseling. Some carriers have a severe vision abnormality, which may lead to a misdiagnosis of autosomal dominant disease. In female carriers, one of the two X chromosomes has a mutant gene. As a result of random X-chromosome inactivation, only one gene is active in each cell (the Lyon hypothesis). Because the mutant gene is retained in some retinal cells during early development, clusters of neighboring cells have the disease, and there are patches of clinical disease that mimic a mild form of the fully expressed male condition in choroideremia, XLRP, and X-linked ocular albinism. Carriers of juvenile retinoschisis, blue cone monochromatism, CSNB, and color vision dichromatism show no fundus changes and no functional vision abnormality. Carriers of autosomal recessive disease rarely show retinal changes or have visual symptoms.

Female carriers of XLRP (Fig. 6.14.7) show one or more small or large retinal patches of typical, intraneural retinal bone-spicule pigmentation and atrophy of the underlying RPE and choriocapillaris in >50% of cases. Many carriers have myopic astigmatism at an oblique axis. Although vision is involved minimally in the majority, some are functionally blind by late





**Fig. 6.14.7** X-linked female retinitis pigmentosa carrier affected by lacunae of disease. Atrophy of retinal pigment epithelium and intraneural retinal bone-spicule pigment result. Acuity is 20/200 (6/60) because of macular atrophy.



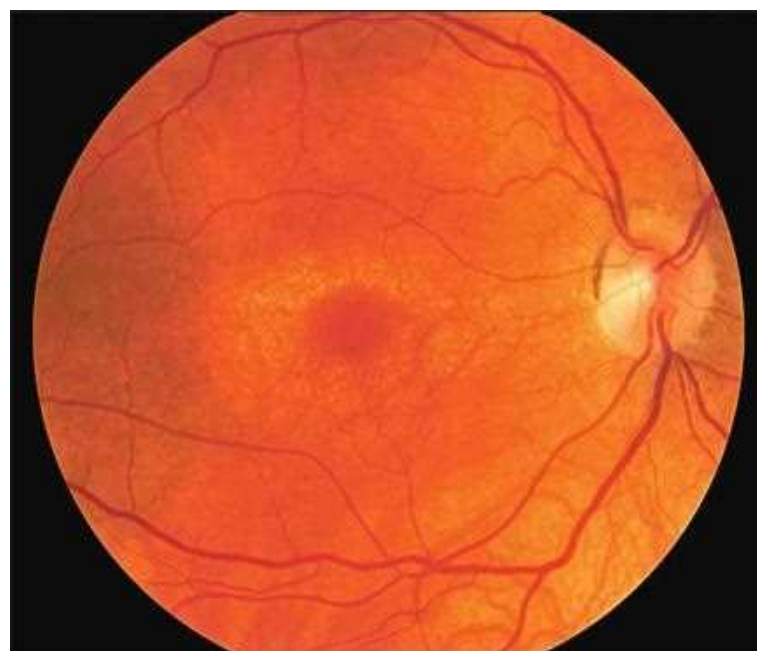
**Fig. 6.14.8** Punctate granularity and attenuation of the normally uniform pigmentation of the retinal pigment epithelium in a female carrier of X-linked ocular albinism. This can often be associated with iris transillumination defects.

middle age or older age. Changes progress with time but generally do so much more slowly than those in XLRP-affected men. An ERG is very helpful, as amplitudes of one or more ERG components are reduced in 80%–95% of XLRP carriers.<sup>49</sup> Furthermore, the ERG amplitudes generally correlate with the expected severity of overall vision loss in later years.

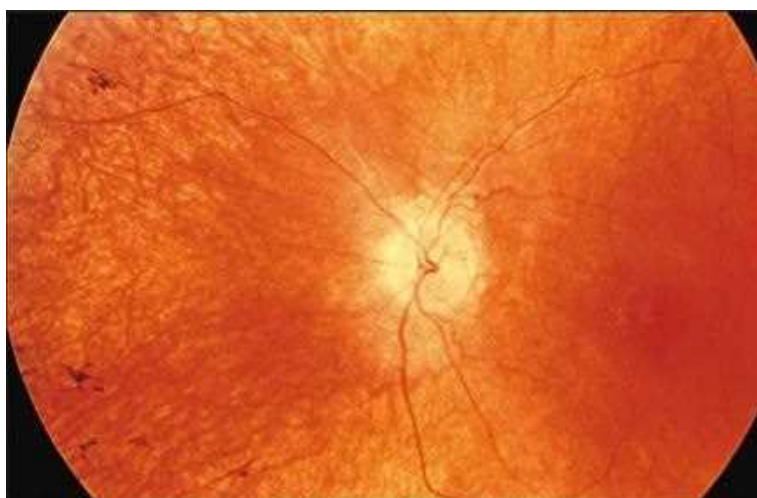
Female carriers of choroideremia also show widespread retinal pigmentary disturbance of the RPE in the periphery and into the macula in 90% of cases. However, very few carriers have any visual symptoms beyond mild glare sensitivity in later age, and visual acuity remains normal. ERG results are affected far less frequently than those of XLRP carriers; fundus examination is the most sensitive means of detection. Most carriers of choroideremia have emmetropia or hyperopia, in contrast to the myopia that is typical of carriers of XLRP. Progression has been observed in some carriers of choroideremia.<sup>49,50</sup> Female carriers of X-linked ocular albinism (Fig. 6.14.8) show punctate RPE pigmentation across the entire fundus and RPE thinning in the periphery (a mild version of changes found in the affected men), which may mimic the “salt and pepper” appearance of congenital rubella retinopathy. Visual acuity is not affected, and the ERG result is normal. Symptoms do not extend beyond mild glare sensitivity to bright light. Carriers of non-X-linked albinism rarely show fundus changes.

## TREATMENT OF RETINAL DEGENERATIONS

No treatment currently has been approved by the U.S. Food and Drug Administration (FDA) for retinal degenerations. Treatment trials to date have spanned vitamin supplementation, medical therapy, gene



**Fig. 6.14.9** Hydroxychloroquine Bull's-Eye Parafoveal Atrophy. This clinical sign is often a late indicator of retinal toxicity. Other testing, such as Humphrey visual field testing and OCT especially, can detect signs of toxicity prior to any clinically observable retinal abnormalities.



**Fig. 6.14.10** Clinical Appearance of Retina in a Patient With Bardet-Biedl Syndrome. Retina demonstrates extensive peripheral retinal pigment epithelium thinning and parafoveal retinal pigment epithelium atrophy.

transfer-based therapy, stem cell-based therapy, and retinal implantation, with many of them currently utilized in practice and many more likely to start in the next few years.

## Vitamin A

A long-term study of oral vitamin A palmitate supplementation (15 000 IU daily) administered to 600 patients who had typical RP showed a modest but positive slowing of vision loss.<sup>51</sup> In all cases in aggregate, vision loss declined to 8.3% per year compared with 10% per year in controls. Such slight slowing of degeneration is rarely noticeable to an individual patient over a short period, but it may provide additional years of vision when spread over a lifetime. The rescue mechanism is unknown, but vitamin A is essential for the formation of light-sensitive rhodopsin. Opsin alone, in the absence of vitamin A, may exhibit a small degree of toxicity and possibly cause photoreceptor demise over a lifetime. In the same study,<sup>51</sup> the administration of vitamin E (400 IU daily) without vitamin A hastened the degeneration by a small but statistically significant amount. However, when combined with vitamin A, low doses of vitamin E did not substantially alter the slowing of progression afforded by vitamin A palmitate alone, and thus the modest amount of vitamin E in multivitamin formulations may not be detrimental when taken along with vitamin A.

If this treatment is suggested, the patient is advised to use vitamin A for the long term and to expect no immediate benefit in vision. Yearly checks of serum liver enzymes and/or vitamin A levels are advisable while vitamin A is taken at high dosage, and discontinuation is necessary if pregnancy is expected. The main caution is to the female patient who must be counseled on the risk of teratogenicity of high doses of vitamin A, and as such, it should not be recommended for women who are pregnant or planning to become pregnant.<sup>52</sup>

## Docosahexaenoic Acid

Docosahexaenoic acid (DHA), a 22:6 fatty acid, is the major lipid component of rod photoreceptor membranes and is important for the maintenance of membrane fluidity required for rods to function. Abnormal cholesterol and serum lipid levels have been reported in some patients with RP,<sup>53</sup> and DHA levels are particularly and somewhat consistently low in patients with XLRP.<sup>54</sup> On the basis that insufficient DHA may affect photoreceptor survival, two randomized clinical trials designed to determine whether DHA dietary supplementation slows progression in retinal degeneration have been completed. The first one included only male patients with X-linked retinitis pigmentosa,<sup>55</sup> and the second one recruited patients regardless of inheritance mode.<sup>56</sup> Unfortunately, these studies did not show a statistically significant effect of DHA on the course of visual loss. A recent study did report that a diet high in long-chain omega-3 fatty acids could slow the rate of visual acuity of patients with RP who were taking vitamin A.<sup>57</sup> Lutein has also been investigated as a potential therapy for RP in addition to vitamin A, with some reported positive effects.<sup>58</sup>

## Carbonic Anhydrase Inhibitors for Cystoid Macular Edema

Some patients with RP have CME, possibly because the efficiency with which fluid is pumped across the RPE is compromised or because of slow retinal vascular leakage. Some studies show that treatment with acetazolamide may be of benefit,<sup>59</sup> with an initial dose of 250 mg daily, increased to 500 mg daily if no effect is apparent. A trial of several weeks is warranted, with successful outcome judged by improved visual acuity on careful repeated measurements or by decreased CME on FA or OCT. If decreased CME is observed by FA after several weeks of use, the continuation of acetazolamide may be considered even if visual acuity has not improved, provided the patient is able to tolerate the drug. Topical carbonic anhydrase inhibitors, such as dorzolamide, have also been used in this setting.

## Gene Therapy

Because RP arises as a consequence of mutations in many genes, one rational approach to therapy relies on correcting the genetic defect. Gene therapy can be broadly divided into three main approaches: (1) delivering a normal copy of the specific affected gene to the retina with a virus vector or other delivery method, (2) inactivating a mutating gene whose gene product has a deleterious effect, and (3) introducing a new gene into a tissue to help fight disease. An example is gene replacement therapy as treatment for autosomal recessive LCA from mutations in the *RPE65* gene. After successful gene therapy in an *RPE65* dog LCA model,<sup>60</sup> this was extended to a human *RPE65* trial, with preliminary evidence of benefit to visual function.<sup>61–63</sup> More long-term study of participants in this study indicate that the effects of treatment are long lasting.<sup>64</sup> Currently, clinical trials involving gene therapy for a number of retinal degenerations, including Stargardt, choroideremia, X-linked retinoschisis, achromatopsia, and *MYO7A* Usher syndrome are currently underway (<http://www.clinicaltrials.gov>).

## Neurotrophic Factors

A report in 1990 showed that intraocular injection of basic fibroblast growth factor effectively slowed photoreceptor degeneration in the RCS rat model of retinal degeneration.<sup>65</sup> These and other results implied that effective therapies may be developed to slow the rate of degeneration radically in these diseases.<sup>66</sup> Ciliary neurotrophic factor (CNTF), delivered intravitreally, has been effective to rescue photoreceptors in multiple animal models of retinal degeneration.<sup>67,68</sup> Small clinical trials in humans have now been done with CNTF delivered by encapsulated cell technology in patients with advanced RP<sup>69,70</sup> and in patients with age-related macular degeneration (AMD) with geographical atrophy.<sup>71</sup> In these small studies, the implants were well tolerated and each reported some positive effects. Long-term follow-up of a cohort of patients with retinitis pigmentosa failed

to show evidence of efficacy in acuity, field sensitivity, or retinal structural measures.<sup>72</sup> Studies using CNTF in the treatment of retinal degenerations are currently underway (<http://www.clinicaltrials.gov>).

## Stem Cell–Based Therapies

The previously mentioned therapies address the function and longevity of existing retinal cells. However, as the name implies, patients with retinal degenerations lose certain cells with time. The two main approaches involving stem cells involve either a regenerative approach, which involves the generation of more differentiated cells to replace a specific cell type that has been lost, or another approach to harness the trophic factors generated by relatively undifferentiated stem cells to provide the molecular boost to fortify existing cells (similar to the previous section). Recently, a recent report on the short-term use of transplanted human-derived RPE cells demonstrated short-term safety.<sup>73</sup> Research is progressing quickly in this area, and future studies are being planned.

## Retinal Prostheses/Implants

Another method to address the loss of retinal cells seen in a range of retinal degenerations has been to use an artificial implant that would detect light, convert light energy into an electrical signal, and then pass on that electrical signal to other cells in the visual system that would get the electrical signal to the brain, where it could be interpreted as vision.<sup>74</sup> Several commercial implant prototypes employing slightly different approaches, with some implants residing in an epiretinal position and others subretinally or suprachoroidal locations, are currently being studied in clinical trials in Europe, Australia, and the United States. Most make use of an external video processing unit, but one device, the Alpha IMS approach, utilizes internal light-sensitive photodiodes and is approved in Europe. A video illustrating the surgical approach as well as patients' perspectives from the Alpha IMS retinal prosthesis can be found on <http://rsnpb.royalsocietypublishing.org/content/280/1757/20130077.figures-only>. Another retinal prosthesis, the Argus II, which utilizes an external video camera and processing unit, is the only retinal prosthesis currently FDA approved for use in the United States, and 5-year data results are available.<sup>75</sup> The concept has been around longer than that of stem cell–based therapies, and several clinical trials using various versions of these implants have been conducted. Progress continues to be made, especially as technology evolves.

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Macular Dystrophies

David G. Telander, Kent W. Small

6.15

**Definition:** The process of premature retinal cell aging and cell death, generally confined to the macula, in which no clear demonstrable extrinsic cause is evident, and a genetically determined defect is confirmed or implicated.

Key Features

- Common to have yellowish material within or beneath the retinal pigment epithelium.
- Loss of macular photoreceptors and retinal pigment epithelial cells causing macular atrophy.
- Loss of central vision.

Associated Features

- Neural retinal, retinal pigment epithelial, and choroidal atrophy commonly limited to the macula.
- Bullseye appearance for some macular dystrophies.
- Pigment clumps in the posterior pole, midperiphery, or far periphery seen rarely.
- Optic atrophy, retinal vascular attenuation, macular edema, and choroidal neovascularization seen rarely.

INTRODUCTION

The macula is the center of all human vision and is critically unique to our visual function. Its irreducibly complex design requires many unique proteins that allow light to be converted to neuronal impulses (phototransduction). Macular dystrophies are rare genetic disorders that can cause severe central vision loss for the individuals affected. Understanding the genetic causes of these dystrophies allow us to see the various types of clinical abnormalities that arise from specific gene defects in a complex system involved in macular function. Molecular genetics has been instrumental in unlocking the secrets of these mechanisms and has given us a better understanding of the macula. The first retinal degeneration mapped by genetic linkage was one type of X-linked retinitis pigmentosa (XLRP) in 1984. Subsequently, linkage of autosomal dominant retinitis pigmentosa (ADRP) to chromosome 3 was achieved by McWilliams et al.<sup>1</sup> The first macular dystrophy to be mapped was North Carolina macular dystrophy in 1992 by Small and colleagues.<sup>2</sup> Since then there have been many important contributions by numerous groups around the world. There are many online resources to catalog these conditions, including Online

Mendelian Inheritance of Man (OMIM, <http://www.ncbi.nlm.nih.gov/omim>), RetNet (<https://sph.uth.edu/Retnet/>), and Retina International (<http://www.retina-international.org/>).

From a clinical perspective, significant phenotypic variations even within a single family are common, making it imperative to examine as many other family members as possible. For example, differences in phenotypes can represent mutations in different genes, different mutations in the same gene, and/or variability in the genetic background in which a single gene/mutation is expressed. In general most macular dystrophies are autosomal dominant and the appearances of the macular abnormality are severe, but the visual acuity is better than one would expect. The autosomal recessive macular dystrophies tend to have worse visual acuities than one would expect from examination.

In contrast to age-related macular degeneration (AMD), which is a multifactorial and multigenic disease, macular dystrophies are usually thought to be caused primarily by a disruption of a single retinal gene. Table 6.15.1 demonstrates how identification of genetic phenotypes has given us insights into macular dystrophies. Table 6.15.2 categorizes the macular dystrophies by the location of the affected cell/gene.

The purpose of this chapter is to highlight the clinical features of some of these macular dystrophies, discuss the pertinent molecular genetics and pathophysiology of these diseases, and correlate the functional consequences of the mutant gene products in the framework of the known anatomy and physiology of the retina and retinal pigment epithelium (RPE). Obviously, every disease cannot be reviewed. However, the intention is to convey certain underlying biological principles that can be extended to understand the molecular pathogenesis of other disease processes.

With the advent of gene therapy, stem cell therapy, artificial vision, and a plethora of new retinal pharmacologicals, proven therapy for these disorders is in the near future. In addition, therapies to halt the progression of choroidal neovascularization have progressed and can benefit some who develop this complication.

STARGARDT DISEASE AND FUNDUS FLAVIMACULATUS

EPIDEMIOLOGY AND PATHOGENESIS

Stargardt disease is the most common macular dystrophy, with an estimated incidence of 1:8000–10 000. Stargardt disease is also known as Stargardt macular dystrophy. It usually presents within the first two decades, but the central vision loss may not occur until later in life.<sup>3</sup>

Stargardt disease (STGD1) most commonly is inherited in an autosomal recessive manner caused by various sequence mutations in adenosine

TABLE 6.15.1 Examples of Cellular Specificity of Macular Dystrophy Genes

Cellular Location	Retinal Dystrophy	Chromosome	Gene
RPE specific	AD Best	11q12.3	VMD2, bestrophin (chloride channel)
	AD Sorsby's macular dystrophy	22q12.3	TIMP3 (tissue inhibitor of metalloproteinase)
	Malattia leventinese (Doyle's honeycomb macular dystrophy)	2p16	EFEMP1 (EGF-containing fibrillin-like extracellular matrix protein 1)
Rod specific	AD Stargardt macular dystrophy	6q14	ELOVL4 (photoreceptor-specific elongation of very long chain fatty acids)
Cone specific	AD cone dystrophy	6p21.1	GUCA1A (guanylate cyclase activator 1A)
Cone-rod specific	AR Stargardt	1p22.1	ABC4 (ATP binding cassette protein found in rods and foveal cones)
	AD adult foveal macular dystrophy	6p21.2	RDS/peripherin (cone and rod outer segment glycoprotein in disc membranes for structural integrity)

AD, Autosomal dominant; AR, autosomal recessive; ATP, adenosine triphosphate; EGF, endothelial growth factor; RPE, retinal pigment epithelium.

TABLE 6.15.2 Macular Dystrophies and Example Genes

Disease Name	Gene	Chromosome	Inheritance
Best 1	VMD2 /TU15B	11	AD
Best 2	VMD2L1	19	
	VMD2L2	1	
Stargardt	ABCA4	1	AR
Stargardt-like macular dystrophy	ELOVL4	6	AD
Pattern dystrophy	PRPH2	6	AD
Adult vitelliform			
VMD3	IMPG1	6q	
VMD 4	IMPG2	3q	
VMD 5			
Sorsby's fundus dystrophy	TIMP3	22	AD
Dominant drusen	EFEMP1	2	AD
North Carolina macular dystrophy			AD
NCMD/(Small's macular dystrophy)			
MCDR1	PRDM13	6q	
MCDR3	IRX1	5	
Enhanced S-cone (Goldmann-Favre)	NR2E3	15	AR
Glomerulonephritis type II and drusen			

AD, Autosomal dominant; AR, autosomal recessive.

triphosphate-binding cassette (*ABCA4*) gene, which has been localized to chromosome 1p21–22.<sup>4–7</sup> *ABCA4* is a very large gene with more than 900 identified disease-causing mutations.<sup>3</sup> While 60%–70% of these patients have a detectable mutation in the *ABCA4* gene, the carrier state is thought to be as frequent as 1:20 people.<sup>3</sup> *ABCA4* normally encodes for a protein involved in the visual cycle. Lipofuscin buildup in the subretinal space appears to be related to a mutation in *ABCA4* and the resulting production of a dysfunctional protein. Lipofuscin is a complex mixture of bisretinoid fluorophores amassed by RPE cells. In the RPE, lipofuscin does not form as a result of oxidative stress, unlike in other cell types. Instead it forms because of a nonenzymatic reaction of vitamin A aldehyde in photoreceptor cells that is transferred to the RPE by the phagocytosis of the photoreceptor outer segments. In recessive Stargardt (STGD1) and *ELOVL4*-related retinal dystrophies (STGD3), the formation of lipofuscin is accelerated, leading to cell death.<sup>8</sup> Carrier parents are unaffected. Interestingly, mutations in this gene can also lead to other retinal diseases such as AMD, retinitis pigmentosa (RP), and autosomal recessive cone–rod dystrophy.<sup>3,8,9</sup> These *ABCA4*-related dystrophies likely represent a spectrum of phenotypes with overlapping retinal changes, just as Stargardt disease itself exhibits great variability in clinical expression.<sup>10–12</sup>

In addition to recessive Stargardt disease, there are other rarer forms inherited as dominant rather than recessive traits. Autosomal dominant Stargardt (STGD3) is a rarer form of this condition and is caused by mutations of the *ELOVL4* gene, which codes for a photoreceptor-specific membrane-bound protein that plays a role in long chain fatty acid biosynthesis.<sup>13</sup> Several other retinal diseases have been mapped near to *ELOVL4*, including retinitis pigmentosa, Leber’s congenital amaurosis, cone–rod dystrophy, North Carolina macular dystrophy, early onset dominant drusen, and progressive bifocal chorioretinal atrophy.<sup>14–16</sup>

OCULAR MANIFESTATIONS AND DIAGNOSIS

The phenotypic variation of mutations in the *ABCA4* gene presents in many forms as described earlier.

Stargardt disease classically is marked by the accumulation of discrete “pisciform” flecks at the level of the RPE (Fig. 6.15.1).<sup>17,18</sup> Early in the disease, patients may have few flecks, but they often will develop more macular flecks along with patches of characteristic central atrophy. Fundus flavimaculatus patients have mutations in the same gene but present with pisciform flecks in the peripheral macula and retina sparing the fovea. Therefore, early in the disease, fundus flavimaculatus patients tend to retain their central vision, but later in life they usually develop central macular atrophy, central vision loss, color vision loss, and photophobia. Stargardt patients, on the other hand, develop a macula with a “beaten bronze” appearance caused by atrophic changes in the RPE. In addition, they also often have a “dark” or “silent” choroid on fluorescein angiography that appears as a prominent retinal circulation against hypofluorescent choroid. Although this finding can be helpful in making the diagnosis.

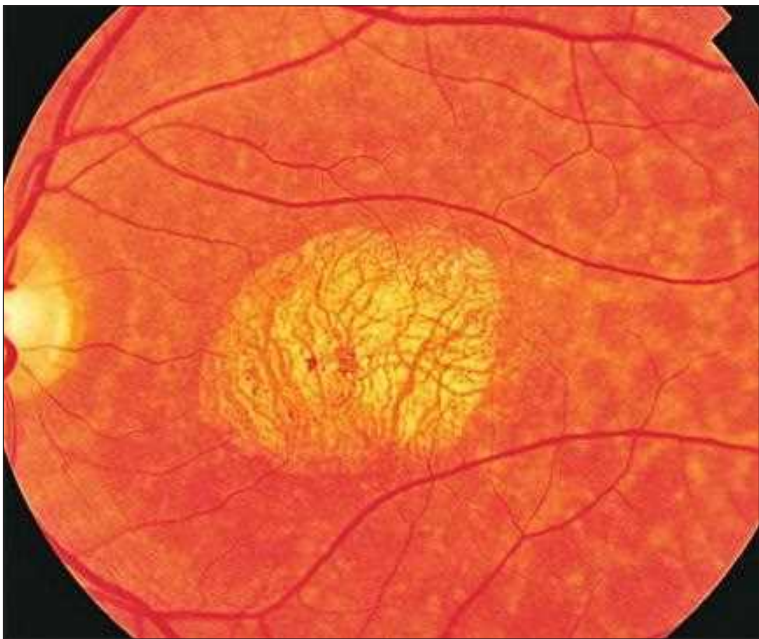


Fig. 6.15.1 Stargardt Disease.

only up to one-fourth of patients have a dark choroid.<sup>19</sup> On angiography the pisciform flecks do not stain. Autofluorescence can be helpful in showing the lipofuscin in flecks and atrophic areas, which will show photoreceptor dysfunction<sup>20</sup> (Fig. 6.15.2). The electroretinogram (ERG) is normal early in the disease but may be reduced in more advanced cases. Of note, the ERG findings do not directly correlate with clinical findings.<sup>21</sup> High-resolution optical coherence tomography (OCT) can show atrophic changes in the photoreceptors and RPE, and lipofuscin deposits can be detected within the parafoveal RPE<sup>22–24</sup> (Fig. 6.15.3). Interestingly, these changes usually precede the occurrence of fundus abnormalities. The OCT can also help with diagnosis and aid in determining the status of the photoreceptor layer in the macula, which is beneficial in the assessment of central vision.<sup>23</sup>

PATHOLOGY

Histological studies reveal that Stargardt patients have a buildup of a lipofuscin-like pigment in the RPE.<sup>25</sup> The mouse model (a knockout *abcr*–/–) of Stargardt disease also has an accumulation of lipofuscin in the RPE. Specifically, the toxic *bisretinoid*, *N-retinylidene-N* retinylethanolamine (A2E) protein builds up, suggesting its role in causing the disease.<sup>4</sup>

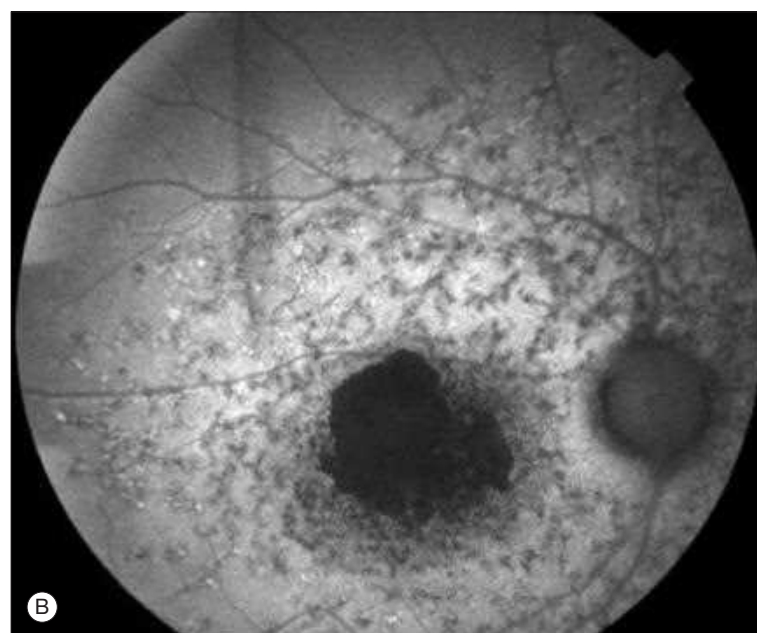
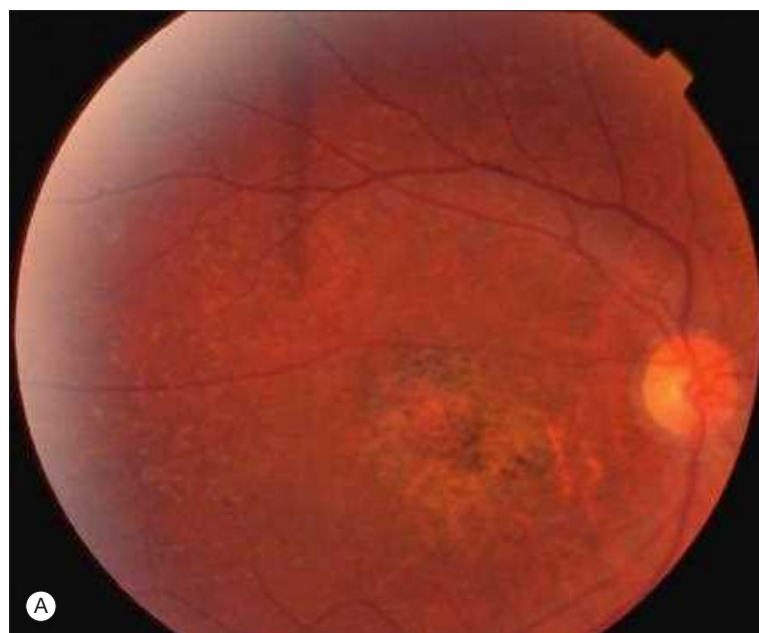
TREATMENT, COURSE, AND OUTCOME

To date there is no known proven treatment for this disease. As *ABCA4* plays a role in vitamin A processing in the visual cycle, additional vitamin A is suspected to make the disease worse. Therefore all forms of vitamin A supplements are discouraged for these patients.<sup>26</sup> Polyunsaturated fatty acids such as docosahexaenoic acid (DHA) have been shown to reduce toxicity of A2E and are therefore recommended especially for patients if they are autosomal dominant Stargardt.<sup>27</sup>

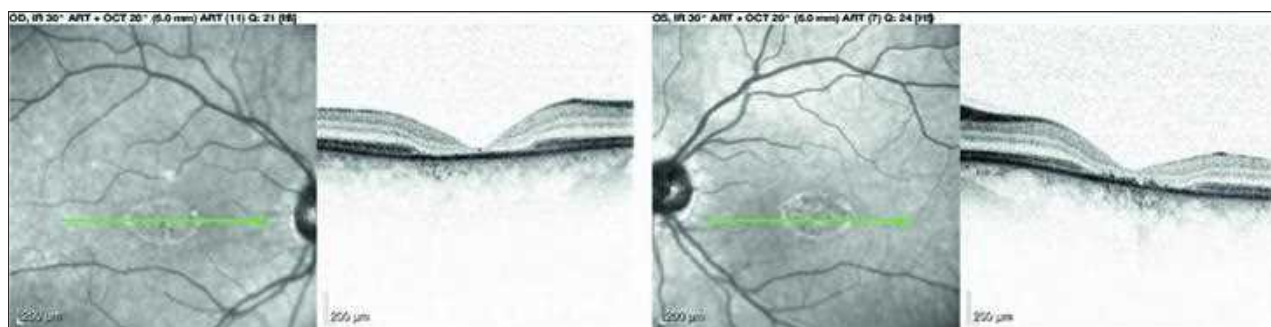
Gene therapy has been initiated for Stargardt, specifically a 48-week phase 1/IIa dose escalation study is currently investigating SAR422459 (a lentiviral vector gene therapy carrying the *ABCA4* gene) for the treatment of Stargardt. Eligible patients must have two pathogenic *ABCA4* gene variants confirmed by segregation analysis of parental samples. (<http://clinicaltrials.gov/ct2/show/NCT01367444>). Another clinical trial has been launched using RPE precursor cells derived from embryonic stem cells injected subretinally for patients with Stargardt disease. Retinal pigment epithelial cells derived from human embryonic stem cells (hESC\_RPE) are surgically implanted in the submacular space.<sup>28</sup> Saffron, ALK-001 (C20-D3-retinyl acetate), MP-4, and DHA are all being studied in additional clinical trials for Stargardt disease (see <https://clinicaltrials.gov/>).<sup>3</sup>

Individual members of families with Stargardt disease often display tremendous variability in presentation, course, and outcome. The visual prognosis ranges from 20/5 to 20/200 as determined by the extent of macular atrophy depending mostly on the extent of macular atrophy for both Stargardt and fundus flavimaculatus.<sup>18,19,29</sup> Choroidal neovascularization is rare but can worsen the prognosis if it occurs.<sup>30</sup>





**Fig. 6.15.2 Fundus Autofluorescence Clearly Delineates Areas of Central Macular Atrophy in Stargardt Disease, Allowing Accurate Measurements of Atrophy.** Color fundus of the right eye (A) can be compared to autofluorescence of the right (B).



**Fig. 6.15.3 Fundus Optical Coherence Tomography Findings Showing Central Retinal Thinning in Stargardt Patient From Photoreceptor and Retinal Pigment Epithelium Cell Loss.**

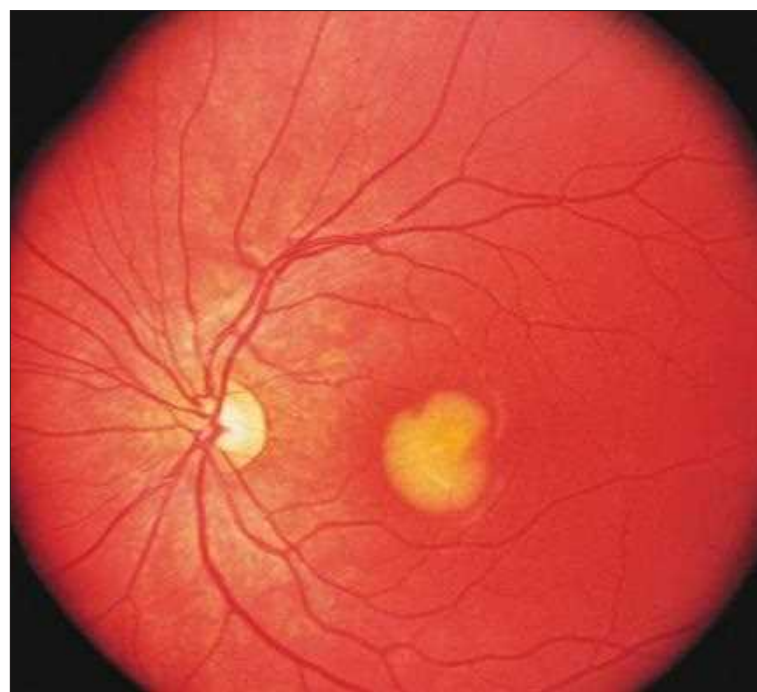
## VITELLIFORM MACULAR DYSTROPHY (BEST DISEASE)

### EPIDEMIOLOGY AND PATHOGENESIS

Vitelliform macular dystrophy is an inherited macular dystrophy in which lipofuscin accumulates in the central macula, causing progressive central vision loss. Vitelliform dystrophy can present early in life (described as Best disease), but the onset of symptoms can vary widely. The adult-onset form of vitelliform dystrophy (described later) usually presents in middle age. Best disease is an autosomal dominant macular dystrophy linked to mutations in the bestrophin (*VMD2*) gene. Like Stargardt, Best patients can be highly variable in clinical phenotype, but is quite rare compared to Stargardt disease. *VMD2* encodes for a transmembrane protein, which acts as an ion exchanger.<sup>31–33</sup> *VMD2* is expressed in the RPE cell membrane and appears to be important in the formation of chloride channels.<sup>34</sup> This leads to the accumulation of lipofuscin through mechanisms that are still unclear. Several mutations within the bestrophin gene have been identified and are associated with both classic Best and adult vitelliform-like presentation.<sup>35</sup> Interestingly, some patients with the mutation can be completely free from any clinically observable retinal changes. Incomplete penetrance by clinical exam alone has been well documented, although electro-oculogram (EOG) generally does demonstrate abnormalities.<sup>36</sup> In fact, Best disease expresses a great deal of phenotypic variability even within a single family.

### OCULAR MANIFESTATIONS AND DIAGNOSIS

Vitelliform dystrophies are characterized by bilateral yellow, yolk-like (vitelliform) macular lesions (Fig. 6.15.4). Although Best disease presents during childhood, adult vitelliform typically presents later in life. In Best, the diameter of the lesion is in the range of 1–5 mm. For Best patients, the lesion will change later in life resulting in macular scarring and atrophy. This may make it more difficult to diagnose later.



**Fig. 6.15.4 Best Disease.** Typical vitelliform lesion from an 11-year-old girl. (Courtesy Ola Sandgren, University Hospital of Umeå, Sweden.)

The stages or evolution of the macular lesions are described as progressing from (1) previtelliform stage to (2) vitelliform stage to the (3) scrambled egg stage with or without hypopyon finally to (4) the atrophic stage. Rarely, the lesions may be multifocal.<sup>37</sup> All Best patients have a light-to-dark (or Arden) ratio of less than 1.5 and often close to 1.1 when tested with the EOG. ERG testing shows only occasionally a reduced C-wave. Therefore



this is the only disease with relatively normal ERG results associated with an abnormal EOG. Moreover, OCT findings appear to be very specific (Fig. 6.15.5). In Best disease, the OCT reveals that the vitelliform material appears as a dome-shaped, hyperreflective, and homogenous lesion (see Fig. 6.15.5) located below the hyperreflective photoreceptor layer.<sup>38</sup>

## **PATHOLOGY**

Best patients have an accumulation of lipofuscin-like material throughout the RPE.<sup>39–42</sup> Unlike with Stargardt disease, despite the accumulation of lipofuscin-like material in the RPE, these patients do not exhibit a dark choroid effect on fluorescein angiography. In addition, Best patients can lose vision from atrophy and scarring in the macula, not from accumulated material in the RPE.

## **TREATMENT, COURSE, AND OUTCOME**

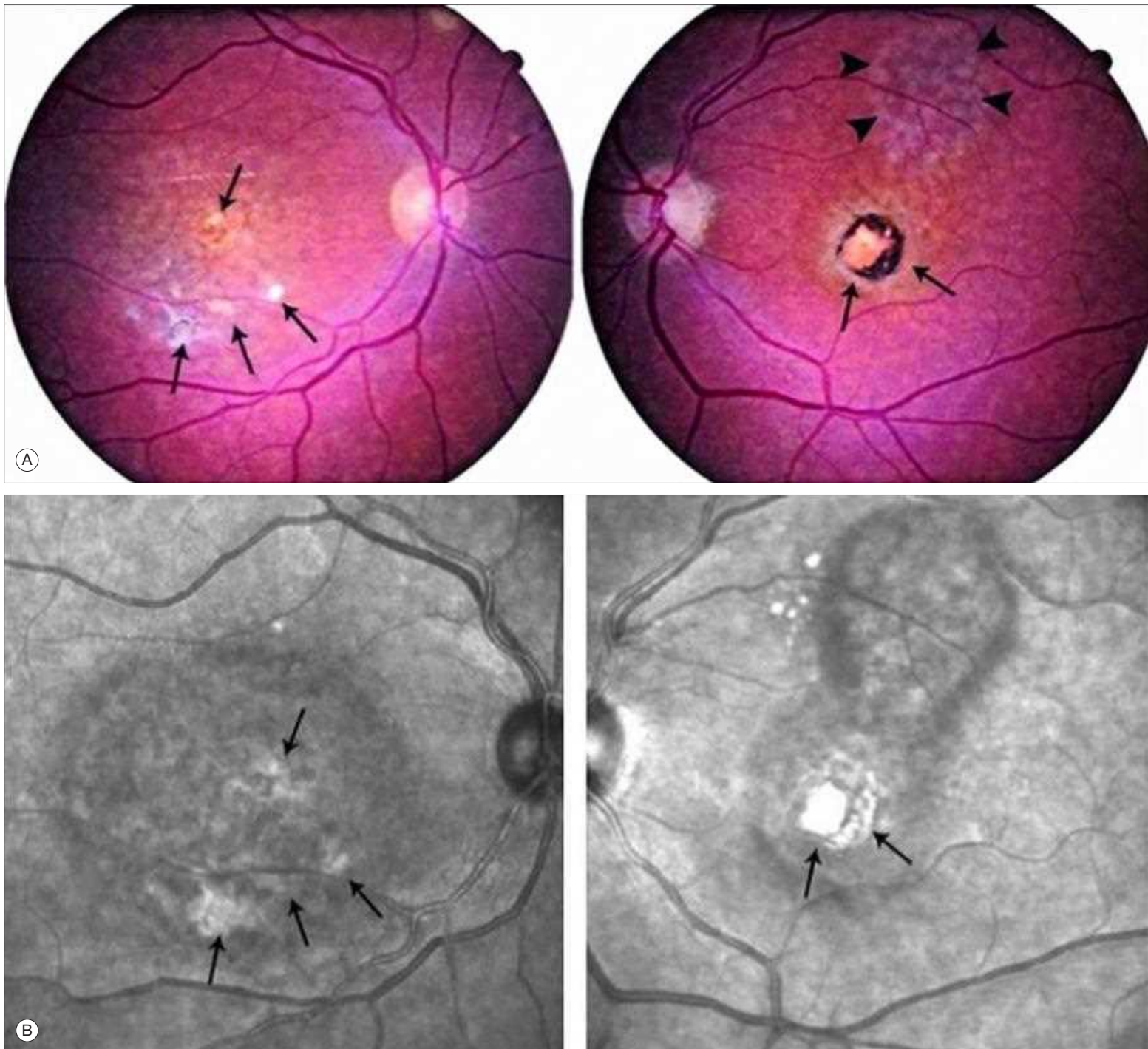
Even though the age of onset of Best disease is variable, most patients present in childhood. Best patients usually have good visual acuity when

the “yolk” remains intact, but the vision drops when macular atrophy begins.<sup>37</sup> Visual acuity can decrease to the 20/200 range, but most patients will keep enough vision in at least one eye to read and drive. Rarely, Best patients develop choroidal neovascular membranes (CNVs).<sup>37</sup>

## **ADULT VITELLIFORM MACULAR DYSTROPHY/ ADULT-ONSET FOVEOMACULAR DYSTROPHY (PATTERN DYSTROPHY)**

### **EPIDEMIOLOGY AND PATHOGENESIS**

Unlike Best disease, the adult-onset form of vitelliform dystrophy usually presents in middle age and typically only causes mild, if any, central vision loss. While these two diseases can be phenotypically similar, the clinical course is highly divergent. While Best is caused by mutations in *VMD2*, adult vitelliform dystrophy has been associated with mutations of both *VMD2* and retinal degeneration slow (*RDS*, *PRPH2*), but the causative



**Fig. 6.15.5** An 80-Year-Old Patient With Best Disease in the Vitelliruptive Stage (Right Eye) and Atrophic Stage (Left Eye). Fundus photos (A), red free (B), fluorescein angiogram (C), optical coherence tomography (D), and histology (E). Note optical coherence tomography findings show characteristic hyporeflective subretinal zone consistent with subretinal deposit at this stage.

*Continued*



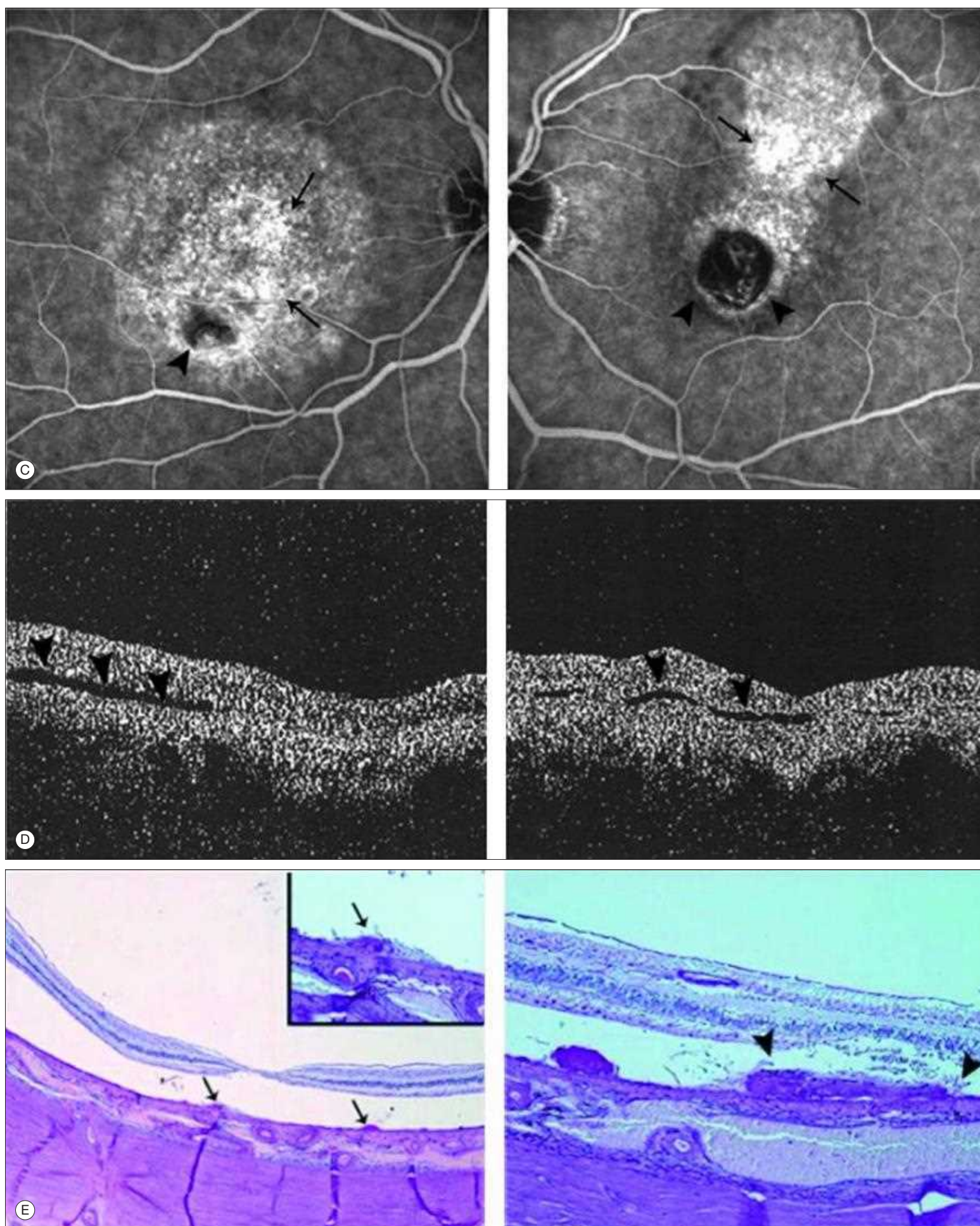
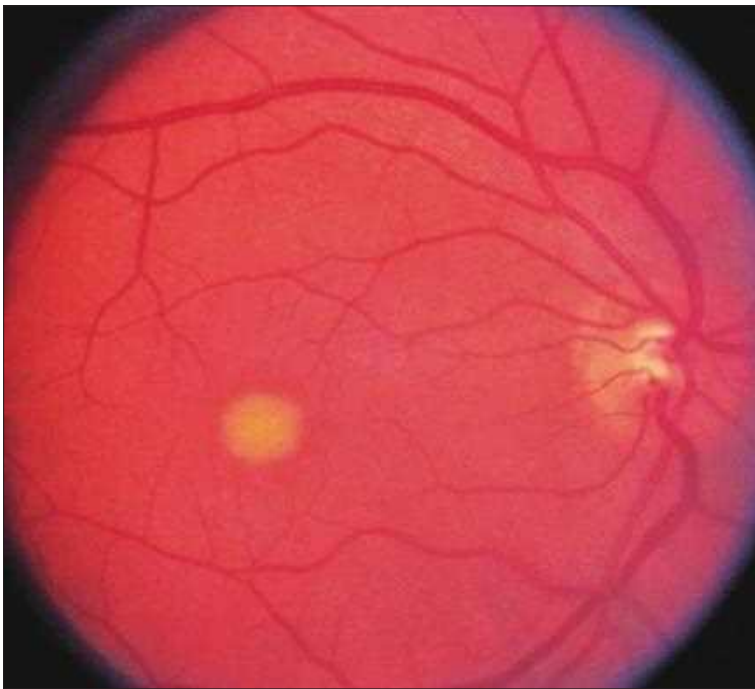
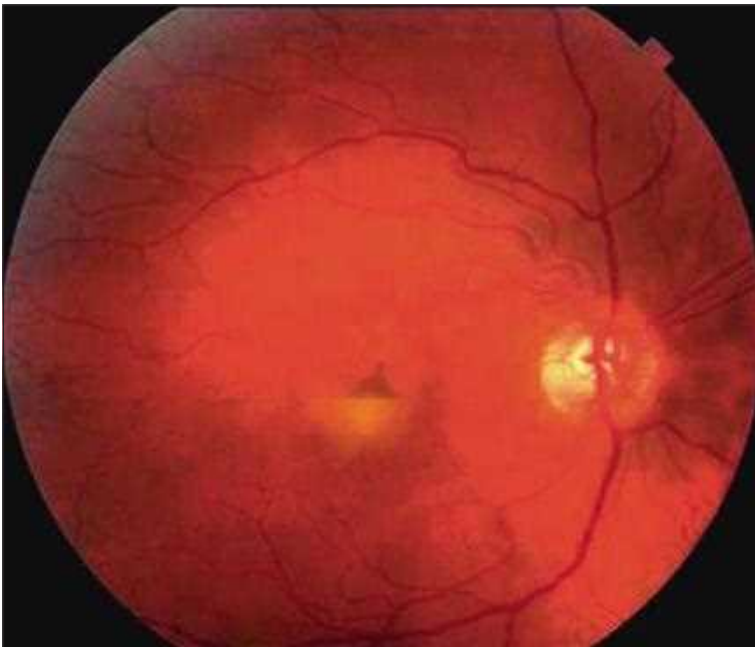


Fig. 6.15.5, cont'd



**Fig. 6.15.6 Adult Vitelliform Macular Dystrophy.** (Reproduced with permission from Feist RM, White MF Jr, Skalka H, Stone BM. Choroidal neovascularization in a patient with adult foveomacular dystrophy. *Am J Ophthalmol* 1994;118:259–60.)

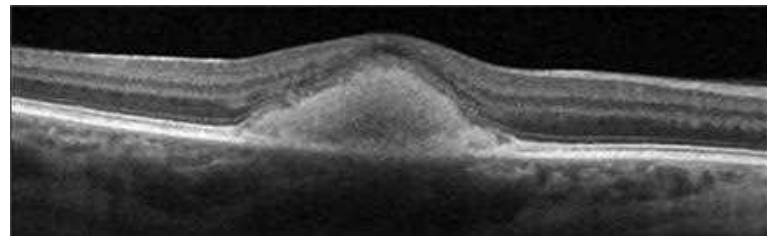


**Fig. 6.15.7 Adult Vitelliform Macular Dystrophy.** Color photograph shows the vitelliform deposit in the macula settled inferiorly, and fundus autofluorescence. (Courtesy Jay S. Duker.)

gene cannot be found in most patients with adult vitelliform dystrophy.<sup>31,43</sup> Interestingly, several mutations within the bestrophin gene have been identified and are associated with both classic Best and adult vitelliform-like presentation.<sup>35</sup> RDS encodes a protein called peripherin. This protein is essential for the normal function of light-sensing (photoreceptor) cells in the retina. How a mutation in RDS only affects the macula and not the remainder of the retina is unclear.

## OCULAR MANIFESTATIONS AND DIAGNOSIS

Adult vitelliform (Figs. 6.15.6) and Best disease can often appear very similar. While Best presents during childhood, adult vitelliform typically presents later in life. In Best the diameter of the lesion is in the range of 1–5 mm, whereas in adult vitelliform the lesion tends to be smaller (Fig. 6.15.7). Adult vitelliform degenerations include foveomacular dystrophy of



**Fig. 6.15.8 Optical Coherence Tomography Shows the Typical Vitelliform Deposit in the Subretinal Space.** (Courtesy Jay S. Duker.)

Gass, and coalescent, widespread, cuticular drusen that form vitelliform lesions in the macula.<sup>44</sup> Adult vitelliform can be differentiated from Best disease by having a near normal EOG (Arden ratio <1.7), but the multifocal ERG may be reduced. Also the OCT will show the absence of subretinal fluid in adult vitelliform dystrophy (Fig. 6.15.8) but not Best disease.<sup>45</sup>

## PATHOLOGY

Adult vitelliform dystrophy patients have damage at the level of the RPE with focal loss of the photoreceptors in the areas of atrophic RPE cells in the fovea. Pigmented material is found between the retina and Bruch's membrane. OCT images localize the vitelliform lesion to the highly reflective photoreceptor-RPE complex.<sup>22</sup> Interestingly, Gass found no abnormal accumulation of lipofuscin in RPE cells in these patients.<sup>44</sup> Other investigators have found high concentrations of lipofuscin in RPE cells and suggest that this accumulation is responsible for the foveal lesion.<sup>40</sup> Moreover, autofluorescence studies support this hypothesis.<sup>46</sup>

## TREATMENT, COURSE, AND OUTCOME

Adult vitelliform dystrophy usually presents during the fourth to sixth decade, and visual symptoms are usually metamorphopsia and mildly blurred vision. Rarely, these patients can also develop CNVs.<sup>47</sup> Interestingly, as in Best disease, adult vitelliform dystrophy patients usually only lose significant vision when atrophy and scarring occur. Best disease should be distinguished from adult vitelliform dystrophy, as there are potential genetic implications that require appropriate counseling.<sup>48</sup>

## DOMINANT DRUSEN (DOYNE'S DRUSEN, MALATTIA LEVENTINESE)

## EPIDEMIOLOGY AND PATHOGENESIS

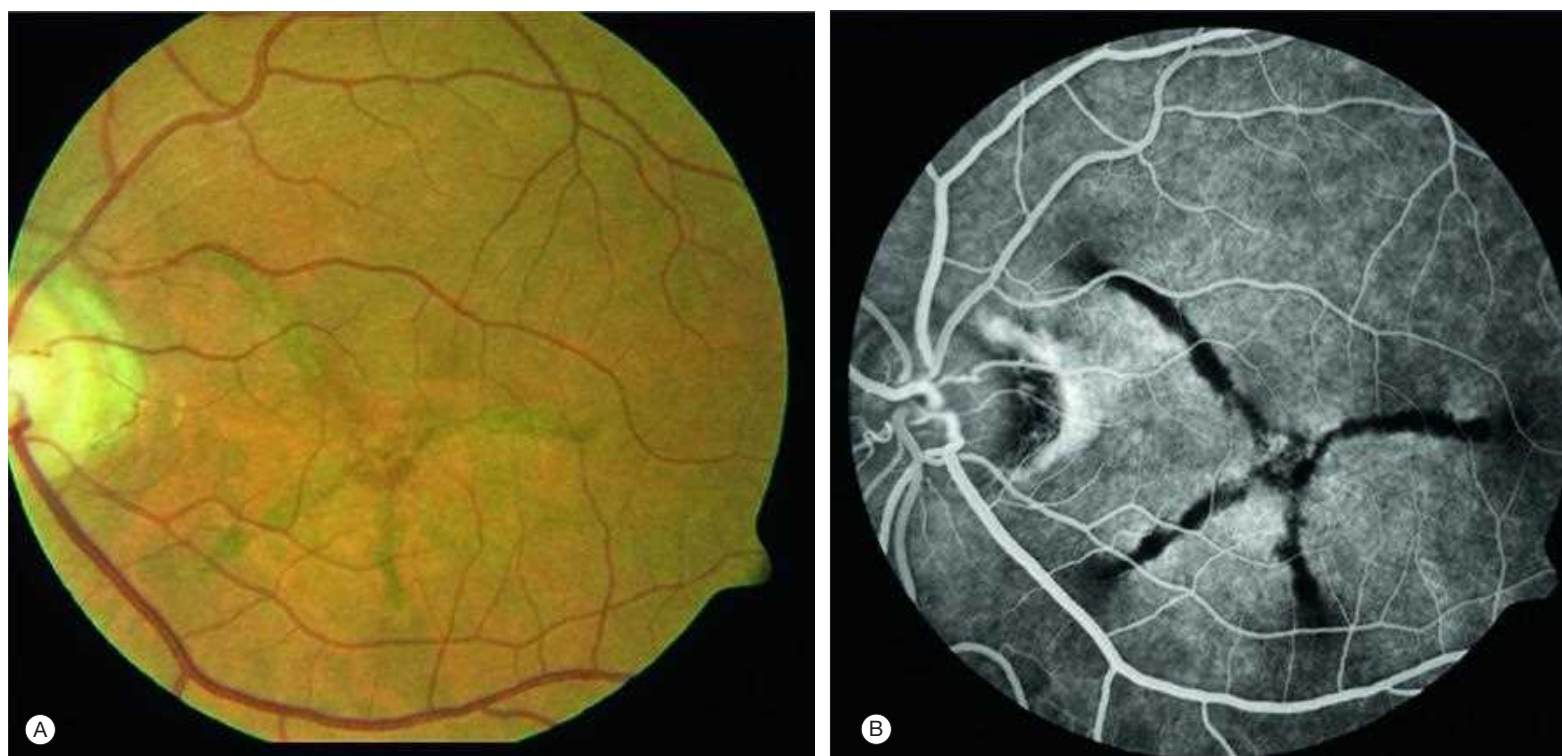
Familial (dominant) drusen is a rare autosomal dominant disease with variable expressivity and age-dependent penetrance.<sup>49</sup> All are due to a single mutation from an arginine to a tryptophan at amino acid 345 in the *EFEMP1* gene.<sup>50</sup> While initially all patients with the R345W mutation had identical haplotypes suggesting a common founder, there were recently reported two separate Japanese and Indian families also with the R345W mutation but with unique haplotypes. This suggests that the same mutation had spontaneously arisen in three different ethnicities.<sup>51,52</sup> The mutant *EFEMP1* is misfolded and secreted inefficiently, thus accumulating within the RPE and causing drusen.<sup>30,53</sup> Another locus on chromosome 6q14 adjacent to the North Carolina dystrophy gene (*MCDRI*) has been identified, also, in those with dominant drusen.<sup>54–56</sup> However, these cases are more consistent with North Carolina macular dystrophy with only drusen present and were misdiagnosed as dominant drusen.

This disease is thought to arise from an inborn error of metabolism localized to the RPE. One hypothesis is that the defect is in an intercellular matrix protein or a structural protein, which leads to the development of abnormal basement membranes.

## OCULAR MANIFESTATIONS AND DIAGNOSIS

Typically, diffuse drusen extend outside the macula and involve retina nasal to the optic disc.<sup>57</sup> The drusen, themselves, may be large and sparse or form a constellation of tiny dots, called *cuticular* or *basal laminar drusen*. Sometimes, basal laminar drusen coalesce to form a vitelliform lesion.<sup>58</sup> The drusen usually first appear around the third or fourth decade of life and become quite numerous by middle age. In the late stages, pigmentations occur, along with atrophy of the RPE, choriocapillaris, and large





**Fig. 6.15.9** This fundus photo (A) and midphase angiogram (B) are of the left fundus of a patient with butterfly pattern dystrophy. The retinal pigment epithelium changes are much easier to notice in the angiogram than in the fundus photo.

choroidal vessels. Flecks in this disorder are whiter and more sharply delineated than those in fundus flavimaculatus.

Fluorescein angiography often highlights atrophy of the RPE, and the drusen appear more extensive than seen clinically. In advanced cases, a central scotoma is seen on visual field examination. OCT reveals a thickening and occasional elevation of the RPE-Bruch's membrane complex.<sup>59</sup> Dark adaptation is usually normal, as are the ERG findings.<sup>60</sup> The EOG findings are normal in the initial stages, but they become subnormal depending on the degree of macular involvement. Familial drusen also exhibit fundus autofluorescence.<sup>61</sup>

## **PATHOLOGY**

Histopathological examinations show round accumulations of hyaline in the pigment epithelium that are continuous with the inner layer of Bruch's membrane. The choroids and neural retina may show atrophy later on, although they appear normal in the earlier stages of the disease.

## **TREATMENT, COURSE, AND OUTCOME**

No known effective treatment exists for diseases in this category. If CNVs occasionally ensue, intravitreal injections of anti-vascular endothelial growth factor (VEGF) agents may improve or stabilize vision. As long as the drusen are relatively discrete and do not affect the fovea markedly, central vision usually is good. When basal laminar drusen coalesce to form a vitelliform cyst, a marked degradation in visual acuity can occur if the yolk degenerates into an atrophic scar. CNVs may occur occasionally.

## **PATTERN DYSTROPHY**

### **EPIDEMIOLOGY AND PATHOGENESIS**

Macular pattern dystrophies are a heterogeneous group of inherited retinal conditions that affect the RPE and are characterized by various patterns of brown, yellow, and orange pigment in the central macula. The incidence of this group of dystrophies has not been determined. There are several different characteristic patterns of pigmentation that are typically inherited in an autosomal dominant pattern.<sup>62,63</sup> Patients from the same family may have different patterns, and some patients can even change patterns or have different patterns in different eyes.<sup>64-66</sup> The pattern dystrophies have been found to be caused by various mutations in the

human RDS/peripherin (*PRPH2*) gene on chromosome 6p21.2.<sup>16,67,68</sup> The peripherin/RDS/*PRPH2* encodes for photoreceptor-specific transmembrane glycoprotein that may play a role in the development and maintenance of photoreceptor outer segments.<sup>67,69-72</sup> Interestingly, some forms of RP and other macular dystrophies are attributed to mutations in this same gene.<sup>72,73</sup>

## **OCULAR MANIFESTATIONS AND DIAGNOSIS**

The age of onset of pattern dystrophies is variable, with many patients remaining asymptomatic until the fifth decade of life; some patients remain asymptomatic throughout life. The pigmentary changes occur at the level of the RPE.<sup>63,74</sup> Drusen and yellow flecks are not characteristic of these dystrophies but pigment is. The clinical phenotypes have many characteristic pigment patterns, including butterfly dystrophy, reticular dystrophy, multifocal pattern dystrophy simulating fundus flavimaculatus, and fundus pulverulentus. The butterfly-shaped pattern dystrophy can most easily be appreciated by fluorescein angiography (FA) and autofluorescence (Fig. 6.15.9). As its name indicates, reticular dystrophy is marked by a reticular network of darkly pigmented lines in the macula. Note that adult vitelliform dystrophy (described earlier) is also included in pattern dystrophies, as this condition is often associated with mutation in the RDS/peripherin/*PRPH2* gene. Fundus pulverulentus is the rarest form, characterized by coarse pigment mottling of the central macula. This dystrophy can be especially difficult to differentiate from AMD and may often be misdiagnosed.<sup>75</sup>

## **PATHOLOGY**

Pattern dystrophies are caused by abnormalities in the RPE of the macula.<sup>74</sup> Reported histological findings are not well documented besides atrophy in the RPE and photoreceptor layers.

## **TREATMENT, COURSE, AND OUTCOME**

Most patients with pattern dystrophies present with only mild metamorphopsia or mildly diminished visual acuity. Many patients are only discovered to have the disorder during routine eye examination. Visual acuity usually remains good through the first five or six decades of life, but later in life it may lead to central macular atrophy, much like advanced AMD. Patients with pattern dystrophies have a small risk of developing choroidal neovascularization later in life.

## DOMINANT CYSTOID MACULAR EDEMA

### EPIDEMIOLOGY AND PATHOGENESIS

Dominant cystoid macular edema is a rare autosomal dominant disease mapped to chromosome 7q.<sup>76</sup> This macular dystrophy is unique in predominantly affecting only the inner nuclear layer of the retina. It is hypothesized that the gene mutation primarily affects Müller's cells, based on histopathological evidence.

### OCULAR MANIFESTATIONS AND DIAGNOSIS

These patients present with central cystoid macular edema, which can cause atrophic changes, and additional vision loss develops.<sup>77</sup> Of note, peripheral pigmentary changes may also be present. FA confirms capillary leakage, with a classic petaloid pattern of dye accumulation in the macula. ERG testing is typically within normal limits, but patients have been found to have decreased Arden (light peak-to-dark trough) ratios on EOG testing. In addition, abnormal dark adaptation studies have been noted for these patients.

### PATHOLOGY

These patients demonstrate macular cysts and disorganization and gliosis of the inner nuclear layer. In addition, they have focal Müller's cell necrosis, RPE and photoreceptor degeneration, epiretinal membrane formation, and abnormal deposition of basement membrane in the perivascular space.<sup>78</sup> Interestingly, the feature of Müller's cell necrosis is unique compared to cystoid macular edema secondary to other causes such as inflammation.

### TREATMENT, COURSE, AND OUTCOME

Dominant cystoid macular edema patients have the onset of symptoms typically in the third decade of life. This will usually slowly progress to cause moderate or severe vision loss. This condition can cause atrophic changes of the macula. No known effective treatment has yet been found.

## SORSBY'S MACULAR DYSTROPHY

### EPIDEMIOLOGY AND PATHOGENESIS

Sorsby's macular dystrophy is a rare, dominantly inherited disorder, with many similarities to AMD except for the age of onset. Sorsby's dystrophy is caused by a mutation in a tissue inhibitor metalloproteinase, *TIMP3*.<sup>79-82</sup> This protein is an important enzyme in the regulation and composition of the extracellular matrix and plays a role in wound healing, bone adaptation, and organ hypertrophy. *TIMP3* has a second function. It encodes a potent angiogenesis inhibitor by blocking the binding of VEGF to VEGF receptor-2. Studies have shown that *TIMP3* overexpression suppresses primary tumor growth and metastasis.<sup>83</sup> This enzyme is expressed in the RPE.<sup>84</sup>

*EFEMP1*, whose mutated gene is responsible for malattia leventinese, was discovered as a strong interacting protein with *TIMP3*. Both these dystrophies have similarities to AMD. This suggests the possibility of a common pathogenetic mechanism for these different forms of macular diseases.

A knockout mouse model of Sorsby's has been created.<sup>85</sup> The model features changes in Bruch's membrane and the RPE that may represent the primary clinical manifestations of Sorsby's.

### OCULAR MANIFESTATIONS AND DIAGNOSIS

Early in the disease, very fine drusen or a large confluent plaque of yellowish material may be noted beneath the central RPE. Then, typically at around 40 years of age, patients develop bilateral exudative maculopathy, which leaves heavily pigmented macular scars and areas of geographical atrophy.<sup>86</sup>

The ERG and EOG results usually are normal early, but decreased photopic and scotopic amplitudes can be seen late in the disease.

### PATHOLOGY

Light and electron microscopic studies show lipid-containing deposits between the basement membrane and the pigment epithelium and the inner collagenous layers of Bruch's membrane.<sup>87</sup>

## TREATMENT, COURSE, AND OUTCOME

Patients typically develop bilateral CNVs at an early age. Severe loss of central visual acuity results from extensive macular scarring related to CNVs. Like patients with AMD, CNVs can be successfully treated with anti-VEGF and has been treated with combined photodynamic therapy and intravitreal triamcinolone.<sup>88,89</sup> Nyctalopia also is a symptom late in the course of disease.<sup>86</sup>

## NORTH CAROLINA MACULAR DYSTROPHY

### EPIDEMIOLOGY AND PATHOGENESIS

North Carolina macular dystrophy (NCMD) is an autosomal dominant, congenital, completely penetrant macular degeneration first reported in a large family in North Carolina, after which the disease was inappropriately named.<sup>90,91</sup> It is rare but is found worldwide in over 40 families (Small, personal communication). Several separate affected families have been discovered in the United States, Europe, Central America, and China. Linkage analysis of the large family from North Carolina mapped the diseased gene to chromosome 6q16.<sup>2,92</sup> This chromosome 6 locus is now known as *MCDR1* (macular dystrophy, retinal subtype, first one mapped). Further genetic analysis reveals that families reported to have central areolar pigment epithelial dystrophy and central pigment and choroidal degeneration are branches of the same family from North Carolina.<sup>93</sup> Indeed, reports of various branches of the single family from North Carolina have resulted in this one disease being given seven different names during the last 25 years. Again, "lumping" diseases together has proven to be more accurate than "splitting." Although there are no accurate names properly describing the anatomic features or pathology, small macular dystrophy could be the best name for this enigmatic disease.<sup>94</sup>

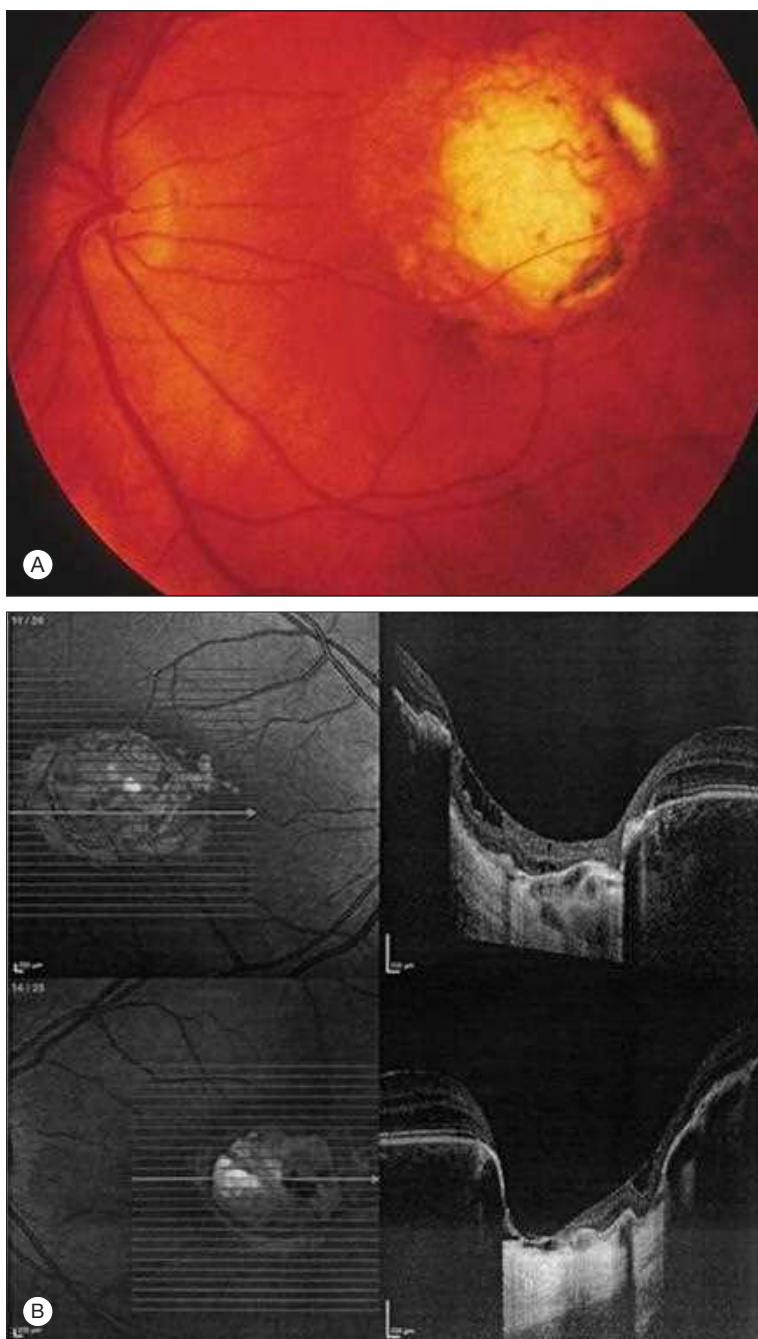
### OCULAR MANIFESTATIONS AND DIAGNOSIS

The most striking features are the huge phenotypic variability within a family and the relatively good vision despite some with severe-appearing macular malformations. About one-third of affected individuals have a macular coloboma-like excavation resembling toxoplasmosis (Fig. 6.15.10A). There is clearly a well-demarcated area of absence of the RPE and choriocapillaris, typically with surrounding subretinal fibrosis—more so on the sharply shelving temporal edge than the more smoothly sloping nasal edge. The patient's fixation is typically on the nasal edge of the lesion rather than in the central area, where the fovea would be expected. This can be quite dramatic appearing on spectral-domain optical coherence tomography (SD-OCT) (Fig. 6.15.10B).

The highly variable expressivity occurs without any particular pattern. Genetic "anticipation" has been evaluated in these families and none was found (Small, personal communication). Some individuals express from birth only a few drusen centrally, whereas others have confluent drusen. Occasionally or rarely a patient will develop choroidal neovascularization with a disciform scar. These are the only patients who experience progressive moderate to severe vision loss and usually only in one eye. CNVs can also occur typically along the temporal edge of the "coloboma." Phenocopies of this disease include drusen of age-related macular degeneration, Best macular dystrophy, and toxoplasmosis. To clinically diagnose NCMD it is imperative to examine other family members in order to appreciate the full spectrum of the disease. Small and his coworkers have believed since 1992 that the *MCDR1* gene is involved in embryonic macular development. This would help explain why the vision is relatively good considering the severe-appearing lesions present in some. The ERG and EOG are normal, as is color vision. As expected, multifocal ERG recordings revealed significant amplitude reductions in the central retina.<sup>95</sup>

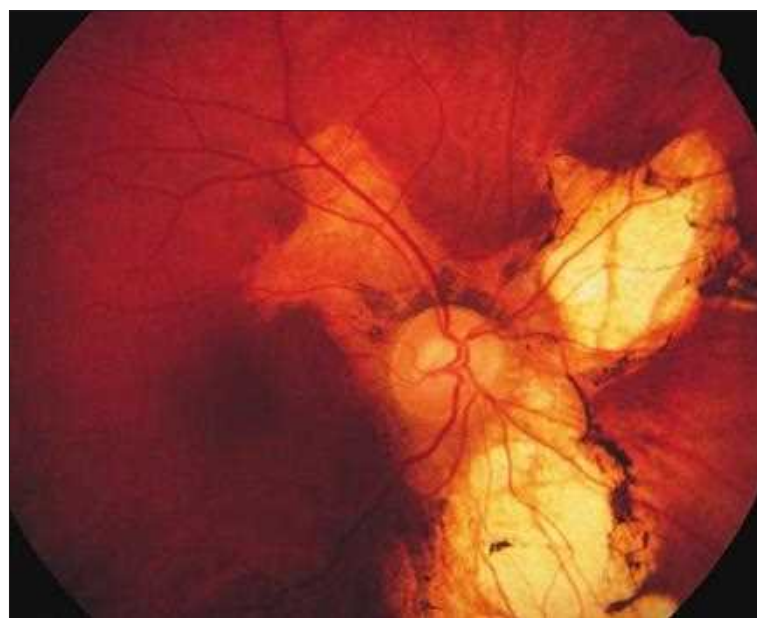
Small and colleagues initially mapped the *MCDR1* locus with the single large family from North Carolina to chromosome 6q12 in 1992.<sup>2</sup> His lab then ascertained additional families from around the world through personal examinations and many collaborators. Eventual linkage analysis of his entire database yielded a LOD score greater than 40, which is perhaps the highest LOD score ever recorded in human genetics.<sup>96-98</sup> Once NEXGEN sequencing became available, Small proceeded with targeted genomic sequencing of the 880 kilobases (Kb) region without any external funding. Overwhelmed with the bioinformatics, Stone and colleagues offered assistance to Small, and shortly thereafter the first mutations were found. Three point mutations were found 12 Kb into a noncoding region in a DNAS1 hypersensitivity binding site that affects regulation of expression





**Fig. 6.15.10 North Carolina Macular Dystrophy.** (A) Macular coloboma-like grade 3 maldevelopment of the macula in an 18-year-old woman with visual acuity of 20/40 (6/12). (B) Optical coherence tomography.

of the neighboring gene, the retinal transcription factor *PRDM13*.<sup>99</sup> A large duplication in the Belizean family also involves *PRDM13*. *PRDM13* is expressed in the fetal retina and dorsal spinal columns and is not expressed in adult tissues. This supports Small's original hypothesis that NCMD is due to a gene involved in the development of the primate macula (only primates have maculae). Because of the duplication, it would appear that the malformation of the maculae (and malformation includes the presence of drusen) is due to overexpression of *PRDM13*. Bowne and colleagues subsequently and independently found another large but different duplication involving *PRDM13* supporting Small and colleagues' earlier work.<sup>99,100</sup> Rosenberg and colleagues had previously mapped a Danish family with the NMCD phenotype to a chromosome 5 locus as MCDR3 showing the presence of some genetic heterogeneity.<sup>94</sup> Using this information from MCDR1, Small with Stone's group found a large duplication involving the *IRX1* gene, which is felt to be a causative mutation. Small and colleagues have a total of 40 families worldwide being studied, making "North Carolina macular dystrophy" a gross misnomer (Small personal communication).<sup>90</sup>



**Fig. 6.15.11 Atrophie Areata in a 37-year-old Man.** (Courtesy Fridbert Jonasson, University Department of Ophthalmology, Landspítalinn, Iceland.)

## PATHOLOGY

Small et al.<sup>101</sup> have studied the histopathology of a mildly affected family member who had bilaterally symmetrical confluent drusen in the central macula. Light microscopy demonstrated a discrete macular lesion characterized by focal absence of photoreceptor cells and RPE. Bruch's membrane was attenuated in the center of the lesion and associated with marked atrophy of the choriocapillaris. Adjacent to the central lesion, some lipofuscin was identified in the RPE.

## TREATMENT, COURSE, AND OUTCOME

The onset is congenital and nonprogressive except for the development of CNVMs. Visual acuity is usually much better than the appearance of the macula suggests. In general, vision is in the 20/20–20/200 range, with a median of 20/60. The CNVMs have been treated successfully with anti-VEGF injections (personal communication B. Bakall).

## ATROPHIA AREATA

## EPIDEMIOLOGY AND PATHOGENESIS

Atrophie areata, also known as helicoid peripapillary choroidal degeneration or Sveinsson chorioretinal atrophy, is a rare autosomal dominant disease reported only in Icelandic families mapped to chromosome 11p15.<sup>102</sup> The encoded protein TEAD1 may alter the expression of genes responsible for the structural and metabolic support of photoreceptors.<sup>103</sup> This is in concordance with electrophysiological testing, which demonstrates normal photoreceptor function but abnormal RPE function.

## OCULAR MANIFESTATIONS AND DIAGNOSIS

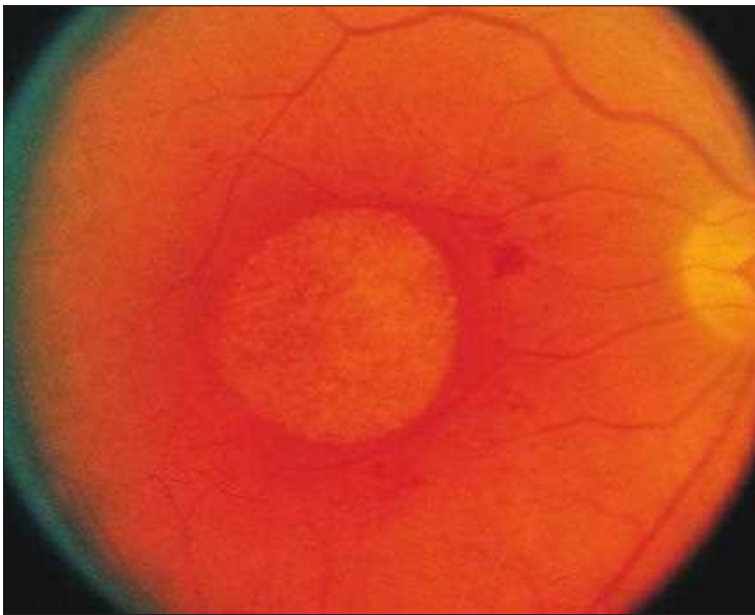
As with most inherited retinal diseases, atrophie areata is a bilateral, symmetrical maculopathy and has an early onset.<sup>102</sup> Marked choroidal atrophy radiates from the optic disc, with two or more ring-shaped extensions that do not follow the major retinal vessels (Fig. 6.15.11). The choroidal vessels drop out in areas of atrophy. This disorder often is associated with high myopic astigmatism. Anterior polar cataracts sometimes are seen in affected persons.

The fundus appearance is quite characteristic, particularly in advanced cases. Color vision usually is normal, and high myopia is a consistent feature.

## TREATMENT, COURSE, AND OUTCOME

Chorioretinal atrophy begins in childhood and is slowly progressive throughout life. Patients present with good visual acuity, but a gradual decline occurs in central vision as macular atrophy ensues.





**Fig. 6.15.12 Cone Degeneration.** (Reproduced with permission from Small KW, Gehrs K. Clinical study of a large family with autosomal dominant progressive cone degeneration. *Am J Ophthalmol* 1996;121:1–12.)

## CONE DYSTROPHY

### EPIDEMIOLOGY AND PATHOGENESIS

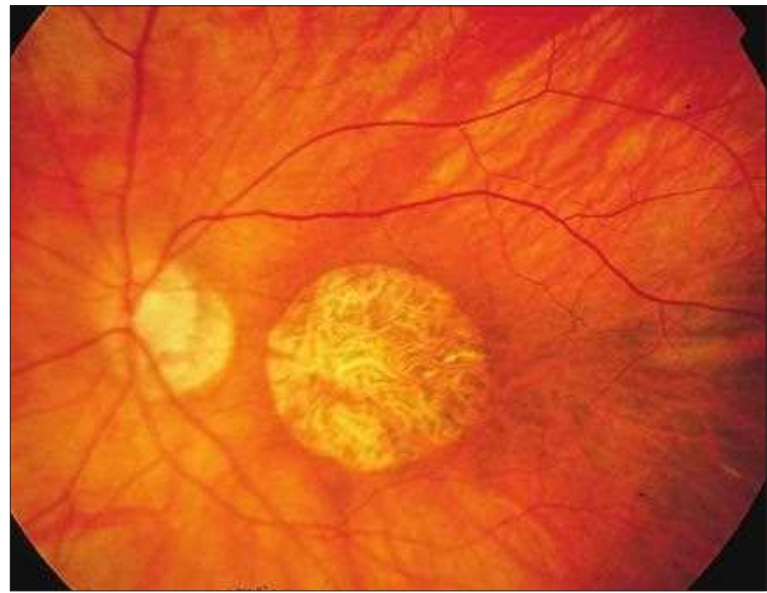
Cone dystrophies are characterized by a specific degeneration of the cone photoreceptor cells. Most genetic causes of cone dystrophies are autosomal dominant, but all types of genetic inheritance have been reported. Small et al. reported a family from Tennessee with autosomal dominant cone degeneration that mapped to chromosome 17p12–13.<sup>104,105</sup> Although this was designated CORD 5 (cone–rod dystrophy 5, although it truly is a predominantly cone dystrophy with little to no rod impairment), the other families reported in the UK with CORD 6 have actually the same disease with similar mutations. In reality, CORD 6 is CORD 5, another misnomer in the literature. The causative gene in this family (and others) was found to be *GUCY2D*. In addition, cone dystrophies have been found to also be caused by mutations in the cone–rod homeobox (*CRX*) as well as the *ABCR* gene.<sup>10</sup>

### OCULAR MANIFESTATIONS AND DIAGNOSIS

Cone dystrophy patients usually present with progressive central acuity loss, color vision disturbances, and photophobia.<sup>106</sup> Patients have retinal changes ranging from subtle, diffuse macular pigment mottling only to focal atrophic macular changes often in a “bullseye” pattern (Fig. 6.15.12).<sup>106</sup> The ERG is essential for making the diagnosis, as it reveals selective diminution of the photopic “B” wave and decreased amplitudes of the 30 Hz flicker. The dark-adapted rod responses, on the other hand, are usually normal or mildly attenuated.<sup>106</sup> Multifocal ERG testing can also be helpful, as it will show low amplitudes or an abnormal foveal-to-parafoveal ratio caused by cone photoreceptors dysfunction. Color vision testing is helpful, which usually reveals dyschromatopsia. Visual field testing reveals full peripheral fields with bilateral central scotomata.

### TREATMENT, COURSE, AND OUTCOME

Cone dystrophies usually present during the first or second decades of life. Not unlike other macular dystrophies, cone dystrophy patients tend to have color vision loss early in the course of the disease. Visual acuity can range from 20/20 to hand movements. Patients experience progressive worsening of their disease with age. To date, this condition remains without a treatment, but gene therapy may be appropriate for these patients.



**Fig. 6.15.13 Central Areolar Choroidal Dystrophy.** (Courtesy Giuliani Silvestri.)

## CENTRAL AREOLAR CHOROIDAL DYSTROPHY

### EPIDEMIOLOGY AND PATHOGENESIS

Central areolar choroidal dystrophy (CACD) is a rare autosomal dominant macular disease mapped to chromosome 17p13.<sup>102,104</sup> Mutations to various loci in this region have been implicated in central areolar dystrophy.<sup>107</sup> Interestingly, several other inherited retinal diseases have been mapped to chromosome 17p, including autosomal dominant cone dystrophy, Leber’s congenital amaurosis, and ADRP. A mutation in the peripherin gene on chromosome 6 also has been associated with central areolar choroidal dystrophy, linking it with the chromosome 6 retinopathies also.<sup>16,107,108</sup> In addition, mutation in guanylate cyclase 2D gene (*GUCY2D*; MIM 600179) and also *GUCA1A* have been implicated in CACD.<sup>109,110</sup> This disease appears to be a primary dystrophy of either the choroidal vessels or the RPE, with secondary involvement of the choriocapillaris.

### OCULAR MANIFESTATIONS AND DIAGNOSIS

The disease is characterized by late onset of the phenotypic manifestations (midlife) with progression occurring over a 3- to 10-year period. It shows variable expressivity among family members.<sup>111</sup> Fundus examination early in the course of the disease reveals nonspecific granular hyperpigmentation of the fovea. Gradually, a sharply demarcated area of RPE atrophy with underlying loss of choriocapillaris leaves intermediate and large choroidal vessels visible (Fig. 6.15.13). As the disease progresses, the macular atrophic area expands in a slow, centrifugal manner. This can appear clinically similar to CORD 5 findings.

FA early in the course of the disease shows background hyperfluorescence from RPE atrophy. When the choriocapillaris becomes lost, this hyperfluorescence disappears, and the intermediate and large choroidal vessels are outlined sharply. The margins of the lesion show hyperfluorescence because of leakage from choriocapillaris at the edges. The ERG and EOG findings range from normal to severely abnormal.<sup>111</sup> Multifocal ERG recordings show significant macular dysfunction that extends beyond the atrophic areas seen clinically.<sup>112,113</sup>

### PATHOLOGY

Histological analysis of the affected area shows an atrophic, fibrosed area, with loss of RPE as well as photoreceptor cells and the underlying choriocapillaris.<sup>114</sup> The rest of the retina and choroid are normal outside of the atrophic zone.

### TREATMENT, COURSE, AND OUTCOME

Patients begin to complain of symptoms of central vision loss during the third to fourth decades of life. Progressive atrophy leads to severe visual dysfunction and absolute scotoma formation by the seventh decade. Some patients, however, may exhibit macular sparing with 20/20 visual acuity.

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# Choroidal Dystrophies

Sandeep Grover, Gerald A. Fishman

# 6.16

## Definitions:

- Choroideremia is a progressive, bilateral, diffuse chorioretinal dystrophy with an X-linked recessive mode of inheritance.
- Gyrate atrophy of the choroid and retina is a progressive, bilateral, diffuse chorioretinal dystrophy with an autosomal recessive mode of inheritance.

## Key Features

### Choroideremia

- Involvement of the choroid, retinal pigment epithelium, and retinal photoreceptors.
- Nyctalopia.
- Midperipheral and, subsequently, far peripheral visual field loss.

### Gyrate Atrophy

- Chorioretinal lesions of atrophic appearance with scalloped margins.
- Nyctalopia.
- Midperipheral and peripheral visual field loss.
- Frequently, they develop cataracts.

## Associated Features

- Choroideremia: often initial macular sparing; characteristic findings in female carriers.
- Gyrate atrophy: systemic hyperornithinemia associated with an ornithine aminotransferase enzyme defect.

## INTRODUCTION

Choroidal dystrophies are a group of progressive, hereditary disorders that are characterized by clinically apparent retinal pigment epithelial (RPE) and choroidal atrophy. Krill and Archer<sup>1</sup> classified such dystrophies into two groups, one with a more regional involvement and the other with a diffuse involvement of the fundus. The regional dystrophies are subclassified further based on the initial or predominant site of the degenerative changes (macular, central areolar, peripapillary, or a combination) and the severity of involvement (involving only the choriocapillaris or, in addition, the larger choroidal vessels). Choroideremia and gyrate atrophy of the choroid and retina represent diffuse forms of choroidal dystrophies. Progressive bifocal chorioretinal atrophy<sup>2</sup> phenotypically shows a regional involvement, but there is a diffuse reduction of retinal function.

## CHOROIDEREMIA

## INTRODUCTION

Choroideremia is an X-linked recessive, bilateral, progressive chorioretinal dystrophy that is characterized by a marked loss of vision at night and progressive loss of peripheral visual fields.

## EPIDEMIOLOGY AND PATHOGENESIS

The exact pathogenesis of the degenerative changes observed in patients and the cells primarily affected in choroideremia are yet to be defined with certainty. In the past, it was thought that this disease was caused primarily by degeneration of RPE cells, the choroid, or both, with photoreceptors degenerating secondarily. It has been suggested that the primary defect

may be in the rod photoreceptor cells of the retina.<sup>3</sup> It has also been proposed that there may be independent degeneration of RPE cells and photoreceptor cells, based on a conditional knockout mouse model.<sup>4</sup> A recent multimodal imaging of photoreceptor structure in choroideremia showed remnants of cone inner segments within “outer retinal tubulations” (ORTs) and the continuity of the ORTs with the preserved retina, thereby suggesting degeneration of RPE earlier than the photoreceptors.<sup>5</sup>

The choroideremia gene (CHM) was isolated by positional cloning techniques and localized to the long arm of the X chromosome (Xq21).<sup>6,7</sup> The CHM gene encodes the Rab escort protein-1 (REP-1)<sup>8</sup> of Rab geranylgeranyl transferase, a two-component enzyme (components REP-1 and REP-2) that modifies Rab proteins. Rab proteins are low-molecular-weight guanosine triphosphatases that regulate intracellular vesicular transport. For Rab proteins to bind to membranes, they undergo lipid modification with the addition of 20 carbon units to the carboxy terminal of the protein, a process known as geranylgeranylation. Of interest, the CHM gene is expressed not only in ocular tissues but also in various cells of nonocular origin. However, CHM gene dysfunction affects only the retina. The proteins REP-1 and REP-2 are 75% identical, and their functions are mutually redundant. The functioning of the majority of the cells in the body that have a REP-1 deficiency can be taken over by REP-2 and, hence, can function adequately. However, the retina has a major Rab protein, Rab 27, which is prenylated more efficiently by REP-1 than REP-2.<sup>9</sup> Since all mutations known so far in the CHM gene create stop codons and, hence, an absence of the gene product REP-1, there is progressive chorioretinal degeneration in patients with choroideremia.<sup>10</sup>

## OCULAR MANIFESTATIONS

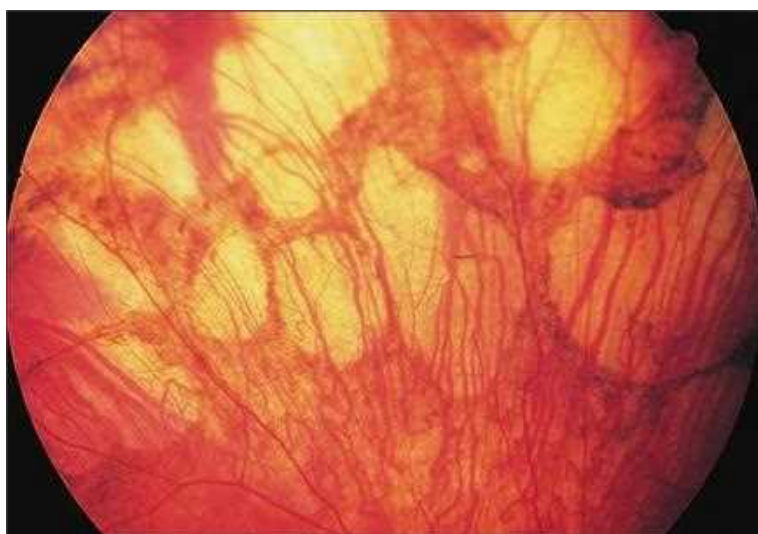
A majority of patients with choroideremia present with progressive impairment of night vision. It usually begins in the first decade of life, although the onset may be delayed. Some patients can, however, have midperipheral visual field loss. The clinical features, including the rate of progression, can show both interfamilial and intrafamilial variability.

The ocular findings in the anterior segment are unremarkable. Posterior subcapsular changes in the lens develop more frequently than in the general population.<sup>11</sup> Even those patients who do not show clinical cataract changes may have subclinical lens changes as demonstrated indirectly by increased light scatter.<sup>12</sup>

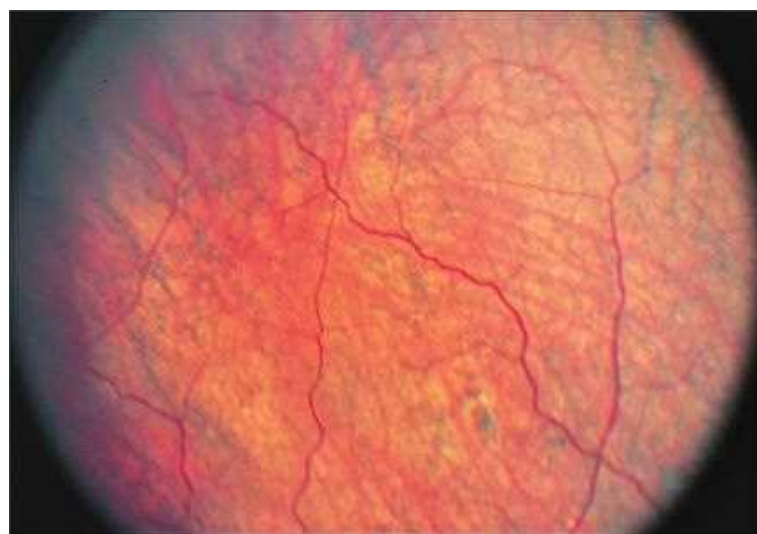
Initial fundus changes most often begin in the midperipheral retina in the form of patches of pigment mottling and hypopigmentation. Nummular areas of patchy RPE and choroidal atrophy can develop subsequently in the midperipheral retina (Fig. 6.16.1). In the intermediate stages of the disease, the atrophy of the RPE and choriocapillaris becomes more diffuse, while the intermediate and the larger choroidal vessels remain relatively more preserved (Fig. 6.16.2). As the disease progresses, both the intermediate- and large-sized choroidal vessels become more atrophic, which exposes the underlying sclera. The macula is often initially relatively spared and is visible as a remaining island of choriocapillaris in the midst of surrounding white sclera (Fig. 6.16.3). The macula can be relatively well preserved even in the late stages of the disease. Only in the more advanced stages do the retinal arterioles become attenuated, while the optic disc does not tend to become as pale or waxy pale as occurs in patients with retinitis pigmentosa.

The loss of visual field often corresponds to the clinically discernible areas of chorioretinal atrophy. Visual field examination initially shows a slightly restricted peripheral field, midperipheral scotomas, or both. With time, these scotomas coalesce to form a ring scotoma.<sup>13</sup> The fields progressively constrict and finally leave a small central island. The visual acuity often is not notably affected and remains favorable until the seventh decade of life or even later.<sup>14</sup> According to another study, there is

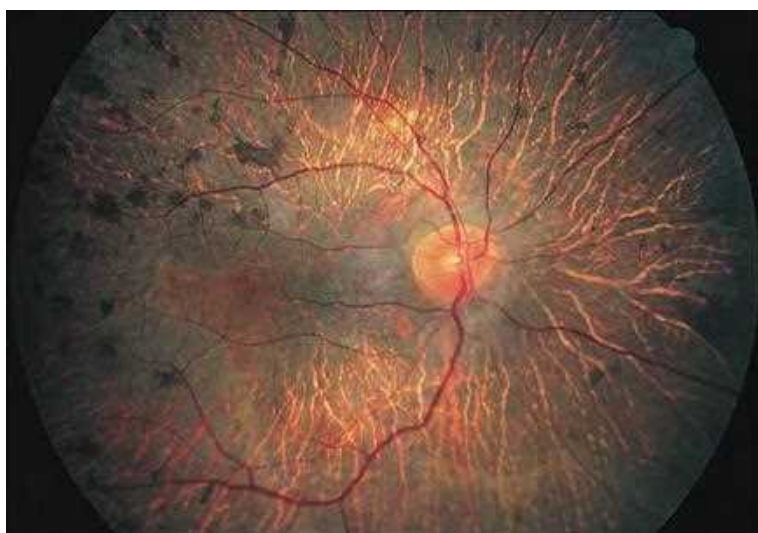




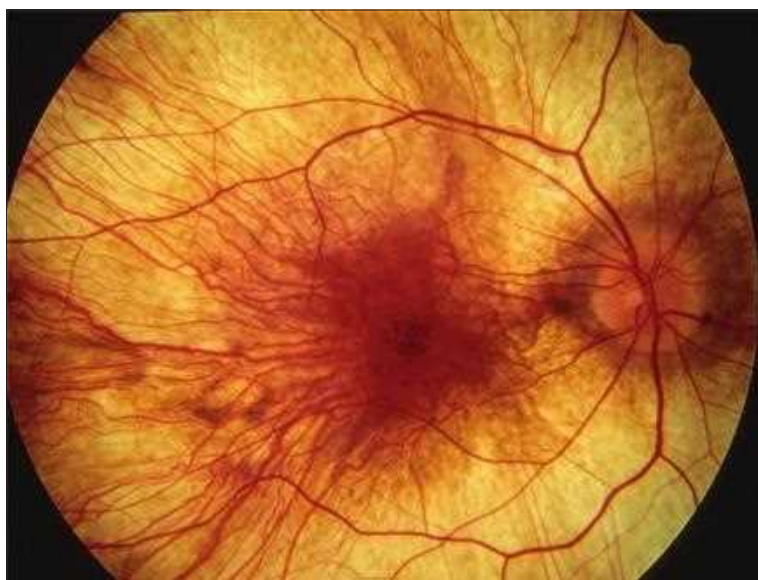
**Fig. 6.16.1 Fundus Changes Found in Choroideremia.** Nummular areas of retinal pigment epithelial and choroidal atrophy in the midperipheral retina are shown.



**Fig. 6.16.4 Peripheral Fundus Changes in a Carrier of Choroideremia.** Note the radial bands of hyperpigmentation and some pigment clumping.



**Fig. 6.16.2 Fundus Changes of the Right Eye in a Patient With an Intermediate Stage of Choroideremia.** Note the diffuse changes of the retinal pigment epithelium and prominent choroidal vessels.



**Fig. 6.16.3 Fundus Changes in the Right Eye in a Patient With Late-Stage Choroideremia.**

a significant decline in visual acuity after age 50 years.<sup>15</sup> Visual acuity may be decreased because of a degenerative maculopathy or the development of posterior subcapsular cataracts. A careful refraction is prudent, because such patients may have various degrees of myopia.

The female carriers are typically asymptomatic. There is a wide spectrum of clinical fundus appearance, which ranges from a fundus of normal appearance to a full-blown picture of choroideremia, as in an affected male. Characteristically, however, pigmentary changes in the fundus, described as *moth-eaten* in appearance, occur predominantly in the midperipheral retina.<sup>16</sup> Areas of hyperpigmentation may be present as radial bands that extend from the midperiphery toward the ora serrata (Fig. 6.16.4). The visual acuity may be decreased and visual fields reduced, depending on the extent of involvement of the photoreceptors. Usually these defects appear late, if at all, and are often mild. Most carriers do not show any electroretinographic amplitude reductions, although those who have more advanced fundus degenerative changes can show appreciable amplitude reductions.

## DIAGNOSIS AND ANCILLARY TESTING

The clinical fundus features are usually diagnostic in the intermediate and late stages of the disease. Good central visual acuity and slowly progressive visual field changes aid in the diagnosis. Both the electroretinogram and electro-oculogram can show marked impairment.<sup>16</sup> The electroretinogram may rarely be normal in amplitude initially (Fig. 6.16.5) or occasionally show only mild impairment in the very early stages. However, with the progression of the disease, there is progressive loss of retinal function (Fig. 6.16.6). The fundus findings initially may be normal or only minimally abnormal (Fig. 6.16.7). Once fundus changes become discernible, however, the electroretinogram is affected, usually notably. It often shows markedly reduced isolated rod responses with prolongation of rod b-wave implicit times in affected men. However, the isolated cone responses are initially either normal or moderately reduced in amplitude, with a delayed b-wave implicit time. The electro-oculogram is markedly abnormal in men with choroideremia<sup>1</sup>; the degree of electro-oculogram abnormality in carriers, although usually normal, varies.

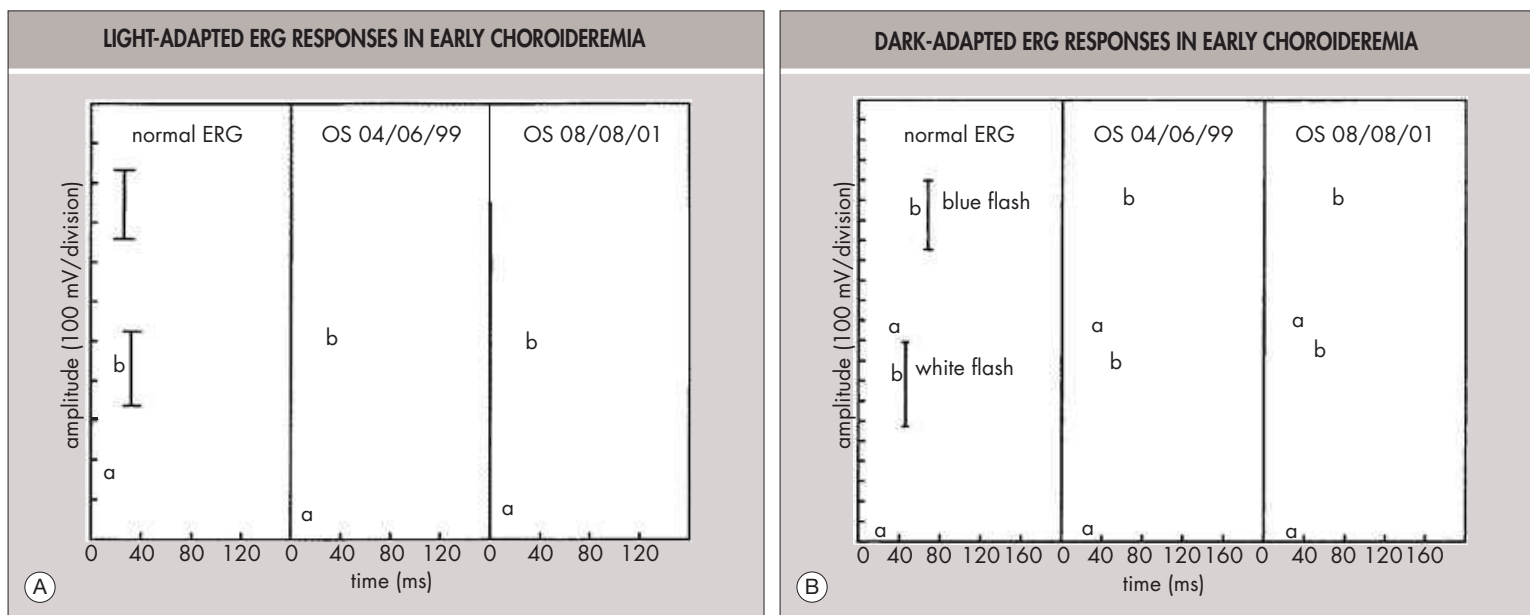
Dark adaptation testing often shows elevated thresholds. In the early stages, only the rod portion of the curve is affected, while cone thresholds subsequently also become elevated.

Spectral-domain optical coherence tomography (SD-OCT) can show cystic macular lesions (Fig. 6.16.8A)<sup>17</sup> and peripapillary nerve fiber layer defects (Fig. 6.16.9),<sup>18</sup> including thickening and thinning in various areas in some patients with choroideremia.

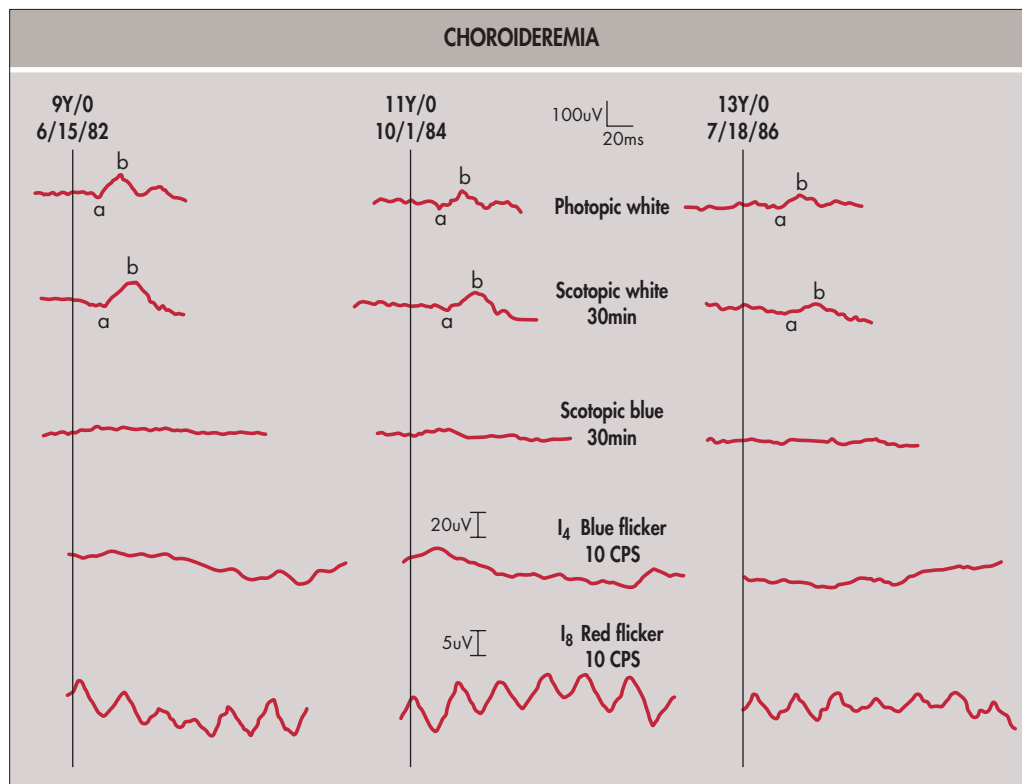
Fluorescein angiography is not useful in the diagnosis of choroideremia. It can, however, define the extent of choriocapillaris atrophy more accurately than ophthalmoscopy. Fluorescein angiography also may be superior to ophthalmoscopy in defining the extent of degenerative changes of the RPE, evident from hyperfluorescence seen on the angiogram.

The clinical diagnosis of choroideremia in the majority of male patients can be confirmed by an immunoblot analysis with anti-REP-1 antibody.<sup>19</sup>





**Fig. 6.16.5** Electoretinographic recordings from a male patient with choroideremia at ages 9 and 11 years showing normal light-adapted flicker and single flash (A) and dark-adapted rod-isolated and maximal (B) responses.



**Fig. 6.16.6** Electoretinographic Recordings From a Male Patient With Choroideremia (as Shown in Fig. 6.16.3) Showing Progressive Decline in Light- and Dark-Adapted Responses.

The value of this test is based on the knowledge that all genetic mutations identified so far create stop codons that result in the absence of REP-1. The predictive value of this test, however, has not yet been established.<sup>19</sup> Also, female carriers cannot be identified with this technique, because their REP-1 expression is not totally absent.

## DIFFERENTIAL DIAGNOSIS

The differential diagnosis for choroideremia includes other night-blinding disorders, particularly retinitis pigmentosa. Fundus features of a pale optic disc, attenuated retinal arterioles, typical bone-spicule-like pigmentation, and a higher prevalence of posterior subcapsular cataracts associated with retinitis pigmentosa usually helps differentiate the latter disease from choroideremia. Nevertheless, some patients who have the X-linked form of retinitis pigmentosa, who can show higher degrees of myopia and prominent choroidal vessels, may have a phenotypic similarity to patients who have choroideremia. However, patients who have X-linked retinitis pigmentosa

have a reduction in central visual acuity early in the course of their disease, while patients with choroideremia do not characteristically manifest bone-spicule-like pigment clumping.

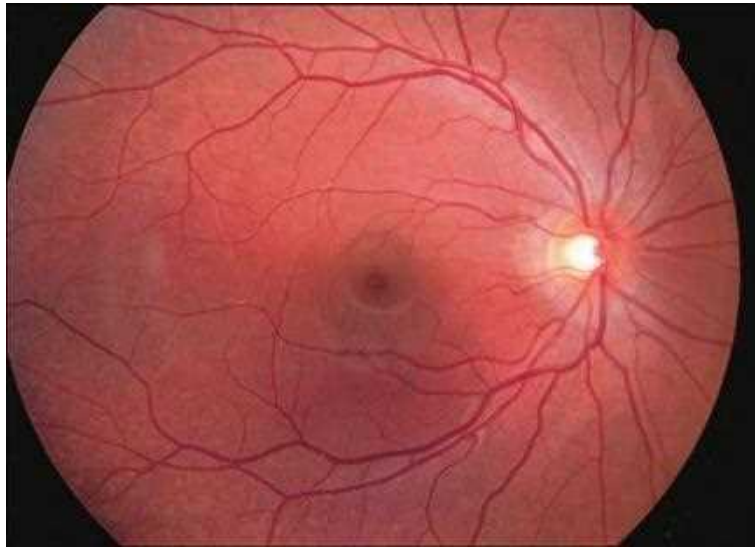
Patients who have ocular albinism may show some degree of phenotypic similarity to those with choroideremia; however, absence of nyctalopia, presence of nystagmus, iris transillumination defects, and normal electoretinographic amplitudes help to differentiate these two disorders.

Features distinguishing gyrate atrophy of the choroid and retina from choroideremia include autosomal recessive inheritance, well-demarcated, scalloped areas of chorioretinal atrophy, and association of hyperornithinemia with the former. It sometimes may be difficult to differentiate end-stage gyrate atrophy from an advanced case of choroideremia.

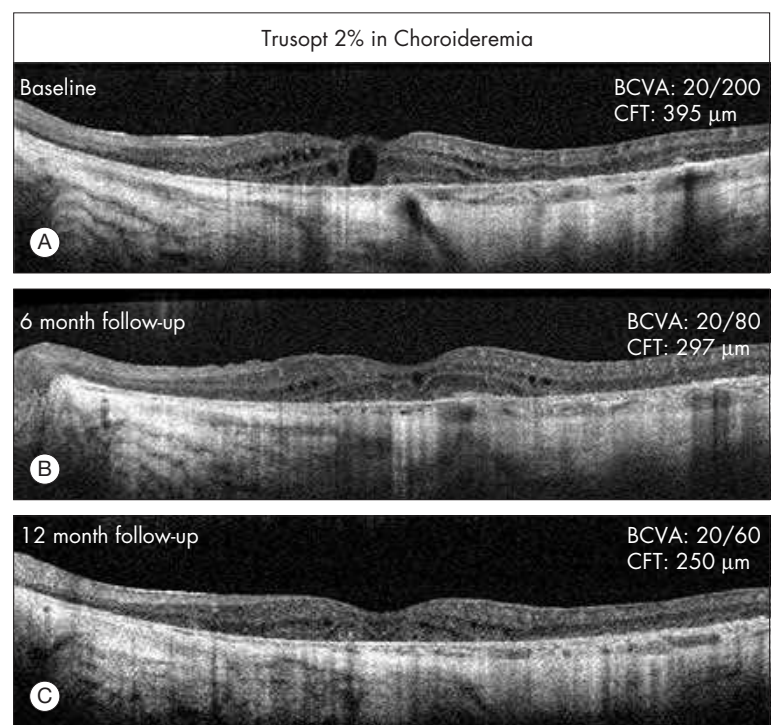
Generalized choroidal atrophy, which may show phenotypic similarities to an intermediate stage of choroideremia, is inherited in an autosomal dominant or occasionally autosomal recessive fashion. The various regional types of choroidal atrophies usually cause a milder visual dysfunction and, in general, can be differentiated easily without notable difficulty.

Another form of a diffuse choroidal dystrophy, progressive bifocal chorioretinal atrophy 2, is an autosomal dominant dystrophy. Its phenotype includes an involvement of the macula from birth, and hence nystagmus and reduced central visual acuity, a relatively higher incidence of retinal detachment and diffuse reduction of rod and cone responses on electroretinography. The phenotype of this disease has a distinctly different fundus appearance, time of onset, and genetics than are observed in choroideremia.

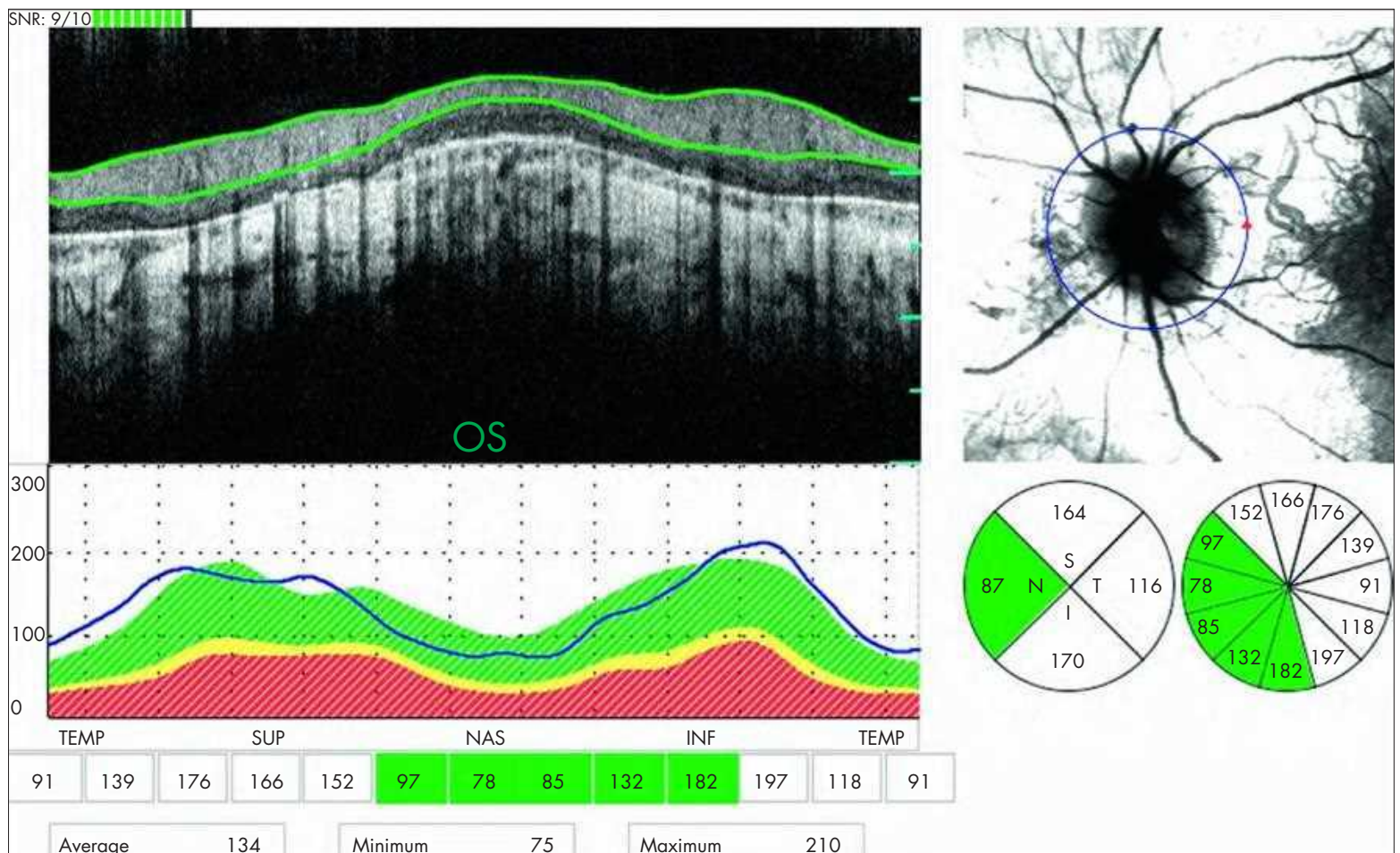
Myopic retinal degeneration sometimes may mimic choroideremia. However, the myopic degeneration usually is not as diffuse as the lesions



**Fig 6.16.7** Fundus Photograph of the Right Eye of the Same Patient as in Fig. 6.16.5 at Age 11 Years, Showing Normal Optic Discs and Retinal Vessels. Also shown is a mild to moderate degree of pigment mottling anterior to the vascular arcades.



**Fig. 6.16.8** Serial images of spectral-domain optical coherence tomography from a patient with choroideremia, showing cystic macular changes and increased macular thickness (A). The other two panels show resolution of cystic changes and decrease in macular thickness 6 months (B) and 12 months (C) after initiation of treatment with topical 2% dorzolamide ophthalmic solution.



**Fig. 6.16.9** Spectral-Domain Optical Coherence Tomography Image Showing the Retinal Nerve Fiber Layer (RNFL) Thickness in a Patient With Choroideremia. It shows some segments (green) where the RNFL thickness is within the normal range and some areas (white) where the RNFL thickness is more than normal.



of choroideremia, and patients with myopic degeneration do not characteristically complain of night blindness.

## SYSTEMIC ASSOCIATIONS

Isolated reports show the association of a choroideremia-like phenotype with mental deficiency, acrokeratosis, anhidrosis, and skeletal deformity; uveal coloboma; obesity and congenital deafness; congenital deafness and mental retardation; hypopituitarism; distal motor neuropathy; and nystagmus, myopia, dental deformities, optic nerve head drusen, and microblepharia.

## PATHOLOGY

In male patients with choroideremia, light microscopy shows widespread chorioretinal atrophy, especially of the choriocapillaris, along with degenerative changes in the RPE, outer retinal layers (especially the photoreceptors), and larger choroidal vessels. A graded atrophy occurs: The equatorial area is most affected while the macular, peripapillary, and ora serrata areas are relatively spared. In the late stages, the far periphery and the central regions also may be severely involved. Retinal bipolar and ganglion cells appear normal. Electron microscopy shows extensive loss of photoreceptors and RPE, especially away from the macula. End-stage disease can show widespread neural retinal gliosis and atrophy.

A histopathological study<sup>3</sup> in an 88-year-old choroideremia carrier showed patchy areas of degeneration of photoreceptors and RPE cells that were not necessarily concordant. The choriocapillaris was normal except where corresponding to areas of severe retinal degeneration, as reported previously. However, immunofluorescence analysis localized the CHM gene product (REP-1 with a mouse monoclonal antibody) to the rod cytoplasm and amacrine cells but not in the cones.<sup>3</sup> This suggests that the primary site of the disease may be in the rods rather than RPE or choroid. This labeling, which was seen in small vesicles in the rod cytoplasm, is consistent with the association of REP-1 with intracellular vesicular transport.

## TREATMENT, COURSE, AND OUTCOME

A phase I/II clinical trial with subretinal injection of an adeno-associated viral gene vector encoding for REP1 (AAV-REP1), showed that this was safe and reported significant visual acuity improvement in 2 of 6 patients enrolled.<sup>20</sup> This improvement in visual acuity was sustained at 3.5 years.<sup>21</sup> Several other similar treatment trials are underway in the United States ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT02341807) Identifier: NCT02341807) and Canada ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT02077361) Identifier: NCT02077361).

The cystic macular changes associated with choroideremia, as seen by SD-OCT, can diminish or resolve when treated with topical 2% dorzolamide, leading to decreased macular thickness (see [Fig. 6.16.8B–C](#)) in at least some patients.<sup>22</sup>

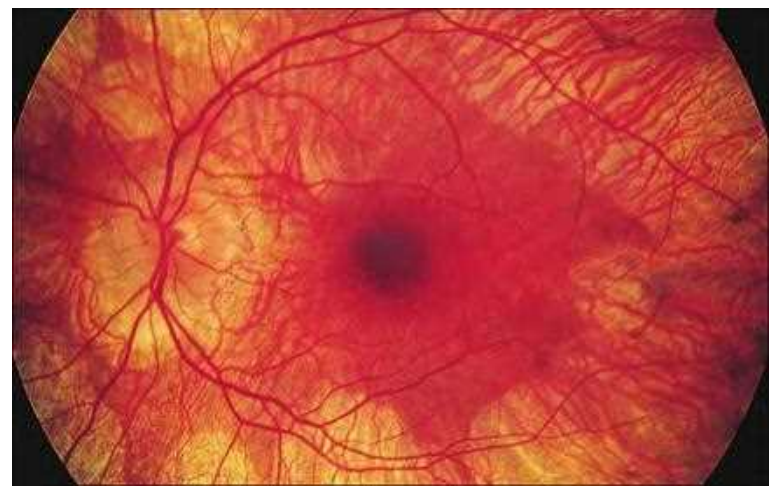
## GYRATE ATROPHY

### INTRODUCTION

Gyrate atrophy of the choroid and retina is a slowly progressive chorioretinal dystrophy, inherited in an autosomal recessive manner. It is characterized by discrete areas of chorioretinal atrophy in the midperipheral retina. These are sharply demarcated from the more posterior retina, which is initially of normal appearance. This dystrophy is associated with hyperornithinemia to levels 10–15 times above normal, shown to be caused by a deficiency of ornithine ketoacid aminotransferase, also known as ornithine aminotransferase (OAT). This enzyme depends on a cofactor, pyridoxal phosphate (vitamin B<sub>6</sub>).

### EPIDEMIOLOGY AND PATHOGENESIS

Simell and Takki<sup>23</sup> in 1973 were the first to report the finding of hyperornithinemia with gyrate atrophy. Sengers et al.<sup>24</sup> first reported a deficiency of the mitochondrial matrix enzyme OAT in patients who have gyrate atrophy. Ornithine, a nonessential amino acid, is an intermediate compound in the formation of urea. The major pathway for utilization of ornithine is by enzymatic conversion into glutamic- $\gamma$ -semialdehyde by OAT, a vitamin B<sub>6</sub>-dependent enzyme, and subsequently to proline. OAT has been found with high activity in the retina, liver, and kidney.



**Fig. 6.16.10 Fundus Changes in the Left Eye of a Patient With an Intermediate Stage of Gyrate Atrophy of the Choroid and Retina.** Note the well-demarcated, scalloped areas of atrophy.

Since OAT is dependent on cofactor B<sub>6</sub>, treatment with oral vitamin B<sub>6</sub> has been tried. Patients who have gyrate atrophy are categorized into two groups, depending on a lowering of plasma ornithine levels in response to vitamin B<sub>6</sub>. The vitamin B<sub>6</sub>-responsive patients, although considerably fewer in number than nonresponders, appear to have a milder disease and better visual function than the nonresponsive group.

The human OAT gene has been cloned and mapped to 10q26.<sup>25</sup> An OAT-deficient mouse model (Oat<sup>-/-</sup>) has been developed by gene targeting that has serum ornithine levels 10–15 times the normal, as in patients with gyrate atrophy.<sup>26</sup> This has improved the potential for a better understanding of the pathogenesis and possible therapeutic outcome of this disease.

## OCULAR MANIFESTATIONS

Patients with gyrate atrophy of the choroid and retina develop nyctalopia during the second to third decade of life. Initially it is mild to moderate in severity and slowly progressive. The earliest appearance may occur in the form of a restriction in peripheral field. Usually, visual acuity is preserved until a later stage. Visual acuity may be decreased from involvement of the macula by the disease itself or secondarily from cystoid macular edema or cataracts.

The fundus shows atrophy of the RPE and choriocapillaris during the earlier and intermediate stages, with sharply demarcated scalloped areas of atrophy ([Fig. 6.16.10](#)) and a tendency for pigment clumping to occur at the margins. The atrophy usually starts in the midperipheral and peripheral areas, often referred to as a *garland-shaped* fashion, and then progresses centrally as well as peripherally. Ultimately it involves the entire fundus, including the peripapillary area, with relative sparing of the macula. With progressive atrophy, the larger choroidal vessels are also involved. The optic disc and retinal arterioles usually are normal until the later stages.<sup>16</sup> Posterior vitreous detachment and epiretinal membranes with cystoid macular edema have been observed with gyrate atrophy of the choroid and retina.<sup>27</sup>

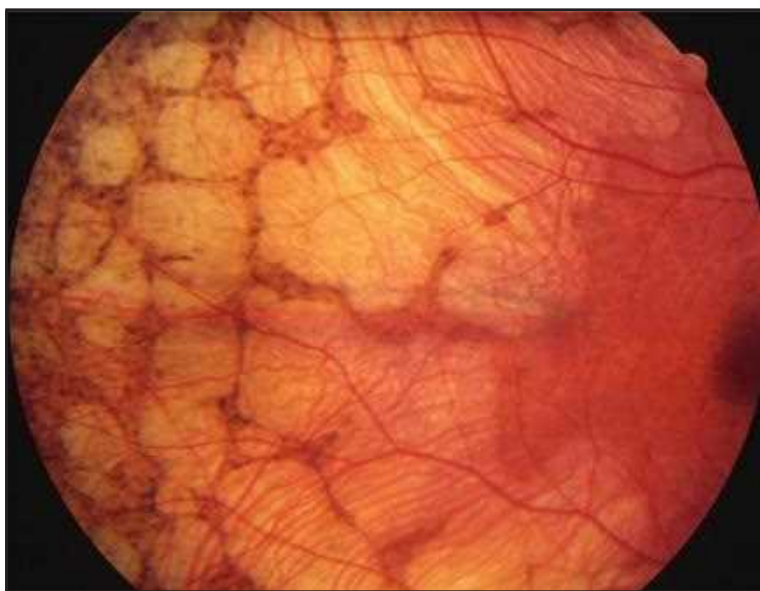
Visual field defects correspond to the atrophic areas in the choroid. The field loss begins in the midperipheral area as regionally dense scotomas, which eventually coalesce to form a ring scotoma. Progressive field loss ultimately leaves the patient with only small residual central fields.

Moderate-to-marked myopia is found in most patients, and lens changes are seen in almost all patients who have this disease.<sup>28</sup> Posterior sutural and subcapsular cataracts and, in isolated cases, anterior subcapsular plaque-like cataracts have been described.<sup>29</sup>

## DIAGNOSIS AND ANCILLARY TESTING

A history of night blindness and the typical fundus feature of scalloped areas of atrophy of the RPE and choroid are suggestive of the diagnosis. The electroretinogram is subnormal in the early stages, with marked reduction or nondetectable a- and b-wave responses in the later stages. The rod responses are affected more severely in the early stages, but later both rods and cones become affected.<sup>30</sup> Some patients also have a delayed cone implicit time response when tested using a 30-Hz flicker stimulus.<sup>30,31</sup> The electro-oculogram is affected mildly or not at all in very early stages of the disease.<sup>30</sup> However, with progression of the disease, electro-oculogram





**Fig. 6.16.11 Fundus Changes in the Right Eye of a Patient With Choroideremia.** The scalloped areas of atrophy resemble the lesions found in gyrate atrophy of choroid and retina.

light-peak to dark-trough ratios become markedly reduced. Overall, the electroretinographic responses, including oscillatory potentials and electro-oculogram light-peak to dark-trough ratios are better maintained in vitamin B<sub>6</sub>-responsive patients.<sup>30</sup> Dark adaptation curves may show a slightly prolonged cone-rod break time. In a vitamin B<sub>6</sub> responder or in early childhood, when the disease is not as severe, notably less extensive changes occur in dark adaptation function. However, in later stages of the disease, more marked elevation of cone, rod, or both thresholds develop.<sup>30</sup>

Fluorescein angiography, not unexpectedly, shows RPE transmission defects in the areas of chorioretinal atrophy. These areas of transmission defects often are larger than the clinically visible atrophic areas.

High ornithine levels are found in the urine, plasma, aqueous humor, and cerebrospinal fluid of these patients, often elevated to 10–20 times the normal levels. No evidence exists of any correlation of age or severity of involvement with the concentration of ornithine in plasma.<sup>32</sup> The 24-hour urine creatine excretion is normal.

## DIFFERENTIAL DIAGNOSIS

Gyrate atrophy of the choroid and retina is diagnosed by means of the typical fundus feature of scalloped areas of chorioretinal atrophy, an autosomal recessive inheritance, and hyperornithinemia. However, a gyrate atrophy-like fundus phenotype with a possible autosomal dominant inheritance pattern and normal plasma ornithine levels has also been described.<sup>33</sup> Gyrate atrophy also can show certain phenotypic similarities to choroideremia, myopic degeneration, and hereditary choroidal atrophy. It is mainly in its later stages that gyrate atrophy of the choroid and retina clinically may most resemble the retinal findings seen in choroideremia. However, in earlier stages of the disease, patients who have choroideremia may show scalloped or nummular areas of RPE and choroidal atrophy (Fig. 6.16.11). Typical retinitis pigmentosa usually can be differentiated from gyrate atrophy, but atypical retinitis pigmentosa sometimes may show certain phenotypic similarities. Bone-spicule pigment in the retina and attenuated retinal arterioles at an earlier stage aid in the diagnosis of retinitis pigmentosa. In gyrate atrophy, the pigment clumps usually are more dense and associated with the atrophic lesions.<sup>32</sup>

## SYSTEMIC ASSOCIATIONS

Electromyograms are abnormal in most tested patients, although only a few complain of slight muscle weakness. Electromyographic observations include a myopathic pattern of short-duration, low-amplitude motor unit action potentials, and increased polyphasic potentials. Muscle biopsy shows atrophic type 2 muscle fibers with tubular aggregates visible on electron microscopy. Abnormal electrocardiographic features may include a broad P-wave, prolonged QT interval, and flattening of the T-wave. Electroencephalograms also may be abnormal in some patients.<sup>31,32</sup> The

changes include an increase in slow activity, focal slow-wave abnormalities, and focal sharp waves.<sup>32</sup>

Various rare associations of a clinical picture that resembles gyrate atrophy have been seen with microcephaly, spinocerebellar ataxia, subluxation of the lens, pituitary dysfunction, and congenital muscular dystrophy. All of these associations were found with normal levels of plasma ornithine.

Reports exist of fine, sparse hair with patches of alopecia, skeletal muscle abnormalities, hepatic mitochondrial changes, and subnormal intelligence. Massive cystinuria and lysinuria with hypermetropia and diabetes also have been observed with gyrate-like atrophy. Chorioretinal lesions that resemble gyrate atrophy have been described in patients with normal plasma ornithine levels.<sup>33</sup>

## PATHOLOGY

Limited information on pathological findings is available on patients with gyrate atrophy.<sup>34</sup> The atrophic areas in the midperipheral retina show a marked atrophy of the choroidal vessels, including the choriocapillaris, RPE, and photoreceptors. The regions of clinically normal appearance in the posterior pole show focal areas of photoreceptor cell loss. The RPE at the posterior pole, however, has been reported to be hyperplastic. The photoreceptors show a shortening of their outer segments in the transitional area and are absent in the atrophic areas.<sup>34</sup> Histological examination of cataractous lenses shows markedly widened spaces at the posterior sutures, filled with denatured proteins.<sup>28</sup>

Electron microscopy shows abnormal mitochondria in the corneal endothelium, smooth muscle of the iris and ciliary body, and epithelium of the ciliary body.<sup>34</sup> Mitochondrial abnormalities include enlarged and dilated mitochondria with an electron-lucent matrix and disruption of cristae. Slight mitochondrial changes are observed in those photoreceptors that look normal structurally but are close to the area of chorioretinal atrophy. Dilated mitochondria are present mainly in rod ellipsoids but also in cone ellipsoids. The mitochondria in the RPE initially are normal.<sup>34</sup>

Histopathological studies in the OAT-deficient mouse model showed earliest changes in the RPE cells in the form of occasional necrotic cells with pale cytoplasm and swollen organelles at 2 months of age. By 7 months, these RPE cells were engorged with phagocytosed outer segment membranes. Photoreceptor cells, which were normal at 2 months of age, lost 33% of their total number and underwent 60% reduction of their outer segment length by 10 months.<sup>26</sup>

## TREATMENT, COURSE, AND OUTCOME

Since ornithine is produced from other amino acids, mainly arginine, some investigators advocate that patients be restricted to a rigid schedule of a low-protein diet, including near-total elimination of arginine, with supplementation of essential amino acids. Administration of high doses of vitamin B<sub>6</sub> has reduced the plasma ornithine level in a limited number of such patients. The results of these forms of treatment have been controversial. Short-term treatment has not shown any convincing evidence of improvement or arrest of the chorioretinal degeneration.<sup>35</sup> However, a long-term study of an arginine-restricted diet in six pairs of affected siblings was encouraging,<sup>36</sup> because it showed that a substantial reduction of ornithine levels occurred when such patients were fed an arginine-restricted diet over a period of 5–7 years.<sup>37</sup> Two of these six sibling pairs, when followed for 16–17 years, showed that the younger sibling in each pair (who was started on this diet at an earlier age than the older sibling) showed a slower progression of chorioretinal lesions and, to a lesser extent, the progressive loss of retinal function. A long-term study in adults also suggested that as long as the plasma ornithine levels can be maintained below an average of 5.29–6.61 mg/dL (about six times the normal range), it may slow the progression of disease as measured by sequential electroretinography.<sup>38</sup> These studies suggest that an arginine-restricted diet may cause a decrease in the progression of the chorioretinal degeneration. Consistent with these observations, correction of ornithine accumulation by an arginine-restricted diet in the Oat<sup>-/-</sup> mouse model entirely prevented retinal degeneration.<sup>39</sup> This suggests that it may not be necessary to restore the activity of the OAT enzyme to metabolize the accumulating ornithine for treating this condition but instead to restrict arginine, the substrate from which ornithine is formed.<sup>39</sup>

As with other inherited retinal degenerative disorders, a better understanding of the pathogenic mechanisms by which the retinal cells degenerate in patients who have various choroidal dystrophies will ultimately lead to more effective treatment strategies in the future.

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# Hereditary Vitreoretinopathies

Alan E. Kimura

# 6.17

**Definition:** A group of rare inherited disorders with primary manifestations that include vitreous and retinal degeneration.

## Key Features

- Range of developmental abnormalities affecting the retinal vasculature through the Wnt signaling pathway in Norrie's disease and familial exudative vitreoretinopathy.
- Range of structural abnormalities in vitreous due to known mutations in Stickler's syndrome and in retina due to known mutations in X-linked recessive juvenile retinoschisis.

## Associated Features

- Autosomal dominant or X-linked recessive inheritance patterns.
- Loss of b-wave on electroretinography in X-linked recessive juvenile retinoschisis.
- Retinal pigment epithelial hyperplasia or atrophy in autosomal dominant vitreoretinopathy.
- Vitreoretinal traction and retinal detachment in Norrie's disease, familial exudative vitreoretinopathy, X-linked juvenile retinoschisis, and Stickler's syndrome.
- Epiphyseal dysplasia with premature degeneration of weight-bearing joints in Stickler's syndrome.
- Osteopenia or osteoporosis in autosomal dominant familial exudative vitreoretinopathy.
- Deafness and mental retardation in many cases of Norrie's disease.

## INTRODUCTION

The hereditary vitreoretinopathies are a diverse group of disorders. Research into these rare diseases continues to illuminate the breadth of mechanisms that can lead to blindness.

Stickler's syndrome is the result of abnormalities in a key structural building block of the connective tissue of the eye, collagen IIa, as well as collagen IXa and collagen XIa. X-linked, recessive, juvenile retinoschisis features abnormalities in the protein retinoschisin, which is believed to play an integral role in cell–cell adhesion within the retinal tissue. Autosomal dominant vitreoretinopathy (ADVIRC) is one of five diseases caused by mutations in the bestrophin gene. The phenotypic range of the bestrophinopathies includes Best disease and ADVIRC. Familial exudative vitreoretinopathy (FEVR) and Norrie's disease are now increasingly understood to share ligand–receptor elements in the important Wnt signaling pathway that is central to vascular development within the eye.

The exact role of the vitreous body in these diseases is unknown and has received little attention. Sebag<sup>1</sup> studied the anatomy of the vitreous body and its role in retinal diseases. Historically, vitreous was believed to play a passive role in the maintenance of the volume of the eye and surgically was avoided because of historically poor outcomes when disturbed. However, therapeutic vitrectomy with refinements in modern guillotine cutters became safe and accepted. As a result of considerable surgical experience, our management of vitreoretinal traction in hereditary retinal diseases is improving.

For each of the entities discussed in this chapter, a McKusick identification number is given. *McKusick's Mendelian Inheritance in Man* is a textbook that is a catalog of genes and genetic disorders in man.<sup>2</sup> The book and online version (*Online Mendelian Inheritance in Man*)<sup>3</sup> are good references for discussing genetic diseases among researchers and clinicians.

Recent advances in molecular biology continue to shed light not only on genes specific to the retina but increasingly reveal the complexity of larger developmental pathways and their exquisite regulation.

## STICKLER'S SYNDROME

### INTRODUCTION

Stickler's syndrome is also known as hereditary arthro-ophthalmopathy. Its inheritance pattern is autosomal dominant with complete penetrance but widely variable expressivity. It is a progressive disorder with a high risk of both ocular and systemic morbidity. The clinical spectrum of affected patients who have Stickler's syndrome includes high myopia, retinal detachments, and premature degenerative changes of cartilage.

### EPIDEMIOLOGY AND PATHOGENESIS

Stickler's syndrome is the most common autosomal dominantly inherited connective tissue disorder in the American Midwest.<sup>4</sup> The strongest case for the argument that vitreous body abnormalities cause retinal pathology arises primarily in Stickler's syndrome. It is hypothesized that the vitreous degeneration is a direct effect of mutations in a structural protein, procollagen II. A significant advance in our understanding of Stickler's syndrome (McKusick No. 120140) was the discovery of a type II collagen gene (COL2A1) mutation on the long arm of chromosome 12 in affected pedigrees. The gene product is a building block in various types of tissue. Structural alterations in the highly ordered vitreous body that arise from COL2A1 gene mutations cause vitreous degeneration and a high rate of complex retinal detachments.<sup>5,6</sup> Translational frameshift mutations are a common pathway by which disease is produced in patients with Stickler's syndrome.<sup>7</sup> The original family of the Wagner's syndrome (early onset cataracts, lattice degeneration of the retina, retinal detachment without involvement of nonocular tissues) is not linked to the COL2A1 gene and may be called Wagner's syndrome type I.

### OCULAR MANIFESTATIONS

High myopia (−8.00 to −18.00 diopters [D]) is the rule, as is an “optically empty” vitreous with abnormal membranes and strands. The optically empty vitreous refers to the presence of early onset, large lacunae of synergetic gel. It is best seen at the slit lamp through a widely dilated pupil. Dilated fundus examination typically reveals perivascular hyperpigmentary changes (Fig. 6.171). Retinal breaks are common and may lead to complicated retinal detachments (50% of eyes in patients with Stickler's syndrome). Giant retinal tears also may occur. Stickler's syndrome–associated retinal detachments are notoriously difficult to repair, due in part to the abnormal adherence between the vitreous and the retina.

Other ocular manifestations include presenile cataracts (in those patients less than 45 years of age, with peripheral, comma-shaped, cortical opacities). Open-angle glaucoma and ocular hypertension are additional problems found in patients with Stickler's syndrome.

### DIAGNOSIS AND ANCILLARY TESTING

Based on ocular findings alone, diagnostic precision can be difficult. Diagnostic criteria for Stickler's syndrome were published by the National Institutes of Health (NIH) in 2005, based on orofacial, ocular, auditory, and skeletal abnormalities with family history or molecular data (COL2A1 mutations).<sup>8</sup> Tests for the underlying gene defect are increasingly available to confirm a clinical diagnosis.



**Fig. 6.17.1 Fundus View of the Eye of a Patient With Stickler's Syndrome.** Note the radial perivascular pigmentary changes.

### BOX 6.17.1 Differential Diagnosis of Hereditary Vitreoretinopathies

#### Stickler's Syndrome

- Wagner's syndrome type I
- Erosive vitreoretinopathy<sup>9,10</sup>
- High myopia (degenerative type)
- Goldmann–Favre disease
- Retinitis pigmentosa

#### X-Linked Juvenile Retinoschisis

- Cystoid macular edema
- Rhegmatogenous retinal detachment
- Stargardt disease (atrophic macula)
- Goldmann–Favre disease
- Senile retinoschisis
- Retinitis pigmentosa

#### Autosomal Dominant Vitreoretinochoroidopathy

- Autosomal dominant neovascular inflammatory vitreoretinopathy<sup>11,12</sup>
- Retinitis pigmentosa
- Paving stone degeneration

#### Familial Exudative Vitreoretinopathy

- Retinopathy of prematurity
- Coats' disease
- Incontinentia pigmenti
- Sickle cell disease

#### Norrie's Disease

- Retinopathy of prematurity
- Persistent fetal vascular syndrome
- X-linked recessive familial exudative vitreoretinopathy

The electroretinography (ERG) changes are commensurate with axial myopia—reducing b-wave amplitudes. No intrinsic abnormality of the generators of the waveforms in the ERG appears to occur. Similarly, the perimetric abnormalities, if any, occur secondary to retinal detachments and do not result from abnormalities in the visual pathway directly. For the differential diagnosis of Stickler's syndrome, see [Box 6.17.1](#).

Differential diagnosis includes VCAN-related vitreoretinopathies of Wagner's syndrome (OMIM #143200) and erosive vitreoretinopathy (ERVR; OMIM \*118661). Versican (VCAN) is the only gene mutation associated with these two autosomal dominantly inherited diseases, characterized by “optically empty vitreous,” myopia, variable night blindness and chorioretinal atrophy, but no systemic associations.<sup>13</sup>

## SYSTEMIC ASSOCIATIONS

Of the diseases discussed in this chapter, both Stickler's syndrome and some autosomal dominant familial exudative vitreoretinopathy patients have systemic complications involving the skeleton. Generalized epiphyseal

dysplasia occurs, with premature degenerative changes in weight-bearing joints. Abnormalities of collagen that affect the head include submucous clefting of the palate and bifid uvula (75%; palpation with a gloved finger may be necessary to diagnose a submucous cleft). Midfacial flattening and the Pierre-Robin anomaly often are subtle, and radiographic studies may be required for diagnosis.<sup>14</sup> Sensorineural hearing loss often may be overlooked, as well as mitral valve prolapse (50%),<sup>15</sup> unless sought after in the systemic evaluation. The hearing loss is progressive and affects most individuals by middle age.

## TREATMENT, COURSE, AND OUTCOME

Early in life, corrective lenses based on a cycloplegic refraction are prescribed to prevent amblyopia. A multidisciplinary evaluation (otolar-yngology, orthopedics) and genetic tests (COL2A1 gene) with genetic counseling are important components of a global approach to the family with Stickler's syndrome. A good example of a growing phenomenon of self-organizing patient support groups is found in the United States at <http://www.sticklers.org/sip/> and in the United Kingdom at <http://www.stickler.org.uk/>. These groups serve multiple purposes, ranging from a source of scientific information to fundraising for research to find cures for the disease. Annual to semiannual retinal evaluation through dilated pupils with prophylactic treatment of new retinal tears is suggested for longitudinal follow-up. If retinal detachment does not occur, the visual morbidity is minimal. Low-vision evaluation may be beneficial for all patients who develop a serious loss of vision that affects activities of daily living.

## X-LINKED JUVENILE RETINOSCHISIS

### INTRODUCTION

X-linked juvenile retinoschisis (OMIM #312700) is a vitreoretinal degeneration affecting males. The cystic, spoke-like foveal changes, visual acuity deterioration, peripheral retinoschisis, and loss of ERG b-wave are bilateral. Despite mutation heterogeneity, there are relatively uniform clinical characteristics, albeit with intrafamilial variation in onset and severity.

### EPIDEMIOLOGY AND PATHOGENESIS

Various deleterious mutations in RS1 encoding for retinoschisin are associated with X-linked juvenile retinoschisis (XLRS; McKusick No. 312700). In a knockout mouse model, the RS1h murine analog seems important in organization of retinal cell layers and structure of the retinal synapse throughout the entire retina, in contrast to macular dominance in humans.<sup>16</sup>

Retinoschisin is a secreted, soluble homo-oligomeric complex that binds tightly to the surface of photoreceptors and bipolar cells to maintain the synapse. Wang et al. hypothesized that missense mutations lead to abnormal protein conformation and intracellular retention of these products.<sup>17</sup>

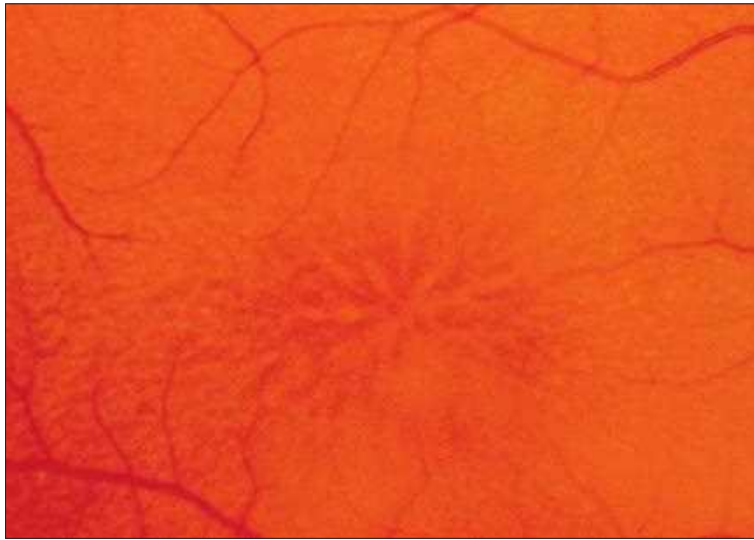
### OCULAR MANIFESTATIONS

Cystic-like, stellate maculopathy, or foveal schisis, is present almost universally in XLRS and may be the only abnormality detected by ophthalmoscopy in one-half of cases ([Fig. 6.17.2](#)). Similar to the findings in Goldmann–Favre disease, no late leakage occurs on fluorescein angiography. In older patients, foveal schisis evolves into an atrophic maculopathy. The average visual acuity is 20/60 (6/18) at age 20 years and 20/200 (6/60) at age 60 years.<sup>18</sup>

The classic histological studies of retinoschisis describe splitting in the anterior layers of the retina ([Fig. 6.17.3](#)), typically in the inferotemporal quadrant, and bilaterally in 40% of patients. The inner layer balloons into the vitreous cavity, and unsupported retinal vessels may lead to recurrent vitreous hemorrhages from associated vitreous traction. Vitreous veils may overlie the retinoschisis.<sup>19</sup> In XLRS, the vitreous exerts an effect on the bullous nature of the retinoschisis lesion. The elevation is seen to flatten after a posterior vitreous detachment has produced a separation between the vitreous face and the internal limiting membrane. It is as if the vitreous releases the inner layers of the retina, which allows them to settle back into an anatomical position.

The Mizuo–Nakamura phenomenon has been described in four unrelated men who suffered from X-linked recessive retinoschisis.<sup>20</sup> Originally described in patients who had autosomal recessive Oguchi's disease, a form





**Fig. 6.17.2 Fundus View of Foveal Schisis Seen in a Man Who Has X-Linked Juvenile Retinoschisis.** This lesion should not be confused with cystoid macular edema.

#### BOX 6.17.2 Diseases With Selective Loss of B-Wave Amplitude on Electroretinographic Testing

- X-linked juvenile retinoschisis
- Congenital stationary night blindness
- Oguchi's disease
- Myotonic dystrophy
- Batten's disease (neuronal ceroid lipofuscinosis)
- Autosomal dominant neovascular inflammatory vitreoretinopathy
- Quinine toxicity
- Methanol toxicity
- Siderosis
- Acute central retinal artery occlusion
- Acute central retinal vein occlusion

of congenital stationary night blindness, this phenomenon also occurs in patients who have an X-linked cone dystrophy.<sup>21</sup>

### DIAGNOSIS AND ANCILLARY TESTING

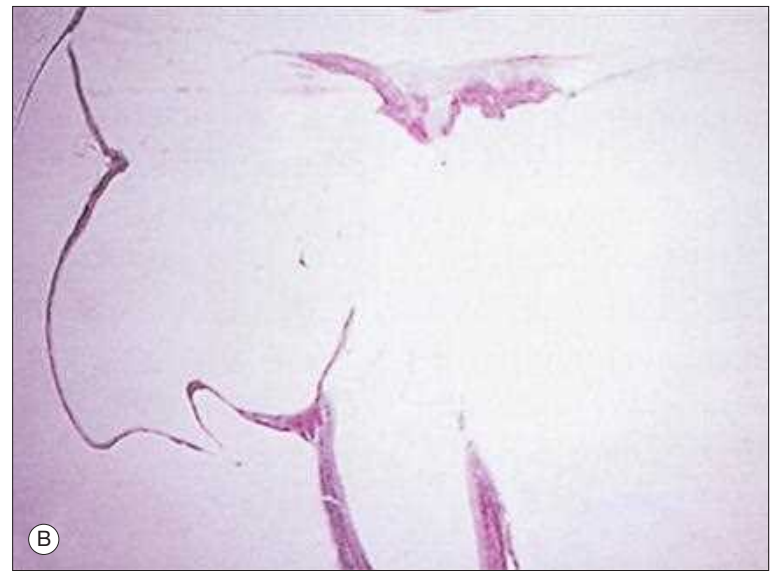
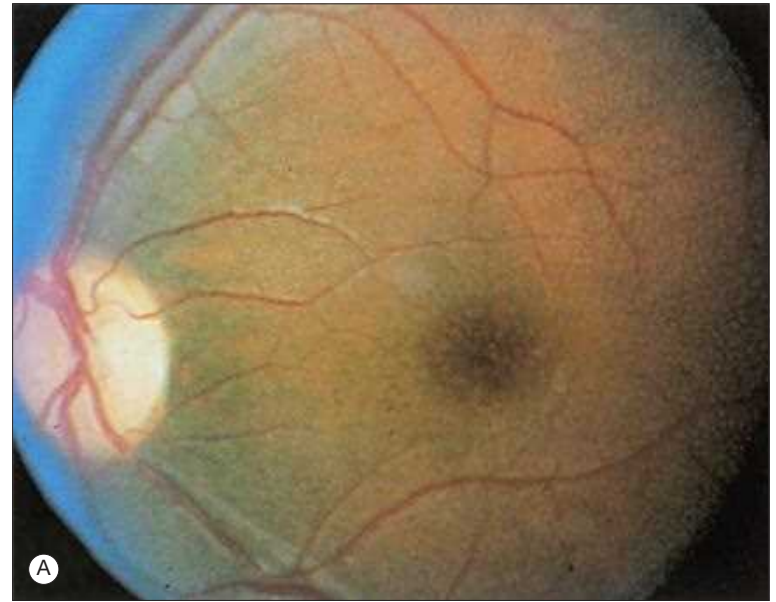
The diagnosis is largely based on clinical examination. In contrast to the histological studies showing anterior layer splitting, spectral domain optical coherence tomography (OCT) shows widespread cystic spaces in both inner and outer macular retina. OCT also reveals subtle structural changes throughout different layers of the retina that vary between the fovea and parafovea. OCT may ultimately improve our understanding of retinoschisis by nondestructively showing disease progression over time and the variation in the depth of retinal splitting by eccentricity from fovea to the periphery. Fluorescein angiography generally shows no leakage of dye or true cystoid macular edema in the posterior pole, whereas the periphery may show slow filling of opacified, dendritic retinal vessels.<sup>22</sup>

The ERG shows selective loss of the b-wave amplitude for the scotopic, nonattenuated flash and loss of the oscillatory potentials (Box 6.17.2). This ERG abnormality suggests a panretinal dysfunction in spite of the ophthalmoscopic appearance of only foveal retinal schisis. No consistent ERG findings are found in female carriers, although sporadic reports of abnormalities exist.

Visual fields demonstrate absolute scotomas in areas of peripheral schisis, because the neural chain of information is interrupted. A relative central scotoma also is seen. Dark adaptation is normal or only minimally affected in X-linked retinoschisis. There are no known systemic associations. For the differential diagnosis of XLRS, see Box 6.17.1.

### TREATMENT, COURSE, AND OUTCOME

Prophylactic treatment of retinoschisis or holes in schisis is not recommended, whereas secondary retinal detachment necessitates intervention. Combined retinal detachment and retinoschisis requires intervention to



**Fig. 6.17.3 Juvenile Retinoschisis.** (A) The characteristic foveal lesion, resembling a polycystic fovea, is shown. Typically, no leakage is present when fluorescein angiography is performed. (Courtesy Dr. A. J. Brocker.) (B) A histological section of another eye shows a large temporal peripheral retinoschisis cavity. (C) A histological section of another area of the same eye shows a splitting in the ganglion and nerve fiber layers of the retina on the earliest finding in juvenile retinoschisis. This pathology of the inner retinal layers is the same as that seen in reticular microcystoid degeneration and retinoschisis. (B–C Courtesy Dr. M. Yanoff.)



close the outer layer holes and full-thickness retinal breaks by vitrectomy, perfluorocarbon reattachment, and panretinal photocoagulation to areas of schisis and detachment, with scleral buckling of the retinal periphery. In young patients who are unable to comply with rigorous postoperative positioning requirements imposed by instillation of long-acting gas, silicone oil tamponade may be preferable.

Genetic counseling is necessary in all cases. Carrier state detection by clinical exam alone is difficult in this disease, although isolated reports exist. Most patients develop a significant loss of macular function in one or both eyes with time. Children need to be examined frequently to rule out amblyopia, vitreous hemorrhage, or retinal detachment.

The National Eye Institute's Study NCT02317887 is a phase 1/2 gene therapy trial in humans using AAV8-scRS/IRBPhRS injected intravitreally. Applied Genetic Technologies is also conducting a human gene therapy trial using rAAV2tYF-CB-hRS1 injected intravitreally.

## AUTOSOMAL DOMINANT VITREORETINOCHOROIDOPATHY

### EPIDEMIOLOGY AND PATHOGENESIS

Mutations in the BEST1 gene cause a range of clinically heterogeneous retinal dystrophies, collectively called bestrophinopathies. These include Best disease (OMIM #153700), adult-onset vitelliform macular dystrophy (OMIM #608161), autosomal recessive bestrophinopathy (OMIM #611809), retinitis pigmentosa (OMIM #26800 and #613194), and ADVIRC (OMIM #193220).<sup>23</sup>

### OCULAR MANIFESTATIONS

The classic finding of ADVIRC is a sharply defined posterior border to an area of abnormal hypopigmentation or hyperpigmentation for 360° bilaterally between the ora serrata and the equator (Fig. 6.174).<sup>24,25</sup> Within this abnormally pigmented area are narrowed retinal arterioles, vascular incompetence, retinal neovascularization, punctate white retinal opacities, and later retinochoroidal atrophy. Cystoid macular edema, if present, is the most significant morbidity, although central retinal pigment epithelial atrophy can be seen in elderly patients. Vitreous hemorrhage and epiretinal membranes also may affect the visual acuity. Profound alterations in the vitreous body are not described, although small numbers of vitreous cells and early posterior vitreous detachments may occur. The condition is slowly progressive and is not associated with retinal detachments. Histopathology has been described in an 88-year-old patient; similar features to retinitis pigmentosa were found, along with some differences.<sup>26</sup>



**Fig. 6.17.4 Fundus View of Retinal Periphery in Autosomal Dominant Vitreoretinopathy.** Note sharply demarcated posterior border to the hyperpigmented peripheral lesion. This border is a useful defining feature of autosomal dominant vitreoretinopathy.

## DIAGNOSIS AND ANCILLARY TESTING

Patients who have ADVIRC generally have no nyctalopia, and ERG findings are normal in younger affected individuals and only moderately depressed in older patients. No known systemic associations exist. For the differential diagnosis of ADVIRC, see Box 6.17.2.

### TREATMENT, COURSE, AND OUTCOME

Annual or biannual dilated fundus examination is suggested unless the disease is symptomatic. Cystoid macular edema typically responds to dorzolamide. The long-term visual prognosis is generally good, though late stage ADVIRC may produce macular RPE atrophy and decreased vision.

## FAMILIAL EXUDATIVE VITREORETINOPATHY

### INTRODUCTION

FEVR, reported initially in 1969 by Criswick and Schepens,<sup>27</sup> has also been called dominant exudative vitreoretinopathy. Both eyes are affected but usually asymmetrically.

### EPIDEMIOLOGY AND PATHOGENESIS

Three genes are associated with autosomal dominantly inherited FEVR (OMIM #133780): FZDD4, encodes the frizzled-4 protein; LRP5, encodes low-density lipoprotein receptor-related protein 5; and TSPAN12, encoding tetraspanin-12.

The frizzled-4 protein is a member of the frizzled family of seven-pass transmembrane receptors that bind Wnt proteins.<sup>28</sup> The norrin gene product acts as ligand for the FZD-4 protein receptor, which in turn activates the Wnt signaling pathway.<sup>29</sup> Among many critical developmental pathways that Wnt affects, it is involved in the blood supply to the retina and inner ear. The LRP5 encodes a single-pass transmembrane receptor, partnering with frizzled-4 to bind Wnt proteins. TSPAN12 encodes a four-pass transmembrane protein, forming a component of the norrin-LRP5-FZD-4 signaling complex. Mutations in these three genes account for less than 50% of adFEVR. Genetic testing is increasingly available with certified genetics counselors knowledgeable of the genetic testing labs. Genetic heterogeneity in FEVR is documented.<sup>30,31</sup> Although rare, FEVR accounts for a significant percentage of all retinal detachments in juvenile and infant patients.

### OCULAR MANIFESTATIONS

The prominent feature is the abrupt cessation of peripheral retinal vessels in a scalloped pattern at the temporal equator (Figs. 6.17.5 and 6.17.6). Dilated retinal vessels may result in peripheral neovascularization with adjacent preretinal hemorrhage and may later evolve into a fibrovascular



**Fig. 6.17.5 Fundus View of a Patient Who Has Familial Exudative Vitreoretinopathy.** Note abnormally straightened retinal vasculature.

scar.<sup>32</sup> Subretinal exudates occur in 10%–15% of eyes and can become massive, resembling Coats' disease.

The majority of retinal detachments occur in the first decade of life, with little progression after 10 years of age.<sup>33,34</sup> Vitreous abnormalities include posterior vitreous detachment and vitreous bands or sheets attached to avascular retina, although milder cases may not show any visible vitreous change. An ectopic macula may be found in 50% of patients. A positive-angle kappa or strabismus is common.

## DIAGNOSIS AND ANCILLARY TESTING

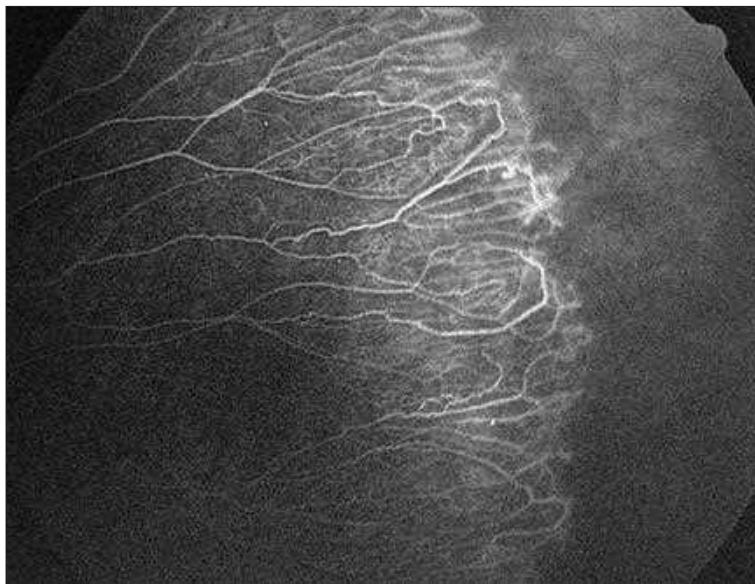
The diagnosis is based on typical clinical findings, a positive family history, the lack of significant prematurity, and the exclusion of other possible causes of peripheral retinal pathology. Fluorescein angiography can be quite helpful because it highlights peripheral, nonperfused retina and shows the characteristic straightening of peripheral retinal vessels.

No significant ERG findings are noted. Even patients who have enough avascular peripheral retina to produce peripheral retinal neovascularization show only minor reductions in b-wave amplitude. No known systemic associations occur. For the differential diagnosis of FEVR, see [Box 6.172](#).

## SYSTEMIC ASSOCIATIONS

Toomes et al. observed osteopenia or osteoporosis on dual X-ray absorptiometry in patients with autosomal dominant FEVR and mutations in *LRP5*.<sup>35</sup> It should be remembered that in Stickler's syndrome, patients with mutations in procollagen II have ocular and skeletal problems as well.

Interestingly, missense mutations within the first few exons of *LRP5* are associated with disorders of high bone mass: high bone mass (OMIM 601884), endosteal hyperostosis (OMIM 144750), and osteopetrosis (OMIM 607634).<sup>36</sup>



**Fig. 6.17.6 Fluorescein Angiogram of a Patient Who Has Familial Exudative Vitreoretinopathy.** Fluorescein angiography is an excellent tool to define the abnormal retinal vasculature in familial exudative vitreoretinopathy. Fluorescein angiography, if available, is particularly useful for peripheral retinal vascular examination.

## TREATMENT, COURSE, AND OUTCOME

Early screening of at-risk individuals is useful to identify nonperfused peripheral retina. Wide-field fluorescein angiography can identify large areas of avascular peripheral retina.

Strabismus from dragged retina must be identified early. Retinal detachments primarily are tractional early in life and combined tractional and rhegmatogenous in the second decade (4%–30% incidence).

## NORRIE'S DISEASE

### INTRODUCTION

Norrie's disease (ND; OMIM #310600) is a rare, bilateral, blinding X-linked recessive disorder, with 30%–50% of patients developing sensorineural deafness and mental retardation.

### EPIDEMIOLOGY AND PATHOGENESIS

The ND gene (NDP \*300658) on chromosome Xp11.4 produces the gene product norrin, a small secreted protein with a cysteine-knot motif. The cysteine-knot motif is highly conserved in many growth factors, such as transforming growth factor beta, human chorionic gonadotropin, nerve growth factor, and platelet-derived growth factor. Norrin acts as a ligand in a Wnt receptor-beta catenin signal transduction pathway that plays a regulatory role in retinal vascular development. FZD-4 gene receptors and LRP-5 gene receptors (see FEVR) are coupled to the beta catenin canonical pathway activating Wnt target genes.<sup>37</sup>

### OCULAR MANIFESTATIONS

The congenitally dysplastic retina presents as a grayish yellow mass known as a pseudoglioma. Partial or complete retinal detachment evolves over the first few months, with typically light perception vision at best.<sup>38</sup>

At birth the anterior segment may be normal, with the pseudoglioma appearance visible behind a clear lens. However, progressive cataract, posterior synechiae, as well as shallowing of the anterior chamber and anterior synechiae may follow. Angle-closure glaucoma and a painful eye may develop, followed by band keratopathy hypotony and phthisis bulbi ([Fig. 6.177](#)).

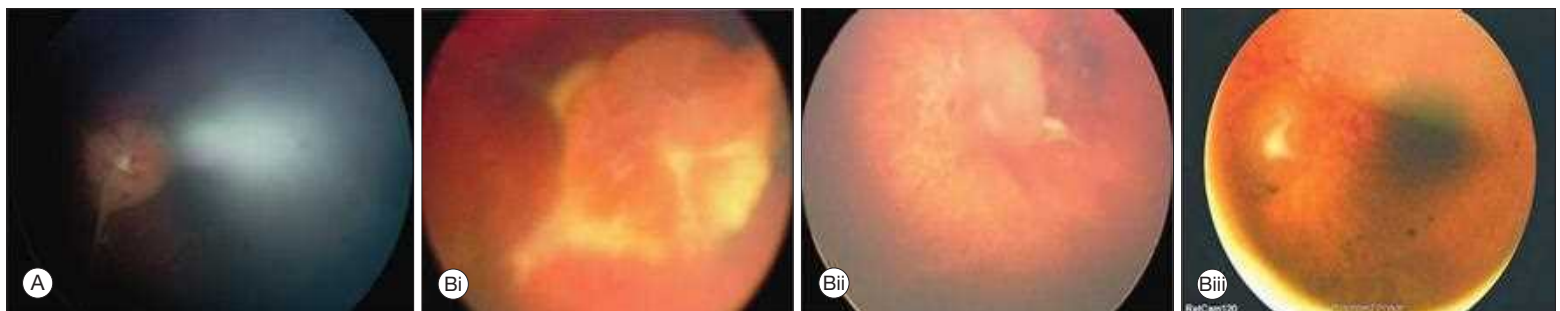
### DIAGNOSIS AND ANCILLARY TESTING

A clinical diagnosis of ND requires the presence of bilateral dystrophic retinas. Increasingly, genetic diagnostic precision is desirable. Prenatal testing is possible for female carriers if the NDP mutation has been identified in a family member. Chorionic villous sampling may be performed at 10–12 weeks' gestation or by amniocentesis at 15–18 weeks' gestation.

Persistent fetal vasculature syndrome (PFVS) is diagnosed in children with findings suggestive of ND but lacking an X-linked recessive inheritance or an ND gene mutation.

### SYSTEMIC ASSOCIATIONS

Sensorineural deafness and mental retardation are present in 30%–50% of patients.



**Fig. 6.17.7 Color Fundus Photograph of Norrie's Disease Patient Showing Profound Retinal Disorganization Arising From Disordered Development (Pseudoglioma).** 'Pumpkin lesion' comprised of vascularized dysplastic retinal mass (pseudoglioma) in posterior pole. (Courtesy Dr. K. A. Drenser.)

## TREATMENT, COURSE, AND OUTCOME

Walsh et al. describe 14 boys with ND who underwent vitrectomy with or without lensectomy prior to 12 months of age. Seven maintained at least light perception in at least one eye, and three had no light perception bilaterally.<sup>39</sup>

A family history and genetic counseling may lead to a high index of suspicion of ND, leading to careful consideration of prenatal amniocentesis fetal-genetic testing. Chow et al. describe a case of induced labor at 37 weeks' gestation, confirmatory examination under anesthesia at 1 day after birth, and bilateral application of laser to avascular retina via binocular indirect ophthalmoscopic delivery. Extraretinal neovascularization regressed fully at one month without retinal detachment. At 23 months, Teller visual acuity was 20/100 OU.<sup>40</sup>

Surveillance for and treatment of hearing loss may include hearing aids and consideration of cochlear implants.

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# Hypertensive Retinopathy

Aleksandra V. Rachitskaya

# 6.18

## CHRONIC HYPERTENSIVE RETINOPATHY

**Definition:** Retinal vascular changes occurring from chronic systemic arterial hypertension.

### Key Features

- Arteriolar narrowing.
- Arteriovenous nicking.
- Microaneurysms.
- Silver/copper wiring.

### Associated Retinal Findings

- Branch retinal vein occlusion.
- Central retinal vein occlusion.
- Macroaneurysm.

## MALIGNANT ACUTE HYPERTENSIVE RETINOPATHY

**Definition:** Retinal, choroidal, and optic nerve changes secondary to acutely elevated systemic arterial blood pressure.

### Key Features

- Retinal hemorrhages.
- Cotton-wool spots.
- Serous retinal detachment.
- Optic disc edema.
- Choroidal ischemia.

### Associated Feature

- Malignant hypertension, encephalopathy, pre-eclampsia, eclampsia, kidney disease, and pheochromocytoma.

## INTRODUCTION

Hypertensive retinopathy represents ophthalmic findings secondary to systemic elevated blood pressure. Retinal as well as choroidal and optic nerve circulations can be affected. Both chronic structural damage and acute changes due to rapid elevation of blood pressure can be observed. Chronic changes include arteriolar narrowing, arteriovenous nicking, and copper and silver wiring. Microaneurysms, retinal blot and flame-shaped hemorrhages, hard exudates, and cotton-wool spots commonly are associated with exudative retinopathy. Acute changes associated with episodes of rapidly elevated blood pressure can include disc edema, choroidal infarction, along with exudative retinopathy.

Hypertensive retinopathy and hypertension are associated with development and progression of such vision-threatening disorders as retinal vein and artery occlusion, macroaneurysms, and diabetic retinopathy. Retinopathy is also an independent risk factor for stroke, cardiovascular

mortality, renal disease, and cognitive decline. Given the high prevalence of hypertension, its association with cardiovascular complications and end organ damage, and poor blood pressure control among particular groups of patients, ophthalmologists play a role in establishing a diagnosis and educating patients about potential ramifications.

## EPIDEMIOLOGY AND PATHOGENESIS

Hypertension (HTN) is defined as systolic blood pressure greater than or equal to 140 mm Hg or diastolic blood pressure greater than or equal to 90 mm Hg.<sup>1</sup> Essential HTN, not secondary to another disease process, is most common. Prevalence of HTN among US adults was 29% in 2011–2014; it increases with age and was found in 65% of those age 60 years and older. HTN prevalence is highest among non-Hispanic African Americans,<sup>1</sup> and affects approximately 1 billion adults worldwide.<sup>2</sup> Systolic blood pressure represents an independent risk predictor for coronary events, stroke, heart failure, and end-stage renal disease.<sup>3</sup> However, among adults with HTN, only 53% had controlled blood pressure during 2011–2014, and young adults aged 18–39 tend to have lower awareness, treatment, and control (37%) of their HTN.<sup>1</sup>

The hypertensive retinal changes are often associated with and masked by the presence of other retinal vascular diseases such as diabetes and vein occlusion. The prevalence of retinopathy has been reported to range from 6.6% to 17.2% and varies with race and ethnicity.<sup>4–7</sup> Retinopathy without diabetes could also be related to increasing age, hyperglycemia, dyslipidemia, higher body mass index, and systemic inflammatory markers.<sup>6</sup> It has, however, been shown that HTN is the major cause of retinopathy without diabetes.<sup>4,8</sup>

HTN itself is a risk factor for development and progression of diabetic retinopathy, retinal vein and artery occlusion, retinal–arteriolar emboli, nonarteritic ischemic optic neuropathy, and retinal arterial macroaneurysm.<sup>9,10</sup> It has also been reported to be a risk factor for age-related macular degeneration and glaucoma.<sup>9–11</sup> Moreover, after risk factors such as systolic blood pressure and diabetes are controlled, advanced retinopathy is independently associated with clinical and subclinical stroke and cardiovascular mortality, congestive heart failure, renal disease, and cognitive decline and dementia.<sup>12–18</sup> The relationship of hypertensive retinopathy with cerebrovascular disease is the strongest.<sup>19</sup>

## OCULAR MANIFESTATIONS

### Hypertensive Retinopathy

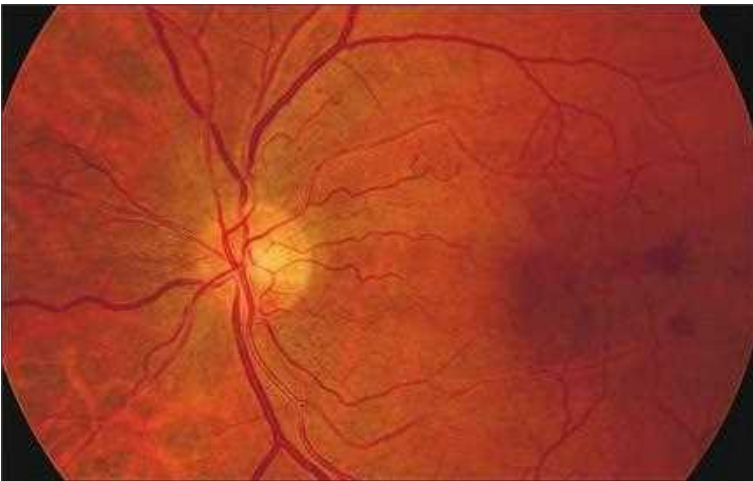
The pathophysiology of hypertensive retinopathy is believed to occur in overlapping and not always sequential phases: a vasoconstrictive phase, an exudative phase, a sclerotic phase, and complications of the sclerotic phase.<sup>20</sup> The arterioles and capillaries are affected.

In the early vasoconstrictive phase, a rise in systemic blood pressure excites pliable and nonsclerotic retinal vessels to increase their vascular tone. It usually presents as generalized retinal arteriolar narrowing.<sup>19–21</sup> Persistently elevated blood pressure leads to intimal thickening, hyperplasia of the media wall, and hyaline degeneration. In this sclerotic stage, there are areas of severe generalized and focal arteriolar narrowing. Arteriovenous nicking occurs due to arteriolar compression of venules at their junctions as they share a common adventitial sheath (Fig. 6.18.1). Alterations in the arteriolar light reflex are described as copper and silver wiring.<sup>21</sup> The complications of the sclerotic phase include formation of macro- and microaneurysms of the retinal artery, artery or vein occlusion, and epiretinal membrane formation (Fig. 6.18.2).<sup>20</sup>

In the exudative phase, which is usually associated with an acute rise in blood pressure, the blood–retinal barrier is disrupted, resulting in



**Fig. 6.18.1 Mild to Moderate Chronic Hypertensive Retinopathy.** Note the nerve fiber layer hemorrhage and sporadic areas of arteriovenous nicking. Blood pressure measured 168/93.



**Fig. 6.18.2 Collateral Vessels in the Superior Macula of a Patient With Hypertensive Retinopathy and a Resolved Branch Retinal Vein Occlusion.** A few microaneurysms and retinal hemorrhages persist from the occlusion.

exudation of blood and lipids and retinal ischemia. Clinically, microaneurysms, focal intraretinal periarteriolar transudates, retinal blot (inner retinal) and flame-shaped (nerve fiber layer) hemorrhages, hard exudates, and cotton-wool spots are seen (Fig. 6.18.3). Cotton-wool spots represent focal ischemic areas of the nerve fiber layer. In cases of acute blood pressure elevation, the swelling of the optic disc and choroidal ischemia may occur as described later.<sup>20-22</sup>

Generalized arteriolar narrowing and arteriovenous nicking is usually seen in chronic hypertensive damage and might correspond to historic and not to current blood pressure levels. On the other hand, focal arteriolar narrowing, retinal hemorrhages, microaneurysms, and cotton-wool spots are associated with concurrently measured blood pressure.<sup>9</sup>

There have been several classification systems of hypertensive retinopathy (Box 6.18.1).<sup>10,23</sup> These have not been extensively utilized, as interobserver variability has been reported. Suggestions have been made to establish a photographic classification of the retinal signs similar to diabetic retinopathy.<sup>18</sup>

For differential diagnosis of hypertension retinopathy, see Box 6.18.2.

## Hypertensive Choroidopathy

Hypertensive choroidopathy usually occurs in association with acutely elevated blood pressure and more frequently affects younger patients whose blood vessels are pliable and not sclerotic.<sup>20</sup> Hypertensive emergencies are



**Fig. 6.18.3 Moderate Hypertensive Retinopathy.** Microaneurysms, retinal blot and flame-shaped hemorrhages, arteriovenous nicking, and cotton-wool spots.

### BOX 6.18.1 Classifications of Hypertensive Retinopathy

#### Keith-Wagener-Barker Classification

- Grade 1: Generalized arteriolar narrowing
- Grade 2: Focal narrowing and arteriovenous nicking/nipping
- Grade 3: Grade 2 plus exudates, hemorrhages, and cotton-wool spots
- Grade 4: Grade 3 plus optic disc swelling

#### Mitchell-Wong Classification

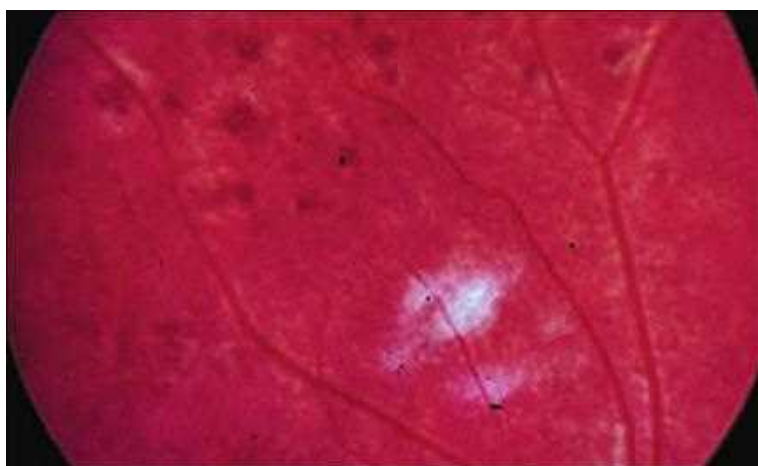
- Mild: generalized and/or focal arteriolar narrowing, arteriovenous nicking/nipping, opacity of arteriolar wall (copper/silver wiring)
- Moderate: retinal hemorrhages (flame, dot, blot), exudates, cotton-wool spots
- Malignant: moderate plus optic disc swelling

### BOX 6.18.2 Differential Diagnosis of Chronic Hypertensive Retinopathy

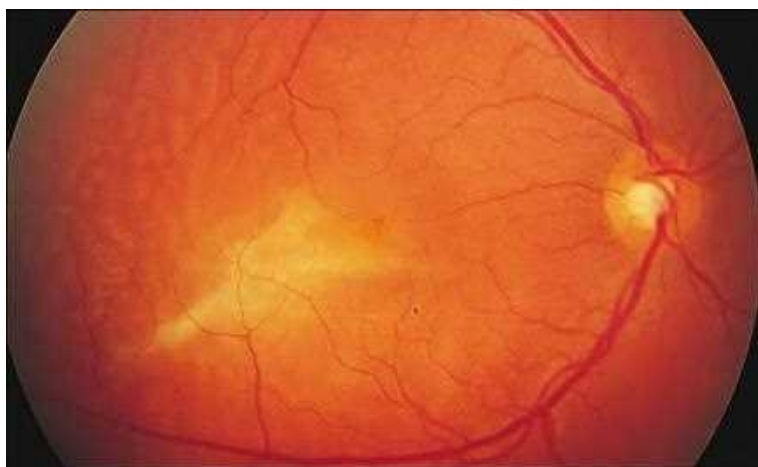
- Diabetic retinopathy
- Retinal venous obstruction
- Hyperviscosity syndromes
- Congenital hereditary retinal arterial tortuosity
- Ocular ischemic syndrome
- Radiation retinopathy

characterized by severe elevations in blood pressure above 180/120 mm Hg.<sup>24</sup> Malignant hypertension and encephalopathy might be present. It can be seen in patients with pre-eclampsia, eclampsia, essential hypertension, kidney disease, and pheochromocytoma.<sup>20</sup> The retinal changes, as described above, include focal intraretinal periarteriolar transudates, microaneurysms, retinal flame-shaped hemorrhages, hard exudates, and cotton-wool spots. Optic nerve swelling can be present as well. Choroidal changes involve patchy perfusion of choriocapillaris. Histologically, it is due to fibrinoid necrosis of the choroidal arteries and arterioles with occlusion of the choriocapillaris.<sup>20</sup> Areas of focal choroidal ischemia called Elschnig's spots appear as pale, yellow, well-demarcated lesions that with time become pigmented as a secondary consequence of tissue infarction (Fig. 6.18.4).<sup>10</sup> Global choroidal dysfunction affects the pumping capacity of the retinal pigment epithelium, leading to exudative retinal detachments that are usually posterior in location (Fig. 6.18.5). Siegrist's streaks are the rarest finding and present as linear configurations of hyperpigmentation that develop over choroidal arteries. The pigmentation has been attributed to hypertrophy and hyperplasia of the retinal pigment epithelium. The streaks usually radiate out to the periphery, passing deep to the retinal vessels along the course of sclerosed choroidal vessels.<sup>25</sup>





**Fig. 6.18.4** Elschnig's Spots.



**Fig. 6.18.5** Serous Detachment of the Retina in a 27-Year-Old Patient Who Has Pregnancy-Induced Hypertension, 3 Days Postpartum. Blood pressure measured 158/100 mm Hg. Note the subretinal fibrin and folds in the retina. (Courtesy Franklin L. Myers.)

## Hypertensive Optic Disc Edema

Optic nerve edema is usually seen in acutely elevated blood pressure. Raised intracranial pressure and concomitant optic nerve ischemia have been implicated to lead to disc swelling (Fig. 6.18.6).<sup>20,26</sup> Subsequent optic nerve pallor can occur. Acute and significant lowering of the blood pressure can result in optic nerve head infarction and subsequent marked optic atrophy and permanent vision loss.<sup>26</sup>

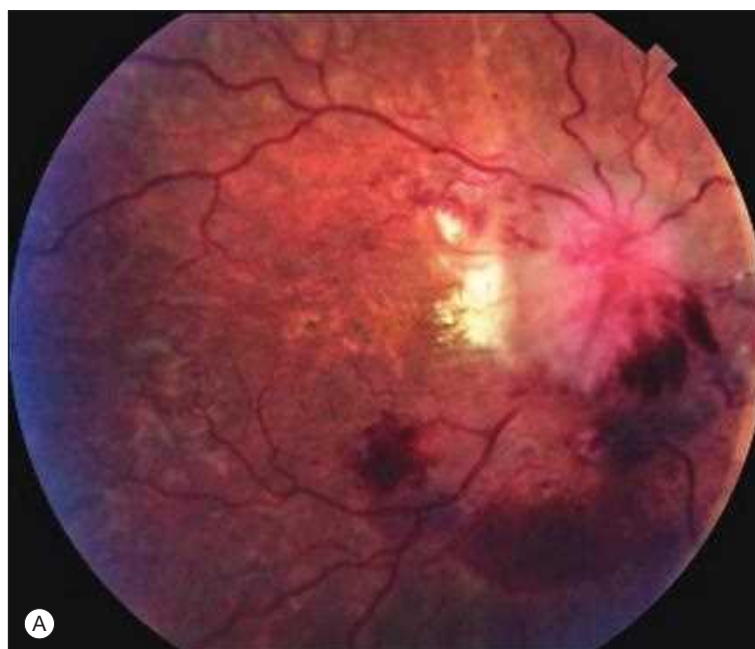
For differential diagnosis of acute hypertension retinopathy, see Box 6.18.3.

## DIAGNOSIS AND ANCILLARY TESTING

Hypertensive retinopathy is a clinical diagnosis made when characteristic retinal vascular, choroidal, or optic disc changes are visualized on slit-lamp biomicroscopy. Ancillary studies can help confirm the diagnosis. Fluorescein angiography (FA) demonstrates narrowing of the retinal arteries, arterioles, and capillary bed, which is the earliest angiographic feature of systemic hypertension. Multiple focal areas of severe retinal ischemia secondary to focal arteriolar narrowing or occlusion are seen. Dilated retinal capillaries and microaneurysms develop at the margins of these areas, which are typically located around the optic disc or along the major retinal vessels (Fig. 6.18.7).<sup>27</sup> In malignant HTN, the optic nerve hyperfluorescence and leakage are seen.<sup>28</sup>

Cotton-wool spots are due to ischemia of the nerve fiber layer. On optical coherence tomography (OCT), they are seen as hyperreflectivity of the nerve fiber layer that subsequently results in permanent damage and thinning.<sup>29,30</sup>

FA and OCT are also useful in conditions associated with HTN and hypertensive retinopathy such as macroaneurysms, retinal artery or vein occlusion, and diabetic retinopathy.



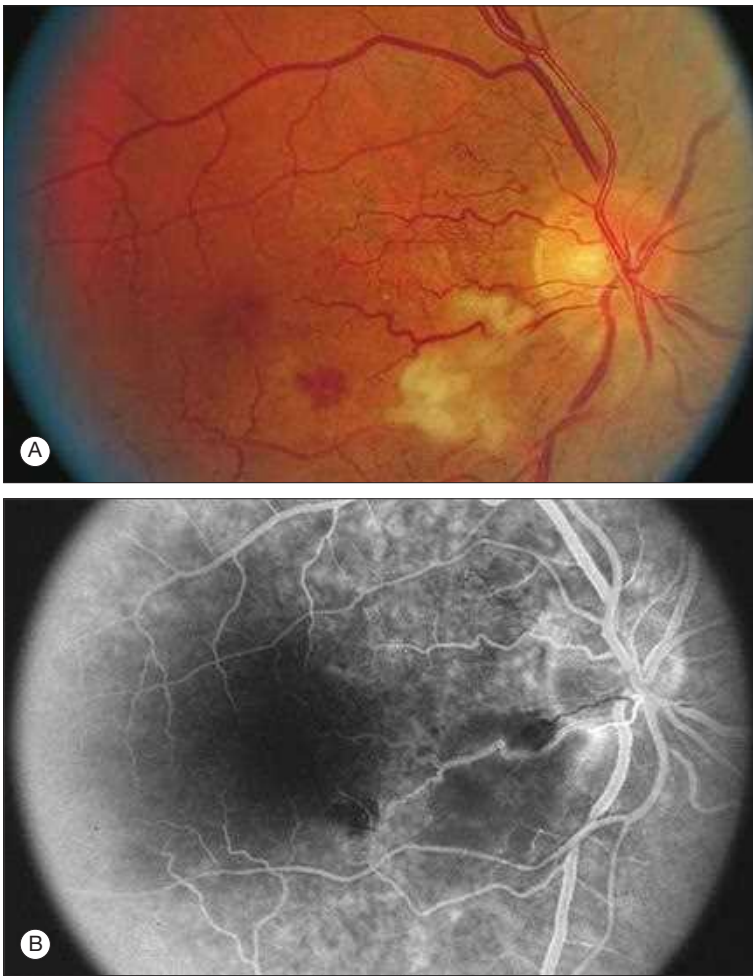
**Fig. 6.18.6** Bilateral Malignant Hypertensive Retinopathy in a Patient With Blood Pressure of 260/140. (A) Right and (B) left eyes. Disc edema, exudate, retinal hemorrhages, venous dilation, narrowing of the arterioles, Elschnig's spots, and Siegrist's streaks are all present. (Courtesy Thomas Hedges III, MD.)

### BOX 6.18.3 Differential Diagnosis of Acute Hypertensive Retinopathy

- Bilateral central serous chorioretinopathy
- Bilateral central retinal vein obstruction
- Collagen vascular diseases
- Diabetic retinopathy (especially in the setting of diabetic papillopathy)

## TREATMENT AND FUTURE DIRECTIONS

The US Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC VII), the Canadian Hypertension Education Program, and the World Health Organization (WHO) International Society of Hypertension identify hypertensive retinopathy as target organ damage.<sup>24,31,32</sup> Documented target organ damage can affect patients' treatment and follow-up schedule. The British Hypertension Society 2004 Guidelines (BHS IV) indicated that severe HTN and grade III–IV retinopathy are suggested indications for specialist referral.<sup>33</sup>



**Fig. 6.18.7** The Right Eye of the Same Patient as Shown in Fig. 6.18.3. (A) A prominent cotton-wool spot in the papillomacular bundle is seen with an adjacent intraretinal hemorrhage. (B) Fluorescein angiography shows capillary nonperfusion in the area corresponding to the cotton-wool patch; note the hypofluorescence of the intraretinal hemorrhage, caused by blockage.

Advanced hypertensive retinopathy is also a risk factor for subclinical and clinical stroke, cognitive decline, and cardiovascular mortality.<sup>12–18</sup>

One of the challenges in hypertensive retinopathy research is a lack of a single classification scheme.<sup>18</sup> Hypertensive changes are often seen in patients with diabetes and arteriosclerotic vascular disease. In the past, it has also been noted that the assessment of retinal microvascular changes varied between observers.<sup>34</sup> Recent advances in digital retinal imaging provide an opportunity to quantify and monitor hypertensive retinopathy, including such imaging biomarkers as retinal vessel width.<sup>19,35</sup> These objective findings could also be utilized in the emerging world of telemedicine.<sup>36</sup>

The newer imaging modalities of wide-field imaging, adaptive optics, and OCT angiography might contribute to our understanding of hypertensive retinopathy. For instance, adaptive optics are used to describe the shapes of microaneurysms and to quantitatively examine the retinal vasculature.<sup>37,38</sup> Study of retinal vessel caliber provides a noninvasive approach that could allow evaluation of systemic microvascular morphology.<sup>39–41</sup>

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# Retinal Arterial Obstruction

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# 6.19

## CENTRAL RETINAL ARTERY OBSTRUCTION

**Definition:** An abrupt diminution of blood flow through the central retinal artery severe enough to cause ischemia of the inner retina.

### Key Features

- Abrupt, painless, severe loss of vision.
- Cherry-red spot.
- Box-carring of blood flow in the retinal vessels.
- Ischemic retinal whitening of the posterior pole.

### Associated Features

- Amaurosis fugax.
- Visible embolus (25%).
- Carotid artery stenosis (33%).
- Giant cell arteritis (5%).
- Neovascularization of the iris (18%).
- Arterial collaterals on the optic disc.

## BRANCH RETINAL ARTERY OBSTRUCTION

**Definition:** An abrupt diminution of blood flow through a branch of the central retinal artery severe enough to cause ischemia of the inner retina in the territory of the affected vessel.

### Key Features

- Retinal whitening in the territory of the obstructed vessel.
- Visible embolus (66%).
- Visual field defect that corresponds to the territory of the obstructed vessels.

### Associated Features

- Carotid artery disease.
- Cardiac valvular disease.
- Cardiac myxoma, long-bone fracture, endocarditis, depot drug injection (rare).
- Systemic clotting disorder or vasculitis (rare).

## CENTRAL RETINAL ARTERY OBSTRUCTION

### INTRODUCTION

Retinal arterial obstructions are divided anatomically into central and branch, depending on the precise site of obstruction. A central retinal artery obstruction occurs when the blockage is within the optic nerve substance itself, and therefore the site of obstruction is generally not visible on ophthalmoscopy. A branch retinal artery obstruction occurs when the site of blockage is distal to the lamina cribrosa of the optic nerve.

Obstructions more proximal to the central retinal artery, in the ophthalmic artery, or even in the internal carotid artery may produce visual loss

as well. Ophthalmic artery obstructions may be difficult to differentiate from central retinal artery obstruction. More proximal obstructions usually cause a more chronic form of visual problem—the ocular ischemic syndrome (see Chapter 6.23).

The majority of retinal arterial obstructions are either thrombotic or embolic in nature. The potential sources and various types of emboli generally do not differ between central retinal artery obstruction and branch retinal artery obstruction, but a branch retinal artery obstruction is far more likely to be embolic than is a central retinal artery obstruction. It has been determined that over two-thirds of branch retinal artery obstructions are caused by emboli, whereas probably less than one-third of central retinal artery obstructions result from emboli.

The retina has a dual circulation with little to no anastomoses. The inner retina is supplied by the central retinal artery, which is an end artery. The outer retina receives its nourishment via diffusion from the choroidal circulation (see Chapter 6.3). Retinal artery obstructions selectively affect the inner retina only.

Because the accompanying visual loss tends to be severe and permanent, it is fortunate that retinal artery obstructions are rare occurrences. As there is a strong association with systemic disease, all patients who suffer retinal artery obstructions should undergo a systemic evaluation.

## EPIDEMIOLOGY AND PATHOGENESIS

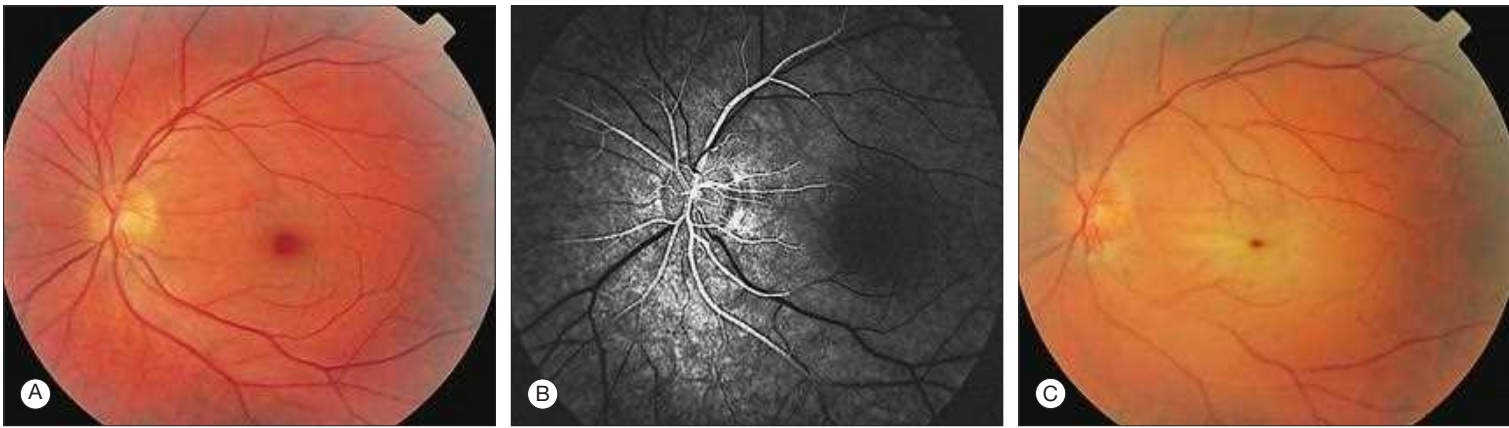
Central retinal artery obstruction is a rare event—it has been estimated to account for about 1 in 10 000 outpatient visits to the ophthalmologist.<sup>1</sup> The incidence was found to be 1.3 per 100 000, or 1.90 per 100 000 when adjusted for age and sex for the white population in the United States.<sup>2</sup> Men are affected more commonly than women, in a ratio of 2:1. The mean age at onset is about 60 years, with a range of reported ages from the first to the ninth decade of life. Right eyes and left eyes appear affected with equal incidence. Bilateral involvement occurs in 1%–2% of cases.

In central retinal artery obstruction, the site of obstruction is not usually visible on clinical examination and, in general, the retrobulbar central retinal artery is too small to image with most techniques. Therefore, the precise cause is speculative. It is currently believed that the majority of central retinal artery obstructions are caused by thrombus formation at or just proximal to the lamina cribrosa. Atherosclerosis is implicated as the inciting event in most cases, although congenital anomalies of the central retinal artery, systemic coagulopathies, or low-flow states from more proximal arterial disease may also be present and render certain individuals more susceptible.

In only 20%–25% of cases are emboli visible in the central retinal artery or one of its branches, suggesting that an embolic cause is not frequent. A more detailed discussion of embolus types is given later in the section on branch retinal artery obstruction. Further indirect evidence against emboli as a frequent cause of central retinal artery obstruction is the 40% or less probability of finding a definitive embolic source on systemic evaluation and the small incidence (approximately 10%) of confirmed associated ipsilateral cerebral emboli in affected patients.<sup>3</sup>

Inflammation in the form of vasculitis (e.g., varicella infection), optic neuritis, or even orbital disease (e.g., mucormycosis) may cause central retinal artery obstruction.<sup>4,5</sup> Local trauma that results in direct damage to the optic nerve or blood vessels may lead to central retinal artery obstruction.<sup>6</sup> Arterial spasm or dissection rarely produces retinal arterial obstruction. In addition, systemic coagulopathies may be associated with both central and branch retinal artery obstructions.<sup>7</sup>

Other rare causes include radiation retinopathy,<sup>8</sup> emboli associated with depot medication injection around the eye,<sup>9</sup> cosmetic facial injection with filler materials,<sup>10</sup> optic disc drusen, and prepapillary arterial loops. Medical examinations and manipulations (e.g., carotid angiography, angioplasty,



**Fig. 6.19.1 The Left Eye of a Healthy 37-Year-Old Man.** The patient had a 3-hour history of visual loss and a visual acuity of 20/60 (6/18). (A) Retinal whitening is very subtle and the retinal vessels appear normal. (B) Fluorescein angiography reveals abnormal arterial filling with a leading edge of dye that confirms central retinal artery obstruction. (C) The same eye 24 hours later. Despite intravenous urokinase, visual acuity dropped to hand movements, and intense retinal whitening with a cherry-red spot is present. Note the interruption in the blood column of the retinal arteries.

### BOX 6.19.1 Other Causes of a Cherry-Red Spot

- Tay–Sachs disease
- Farber’s disease
- Sandhoff’s disease
- Niemann–Pick disease
- Goldberg’s syndrome
- Gaucher’s disease
- Ganglioside GMI, type 2
- Hurler’s syndrome (mucopolysaccharidosis 1 H)
- $\beta$ -Galactosidase deficiency (mucopolysaccharidosis VII)
- Hallevorden–Spatz disease
- Batten–Mayou–Vogt–Spielmeyer disease

chiropractic neck manipulation) rarely result in emboli to the central retinal artery.<sup>11,12</sup> Although elevated intraocular pressure has been implicated as a cause of central retinal artery obstruction, it is unlikely that intraocular pressure can be raised high enough to block arterial inflow to the eye.

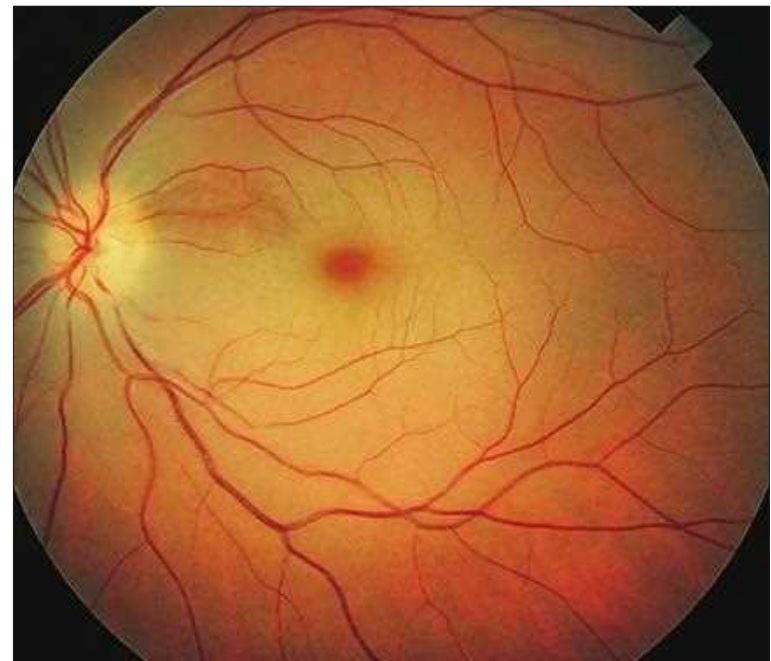
## OCULAR MANIFESTATIONS

The hallmark symptom of acute central retinal artery obstruction is abrupt, painless loss of vision.<sup>13</sup> Pain is unusual and suggests associated ocular ischemic syndrome (OIS). Amaurosis fugax precedes visual loss in about 10% of patients. Rarely, in cases associated with arterial spasm, a relapsing and remitting course of visual loss precedes central retinal artery obstruction.<sup>14</sup>

Examination typically reveals a visual acuity of 20/800 (6/240) or worse.<sup>15</sup> Hand motion or light perception vision can occur, but no light perception vision is uncommon except in the setting of an ophthalmic artery obstruction or temporal arteritis. If a patent cilioretinal artery is present and perfuses the fovea, normal central acuity may be present. An afferent pupillary defect on the affected side is the rule. Anterior segment examination is normal except in the setting of concurrent OIS with neovascularization of the iris.

Within the first few minutes to hours after the obstruction, the fundus may appear relatively normal (Fig. 6.19.1A–B). Eventually, the decreased blood flow results in ischemic whitening of the retina in the territory of the obstructed artery, which is most pronounced in the posterior pole (where the nerve fiber layer of the retina is thickest). Acutely, the arteries appear thin and attenuated. In severe blockages, both veins and arteries may manifest “box-carring” or segmentation of the blood flow.

A cherry-red spot of the macula is typical and arises in this area because the nerve fiber layer is thin. Transmission of the normal choroidal appearance, therefore, is not diminished, which contrasts distinctly with the surrounding area of intense retinal whitening that blocks transmission of the normal choroidal coloration. Although other conditions may be associated with a macular cherry-red spot (Box 6.19.1), these are usually differentiated easily from central retinal artery obstruction. Splinter retinal hemorrhages on the disc are common, but more extensive retinal hemorrhaging suggests an alternative diagnosis. If pallid swelling is present, temporal



**Fig. 6.19.2 A Central Retinal Artery Obstruction.** A prominent cherry-red spot with cilioretinal artery sparing in the papillomacular bundle.

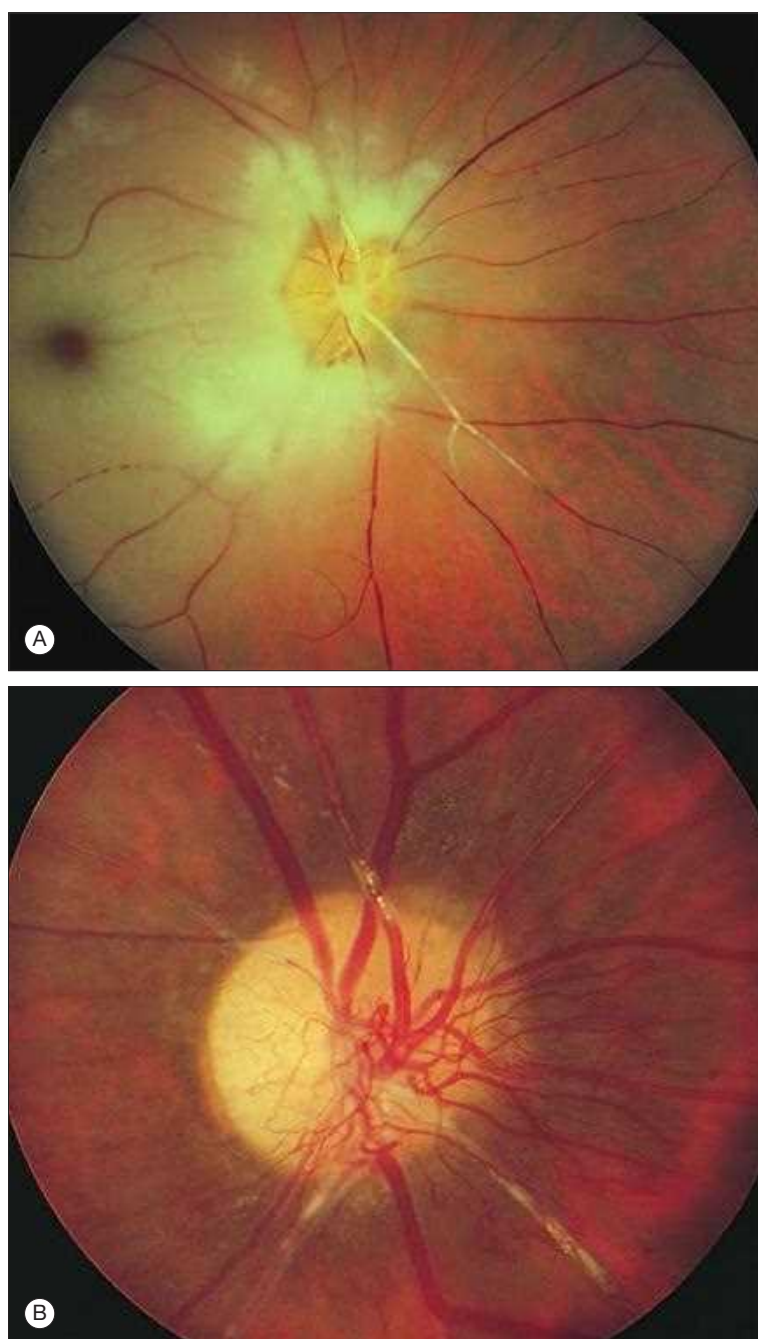
arteritis must be ruled out. A patent cilioretinal artery results in a small area of retina that appears normal (Fig. 6.19.2).

By 6 weeks after the acute event, the retinal whitening typically resolves, the optic disc develops pallor, and arterial collaterals may form on the optic disc. No foveolar light reflex is apparent, and fine changes in the retinal pigment epithelium may be visible. Secondary ocular neovascularization is not uncommon after central retinal artery obstruction and tends to occur around 8 weeks after the obstruction (range 2–16).<sup>16</sup> Iris neovascularization occurs in about 18% of patients,<sup>17,18</sup> with many of these eyes going on to neovascular glaucoma. Panretinal photocoagulation appears to reduce the risk of neovascular glaucoma moderately.<sup>19</sup> Neovascularization of the optic disc occurs after about 2% of central retinal artery obstruction (Fig. 6.19.3).<sup>20</sup> Vitreous hemorrhage may ensue.

## DIAGNOSIS AND ANCILLARY TESTING

Diagnosis of central retinal artery obstruction is straightforward when diffuse ischemic retinal whitening is present in the setting of abrupt, painless visual loss. Fluorescein angiography may help if the diagnosis is in doubt. A delayed arm-to-retina time with a leading edge of dye visible in the retinal arteries is typical (see Fig. 6.19.1B). In some cases, it may be minutes before the retinal arterial tree fills with fluorescein. Arteriovenous transit is delayed as well, and late staining of the disc is common. Retinal oximetry may aid in early diagnosis and have utility for follow-up as it can demonstrate the return of blood flow, but this emerging modality requires further clinical testing.<sup>21</sup>





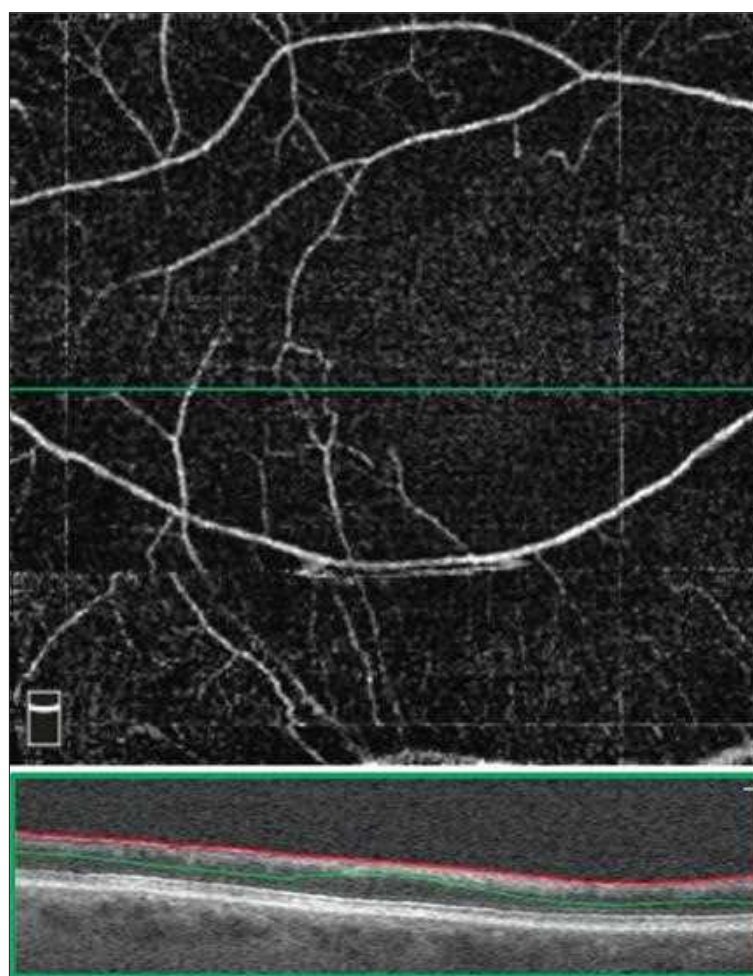
**Fig. 6.19.3** A 26-Year-Old Diabetic Man. (A) Central retinal artery obstruction caused by a platelet-fibrin embolus. (B) After 3 months, extensive neovascularization of the disc is present. (Courtesy Larry Magargal, MD.)

Macular optical coherence tomography (OCT) in the acute phase shows inner retinal thickening with shadowing of the outer retina that can be mistaken for subretinal fluid. When the retinal whitening resolves, OCT reveals severe inner retinal thinning.<sup>22</sup> OCT angiography of prior central retinal artery obstruction demonstrates decreased retinal vascularity and attenuation of vessels in the macula (Fig. 6.19.4). Electroretinography characteristically reveals a decreased to absent b-wave with intact a-wave. Visual fields show a remaining temporal island of peripheral vision. If a patent cilioretinal artery is present, a small intact central island is found as well.

Color Doppler imaging is a form of ultrasonography that can help to determine the blood flow characteristics of the retinobulbar circulation. Color Doppler studies of acute central retinal artery obstruction show diminished to absent blood flow velocity in the central retinal artery, generally with intact flow in the ophthalmic and choroidal branches. Color Doppler imaging can be used to detect calcific emboli at the lamina cribrosa and may be used to monitor blood flow changes induced by therapy.

## DIFFERENTIAL DIAGNOSIS

The differential diagnosis of central retinal artery obstruction is given in Box 6.19.2.



**Fig. 6.19.4** Optical Coherence Tomography Angiography and Corresponding Optical Coherence Tomography Structural B-Scan From an Eye With a Prior Central Retinal Artery Obstruction. Note the paucity of small retinal vessels in the macula and the attenuation of the large retinal vessels. Structural B-scan shows loss of inner retinal tissue.

### BOX 6.19.2 Differential Diagnosis of Central Retinal Artery Obstruction

- Single or multiple branch retinal artery obstruction
- Cilioretinal artery obstruction
- Severe commotio retinas
- Necrotizing herpetic retinitis

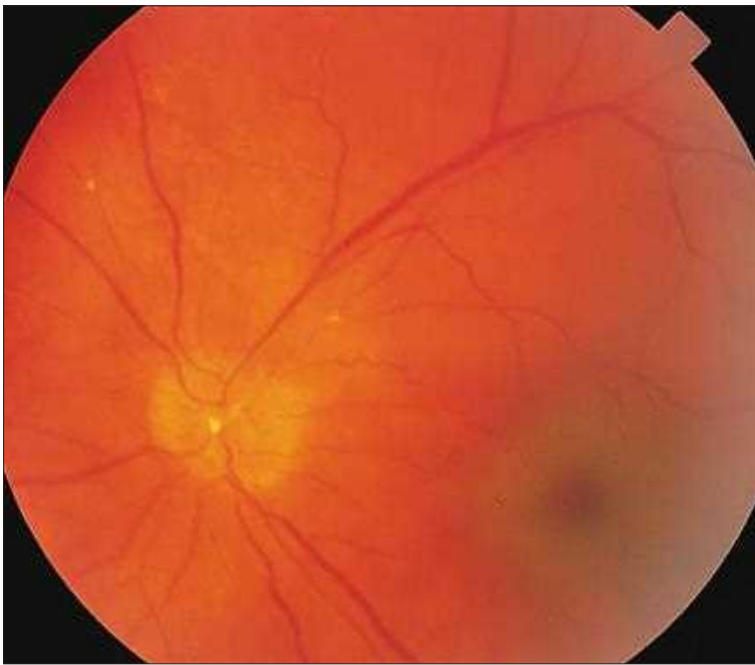
## SYSTEMIC ASSOCIATIONS

Although systemic diseases commonly are found in patients who suffer from retinal artery obstruction, the true cause and effect may not be clear. About 50%–60% of patients have concurrent systemic arterial hypertension, and diabetes is present in 25%. Systemic evaluation reveals no definite cause for the obstruction in over 50% of affected patients. Potential embolic sources are found in less than 40% of cases.<sup>23,24</sup>

The most common pathogenetic association uncovered is hemodynamically significant ipsilateral carotid artery disease, which is present in about one-third of affected patients. Carotid noninvasive testing should be considered for all patients who have central retinal artery obstruction, although disease in those younger than 50 years of age is quite rare (Fig. 6.19.5). An embolic source from the heart is present in less than 10% of patients with central retinal artery obstruction, but echocardiography and Holter monitoring should be performed, especially in younger patients. In some cases, transesophageal echocardiography is necessary to reveal embolic sources.<sup>25</sup> In a large, population-based study, subjects with history of retinal artery obstruction were two times more likely to have a stroke than controls.<sup>26</sup>

Even though it is present in less than 5% of cases, it is of paramount importance that temporal arteritis be ruled out in all patients older than 50 years who have a central retinal artery obstruction. An immediate erythrocyte sedimentation rate must be obtained, and if it is elevated or if clinical





**Fig. 6.19.5 Acute Central Retinal Artery Obstruction.** Secondary to an embolus at the lamina cribrosa. Note two other emboli in the superior retinal vessels. Ipsilateral carotid artery disease was present.

suspicion exists, corticosteroid therapy and a temporal artery biopsy are considered.

Other rare associated systemic diseases include blood-clotting abnormalities such as antiphospholipid antibodies, protein S deficiency, protein C deficiency, and antithrombin III deficiency.<sup>27,28</sup> A list of systemic associations for retinal artery obstructions is given in [Box 6.19.3](#).

## **PATHOLOGY**

Histopathological examination shows coagulative necrosis of the inner retina. Acute, early, intracellular edema is followed by complete loss of the inner retinal tissue. Chronically, a diffuse acellular zone replaces the nerve fiber layer, ganglion cell layer, and inner plexiform layer. The outer retinal cells remain relatively intact. Sections of the obstructed central retinal artery may reveal a thrombus or embolus that is often recanalized ([Fig. 6.19.6](#)).

## **TREATMENT**

No proved treatment exists for central retinal artery obstruction, but treatment strategies center around the following goals:

- Increase retinal oxygenation.
- Increase retinal arterial blood flow.
- Reverse arterial obstruction.
- Prevent hypoxic retinal damage.

Theoretically, retinal oxygenation can be increased by breathing carbogen (95% oxygen, 5% carbon dioxide). No clinical study indicates efficacy for carbogen therapy, and one retrospective study suggests that it has no beneficial effect.<sup>29</sup> It is rarely used currently.

An increase in retinal arterial blood flow is attempted by lowering intraocular pressure. This is accomplished by ocular massage, paracentesis,

### **BOX 6.19.3 Systemic Conditions Associated With Retinal Artery Obstructions**

#### **Atherosclerotic Cardiovascular Disease**

- Ophthalmic artery plaques, stenosis, or dissection
- Carotid artery plaques, stenosis, or dissection
- Aortic plaques, stenosis, or dissection

#### **Cardiac**

- Valvular disease (including rheumatic fever)
- Ventriculoseptal defects
- Patent foramen ovale
- Papillary fibroelastoma
- Cardiac myxoma
- Mural thrombus
- Arrhythmias
- Subacute bacterial endocarditis

#### **Coagulopathies**

- Antiphospholipid antibodies
- Lupus anticoagulant
- Protein C deficiency
- Protein S deficiency
- Antithrombin III deficiency
- Elevation of platelet factor 4
- Prothrombin deficiency
- Sickle cell disease

#### **Oncological**

- Metastatic tumors
- Leukemia
- Lymphoma

#### **Radiological and Medical Procedures**

- Angiography
- Angioplasty
- Chiropractic neck manipulation
- Depot corticosteroid injection

#### **Systemic Vasculitis**

- Susac's disease
- Systemic lupus erythematosus
- Polyarteritis nodosa

- Temporal arteritis
- Scleroderma
- Sneddon–Wilkinson disease
- Wegener's granulomatosis
- Inflammatory bowel disease
- Kawasaki syndrome

#### **Systemic Infections**

- Syphilis
- Mediterranean spotted fever
- Loiasis
- Bartonella
- Dengue fever

#### **Local Trauma**

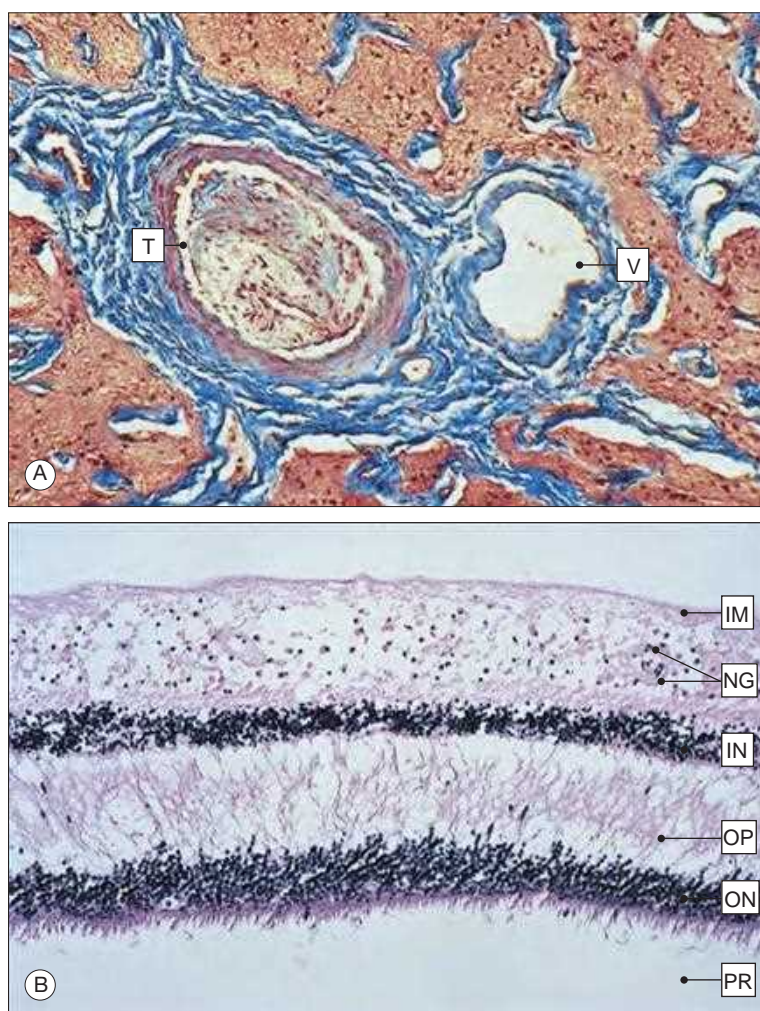
- Direct ocular compression
- Penetrating injury
- Retrobulbar injection
- Peribulbar injection
- Postretinal detachment repair
- Orbital trauma
- Retrobulbar hemorrhage
- Purtscher disease

#### **Local Ocular**

- Prepapillary arterial loops
- Optic nerve drusen
- Necrotizing herpetic retinitis
- Orbital mucormycosis
- Toxoplasmosis

#### **Miscellaneous**

- Amniotic fluid embolism
- Pancreatitis
- Migraine
- Pregnancy
- Oral contraceptives
- Cocaine abuse
- Intravenous drug use
- Viperine snakebite



**Fig. 6.19.6 Central Retinal Artery Occlusion.** (A) A trichrome-stained section shows an organized thrombus (T) that occludes the central retinal artery within the optic nerve (V, vein). (B) A histological section at the early stage shows edema of the inner neural retinal layers and ganglion cell nuclei pyknosis. Patient had a cherry-red spot in the fovea at time of enucleation. IM, Internal limiting membrane; IN, inner nuclear layer; NG, swollen nerve fiber and ganglion layers; ON, outer nuclear layer; OP, outer plexiform layer; PR, photoreceptors.

and the administration of ocular antihypertensive medications. Medical attempts to dilate retinal arteries or block vascular spasm have been tried as well. Hemodilution, sublingual nitroglycerin, pentoxifylline (oxpentifylline), calcium-channel blockers, and  $\beta$ -blockers have all been used with no proof of efficacy.<sup>30,31</sup>

Reversal of arterial obstruction through the use of anticoagulation or fibrinolytic medications has been reported. To date, the utility of these interventions has not been proved by controlled clinical trials. The only prospective, controlled trial of intra-arterial thrombolysis (EAGLE Study) was unable to show a benefit compared to conventional therapy although the power of the study was low.<sup>32</sup>

Thrombolysis can also be achieved intravenously as per stroke thrombolysis protocol. An interventional case series demonstrated that intravenous tPA with concomitant intravenous heparin resulted in visual improvement of three Snellen lines or more in 50% of subjects if given within 6.5 hours after onset of symptoms.<sup>33</sup> The results of a small, randomized, controlled trial also suggest that intravenous tPA is efficacious only when given within 6 hours of onset of symptoms.

At present, prevention of hypoxic damage to the retina is only theoretically possible.<sup>34</sup> Antioxidant medications (e.g., superoxide dismutase) and *N*-methyl-D-aspartate (NMDA) inhibitors are two classes of compounds that may accomplish retinal rescue pharmacologically and are under study. Hyperbaric oxygen therapy with hemodilution can also be used.<sup>35</sup>

Cases of central retinal artery obstruction associated with temporal arteritis are treated emergently with high-dose corticosteroids. Without therapy, the risk to the second eye is great. Although the first affected eye rarely recovers, instances exist in which high-dose intravenous methylprednisolone induced visual recovery from central retinal artery obstruction associated with temporal arteritis.<sup>36</sup>

## COURSE AND OUTCOME

Most central retinal artery obstructions result in severe, permanent loss of vision. About one-third of patients experience some improvement in final vision in terms of presentation acuity either with or without conventional treatment. Three or more Snellen lines of improved visual acuity occur in only about 10% of untreated patients.

Experimentally, if an obstruction exists in the primate retina for more than 240 minutes, complete irreversible death of the inner retina occurs.<sup>37</sup> In practice, a rare patient has experienced total spontaneous recovery even after several days of documented visual loss.<sup>38</sup> Spontaneous recovery may be more common in young children.

## BRANCH RETINAL ARTERY OBSTRUCTION

### INTRODUCTION

Branch retinal artery obstruction represents a rarely encountered retinal vascular disorder. Although current treatments are not effective, in the majority of cases the source of the obstruction can be determined. As associated systemic implications occur, diagnosis and systemic evaluation of these patients are critical.

### EPIDEMIOLOGY AND PATHOGENESIS

Branch retinal artery obstruction is a rare event, even less common than central retinal artery obstruction overall. The exception to this comparative incidence is with young patients, in whom branch retinal artery obstruction is the more common type of retinal artery obstruction.<sup>39</sup> Overall, men are more affected than women by a 2:1 ratio, which reflects the higher incidence of vasculopathic disease in men. In the subset of young patients (less than 50 years of age), women and men are affected equally. The mean age of affected patients is 60 years, with a range from the second decade of life to the tenth. The great majority of patients are in the sixth or seventh decade of life. The right eye (60%) is affected more commonly than the left (40%), which probably reflects the greater possibility of cardiac or aortic emboli traveling to the right carotid artery. Branch retinal artery obstruction strikes the temporal retinal circulation far more frequently than the nasal, consistent with the greater blood flow to the macular retina.<sup>40</sup>

Over two-thirds of branch retinal artery obstructions are secondary to emboli to the retinal circulation.<sup>41</sup> In most cases, the emboli are clearly visible in the arterial tree. Emboli to the retinal circulation may originate at any point in the proximal circulation from the heart to the ophthalmic artery. Risk factors reflect the vasculopathic mechanisms that produce disease within the cardiovascular system. These include predisposing family history, hypertension, elevated lipid levels, cigarette smoking, and diabetes mellitus.

Three main types of retinal emboli have been identified:

- Cholesterol (Hollenhorst plaque).
- Platelet-fibrin.
- Calcific.

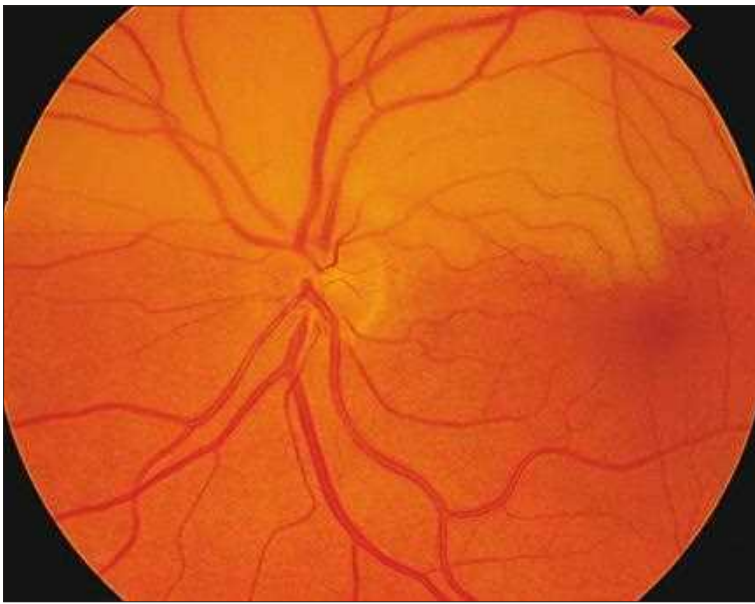
Cholesterol emboli typically emanate from atheromatous plaques of the ipsilateral carotid artery system, although the aorta or heart valves may also be a source. They are yellow-orange in color, refractile, and globular or rectangular in shape. They may be small and can on occasion be seen intravascularly without blockage of blood flow. Platelet-fibrin emboli are long, smooth, white-colored, intra-arterial plugs that may be mobile or break up over time. Usually they are associated with carotid or cardiac thromboses. Calcific emboli are solid, white, nonrefractile plugs associated with calcification of heart valves or the aorta.

Less commonly seen embolic types include tumor cells from atrial myxoma<sup>42</sup> or a systemic metastasis, septic emboli associated with septicemia or endocarditis, fat emboli associated with large bone fractures, emboli dislodged during angioplasty or angiography, and depot drug preparations from intra-arterial injections around the eye or face.

Rarely, local ocular conditions produce branch retinal artery obstruction. These include inflammatory diseases such as toxoplasmosis<sup>43</sup> or acute retinal necrosis, mechanical compression from anterior ischemic optic neuropathy,<sup>44</sup> or structural entities such as optic disc drusen or prepapillary arterial loops.

Systemic hematological or clotting problems may induce isolated branch retinal artery obstruction or even multiple recurrent branch retinal artery obstruction.<sup>45,46</sup> Systemic vasculitides, such as polyarteritis nodosa





**Fig. 6.19.7 Superior Hemispheric Branch Retinal Artery Obstruction.** The site of obstruction is probably within the optic nerve substance itself. Note that the dual trunk of the central retinal artery obstruction has separated proximal to the lamina. Only the superior trunk was affected.

or local vasculitis associated with varicella infection, may be associated with branch retinal artery obstruction. Oral contraceptive use and cigarette smoking have been implicated as possible risk factors, especially in young, otherwise healthy women.

## OCULAR MANIFESTATIONS

Abrupt, painless loss of vision in the visual field corresponding to the territory of the obstructed artery is the typical history of presentation. Amaurosis fugax occurs in about one-fourth of patients prior to frank obstruction, especially in the setting of carotid disease. Rarely, patients develop bilateral simultaneous branch retinal artery obstruction, which can mimic homonymous field defects.

Acutely, examination reveals intact central acuity in about 50% of patients. A relative afferent pupillary defect is common, the presence of which is determined by the extent of retinal involvement.

Retinal whitening that corresponds to the areas of ischemia is the most notable finding. The whitening stops at adjacent retinal veins, as these vessels mark the extent of the territory of the retinal arteries (Fig. 6.19.7). Retinal emboli are seen in over two-thirds of branch retinal artery obstructions. Flame hemorrhages at the margins of the retinal ischemia are not uncommon, and local areas of more intense inner retinal whitening that resemble scattered cotton-wool spots can develop. Other areas with less intense retinal whitening may represent paracentral acute middle maculopathy (PAMM) lesions.<sup>47</sup>

A syndrome of multiple, recurrent, bilateral branch retinal artery obstruction in young, otherwise healthy patients has been reported. A few of the patients also manifest vestibuloauditory symptoms.<sup>48</sup> Although the underlying pathology in this subset of patients is probably heterogeneous, some probably have Susac's syndrome, a rare disorder that manifests as a microangiopathy of the central nervous system. Others probably have various types of systemic clotting abnormalities.<sup>49</sup>

In the chronic phase, when the retinal whitening has diminished, a loss of the nerve fiber layer in the affected area may be apparent. In most instances, the affected retina appears normal. At the site of obstruction, localized sheathing of the arteriole is common. Arteriolar collaterals on the optic disc or at the site of obstruction may develop.

## DIAGNOSIS AND ANCILLARY TESTING

Ancillary testing is not usually necessary to make the diagnosis. Fluorescein angiography (FA) reveals an abrupt diminution in dye at the site of the obstruction and distally. Filling in the adjacent retinal veins is slow to absent, and late staining or even leakage from the embolus site may occur. OCT initially reveals thickening and hyperreflectivity consistent with intracellular edema of the inner retina in the territory of the obstructed artery.<sup>50</sup> Over time, the corresponding inner retina will be severely thinned. OCT

### BOX 6.19.4 Differential Diagnosis of Branch Retinal Artery Obstruction

- Cotton-wool spot(s)
- Central retinal artery obstruction
- Cilioretinal artery obstruction
- Retinal astrocytoma
- Inflammatory or infectious retinitis

angiography demonstrates vascular features that correlate with FA and provide improved visualization of the microvasculature compared to FA, suggesting potential utility in monitoring branch retinal artery obstruction resolution.<sup>51</sup>

Visual field testing can confirm the extent of visual loss and may pick up contralateral field loss from previous emboli or other associated conditions.

## DIFFERENTIAL DIAGNOSIS

The differential diagnosis of branch retinal artery obstruction is given in Box 6.19.4.

## SYSTEMIC ASSOCIATIONS

Systemic evaluation of patients who have branch retinal artery obstruction discloses evidence of an embolic source from the carotid arteries or the heart, in many cases. Other rare systemic conditions associated with branch retinal artery obstruction include amniotic fluid embolism, pancreatitis, sickle-cell disease, homocystinuria, and Kawasaki disease. Young patients, especially those who have multiple or recurrent branch retinal artery obstruction, should be evaluated for systemic clotting abnormalities.

Branch retinal artery obstruction associated with temporal arteritis is exceedingly uncommon.<sup>52</sup> It is not usually necessary to obtain an erythrocyte sedimentation rate unless other evidence of temporal arteritis exists. Box 6.19.3 lists the systemic conditions most commonly associated with retinal artery obstructions.

## PATHOLOGY

Early coagulative necrosis of the inner layers of the neural retina, which are supplied by the retinal arterioles, is manifest by edema of the neuronal cells during the first few hours after arterial occlusion and becomes maximal within 24 hours. The intracellular swelling accounts for the gray retinal opacity seen clinically. If the area of coagulative necrosis is small and localized, it appears as a cotton-wool spot, the clinical manifestation of a microinfarct of the nerve fiber layer of the neural retina. The cytoïd body observed microscopically is a swollen, interrupted axon in the neural retinal nerve fiber layer. Histologically, the swollen end bulb superficially resembles a cell, hence the term cytoïd body. A collection of many cytoïd bodies, along with localized edema, marks the area of the microinfarct. A cotton-wool spot represents a localized accumulation of axoplasmic debris in the neural retinal nerve fiber layer and results from interruption of the orthograde or retrograde organelle transport in ganglion cell axons, that is, obstruction of axoplasmic flow.

The outer half of the neural retina is well preserved. The inner half of the neural retina, however, becomes "homogenized" into a diffuse, relatively acellular zone, which generally contains thick-walled retinal blood vessels. Because the glial cells die along with the other neural retinal elements, gliosis does not occur.

## TREATMENT

No proven treatment exists for branch retinal artery obstruction. Because the visual prognosis is much better for branch retinal artery obstruction than for central retinal artery obstruction, invasive therapeutic maneuvers of dubious utility are not typically performed. Rarely, ocular massage or paracentesis will successfully dislodge an embolus. Laser treatment has been employed to disrupt emboli, in some cases with improvement in the vision.<sup>53,54,55</sup>

One report suggests that hyperbaric oxygen therapy may improve the visual loss associated with multiple branch retinal artery obstruction in Susac's syndrome.<sup>56</sup>



In the rare patient who has branch retinal artery obstruction accompanied by a systemic clotting disorder, systemic anticoagulation may prevent further events.

## COURSE AND OUTCOME

Most patients remain with a fixed visual field defect but intact central acuity. About 80% of eyes recover to 20/40 (6/12) or better central acuity. Retinal neovascularization has been reported but is distinctly uncommon. Iris neovascularization does not occur. In retrospective studies, greater foveal and outer nuclear layer thickness on OCT during the acute phase were positively correlated with improved vision in resolved branch retinal artery obstruction and thus may be useful prognostic factors.<sup>57,58</sup>

## OPHTHALMIC ARTERY OBSTRUCTION

Acute simultaneous obstruction of both the retinal and choroidal circulations is referred to as an ophthalmic artery obstruction. In some cases a single site of blockage in the ophthalmic artery is present, and in others simultaneous interruption of the retinal and posterior choroidal circulations with multiple blockage sites is found.

Ophthalmic artery obstructions can be differentiated clinically from central retinal artery obstruction by the following features:<sup>59</sup>

- Severe visual loss—bare or no light perception.
- Intense ischemic retinal whitening that extends beyond the macular area.
- Little to no cherry-red spot.
- Marked choroidal perfusion defects on fluorescein angiography.
- Nonrecordable electroretinogram.
- Late retinal pigment epithelium alterations.

Cases of ophthalmic artery obstruction usually have associated local orbital or systemic diseases, which include orbital mucormycosis, orbital trauma, retrobulbar anesthesia, depot corticosteroid injection, atrial myxoma, or carotid artery disease. Temporal arteritis usually does not produce ophthalmic artery obstruction in the absence of ipsilateral ischemic optic neuropathy.

As with central retinal artery obstruction, no proven therapy exists and significant visual recovery usually does not occur. In the absence of local causes, systemic evaluation must include testing for temporal arteritis, carotid artery disease, and cardiac disease.

## CILIORETINAL ARTERY OBSTRUCTION

A cilioretinal artery exists in about 30% of individuals. It is a vessel that perfuses the retina and is derived directly from the posterior ciliary circulation rather than from the central retinal artery. For this reason, it may remain patent in the setting of a central retinal artery obstruction. Such vessels are usually observed to emanate from the temporal disc margin. They may be multiple and can also perfuse the nasal retina. On fluorescein angiography, they fill 1–3 seconds prior to the retinal circulation. Cilioretinal artery obstruction exists in three clinical variations:

- Isolated
- Cilioretinal artery obstruction combined with central retinal vein obstruction
- Cilioretinal artery obstruction combined with ischemic optic neuropathy

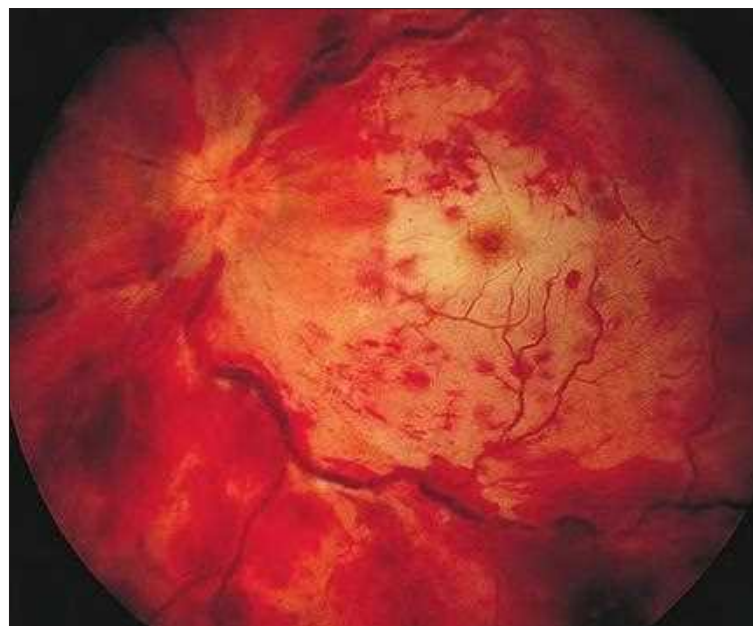
Isolated cilioretinal artery obstructions usually occur in young patients in the setting of collagen vascular disorders. They carry a good visual prognosis, with 90% of eyes left with 20/40 (6/12) or better vision.<sup>60</sup>

Cilioretinal artery obstruction combined with central retinal vein obstruction is not an uncommon variant in young patients (Fig. 6.19.8). It generally behaves as a nonischemic central retinal vein obstruction with a good central visual prognosis. The scotoma from the artery obstruction is usually permanent. Although the mechanism of this association is unclear, it is hypothesized that some eyes harbor a primary optic disc vasculitis (papillophlebitis) that affects both the arterial and venous circulation.<sup>61</sup> It is more common in men than in women. Patients are generally healthy, but this entity has been associated with inflammatory bowel disease and leukemia.

In contrast to the first two groups discussed before, cilioretinal artery obstruction with ischemic optic neuropathy carries a grim visual prognosis and a strong association with temporal arteritis.



**Fig. 6.19.8 Cilioretinal Artery Obstruction in Conjunction With Mild Nonischemic Central Retinal Vein Obstruction.** Note the retinal whitening just inferior to the fovea in the distribution of the cilioretinal artery.



**Fig. 6.19.9 Combined Central Retinal Artery Obstruction and Central Retinal Vein Obstruction.** Visual acuity in this 21-year-old woman who had lupus was light perception, and neovascularization of the iris ensued.

## COMBINED ARTERY AND VEIN OBSTRUCTIONS

Central retinal artery obstruction combined with simultaneous central retinal vein obstruction rarely occurs. Patients typically present with acute, severe loss of vision. Examination shows a cherry-red spot combined with features of a central retinal vein obstruction, which include dilated, tortuous veins that have retinal hemorrhages in all four quadrants (Fig. 6.19.9).<sup>62</sup> Associated systemic or local disease is the rule—collagen vascular disorders, leukemia, orbital trauma, retrobulbar injections, and mucormycosis have been implicated. The visual prognosis is generally poor and the risk of neovascularization of the iris is about 75%. In exceptional cases, a patient may manifest spontaneous improvement.<sup>63</sup>

Branch retinal artery obstruction combined with simultaneous central retinal vein obstruction has also been reported.<sup>64</sup> This rare entity behaves as a central retinal vein obstruction. Interferon has been implicated.<sup>65</sup> Neovascularization of the iris is possible, but systemic associations other than hypertension and diabetes have not been confirmed. Treatment with hyperbaric oxygen and nadroparin calcium has been described.<sup>66</sup>

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## Venous Occlusive Disease of the Retina

6.20

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## CENTRAL RETINAL VEIN OCCLUSION

**Definition:** Occlusion of the central retinal vein at the lamina cribrosa.

## Key Features

- Retinal hemorrhages in all four quadrants.
- Dilated, tortuous veins in all four quadrants.

## Associated Features

- Optic disc edema.
- Macular edema.
- Submacular fluid.
- Cotton-wool spots.
- Capillary nonperfusion.
- Neovascularization of the iris, retina, or optic disc.
- Vitreous hemorrhage.
- Neovascular glaucoma.
- Optic disc venous – venous collateral vessels (opticociliary collateral vessels).

## BRANCH RETINAL VEIN OCCLUSION

**Definition:** Occlusion of a branch retinal vein.

## Key Features

- Retinal hemorrhages in the distribution of the obstructed branch retinal vein.
- Dilated, tortuous retinal vein in the distribution of the obstructed branch.

## Associated Features

- Optic disc edema.
- Macular edema.
- Submacular fluid.
- Cotton-wool spots.
- Capillary nonperfusion.
- Retinal neovascularization.
- Vitreous hemorrhage.
- Sheathing of vasculature.
- Lipid exudates.
- Microvascular changes including microaneurysms and collateral vessels.
- Pigmentary macular disturbances.
- Subretinal fibrosis.

## INTRODUCTION

Venous occlusive disease of the retina is the second most common retinal vascular disorder, behind diabetic retinopathy.<sup>1</sup> It is believed to be caused by external compression of the vein by an atherosclerotic artery, intraluminal thrombosis, or inflammation of the vein<sup>2,3</sup> and typically affects patients 50 years of age or older. Retinal vein occlusions are usually recognized by

their characteristic clinical appearance, and treatment options have been investigated thoroughly with large, multicenter, randomized clinical trials.

Retinal vein occlusions are classified according to whether the central retinal vein or one of its branches is obstructed. Central retinal vein occlusion (CRVO) and branch retinal vein occlusion (BRVO) differ with respect to pathophysiology, underlying systemic associations, clinical course, and therapy. Branch retinal vein occlusions occur more frequently than CRVO.

## EPIDEMIOLOGY

The global impact of RVOs is significant, with an estimated 16.4 million adults affected worldwide—2.5 million affected by CRVO and 13.9 affected by BRVO.<sup>4,5</sup> Large, population-based studies have shown that the cumulative incidence of RVO over a 9–15 year period is 1.6%–3.0% in the elderly population,<sup>1,6</sup> with a 9–15 year cumulative incidence of CRVO at 0.3%–0.5% and BRVO at 1.6%–2.7%.<sup>6–8</sup> Using pooled data from populations in the United States, Europe, Asia, and Australia, the estimated prevalence of BRVO is 4.42 per 1000 people and CRVO is 0.8 per 1000 people, increasing with age.<sup>4</sup> Additionally, CRVO is associated with an increase in mortality because of its statistical association with comorbid diabetes or cardiovascular disease.<sup>9</sup> The presence of glaucoma is frequently found to be a risk factor for the development of both CRVO and BRVO, with an odds ratio of 2.53 and 9.28, respectively<sup>6</sup>; however, the Beijing Eye Study did not find such an association.<sup>7</sup> Variations in the population-based studies are likely due to significant variations in sample ethnicity as well as differences in age eligibility for subjects. Bilaterality is uncommon in both CRVO and BRVO, with a coincident second RVO occurring in 6.3% eyes in the 15-year Beaver Dam Eye Study cohort,<sup>6</sup> in 6.4% of eyes after 5 years in the Blue Mountains Eye Study.<sup>1</sup> The risk of any vascular occlusion in an unaffected fellow eye has also been estimated to be 0.9% per year.<sup>10</sup>

Data on the economic burden of vein occlusions is limited. Using the Beaver Dam Eye Study estimates of prevalence in conjunction with a study on the Medicare cost per CRVO diagnosis based on 2006 dollars,<sup>11</sup> the total costs to the U.S. Medicare population are estimated to be \$1.3 billion annually for CRVO.<sup>12</sup>

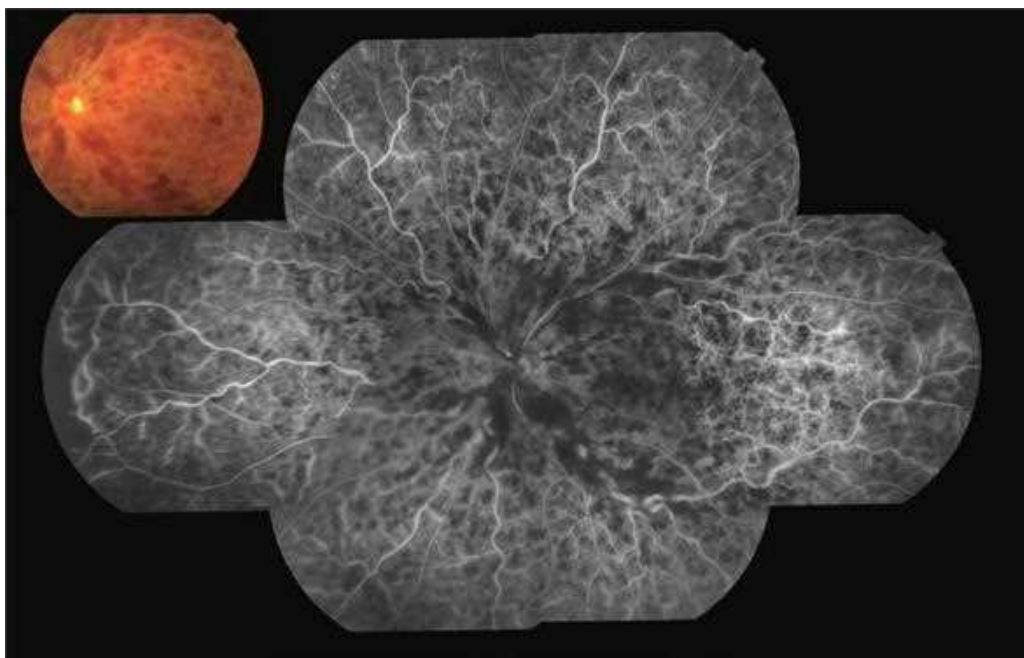
## CENTRAL RETINAL VEIN OCCLUSION

## PATHOGENESIS

The occlusion is believed to be the result of a thrombus in the central retinal vein at or posterior to the lamina cribrosa. Arteriosclerosis of the neighboring central retinal artery that causes turbulent venous flow and then endothelial damage often is implicated. Endothelial cell proliferation has been suggested also. An alternative theory is that thrombosis of the central retinal vein is an end-stage phenomenon, induced by a variety of primary insults such as compressive or inflammatory optic nerve or orbital problems, structural abnormalities in the lamina cribrosa, or hemodynamic changes.

## OCULAR MANIFESTATIONS

The diagnosis of a CRVO is based on the characteristic fundus findings of dilated and tortuous retinal veins in all four quadrants of the retina in association with intraretinal hemorrhages, cotton-wool spots, retinal exudations, disc edema, and/or concurrent signs of hypertensive retinopathy (Fig. 6.20.1).<sup>13</sup> Macular edema and ischemia are the most common causes of vision loss; however, the presence of intraretinal hemorrhage and exudates in the fovea can also affect vision. Patients generally present with acute onset painless blurry vision although an incidental finding of a mild



**Fig. 6.20.1 Central Retinal Vein Occlusion.** Fluorescein angiogram with peripheral sweeps showing dilated and tortuous retinal veins with widespread blocking defects from intraretinal hemorrhage (see color fundus photograph inset) and far peripheral nonperfusion.

CRVO is possible. Rarely, patients can present with a combined retinal vein and artery occlusion, which typically lead to a poor visual prognosis.<sup>14,15</sup>

The severity of CRVOs often corresponds to the amount of retinal nonperfusion, which can easily be appreciated on fluorescein angiography. Vision for minimally nonperfused CRVOs can be mild to moderate, whereas highly nonperfused eyes can have an afferent pupillary defect with significant vision loss. Traditionally, CRVOs were categorized as non-ischemic CRVOs, which is defined as less than 10 disc areas of ischemia as seen on the traditional seven standard field fluorescein angiography, versus ischemic CRVOs, which encompasses all other eyes. This distinction between the two types of CRVOs remains somewhat arbitrary, representing a continuum of disease severity but has been an important separation in literature describing CRVO outcomes. Of all patients with CRVO, 75%–80% can be considered classically nonischemic (Fig. 6.20.2), whereas classic ischemic CRVOs account for 20%–25% of all CRVOs (Fig. 6.20.3). The Central Vein Occlusion Study (CVOS) Group found that 34% of nonischemic CRVOs progressed to become ischemic within 3 years.<sup>10</sup>

Ischemic CRVOs tend to have higher rates of neovascularization of the iris and/or angle,<sup>16,17</sup> which typically occur within 3 months of disease onset (90-day glaucoma), and the subsequent rate of neovascular glaucoma ranges from 20%–63% (compared to 0% in nonischemic CRVOs).<sup>18</sup> In the absence of neovascularization, the pathological clinical features of CRVOs may decrease or resolve 6–12 months after diagnosis. During the resolution phase, the optic nerve can show pallor and develop optociliary collateral vessels. Permanent macular changes can develop that include pigmentary changes, epiretinal membrane formation, and subretinal fibrosis. Macular ischemia or sequelae from persistent macular edema may ultimately limit final visual acuity, especially if there is significant peripheral nonperfusion.

In about 20% of eyes, the central retinal vein enters the optic nerve as two separate branches (superior and inferior) before merging as a single trunk posterior to the lamina cribrosa. In these eyes, occlusion of one of the dual trunks within the substance of the optic nerve results in a hemispheric CRVO. Although only one half of the retina is involved, these occlusions act like CRVOs in terms of visual outcome, risk of neovascularization, and response to treatment.

Some mild CRVOs in patients younger than 50 years are classified as papillophlebitis, a term that suggests a benign course. An inflammatory optic neuritis or vasculitis is hypothesized as the cause. These eyes tend to have optic disc edema out of proportion to the retinal findings, cotton-wool spots that ring the optic disc, and occasionally cilioretinal artery occlusions or even partial central retinal artery occlusions. Although spontaneous improvement is common, the course is not always benign. Up to 30% of these patients may develop the ischemic type of occlusion with a final visual acuity of 20/200 (6/60) or worse.<sup>19</sup>

## ANCILLARY TESTING

Fluorescein angiography for CRVOs show a delayed filling of the retinal veins and is the most useful ancillary test for the evaluation of nonperfusion

and neovascularization. The risk of a neovascular event increases with the extent of nonperfusion, particularly above 5.5 disc areas.<sup>20</sup> The CVOS Group reported that 35% of ischemic and 10% of nonischemic CRVOs demonstrated anterior segment (iris or angle or both) neovascularization at or before the 4-month follow-up.<sup>10</sup> They found the greatest predictors of anterior segment neovascularization were visual acuity and degree of nonperfusion on fluorescein angiography, the worst prognostic groups being patients with visual acuity worse than 20/200 (6/60) or 30 or more disc areas of nonperfusion.<sup>10</sup>

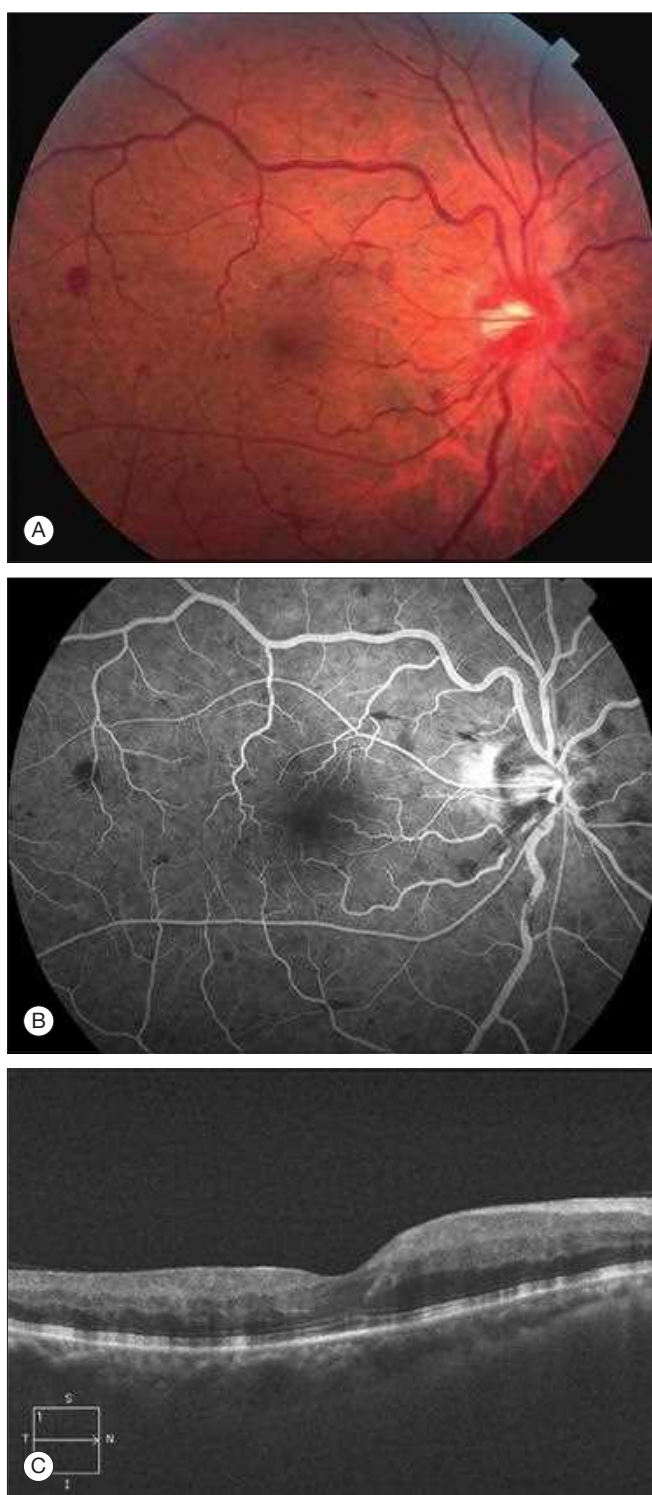
Fluorescein angiography in ischemic CRVOs may show marked hypofluorescence (see Fig. 6.20.3), which is secondary to either blockage from intraretinal hemorrhages or to retinal capillary nonperfusion. When extensive hemorrhages are present, grading the degree of ischemia can be difficult. However, as the hemorrhages clear, the degree of capillary nonperfusion typically becomes more apparent. A greater amount of initial hemorrhages is associated with a higher level of ischemia. Angiography can also reveal optic nerve head leakage and perivenous staining, and in the late stages of the disease, collateral vessels and microaneurysms can be seen. The macular region may also show persistent edema or pigmentary degeneration. With nonischemic CRVOs, fluorescein angiography can reveal staining along the retinal veins, microaneurysms, and dilated optic nerve head capillaries. Retinal capillary nonperfusion (see Fig. 6.20.2) is minimal or absent. As the nonischemic CRVO resolves, angiography may become normal. The appearance of atypical findings on fluorescein angiography, such as choroidal nonperfusion, should prompt consideration of other diagnoses.

The original definitions of ischemic and nonischemic CRVOs in the CVOS study relied on fluorescein angiography from the seven standard field images as defined by the Early Treatment of Diabetic Treatment Study.<sup>21</sup> With the advent of ultra-wide field imaging that can image up to 200° in one capture,<sup>22</sup> a growing number of studies are looking at the utility of assessing nonperfusion on a continuum. Different measurements of nonperfusion, including the ischemic index, total area of nonperfusion, and radial extent of nonperfusion, have all been proposed.<sup>22–25</sup>

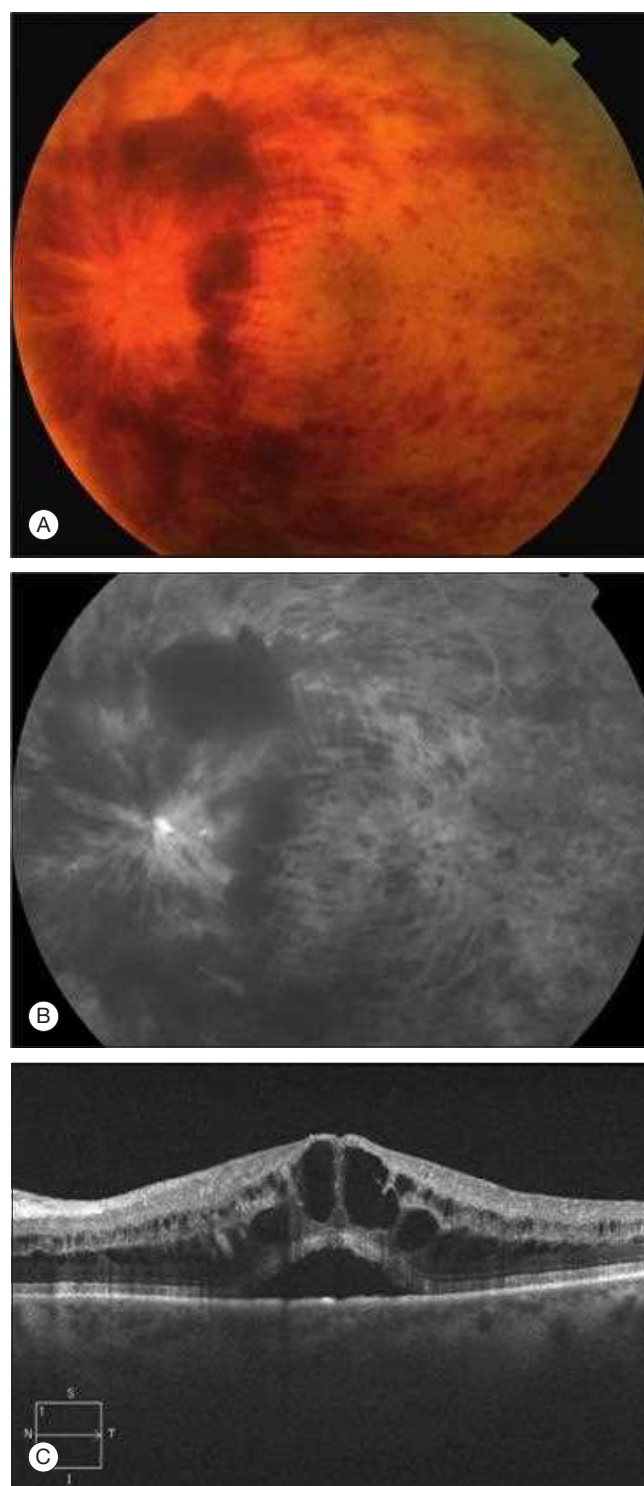
Macular edema is the most common cause of visual loss in RVOs and can occur more severely in ischemic cases. Macular edema is best imaged by optical coherence tomography (OCT), which is useful in quantifying and monitoring macular edema in patients with RVOs.<sup>26,27</sup> OCT commonly shows subclinical serous detachments of the macula in up to 80% of patients.<sup>28</sup> ERM is also a common feature on OCT testing in the setting of an RVO.

## DIFFERENTIAL DIAGNOSIS

The differential diagnosis for CRVOs includes ocular ischemic syndrome, diabetic retinopathy, radiation retinopathy, hyperviscosity retinopathy, and hypertensive retinopathy with possible multiple contributing factors. Ocular ischemic syndrome often presents with attenuated vessels rather



**Fig. 6.20.2 Nonischemic Central Retinal Vein Occlusion.** (A) Fundus photograph and (B) fluorescein angiogram showing scattered intraretinal hemorrhages, mild optic nerve head edema and hyperemia, and dilated and tortuous veins. (C) Optical coherence tomography showing no significant macular edema.



**Fig. 6.20.3 Ischemic Central Retinal Vein Occlusion.** (A) Fundus photograph and (B) fluorescein angiogram showing extensive intraretinal hemorrhages. The vasculature is barely discernable. (C) Optical coherence tomography showing cystoid macular edema with subretinal fluid.

than dilated and tortuous veins, can have choroidal in addition to retinal nonperfusion, and can be associated with hypotony from ciliary body ischemia. Additionally, the retinal hemorrhages seen in ocular ischemic syndrome tend to localize to the midperiphery instead of the posterior pole as seen in CRVO. Diabetic retinopathy requires the concurrent diagnosis of diabetes and is generally a bilateral disease. Radiation retinopathy requires an antecedent history of radiation affecting the periorbital region.

Hyperviscosity syndromes may produce a retinopathy similar to CRVO or BRVO. Simultaneous bilateral disease is an unusual finding in RVOs but occurs more commonly in hyperviscosity states seen in diseases like Waldenström's macroglobulinemia, polycythemia vera, leukemia, and multiple myeloma. Additionally, vasculitis that may be associated with

systemic inflammatory disease, such as sarcoidosis, Behçet's, and polyarteritis nodosa, can also masquerade as a CRVO.

When a patient presents with a CRVO in the absence of clear risk factors or presents with bilateral disease, the medical and laboratory evaluation should include a targeted search for evidence of diabetes, hyperviscosity syndromes, or inflammatory disease. Treatment of the primary disease can help improve the course of the retinopathy. For instance, plasmapheresis can be effective in reversing the retinopathy seen in cases of acute hyperviscosity syndrome.<sup>29</sup> Severe anemia with thrombocytopenia can also cause a retinopathy that resembles CRVO, which can be treated with transfusions. Lastly, acute hypertensive retinopathy with disc edema may resemble bilateral CRVO and require immediate lowering of blood pressure to prevent end-organ damage throughout the body.



**BOX 6.20.1 Medical and Ophthalmic Workup for Central Retinal Vein Occlusion and Branch Retinal Vein Occlusion****Central Retinal Vein Occlusion**

- Complete history and physical examination
- Complete ophthalmic examination
- Fluorescein angiography
- Optical coherence tomography
- Gonioscopy to look for iris and/or angle neovascularization
- Blood pressure
- Complete blood count
- Chemistry profile
- Coagulation factors
- Fasting blood glucose
- Lipid profile

**Branch Retinal Vein Occlusion**

- Complete history and physical examination
- Complete ophthalmic examination
- Fluorescein angiography
- Optical coherence tomography
- Blood pressure

**SYSTEMIC ASSOCIATIONS AND LABORATORY EVALUATION**

CRVO has been clearly associated with age greater than 50 years and hypertension. The association with hyperlipidemia, diabetes mellitus, and cardiovascular disease has been demonstrated in some studies but not others. These are the most common associations of CRVO, and in a patient over the age of 50 known to have one of these conditions, no further workup is necessary.

The absence of the above known risk factors, especially in a young patient,<sup>30</sup> should prompt a general medical evaluation, which can include a medical history and physical examination with blood pressure evaluation (Box 6.20.1). Basic laboratory evaluation may include a complete blood count, chemistry profile, coagulation factors, hemoglobin A1C, and lipid profile. If a systemic clotting diathesis, blood dyscrasia, or hyperviscosity is suspected based on medical history and concurrent signs, further hematological work up is required. The workup should be driven by medical history and may need to be done in conjunction with a hematologist or rheumatologist. Relevant labs may include lupus anticoagulant, antiphospholipid antibody, anticardiolipin antibody, antithrombin III, factor V Leiden, serum protein electrophoresis, complement factors, and protein S and protein C levels. Elevated levels of homocysteine have also been associated with the development of retinal vascular occlusive disease.<sup>31</sup> If there are signs of inflammation, an autoimmune vasculitis must be ruled out with laboratory work and/or imaging. Oral contraceptive use in women has also been associated with CRVO.<sup>32</sup>

**PATHOLOGY**

Green et al.<sup>2</sup> evaluated histological sections of 29 eyes in 28 patients who had CRVO. All 29 eyes had the formation of a fresh or recanalized thrombus at or just posterior to the lamina cribrosa. There was a mild lymphocytic infiltration with prominent endothelial cells within the thrombi. Further, there was loss of the inner retinal layers consistent with inner retinal ischemia. Alterations in blood flow, hyperviscosity, and vessel wall abnormalities may produce CRVOs by enabling a thrombus of the central retinal vein to form. It has been hypothesized that glaucoma, a risk factor for CRVO, causes stretching and compression of the lamina cribrosa, which results in vessel distortion, increased resistance to flow, and, ultimately, thrombosis.<sup>2</sup>

**TREATMENT**

No known treatment reverses the pathology seen in CRVO. It is prudent to advise risk factor reduction along with a healthy diet and exercise. Several therapies have been proposed but none have proven efficacious, including aspirin; systemic anticoagulation with warfarin, heparin, and recombinant tissue plasminogen activator; local anticoagulation with intravitreal recombinant tissue plasminogen activator; corticosteroids; anti-inflammatory agents; isovolemic hemodilution; plasmapheresis; and optic nerve sheath

**BOX 6.20.2 Treatment Guidelines for Patients Who Have Central Retinal Vein Occlusion**

- Treat any associated intraocular neovascularization with panretinal photocoagulation.
- Treat associated macular edema, if visually significant, with an intravitreal anti-vascular endothelial growth factor (VEGF) agent or corticosteroid.
- Visual acuity loss from macular edema does not improve with grid laser.
- Lower intraocular pressure if elevated.
- Treat underlying medical conditions.

decompression. However, certain complications of CRVO, such as macular edema and neovascularization may be treatable (Box 6.20.2).

**Neovascular Glaucoma**

Neovascular glaucoma (NVG) is a severe complication of ischemic CRVO, and its hallmark is abnormal neovascularization of the iris (NVI) and angle (NVA). This may result in intractable glaucoma, blindness, and pain necessitating enucleation. The 3-year cumulative incidence of NVI or NVG in CRVO is 8.5%.<sup>20</sup> The CVOS Group investigated whether prophylactic panretinal photocoagulation (PRP) was effective in preventing the development of NVI or NVA in patients with ischemic CRVO.<sup>33</sup> The study found that prophylactically treated ischemic eyes developed NVI less frequently than ischemic eyes that were not treated prophylactically (20% in the treatment group versus 35% in the no-early-treatment group), although the difference was not statistically significant. However, PRP was more likely to result in prompt regression of NVI in the previously untreated group versus the prophylactically treated group (56% versus 22%, respectively, after 1 month). As a result, for ischemic CRVO, frequent follow-up examinations during the early months and prompt PRP if NVI develops is the recommended treatment strategy to reduce the risk of developing NVG. Ultra-wide field angiography provides extensive visualization of peripheral nonperfusion in eyes with CRVO allowing for calculation of an “ischemic index,” which may be helpful to identify eyes earlier at highest risk for NVG.<sup>34</sup>

Identification of early NVI at the pupillary border is critical; examination of the undilated pupil is recommended. Routine gonioscopy also is suggested, because NVA can occur without NVI. Intravitreal anti-vascular endothelial growth factor (VEGF) drugs such as bevacizumab have become a useful adjunctive therapy in quickly reducing or eliminating neovascularization from the anterior segment in CRVO.<sup>35</sup> It is important to note that the effect of intravitreal anti-VEGF therapy is limited by the half-life of the drug.

**Macular Edema**

Cystoid macular edema (CME) and resulting macular dysfunction occur in virtually all patients with ischemic CRVO and in many patients with nonischemic CRVO. The CVOS evaluated the efficacy of macular grid photocoagulation in patients with CRVO and macular edema.<sup>36</sup> Although macular grid laser treatment reduced angiographic CME, the study did not find a difference in visual acuity between the treated and untreated groups. As a result, it is not recommended that macular grid photocoagulation be employed for the treatment of CME in CRVO (as opposed to BRVO, see later).

Local administration of a corticosteroid, particularly intravitreal triamcinolone, is commonly used off label to treat CME associated with CRVO.<sup>37</sup> The Standard Care Versus Corticosteroid for Retinal Vein Occlusion (SCORE) study evaluated 1 mg and 4 mg doses of preservative-free intravitreal triamcinolone compared to observation for the treatment of CME in CRVO.<sup>38</sup> They found significant improvements in visual acuity in both treatment groups compared to observation at 1 year ( $\geq 15$  letter gains in 27% of eyes in 1 mg group, 26% in 4 mg group, 7% in untreated group). Incidence of cataract formation and intraocular pressure rise was highest in the 4 mg group (33% and 35% respectively). The effect of intravitreal triamcinolone was temporary, requiring an average of 2.2 and 2.0 injections after 8 months in the 1 mg and 4 mg treatment groups, respectively, to maintain efficacy. This limited duration of efficacy of intravitreal triamcinolone prompted the development of sustained-release intravitreal corticosteroids. A sustained-release intravitreal dexamethasone implant

has gained U.S. Food and Drug Administration (FDA) approval for CME in CRVO and BRVO.<sup>39</sup> One year following treatment with a 0.7 mg implant at baseline and at 6 months, 29% of eyes with CRVO or BRVO experienced a visual acuity gain of 15 or more letters. In a subanalysis, the peak improvement in mean visual acuity in CRVO eyes was 8.7 letters and occurred 60 days following injection. Corticosteroid-induced intraocular pressure rises and cataract formation occurred but generally less frequently compared to those in the SCORE trial.

Prospective studies have proven the efficacy of anti-VEGF agents including bevacizumab,<sup>40,41</sup> which is used off label, and both ranibizumab<sup>42</sup> and aflibercept,<sup>43</sup> which are FDA approved, for the treatment of CME secondary to CRVO. Bevacizumab dosed every 6 weeks for 6 months significantly improved visual acuity compared to sham injection (14.1 letter gain versus 2.0 letter loss).<sup>41</sup> The ranibizumab for the treatment of macular edema after Central Retinal Vein Occlusion Study (CRUISE) found similar gains of 12.7 (0.3 mg group) and 14.9 (0.5 mg group) letters with monthly ranibizumab compared to 0.8 letters in the sham group at 6 months.<sup>42</sup> The HORIZON trial (open-label extension trial of ranibizumab for choroidal neovascularization) included 60% of patients who completed the 12-month CRUISE trial.<sup>44</sup> During the first 12 months of HORIZON, patients were treated as needed with 0.5 mg ranibizumab; the patients originally in the 0.5 mg ranibizumab arm of CRUISE required a mean of 3.5 injections during HORIZON. Some of the visual and anatomical gains achieved during monthly treatment were lost during as-needed treatment. The CRUISE and HORIZON results together have shown that long-term use of ranibizumab is well tolerated, and regular follow-up and treatment are required for optimal visual and anatomic outcomes. The COPERNICUS trial investigated intravitreal aflibercept dosed every 4 weeks for 6 months compared to sham and found significant visual acuity gains compared to sham (6 months: 17.3 letter gain versus 4.0 letter loss). Patients were then dosed as needed for an additional 6 months in both groups, and the initially sham-treated group never caught up in visual acuity gains (12 months: 16.2 letter gain versus 3.8 letter gain), suggesting a benefit of earlier initiation of treatment.<sup>43</sup> The CRYSTAL study also showed that patients with earlier initiation of treatment after the onset of CRVO had better overall visual acuity outcomes.<sup>45</sup> The GALILEO study showed 60.2% of patients treated with aflibercept monthly for 6 months gained 15 or more letters as compared to 20.1% in the sham arm.<sup>46</sup> Finally, the NEWTON study demonstrated that patients previously treated with bevacizumab and ranibizumab experienced a longer edema-free interval on aflibercept (62 days on aflibercept vs. 39 days on bevacizumab/ranibizumab).<sup>47</sup> Anti-VEGF therapy has become the standard of care for the treatment of CME secondary to CRVO due to the convincing results of these trials.

## COURSE AND OUTCOME

The prognosis for visual recovery is dependent on the subtype of CRVO. In general, the visual prognosis can be predicted from the visual acuity during initial evaluation. Patients who have nonischemic CRVOs may experience a complete recovery of vision, although this occurs in less than 10% of cases.<sup>48</sup> In the CVOS, which established natural history data on CRVO, baseline visual acuity tended to (but did not always) predict eventual visual acuity outcome, which in turn reflected the perfusion status of the retina.<sup>10</sup> For example, for eyes with presenting visual acuity of 20/40 or more, 65% maintained this range of visual acuity, whereas for eyes with presenting visual acuity of less than 20/200, 80% had visual acuity remaining this poor at the conclusion of the study. With newer treatment modalities (particularly anti-VEGF agents), the natural course of CRVO is being curtailed, and better visual acuity outcomes are now possible compared to the era of the CVOS, as evidenced by the SCORE and CRUISE studies.

In the era of the CVOS study, recommended follow-up examination intervals depended on the presenting visual acuity and degree of ischemia.<sup>10,33,49</sup> With the advent of anti-VEGF therapy, most patients with CRVO are followed monthly, at least initially, while undergoing monitoring and treatment for CME.

## BRANCH RETINAL VEIN OCCLUSION

### PATHOGENESIS

BRVOs occur approximately three times more commonly than CRVOs. Most epidemiological and histopathological evidence implicates arteriolar disease as the underlying pathogenesis. BRVO almost always occurs at an

arteriovenous crossing, where the artery and vein share a common adventitial sheath. The artery typically is anterior (innermost) to the vein.<sup>50</sup> It is postulated that a rigid, arteriosclerotic artery compresses the retinal vein, which results in turbulent blood flow and endothelial damage, followed by thrombosis and occlusion of the vein.

Rarely, local ocular diseases, especially of an inflammatory nature, can result in a secondary BRVO. This has been reported in diseases such as toxoplasmosis, Eales' disease, Behçet's syndrome, and ocular sarcoidosis. When an occlusion does not occur at the arteriovenous crossing, the possibility of an underlying retinochoroiditis or retinal vasculitis should be considered. Macroaneurysms, Coats' disease, retinal capillary hemangiomas, and optic disc drusen are also linked to BRVO.

## OCULAR MANIFESTATIONS

BRVO is a common retinal vascular disorder of the elderly, at least three times more common than CRVO. Visual loss from a BRVO usually is caused by macular edema, macular ischemia, or secondary effects of neovascularization. Patients with BRVO usually complain of sudden onset of blurred vision or a visual field defect. Flame-shaped intraretinal hemorrhages confined to the distribution of a retinal vein are characteristic (Figs. 6.20.4A and 6.20.5A). The distribution of the hemorrhages usually assumes a triangular configuration with the apex at the site of blockage. Mild occlusions are associated with a relatively small amount of hemorrhage, whereas complete occlusions result in extensive hemorrhages, cotton-wool spot formation, and widespread capillary nonperfusion. If the macula is involved, macular edema and ischemia may cause decreased visual acuity. Visual acuity typically ranges from 20/20 (6/6) to counting fingers. If the macula is spared, a BRVO may be asymptomatic. Occasionally a partial BRVO with little hemorrhage and edema may progress to a complete BRVO, with an increase in hemorrhage and edema with a corresponding decrease in visual acuity. BRVOs occur superotemporally 52.3% of the time, inferotemporally 38.5% of the time, and in the nasal quadrant 9.2% of the time.<sup>6</sup> Nasal quadrant BRVOs are likely underrepresented, as most are asymptomatic and thus these patients might not seek ophthalmic attention.

Retinal neovascularization occurs in approximately 20% of cases, but anterior segment neovascularization (NVI/NVA) and NVG are exceedingly rare, in contrast to CRVO. The incidence of retinal neovascularization rises with increasing area of retinal nonperfusion.<sup>51</sup> Retinal neovascularization typically develops within the first 6–12 months but may occur years later. Vitreous hemorrhage and tractional retinal detachment can result, which may require vitrectomy. Microaneurysm formation and lipid exudation may also be present. Capillary nonperfusion is seen best on fluorescein angiography in the later stages after the hemorrhages have cleared. Localized serous retinal detachment can also be seen in the acute setting of a BRVO, a feature that has become more apparent with the advent of OCT.<sup>52</sup>

Over time, the clinical features of an acute BRVO can become subtler so that the fundus can look almost normal. Collateral vessels and microvascular abnormalities usually develop. Collateral vessels crossing the horizontal raphe are a salient feature of BRVO, and their presence should prompt consideration of remote BRVO. The retinal vein may become sclerotic proximal to the site of blockage while the retinal artery that feeds the affected zone may become narrowed and sheathed. Epiretinal membrane and macular retinal pigment epithelial changes as a result of chronic CME sometimes are seen in the late phase of a BRVO.

## ANCILLARY TESTING

Fluorescein angiography is a helpful adjunct for both establishment of the diagnosis and guidance for treatment of a BRVO. Arteriolar filling may be slowed in a severe BRVO, but venous filling in the affected vessel is almost always delayed in the acute phase. Hypofluorescence caused by hemorrhage and capillary nonperfusion are common findings, and dilated, tortuous capillaries are seen. Collateral vessels may cross the horizontal raphe. The retinal vessels, particularly the vein walls near the site of the occlusion, may stain with fluorescein. If neovascularization is present, there is profuse localized leakage on the angiogram. In contrast, collateral vessels do not leak fluorescein. Macular edema, if present, is revealed clearly by fluorescein angiography and may involve the entire fovea or just several clock hours, depending on the distribution of the occlusion. Optical coherence testing has become essential for diagnosing and managing macular edema in patients with BRVO (see Figs. 6.20.4B and D and 6.20.5B and D).





**Fig. 6.20.4 Branch Retinal Vein Occlusion Treated With Focal Laser.** (A) Fundus photograph of localized intraretinal hemorrhages and cotton-wool spots in a segmental distribution along a superotemporal retinal vein. (B) Corresponding optical coherence tomography and thickness map reveal macular edema. (C) Fundus photograph 2 years following treatment with focal grid laser photocoagulation to area of leakage shows resolution of hemorrhage. (D) Corresponding optical coherence tomography and thickness map show resolution of macular edema. (Images courtesy Jay S. Duker, MD.)

## DIFFERENTIAL DIAGNOSIS

The differential diagnosis of BRVO is shown in [Box 6.20.3](#).

## SYSTEMIC ASSOCIATIONS

Many associations have been made with BRVO, the most common being systemic cardiovascular disorders and age.<sup>53</sup> Others include peripheral vascular disease, increased body mass index, and glaucoma. Interestingly, as with CRVO, there is significant discrepancy in regards to definitive risk factor identification among various epidemiological studies of BRVO.

## PATHOLOGY

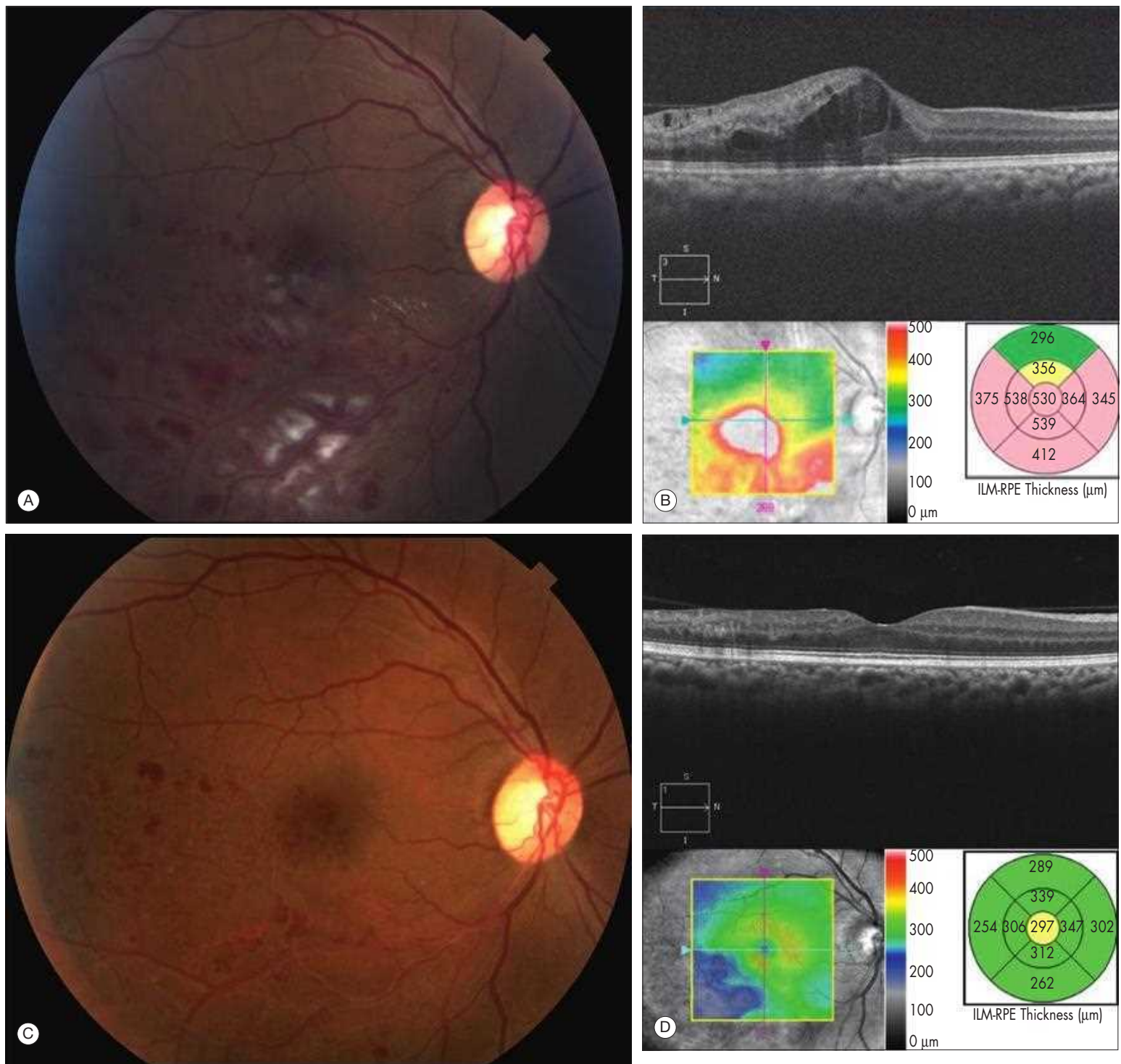
A histopathological study of nine BRVOs showed a fresh or recanalized thrombus at the site of the vein occlusion in all eyes.<sup>3</sup> Ischemic atrophy

of the retina was found in the distribution of the occlusion in most of the eyes. All eyes showed varied degrees of arteriosclerosis. No thrombus was noted in any of the arteries. Neovascularization of the disc and retina was noted in four eyes, and CME was present in five eyes.

## TREATMENT

The Branch Vein Occlusion Study (BVOS) was designed to evaluate the effect of laser photocoagulation on neovascularization, vitreous hemorrhage, and macular edema in BRVO.<sup>51,54</sup> Peripheral sectoral scatter laser photocoagulation reduced the rate of development of both neovascularization and vitreous hemorrhage.<sup>51</sup> There was no advantage in treatment before neovascularization occurred, even if extensive capillary nonperfusion existed. If laser is applied to all nonperfused BRVOs, a large percentage of patients will be treated unnecessarily ([Boxes 6.20.4](#) and [6.20.5](#)). When peripheral laser is indicated, fluorescein angiography can be helpful





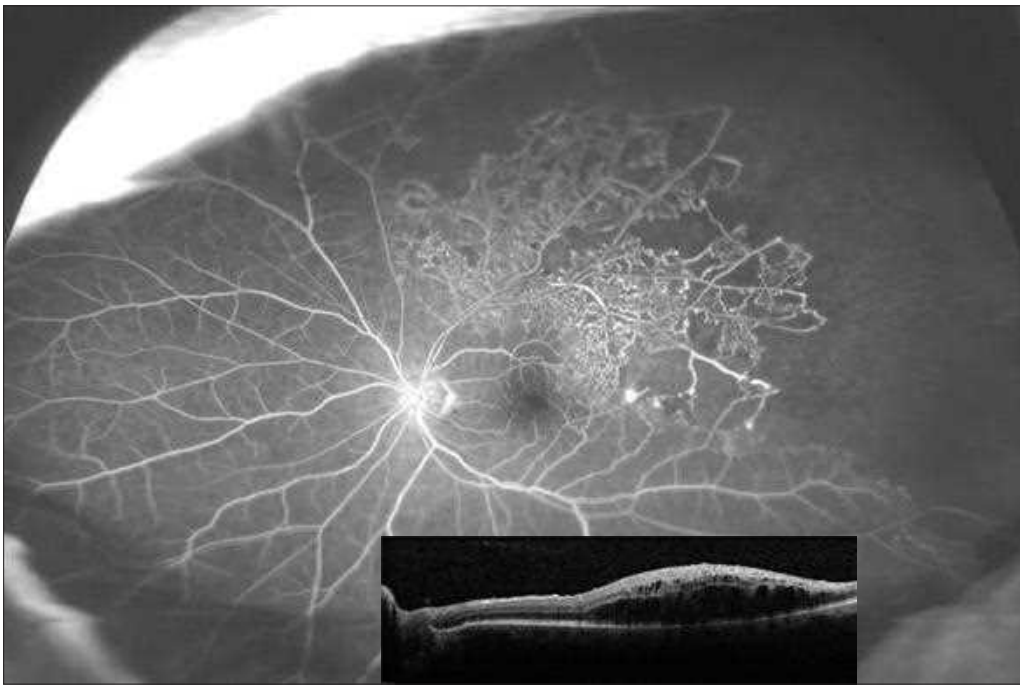
**Fig. 6.20.5 Branch Retinal Vein Occlusion Treated With Combination Focal Laser and Intravitreal Bevacizumab.** (A) Fundus photograph of intraretinal hemorrhages and cotton-wool spots along the inferotemporal retinal vein. (B) Corresponding optical coherence tomography and thickness map reveal significant macular edema. (C) Fundus photograph 6 months following combination treatment with focal grid laser photocoagulation and intravitreal bevacizumab. (D) Corresponding optical coherence tomography and thickness map show resolution of macular edema with mild infratemporal retinal thinning. (Images courtesy Caroline R. Bauml, MD.)

#### BOX 6.20.3 Differential Diagnosis of Branch Retinal Vein Occlusion

- Hypertensive retinopathy
- Diabetic retinopathy
- Radiation retinopathy
- Macular telangiectasia
- Retinal angiomatous proliferation

#### BOX 6.20.4 Treatment Guidelines for Branch Retinal Vein Occlusion and Macular Edema

- Determine if decreased visual acuity is caused by macular edema versus macular nonperfusion based on fluorescein angiography.
- If macular edema explains visual loss, consider early treatment with intravitreal anti-vascular endothelial growth factor (VEGF) therapy.
- Macular edema can resolve spontaneously by 3 months in one-third of patients. Consider grid macular photocoagulation as an adjunct to intravitreal anti-VEGF therapy if needed.
- Intravitreal corticosteroid implants can be considered, especially in pseudophakic patients.
- If capillary nonperfusion explains decreased visual acuity, laser treatment is not advised.



**Fig. 6.20.6 Wide Field Angiography in Branch Retinal Vein Occlusion.** Ultra-wide field fluorescein angiogram shows extensive peripheral nonperfusion in the superior and temporal periphery. Corresponding optical coherence tomography (inset) shows superior macular edema.

#### **BOX 6.20.5 Treatment Guidelines for Branch Retinal Vein Occlusion and Neovascularization**

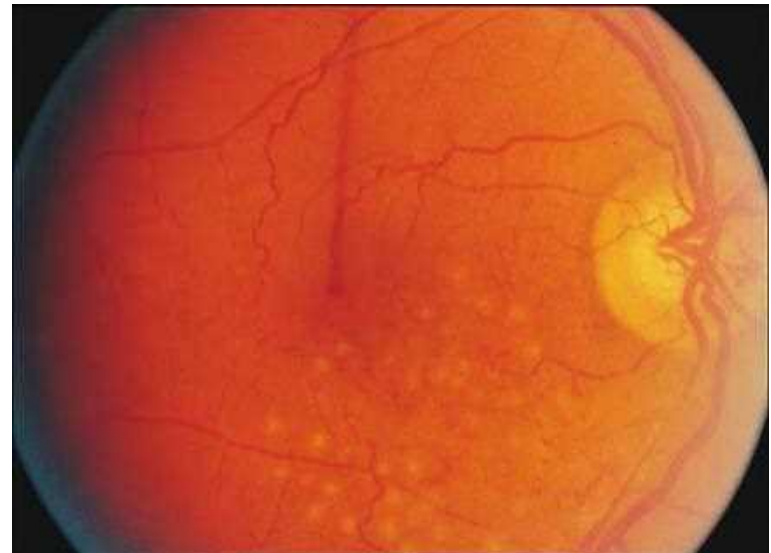
- Obtain a good-quality fluorescein angiography after retinal hemorrhages have cleared sufficiently.
- If more than five disc diameters of nonperfusion are present, the patient should be followed at 4-month intervals to see if the development of neovascularization occurs.
- If neovascularization develops, panretinal photocoagulation to the involved retinal sector should be applied using argon laser.

in guiding laser treatment by defining areas of peripheral capillary nonperfusion (Fig. 6.20.6). A scatter pattern of laser is performed in the affected sector. Vitreous surgery is employed occasionally for nonclearing vitreous hemorrhages, epiretinal membrane, or tractional retinal detachment with macular involvement.

Additionally, BVOS patients who had 20/40 (6/12) or worse vision and macular edema on fluorescein angiography were treated with focal laser in a grid pattern over the area of leakage (as seen with fluorescein angiography). Treated patients had reduced macular edema and improved visual acuity compared to untreated controls.<sup>54</sup> Because visual acuity and macular edema may improve spontaneously, patients were not treated with laser for at least 3 months after the development of the BRVO. Photocoagulation did not extend closer than the edge of the foveal avascular zone, nor did it extend peripherally beyond the major vascular arcades. A grid pattern of laser was applied to the area of capillary leakage (Fig. 6.20.7).

In patients with macular edema, one or multiple focal laser treatments (see Fig. 6.20.4) may be necessary to achieve efficacy.<sup>55</sup> There is some evidence that peripheral nonperfusion, which is best visualized with ultra-wide field angiography (see Fig. 6.20.6), plays a pathogenic role in cases with persistent macular edema despite macular grid laser.<sup>56</sup> Scatter laser to the nonperfused peripheral retina may assist in reducing macular edema in these cases.

As in CRVO, prospective randomized trials have been performed to evaluate intravitreal corticosteroids and intravitreal anti-VEGF agents in the treatment of macular edema associated with BRVO. The SCORE study for BRVO found no improvement in visual acuity outcomes with intravitreal triamcinolone compared to standard grid macular laser treatment for macular edema.<sup>57</sup> Investigators did find higher rates of adverse events (cataract and elevated intraocular pressure) in the corticosteroid groups. The dexamethasone sustained release implant is approved for the treatment of macular edema in BRVO as well as CRVO, and a subanalysis for BRVO showed that nearly 30% of patients gained three or more lines of vision at 60 days, gaining an average of 10.3 letters. The rate of cataract progression



**Fig. 6.20.7 Branch Retinal Vein Occlusion.** Immediate posttreatment view of grid laser treatment for macular edema secondary to a BRVO.

and intraocular pressure elevation was lower for the dexamethasone implant than in the SCORE study, although data in the dexamethasone studies was only available for 6 months, after a maximum of two injections of the implant.

The ranibizumab for the treatment of macular edema following Branch Retinal Vein Occlusion (BRAVO) clinical trial found gains of 16.6 (0.3 mg group) and 18.3 (0.5 mg group) letters in the monthly ranibizumab groups compared with 7.3 in the sham group at 6 months.<sup>58</sup> As for CRVO, the HORIZON study was an open-label extension trial that included 67% of BRVO patients completing the 12-month BRAVO trial. Patients originally randomized to the 0.5 mg ranibizumab arm in BRAVO received a mean of 2.1 injections during 12 months of as-needed treatment in HORIZON.<sup>44</sup> Mean BCVA remained stable for the first 12 months of the HORIZON trial for BRVO patients. The reduction in frequency of ranibizumab injections (as needed compared to monthly) during this second year of follow-up had minimal functional or anatomical effect in BRVO patients, in contrast to the diminished gains observed in CRVO patients (see earlier). This difference may be due to the lower overall ischemic burden and concomitant VEGF load seen in BRVOs compared to CRVOs. The use of grid laser in some of the BRVO patients also may have contributed to better stability by decreasing the VEGF load.<sup>44</sup> In addition to ranibizumab, bevacizumab,

which is used off label, is also widely used in the treatment of macular edema due to BRVO.<sup>59</sup>

Given multiple treatment options, recent studies have compared the efficacy of laser versus injections. The VIBRANT study compared treatment with monthly aflibercept vs. grid laser for BRVO-related CME. At 24 weeks, BCVA was improved 17.0 letters in the aflibercept group vs. 6.9 letters in the grid laser group.<sup>60</sup> The RELATE trial also evaluated the benefit of grid laser.<sup>61</sup> This study initially randomized patients to receive ranibizumab vs. sham for macular edema secondary to BRVO. Twenty-four weeks after randomization, patients could receive combination of grid and scatter laser. The study found no additional benefit of laser in terms of improvement in vision, resolution of macular edema, or reduced number of intravitreal injections. Finally, the BRIGHTER trial compared grid laser monotherapy vs. ranibizumab monotherapy vs. ranibizumab plus grid laser. This study found no additional benefit to using grid laser vs. ranibizumab alone.<sup>62</sup>

In light of these studies, anti-VEGF therapy has become the standard treatment of CME due to BRVO (see Fig. 6.20.5). Questions remain regarding treatment duration and frequency, with long-term studies still being conducted.

## COURSE AND OUTCOME

Without treatment, one third of patients with BRVO end up with visual acuity better than 20/40 (6/12). However, two thirds have decreased visual acuity secondary to macular edema, macular ischemia, macular hemorrhage, or vitreous hemorrhage. As noted earlier, laser treatment for macular edema significantly enhances the chance that the patient's baseline visual acuity will improve by two lines (65% versus 37%).<sup>54</sup> With the advent of anti-VEGF therapy, treatment is often initiated earlier, and visual acuity outcomes are potentially more robust compared with treatment with focal laser alone. Poor visual prognostic factors include advancing age, male sex, worse baseline visual acuity, and an increased number of predisposing risk factors.<sup>63</sup>

Approximately 20% of patients with BRVO will develop neovascularization. Of these patients, about 60% will have episodic vitreous hemorrhages, the incidence of which can be reduced by sectoral PRP.

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# Retinopathy of Prematurity

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## 6.21

**Definition:** A proliferative retinopathy of premature infants.

### Key Features

#### Avascular Retina

- Stage 1: demarcation line between normal and avascular retina.
- Stage 2: elevated ridge between normal and avascular retina.
- Stage 3: extraretinal fibrovascular proliferation on the ridge.
- Stages 4 and 5: tractional retinal detachment due to contraction of extraretinal fibrovascular proliferation.

### Associated Features

- Low birth weight and gestational age.
- Dilated and tortuous arteries and veins in the posterior pole (plus disease).
- Macular ectopia and distortion.
- Tractional retinal detachment.
- Retinal fold.
- Leukocoria.

## INTRODUCTION

First described in 1942, retinopathy of prematurity (ROP) is a proliferative retinopathy affecting premature infants of low birth weight (BW) and young gestational age (GA).<sup>1</sup> Despite—and partly due to—major advances in neonatology, ROP remains a leading cause of lifelong visual impairment among children in developed countries. About 1100–1500 infants annually in the United States develop ROP that is severe enough to require medical treatment, and of them 400–600 infants each year in the United States become legally blind from ROP.<sup>2</sup>

## PATHOGENESIS

The pathogenesis of ROP is multifactorial where developmental, genetic, and environmental factors come into play. During normal retinal development, vasculogenesis transforms precursor mesenchymal cells into capillary networks beginning at about 16 weeks of gestation.<sup>3</sup> Mature vessels differentiate from these networks and reach the nasal and temporal ora serrata at about 36 and 39–41 weeks, respectively. Therefore, full retinal vascular development is mostly accomplished in utero, where the fetus is in a relatively hypoxic environment (average PaO<sub>2</sub> is 25–35) and exposed to the placental and maternal cytokines and growth factors. In addition, several pivotal cell-signaling pathways and growth factors involved in retinal vasculogenesis and neural development—including the VEGF-signaling pathway,<sup>4</sup> insulin-like growth factor 1 (IGF-1),<sup>5</sup> and the Wnt-signaling pathway<sup>6</sup>—are disrupted by premature birth and the ex utero hyperoxic environment. Taken together, premature birth disrupts this well-orchestrated process, as the fetus is exposed to a new environment, and the ophthalmoscopic findings of ROP stem from this arrested development and aberrant retinal tissue response to it.

High oxygen administration at birth was among the first factors to be found critical to the pathogenesis of ROP.<sup>7</sup> Excessively high levels of oxygen in incubators, used to save the lives of premature infants, led to an ROP epidemic and the realization that reducing the level of oxygen given to premature babies reduces the incidence of ROP.<sup>8</sup> The detrimental effects of high and/or fluctuating oxygen concentrations were validated in the oxygen-induced retinopathy models, where alternating

oxygen concentrations induce retinal neovascularization.<sup>9,10</sup> Although these models lack significant features of human ROP [absence of ridge tissue, involution of retinal neovascularization (RNV), and absence of neovascular complications such as hemorrhage and tractional retinal detachment], they have been instrumental in the dissection of the molecular mechanisms involved in ROP and retinal neovascular diseases in general.

The association between high oxygen levels and ROP led to the development of the two-phase hypothesis for ROP almost 30 years before the classification of human ROP in zones and stages. According to this, in the first phase there is a delay or halting in physiological retinal vascular development due to prematurity as well as hyperoxia-induced endothelial cell damage and subsequent vasoattenuation. As the peripheral avascular retina continues to develop in the absence of a developing vascular bed, it becomes relatively hypoxic and secretes proangiogenic factors, which promote retinal neovascularization and abnormal vasoproliferation in the vitreous (second phase).

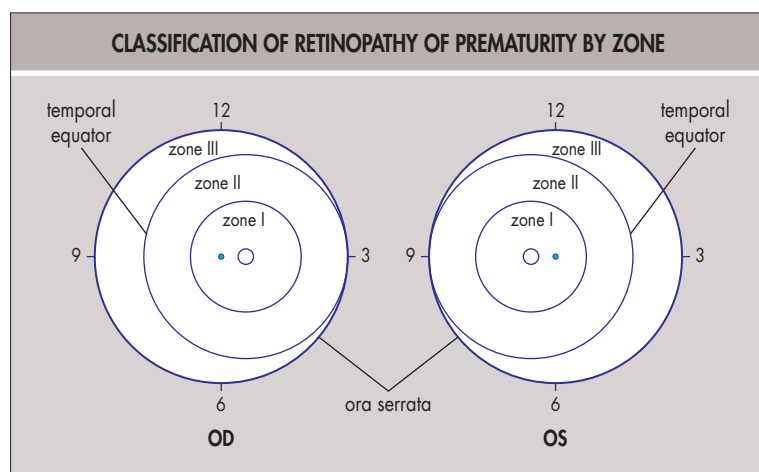
Given its pivotal role in other retinal neovascular diseases, increasing attention has been focused on vascular endothelial growth factor (VEGF).<sup>11</sup> In ROP, VEGF has been shown to be elevated in both the vitreous<sup>12</sup> and serum<sup>13</sup> of infants with ROP, and the importance of VEGF upregulation in the proliferative phase of this disease has been shown in humans, since blockade of VEGF with anti-VEGF antibodies (bevacizumab) has considerable efficacy.<sup>14</sup> However, this dual role of VEGF in development and disease raises concerns about the timing and safety of VEGF inhibition in ROP (discussed later).

Genetic factors may play a role in the development of severe ROP as well.<sup>15</sup> Some clinical features of ROP noted in near-term and full-term infants may resemble those seen in familial exudative vitreoretinopathy (FEVR), the X-linked form of which is associated with mutations in the Norrie's disease (NDP) gene.<sup>16</sup> Shastri et al. investigated a cohort of 16 premature infants with ROP and found missense mutations in four infants with advanced disease.<sup>17</sup> None of the parents or 50 healthy controls had mutations.<sup>17</sup> The NDP gene product, norrin, is a ligand that activates a signal transduction pathway necessary for early retinal development and vasculogenesis.<sup>18</sup> Subsequent studies have suggested up to 2% of infants with ROP have NDP mutations.<sup>19,20</sup> It is likely that other genes involved in this signal transduction pathway may harbor mutations or polymorphisms that predispose premature babies to increased rates of ROP.<sup>21</sup>

## CLINICAL FEATURES AND CLASSIFICATION

The International Classification of Retinopathy of Prematurity (ICROP) was instrumental in establishing the standards and nomenclature for the clinical assessment of ROP based on the anatomical location (zone) and severity (stage) of disease.<sup>22</sup> Zone I is defined as a circle, the center of which is the disc and the radius of which is twice the distance of the disc to the fovea. Zone II is a doughnut-shaped region that extends from the anterior border of zone I to within one disc-diameter of the ora serrata nasally and to the anatomical equator temporally. Zone III encompasses the residual temporal retina (Fig. 6.21.1).

The first sign of ROP (stage 1) is the appearance of a thin, flat, white structure (termed a demarcation line) at the junction of vascularized retina posteriorly and avascular retina anteriorly (Fig. 6.21.2A). Stage 2 ROP occurs as the demarcation line develops into a pink or white elevation (ridge) of thickened tissue (Fig. 6.21.2B); small tufts of vessels may be seen posterior to the ridge. Vessel growth into and above the ridge (extraretinal fibrovascular proliferation) characterizes stage 3 ROP (Fig. 6.21.2C). This fibrovascular proliferation may extend into the overlying vitreous and cause preretinal or vitreous hemorrhage (Fig. 6.21.2C). Contraction of fibrovascular proliferation exerts traction on the retina, leading to partial retinal detachment (stage 4 ROP), either without foveal involvement (stage



**Fig. 6.21.1 Anatomical Classification of Retinopathy of Prematurity by Zone.** The temporal edge of zone II coincides with the equator.

4A) (Fig. 6.21.2D) or with foveal involvement (stage 4B) (Fig. 6.21.2E). Stage 5 ROP denotes a total retinal detachment (Fig. 6.21.2F). Stage 5 detachments are funnel shaped and described as open or closed anteriorly and open or closed posteriorly. The term *retrolental fibroplasia*, originally coined by Terry in 1942,<sup>87</sup> refers to what we know today as stage 5 ROP.

In its acute (neovascular) phase, ROP is a progressive vascular disease with increasing dilatation and tortuosity of peripheral retinal vessels, engorgement of iris vessels, and pupillary rigidity. “Plus disease” refers to the presence of marked venous dilatation and arterial tortuosity in the posterior pole (Fig. 6.21.3A) secondary to arteriovenous shunting at the level of the ridge and constitutes the hallmark of progressive, treatment-warranting ROP. In the CRYO-ROP Study, plus disease was defined as significant dilation and tortuosity in all four vascular arcade quadrants, yet in subsequent studies<sup>23</sup> (STOP-ROP, ET-ROP) and current practice, the diagnosis of plus disease is made if sufficient vascular dilation and tortuosity are present in at least two quadrants of the eye. The term pre-plus disease was introduced later<sup>24</sup> to highlight the fact that plus disease does not appear as an all-at-once phenomenon but as a continuum of progressively increasing neovascular activity at the ridge manifested with arborization and tortuosity of the blood vessels (Fig. 6.21.3B). To this aim, pre-plus disease is defined as increased dilation and/or tortuosity of retinal arteries and/or veins in at least two quadrants, of insufficient severity for the diagnosis of plus disease. The presence of pre-plus disease can be predictive of progression to severe ROP requiring laser treatment.<sup>25</sup>

Aggressive posterior ROP (AP-ROP) is an uncommon severe form of ROP encountered in extremely premature infants (23–26 GA on average in some series<sup>26</sup>) that is characterized by very posterior (zone I) disease, neovascular fronds that lie flat on the retinal surface (flat neovascularization), absence of ridge tissue, and dilated tortuous vessels in a syncytial pattern (Fig. 6.21.3C).<sup>24</sup> AP-ROP can progress rapidly to stage 4 and 5 if left untreated, and eyes with AP-ROP have poorer prognosis than classic (zone II disease) ROP, with retinal detachment rates as high as 45%.<sup>27,28</sup>

Finally, the definition of “threshold” ROP has varied in successive clinical trials. In the CRYO-ROP study it was defined as the severity of ROP for which there was an equal chance of spontaneous regression or progression to an unfavorable outcome.<sup>29</sup> This was defined as stage 3+ ROP in zones I or II, occupying at least five contiguous clock-hours or eight noncontiguous clock-hours of retina.<sup>29</sup> For eyes with zone II ROP, this estimation proved quite precise: 62% of untreated eyes with threshold ROP went on to an untoward visual outcome.<sup>30</sup> However, untreated threshold zone I eyes had a 90% chance of unfavorable outcome. Roughly 44% of eyes with zone II ROP in the CRYO-ROP had an unfavorable outcome despite appropriate intervention.<sup>31</sup> To address this problem, the multicenter study of Early Treatment for Retinopathy of Prematurity (ETROP)<sup>32</sup> compared early treatment of high-risk eyes (prethreshold type 1) versus treatment at threshold to show that early laser treatment improves both structural and visual outcomes. Two categories of prethreshold disease were created and management dictated by high-risk (type 1) or low-risk (type 2) prethreshold disease. ETROP findings suggest that type 1 prethreshold ROP receive laser ablation of the peripheral avascular retina. Type 2 prethreshold ROP is observed weekly or twice weekly based on the extent of ROP noted. When compared to the results of the CRYO-ROP study, the ETROP study suggests that early treatment of high-risk prethreshold ROP significantly

decreases unfavorable visual acuity outcomes (19.5%–14.5%;  $p = 0.01$ ) and structural outcomes (15.6%–9.1%;  $p < 0.001$ ).

## DIAGNOSIS AND SCREENING

Initial examination of the anterior segment is performed with specific attention to the iris vessels, lens, and tunica vasculosa lentis. Poor pupillary dilation and iris vascular engorgement can be a sign of plus disease.<sup>22</sup> After pupillary dilation, fundus examination is performed with an indirect ophthalmoscope and a 28.00 diopter (D) or 30.00 D lens. The posterior pole is examined without depression for plus disease. Clinically, the entire zone I can be seen through a 28.00 D lens when the view is centered on the optic nerve. Scleral depression is then used to examine the temporal retina, followed by the nasal retina, to establish the proximity of retinal vessels to the ora serrata.

Given the progressive nature of ROP, as well as the proven benefits of early diagnosis and timely intervention to minimize the risk of severe visual loss, a joint statement outlining the principles of a screening program for ROP has been set forth:

- Screening for ROP should be performed in all infants with a birth weight at or above 1500 g or gestational age of 30 weeks or less (as defined by the attending neonatologist) and selected infants with a birth weight between 1500 and 2000 g or gestational age of more than 30 weeks with an unstable clinical course.
- In most cases, at least two examinations should be performed. One examination may suffice if it shows unequivocally that retinal vascularization is complete bilaterally. The first examination should be performed between 4 and 6 weeks of chronological (postnatal) age or between 31 and 33 weeks of postmenstrual age (PMA) (calculated as GA plus chronological age), whichever is later.
- Infants with immature retinas (no ROP) vascularized into zone II or III may be examined at 2-week intervals.
- Infants with type 2 prethreshold disease require weekly or twice weekly exams.
- Infants with type 1 prethreshold disease should be considered for peripheral laser ablation.

## ROLE OF TELEMEDICINE IN ROP SCREENING

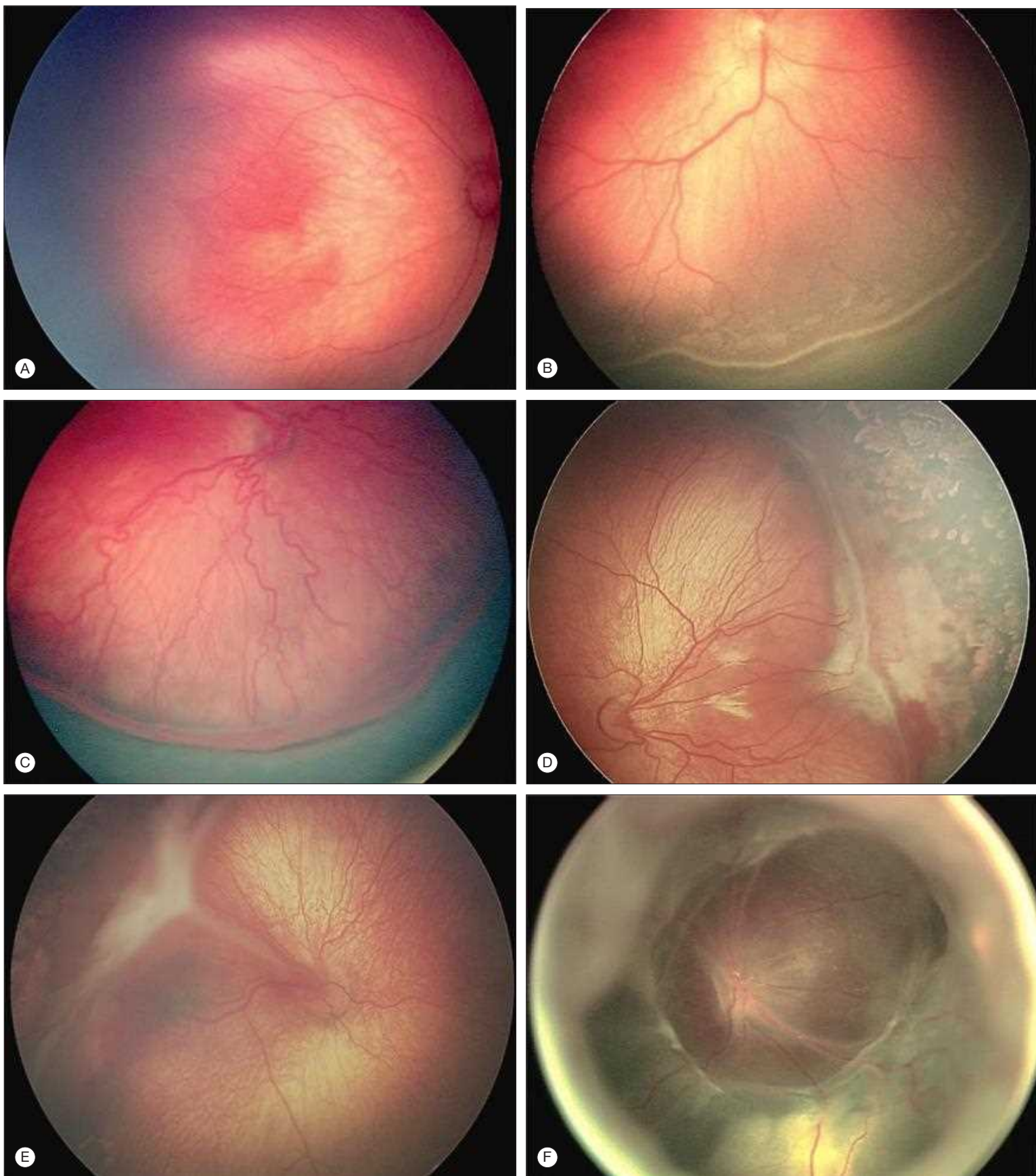
The historical gold standard method for ROP screening has been bedside examination with binocular indirect ophthalmoscopy (BIO). However, a significant limitation of bedside examination is the subjectivity of the examiner’s impression of the BIO findings with its subsequent documentation. Several studies have shown a wide range of disagreement of ROP diagnosis and severity among healthcare professionals screening for ROP.<sup>33,34</sup> In the pivotal CRYO-ROP trial, there was disagreement between two unmasked, certified examiners as to whether threshold disease was present in 12% of eyes. Moreover, accurate documentation of retinal pathology in ROP is critical for longitudinal comparison and demonstration of sound clinical practice, especially in the complex medicolegal climate that surrounds ROP.

The feasibility of remote digital fundus imaging in screening for ROP was first demonstrated in 2000,<sup>35</sup> and since then numerous studies<sup>36</sup> clinical trials,<sup>37</sup> and live telemedicine programs<sup>38</sup> have validated the accuracy and sensitivity of “store-and-forward” telemedicine in effectively detecting treatment and/or referral-warranted ROP using contact wide-field digital cameras. These results are fairly consistent among different camera operators, including trained ophthalmologists,<sup>39,40</sup> trained neonatal personnel,<sup>41,42</sup> and ophthalmic photographers.<sup>40,43</sup> The latter is of great importance for communities with limited access to ROP providers and geographically restricted neonatal intensive care units and for connecting ROP screeners with experts for management of complex cases.

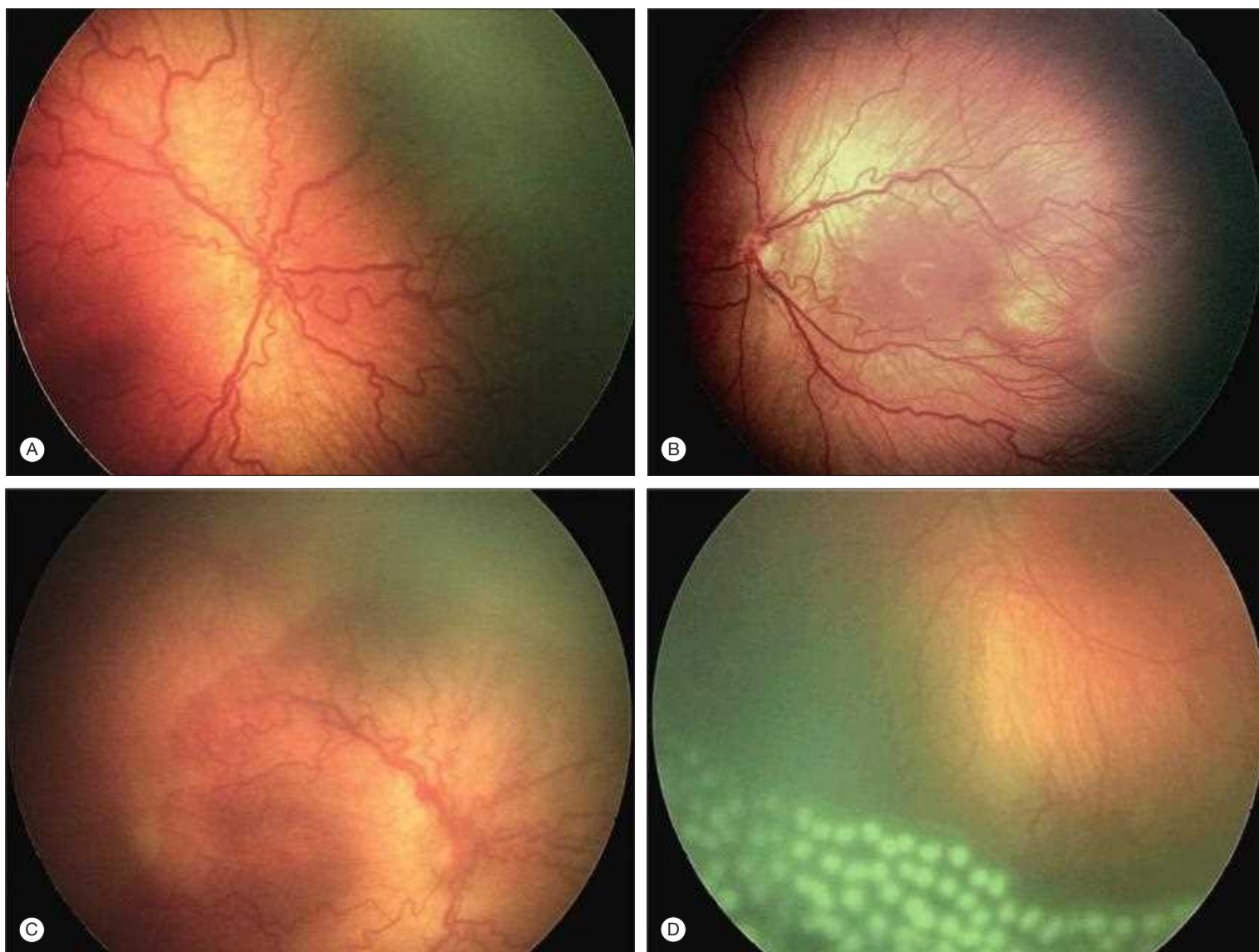
## DIFFERENTIAL DIAGNOSIS

In a premature infant of low BW with characteristic findings of immature retinal development, the diagnosis of ROP is generally straightforward. FEVR is the main masquerader that may mimic ROP in infancy. With its characteristic skin findings and gender predilection, incontinentia pigmenti is another pediatric retinal vasculopathy that shares similar clinical features with ROP. On the other hand, if a premature infant has not been screened or treated appropriately, the presenting finding may be leukocoria due to retrolental fibrous proliferation. In such infants, the differential diagnosis is broader and includes:





**Fig. 6.21.2** (A) **Stage 1.** The flat white border between avascular and vascular retina seen temporally is called a demarcation line. (B) **Stage 2.** The elevated mesenchymal ridge has height. Highly arborized blood vessels from the vascularized retina dive into the ridge. (C) **Stage 3.** Vessels on top of the ridge project into the vitreous cavity. This extraretinal proliferation carries with it a fibrovascular membrane. Note the opalescent avascular retina anterior to the ridge. Hemorrhage on the ridge is not uncommon. (D) **Stage 4.** Retinal detachment sparing the fovea. (E) **Stage 4B.** Detachment involves the fovea with an early retinal fold formation. (F) **Stage 5.** Depiction of an open anterior configuration secondary to fibrovascular proliferation that pulls the peripheral retina anteriorly.



**Fig. 6.21.3** (A) An example of moderate plus disease. Dilated retinal veins and tortuous arteries may be seen in the posterior pole. (B) Pre-plus disease. (C–D) Aggressive posterior retinopathy of prematurity.

- Retinoblastoma.
- Persistent fetal vasculature (formerly called persistence of primary hyperplastic vitreous; usually unilateral and associated with microphthalmia and prominent ciliary processes).
- Exudative retinal detachment (most commonly from Coats' disease; usually unilateral and more common in boys).
- Infectious causes such as endogenous endophthalmitis, toxocariasis, or toxoplasmosis (all of which may be diagnosed by appropriate microbiological and immunological testing).
- Coloboma of the optic disc or choroid.
- Cataract.
- Genetic syndromes, such as trisomy 13, Norrie's disease, and Warburg syndrome (all of which may be diagnosed by genetic testing and/or characteristic systemic physical findings).

## **PATHOLOGY**

Earlier histological studies demonstrated that the ridge in ROP consists of a larger anterior collection of spindle-shaped cells in the nerve fiber layer (the “vanguard”) and a variably present smaller posterior vascularized rear-guard.<sup>44</sup> These spindle-shaped cells are predominantly astrocyte precursors and, to a far lesser extent, mature astrocytes.<sup>45</sup> Stage 1 ROP is characterized by hyperplasia of the primitive spindle-shaped cells of the vanguard mesenchymal tissue at the demarcation line, whereas stage 2 consists of further hyperplasia of the spindle cells along with proliferation of the endothelial cells of the rear-guard mesenchymal tissue. In stage 3, extraretinal vascular tissue emanates from the ridge.<sup>44</sup> Proliferation of endothelial cells and small, thin-walled vessels occurs and represents abnormal angiogenesis. Equally important is the condensation of vitreous into sheets and

strands oriented anteriorly toward the equator of the lens. Vitreous tractional forces draw the retina anteriorly leading to foreshortening, folding, and subsequent retinal detachment.<sup>46</sup>

## **TREATMENT**

The goals of any acute ROP treatment is the abolishment of the angiogenic response driven by the avascular retina, which can be achieved by cryotherapy, laser photocoagulation, and pharmacological blockade of VEGF. Surgical intervention is reserved for the cicatricial stages of ROP leading to retinal traction, hemorrhage, and detachment.

## **ABLATION OF PERIPHERAL AVASCULAR RETINA**

Peripheral retinal ablation has been the mainstay of therapy for vasoproliferative retinopathy of prematurity dating back to the CRYO-ROP study. Cryotherapy has been employed to achieve peripheral retinal ablation for ROP since the 1970s<sup>29</sup> but has largely been supplanted by laser.<sup>47</sup> Indications for utilizing cryotherapy include poor fundus visibility, lack of laser availability, and physician's unfamiliarity with indirect laser techniques.

Laser photocoagulation has been shown to be at least as effective as<sup>48</sup>—if not more effective<sup>49</sup> than—cryotherapy for threshold disease.<sup>50</sup> In the largest prospective, randomized comparison of laser photocoagulation with cryotherapy (25 infants followed for at least 4 years), eyes treated with laser were significantly more likely to have visual acuity of 20/50 or better and were significantly less myopic.<sup>51,52</sup> The advantage of laser is greatest for eyes with zone I disease. Favorable anatomical results have been reported in 83%–85% of all eyes<sup>53,54</sup> versus only 25% of eyes with zone I disease treated with cryopexy.<sup>35</sup>



Advantages of laser photocoagulation over cryotherapy include ease of treatment, portability, and fewer systemic complications. Photocoagulation is delivered through a dilated pupil with a 20.00 D or 28.00 D lens. The endpoint is near-confluent ablation with burns spaced one-half burn width apart from the ora serrata up to (but not including) the ridge for 360°<sup>56</sup> (Fig. 6.21.3D). The retina should be inspected for skip areas, and the infant should be re-examined within 1 week. Persistent plus disease or fibrovascular proliferation are indications for additional treatment. Complications of laser treatment include anterior segment ischemia, cataract, high myopia, and burns of the cornea, iris, or tunica vasculosa lentis.<sup>57–59</sup>

The limitations of peripheral retinal ablation include the irreversible and extensive destruction of peripheral retina, concomitant reduction in visual fields, the laborious nature of the treatment, and the high level of training required to administer and monitor the treatment.

## ROLE OF ANTI-VEGF THERAPY IN ROP TREATMENT

The off-label use of anti-VEGF agents (bevacizumab or ranibizumab) in eyes with advanced ROP is supported by more than 50 case reports/case series<sup>60</sup> and one randomized, controlled clinical trial.<sup>61</sup> A systematic analysis<sup>62</sup> and an evidence-based meta-analysis<sup>63</sup> of VEGF inhibition as a treatment for ROP concluded that there is considerable variability in treatment indications, dosage, treatment timing, and treatment frequency; thus extrapolation of safe guidelines is challenging. In addition, although the BEAT-ROP study provided the first evidence in the context of a prospective, randomized controlled clinical trial of the prevailing concept that VEGF inhibition has a role in acute zone I ROP, it also raised significant questions, mostly due to a population bias of patients enrolled in the study, unusually high failure rate of laser treatment compared to ETROP standards, and higher number of deaths in the bevacizumab group (although the study was not powered for evaluation of safety).<sup>61</sup>

The dual role of VEGF in development and disease also makes employment of anti-VEGF therapy more challenging because the optimal dosing and choice of drug are still unknown. In the BEAT-ROP trial and the majority of published case series, a dose of 0.625 mg/0.025 mL was employed, which according to preclinical data delivers a dose of more than 10<sup>4</sup> as much anti-VEGF antibody as VEGF present in the vitreous of infants with ROP.<sup>12,64</sup> Indeed, a dose of bevacizumab as low as 0.031 mg has been shown to be effective in a recent phase 1 study for type 1 ROP.<sup>65</sup> It is also hoped that the RAINBOW study (RAnibizumab Compared With Laser Therapy for the Treatment of INfants BOrn Prematurely With Retinopathy of Prematurity; NCT02375971), which is an ongoing, phase 3, randomized, multicenter, prospective clinical trial that investigates the efficacy and safety of ranibizumab (Lucentis; Genentech, South San Francisco, CA) in infants with type 1 ROP compared with laser therapy, will provide better information on the dosing regimen (0.2 mg and 0.1 mg ranibizumab) as well. The latter has important implications given the systemic absorption of anti-VEGF agents and their potential impact on neurodevelopmental outcomes.<sup>66,67</sup>

In summary, the current available evidence for the follow-up, safety, and efficacy of anti-VEGF treatment is on a much lower level than the evidence for laser therapy, which has been established for more than four decades. Certainly there are advantages of anti-VEGF, such as ease of administration, fewer refractive errors compared to laser,<sup>68</sup> and allowance of centrifugal vascular retinal growth, but these await robust clinical trials

to be carefully evaluated under the scope of systemic safety and critical role of VEGF in retinal development. In the current clinical practice, however, anti-VEGF injections can be particularly helpful in the following scenarios:

- Treatment-naïve eyes with vascular congestion of the anterior segment precluding adequate visualization for laser treatment.
- Primary monotherapy (without adjuvant retinal ablation) for eyes with posterior or aggressive disease.<sup>69</sup>
- Infants unable to tolerate general anesthesia for intubation and laser treatment.

## SURGERY IN ROP TREATMENT

Although retinal ablation is effective in a majority of cases of ROP, some eyes will progress to retinal detachment (RD) at a mean of 41 weeks PMA after effective laser ablation.<sup>70</sup> ROP RD is most commonly tractional, originating at the ridge in a circumferential, purse-string pattern that draws the retina anteriorly and centrally. The surgical goal is interrupting the traction resulting from fibrous proliferation, and several tractional vectors must be addressed for surgical success (Fig. 6.21.4A–D).

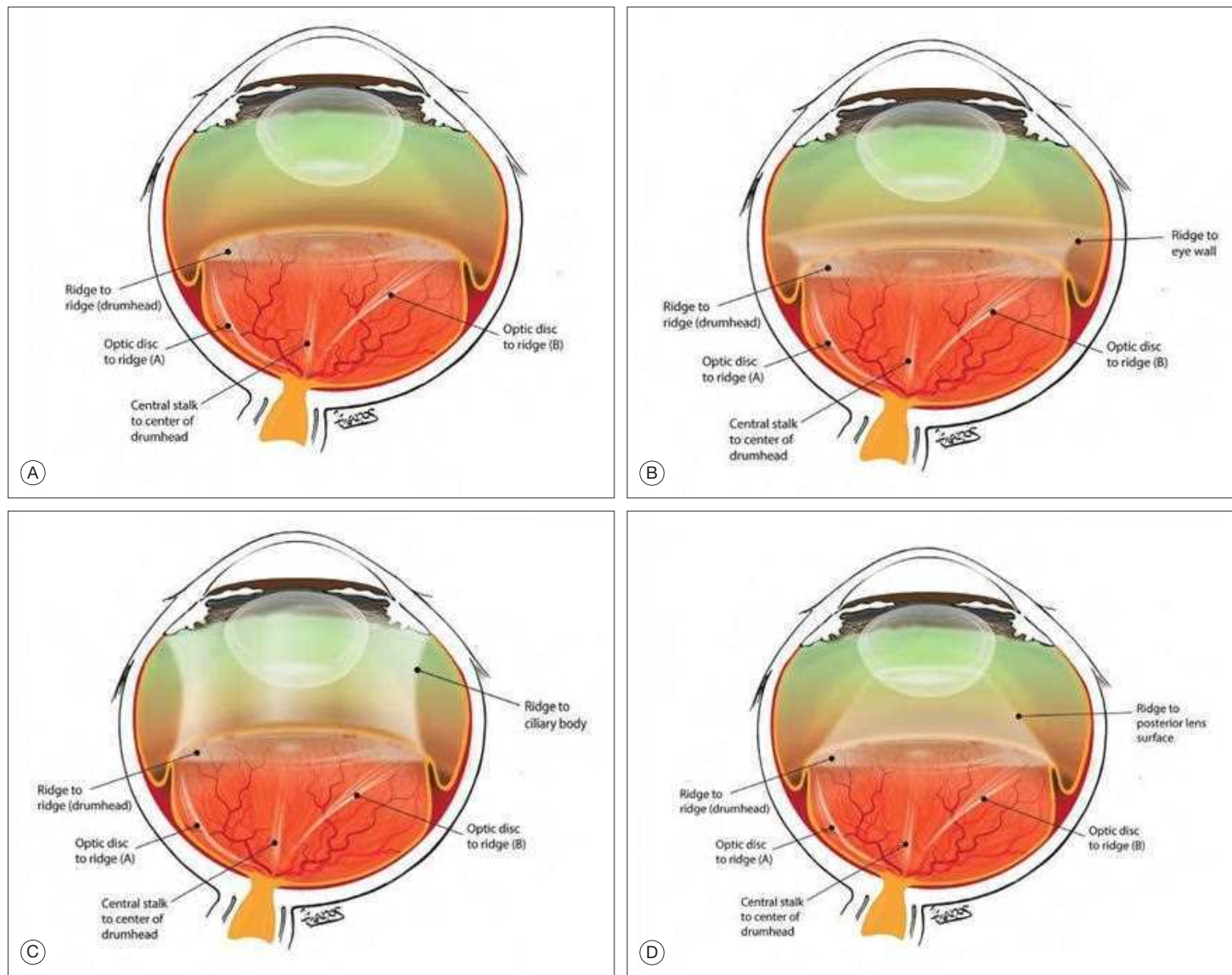
The goal of intervention for ROP-related RD varies with the severity of the detachment. The goal for extramacular retinal detachment (stage 4A ROP) is an undistorted or minimally distorted posterior pole, total retinal reattachment, and preservation of the lens and central fixation vision. Scleral buckling<sup>71,72</sup> and vitrectomy<sup>73</sup> have been used to manage stage 4A ROP. Disadvantages of scleral buckling for stage 4A ROP are the dramatic anisometropic myopia and the second intervention required for transection or removal so that the eye may continue to grow.<sup>74</sup> Lens-sparing vitrectomy can interrupt progression of ROP from stage 4A to stages 4B or 5 by directly addressing transvitreal traction resulting from fibrous proliferation and has become the method of choice.<sup>75,76</sup> Data from several centers dedicated to surgery for advanced ROP have shown that in experienced hands, lens-sparing vitrectomy allows primary retinal reattachment in 60%–90% of eyes with stage 4 ROP.<sup>73,77</sup> Visual results following vitrectomy for stage 4A can be very rewarding, with mean visions on the order of 20/60.<sup>78</sup>

Surgery for tractional RD involving the macula (stage 4B ROP) is performed to minimize retinal distortion and prevent total detachment (stage 5). The functional goal is ambulatory vision.<sup>79</sup> In earlier studies, visual outcome for retinal detachment beyond stage 4A was quite poor. More recent reports demonstrate that form-vision can be obtained by vitrectomy for stage 5 ROP.<sup>80,81</sup> Maximal recovery of vision following macula-off RD and interruption of visual development in infants may take years.

## LATE COMPLICATIONS OF ROP

Retinopathy of prematurity is a disease with lifelong ocular sequelae and adults with history of prematurity have increased prevalence of amblyopia, myopia, strabismus, early nuclear sclerotic cataract, and glaucoma.<sup>82</sup> Common retinal findings of regressed ROP include perivascular straightening, pigmentary changes, peripheral cicatricial changes, vascularization over a regressed ridge tissue, and lattice degeneration. Higher retinal complication rates after cataract surgery<sup>83,84</sup> and failure rates after retinal tears/detachment treatment in this patient population are attributable to an abnormal vitreoretinal interface, specifically the posterior border of the vitreous base, which demonstrates significant organization and tight adherence to the retina.<sup>85,86</sup>





**Fig. 6.21.4 Tractional Vectors Occurring in Retinopathy of Prematurity-Related Detachments.** The primary tractional vectors in retinopathy of prematurity related retinal detachments are ridge to ridge (drumhead) and optic disc to ridge (A), ridge to eye wall (B), ridge to ciliary body (C), and ridge to posterior lens surface (D).

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# Diabetic Retinopathy

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# 6.22

**Definition:** Progressive dysfunction of the retinal vasculature caused by chronic hyperglycemia resulting in structural damage to the neural retina.

## Key Features

- Microaneurysms.
- Retinal hemorrhages.
- Retinal lipid exudates.
- Cotton-wool spots.
- Capillary nonperfusion.
- Macular edema.
- Neovascularization.

## Associated Features

- Vitreous hemorrhage.
- Retinal detachment.
- Neovascular glaucoma.
- Early onset cataract.
- Cranial nerve palsies.

## INTRODUCTION

Successful management of diabetic retinopathy requires not only local treatment (laser therapy, intravitreal pharmacotherapy, and vitrectomy) but also systemic control of hyperglycemia, blood pressure, and lipids. If fundus examinations are initiated before the development of significant retinopathy and repeated periodically—and if the recommendations of the Early Treatment Diabetic Retinopathy Study (ETDRS) and recent anti-vascular endothelial growth factor (VEGF) clinical trials results are applied in the management of diabetic macular edema or neovascularization—the risk of severe visual loss is less than 5%. However, diabetic retinopathy remains the number one cause of new blindness in most industrialized countries because of delays in seeking treatment. The vast majority of diabetic individuals who lose vision do so not because of an inability to treat their disease but due to a delay in seeking medical attention. In addition, in many countries, the incidence of diabetes is increasing dramatically.

## EPIDEMIOLOGY

Duration of retinopathy is most closely associated with the incidence of diabetic retinopathy and remains the best predictor of diabetic retinopathy.<sup>1</sup> The first five years of type 1 diabetes has a very low risk of retinopathy. However, 27% of those who have had diabetes for 5–10 years and 71%–90% of those who have had diabetes for longer than 10 years have diabetic retinopathy.<sup>2</sup> After 20–30 years, the incidence rises to 95%, and about 30%–50% of these patients have proliferative diabetic retinopathy (PDR).

Yanko et al.<sup>3</sup> found that the prevalence of retinopathy 11–13 years after the onset of type 2 diabetes was 23%; after 16 or more years, it was 60%; and 11 or more years after the onset, 3% of the patients had PDR. Klein et al.<sup>2</sup> reported that 10 years after the diagnosis of type 2 diabetes, 67% of patients had retinopathy and 10% had PDR.

The duration of diabetes after the onset of puberty appears to be most important. For example, the risk of retinopathy is roughly the same for two 25-year-old patients, one of whom developed diabetes at the age of 6 and the other at the age of 12 years.<sup>4</sup> The risk of retinopathy in children diagnosed prior to the age of 2 years has a negligible risk of retinopathy for the first 10 years.<sup>5</sup>

The Diabetes Control and Complications Trial (DCCT) showed that type 1 diabetics who closely monitored their blood glucose via tight control (four measurements per day = tight control) had a 76% reduction in the rate of development of any retinopathy (primary prevention cohort) and a 54% reduction in progression of established retinopathy (secondary intervention cohort) as compared with the conventional treatment group (one measurement per day).<sup>6</sup> For advanced retinopathy, however, even the most rigorous control of blood glucose may not prevent progression. The DCCT was halted early after 6.5 years when the benefit of tight control was deemed unlikely to be reversed with time. Most of the participants were followed in the Epidemiology of Diabetes Interventions and Complications (EDIC) study. The EDIC study showed continued benefit for the former tight control group over the former conventional treatment group, despite normalization of glucose control even after 7 years of follow-up.<sup>7</sup> The value of intensive treatment has also been demonstrated for type 2 diabetes. The United Kingdom Prospective Diabetes Study (UKPDS) revealed a 21% reduction in the 1-year rate of progression of retinopathy.<sup>8</sup> The DCCT has shown that for every 1% decrease in the hemoglobin A1C (HbA1C) level, the incidence of diabetic retinopathy decreases 28%.<sup>9</sup>

It is important to realize that many patients with diabetes are unaware of their diabetic retinopathy. A Joslin Diabetes Center study on self-awareness of diabetic retinopathy found that 83% of patients with diabetic retinopathy and 78% of those with vision-threatening disease were unaware they had diabetic retinopathy at their first visit. Communication and education of the patient are very important.<sup>10</sup> The Diabetic Retinopathy Clinical Research Network (DRCR) evaluated the effect on retinopathy of educating the diabetic patient about their HbA1C and blood pressure levels at their regular retinal examination visits.<sup>11</sup> Despite physician-initiated discussion of in-office measurements of HbA1C and blood pressure readings with patients at their scheduled visits, the HbA1C levels did not significantly change from baseline. This suggests that more frequent and/or intensive intervention is needed than checking of these levels and discussing the results during a routine retinal evaluation. Renal disease, as evidenced by proteinuria, elevated blood urea nitrogen levels, elevated blood creatinine levels, and even microalbuminuria, is an excellent predictor of the presence of coexisting retinopathy.<sup>1,12</sup> Among patients with symptomatic retinopathy, 35% have proteinuria, elevated blood urea nitrogen values, or elevated creatinine levels. Systemic hypertension is another independent risk factor for diabetic retinopathy. The UKPDS demonstrated that tighter blood pressure control significantly reduced the progression of diabetic retinopathy.<sup>13</sup>

In pregnant diabetic women without retinopathy, the risk of developing nonproliferative diabetic retinopathy (NPDR) is about 10%. In contrast, those with NPDR and systemic hypertension at the onset of pregnancy—or those who develop systemic hypertension—are likely to show progression, with increased hemorrhages, cotton-wool spots, and macular edema.<sup>8</sup> Fortunately, there is usually some regression after delivery. About 4% of pregnant women with NPDR progress to PDR. Those with untreated PDR at the onset of pregnancy frequently do poorly unless they are treated with panretinal photocoagulation (PRP). Previously treated PDR usually does not worsen during pregnancy. Women who begin pregnancy with poorly controlled diabetes who are suddenly brought under strict control frequently have severe deterioration of their retinopathy and do not always recover after delivery.<sup>14</sup> It is very important to monitor pregnant patients carefully and closely, with some clinicians advocating quarterly examinations. Anti-VEGF treatment has not been studied in pregnant women. Laser or other non-anti-VEGF treatment is recommended. In addition, fluorescein dye is known to cross the placenta and is also excreted in breast milk for up to 72 hours.<sup>15</sup>

Some drugs have been implicated in worsening retinopathy and in particular diabetic macular edema (DME). Glitazones are associated with an

increased risk of worsening of DME.<sup>16</sup> A study of 170 000 patients in the Kaiser Permanente database showed that patients treated with glitazones had a significantly higher risk of developing DME (odds ratio 2.6, 95% confidence interval 2.4–3.0) in a univariate analysis.<sup>17</sup> After adjusting for confounding factors, the odds ratio was 1.6, 95% confidence interval 1.4–1.8. Some clinical trials have shown a higher risk of DME in patients taking insulin and glitazones (Actos package insert. Deerfield IL: Takeda Pharmaceutical America, Inc, 2011). It is therefore important to review a patient's drug history when evaluating diabetic patients with macular edema. The glitazone rosiglitazone, however, was shown to lower the risk of progression to PDR and to have similar rates of DME as controls at 3 years.<sup>18</sup> In The Health Improvement Network (THIN) database, a large retrospective cohort study of 103 368 patients with type II diabetes mellitus and no DME at baseline, an increased risk of DME was found at both 1 and 10 years for users of thiazolidinediones compared to nonusers. The adjusted odds ratio was 2.3 at 1 year and the adjusted hazard ratio was 2.3 at 10 years.<sup>19</sup>

## PATHOGENESIS

The final metabolic pathway that causes diabetic retinopathy is unknown. There are several theories that are not mutually exclusive.

### Aldose Reductase

Aldose reductase converts sugars into their alcohols. For example, glucose is converted to sorbitol and galactose is converted to galactitol. However, sorbitol and galactitol cannot easily diffuse out of cells, causing increased intracellular concentration. Osmotic forces then cause water to diffuse into the cell. The resultant damage to lens epithelial cells, which have a high concentration of aldose reductase, is responsible for the cataract seen in children.<sup>20</sup> Because aldose reductase is also found in high concentration in retinal pericytes and Schwann cells, some investigators suggest that diabetic retinopathy and neuropathy may be caused by aldose reductase-mediated damage. Despite these theoretical benefits, clinical trials have thus far failed to show a reduction in the incidence of diabetic retinopathy or of neuropathy by aldose reductase inhibitors, possibly because an effective aldose reductase inhibitor with few systemic side effects has yet to be developed.<sup>19</sup>

### Vasoproliferative Factors

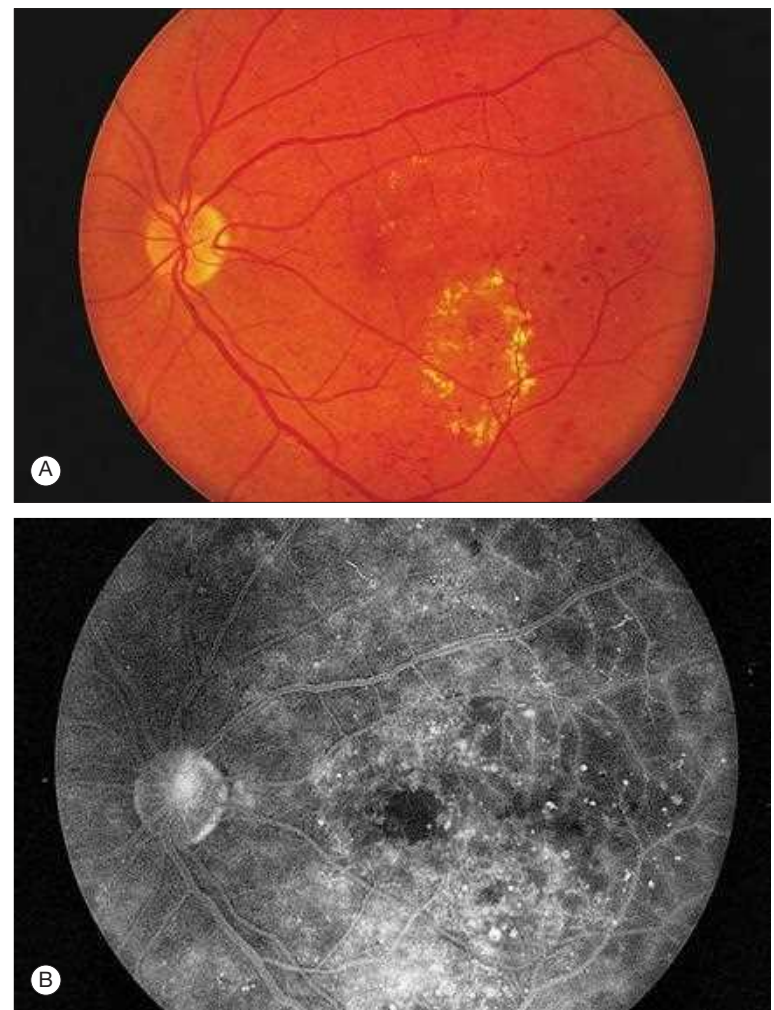
The retina and retinal pigment epithelium release vasoproliferative factors, such as VEGF, which induce neovascularization. VEGF has a direct role in the proliferative retinal vascular abnormalities that are found in diabetes. Animal models have demonstrated that VEGF expression correlates with the development and regression of neovascularization.<sup>21</sup> The concentration of VEGF in aqueous and vitreous directly correlates with the severity of retinopathy.<sup>22</sup> VEGF is a potent vasopermeability factor and is responsible for DME.<sup>23</sup> Several randomized controlled clinical trials have shown efficacy of anti-VEGF treatments for DME. There are other vasoactive cytokines released in diabetic eyes. These include tissue growth factor beta and connective tissue growth factor. The inflammatory component results from macrophage and complement activation. Extensive, dense deposition of C5b-9 as well as vitronectin were found in the connective matrix of the choriocapillaris. It is believed that complement activation results in increased neutrophils, which then cause endothelial damage. Lipids and proteins leak out of the capillaries. Extracellular matrix deposition may be triggered by the complement cascade's effects on neighboring cells and result in thickened choriocapillaris and Bruch's membrane.<sup>24</sup> Inflammation thus plays a role in macular edema and diabetic retinopathy. It is believed that long-standing DME may have more of an inflammatory component and be more responsive to corticosteroids, which are also antiangiogenic.<sup>25</sup>

### Platelets and Blood Viscosity

Diabetes is associated with abnormalities of platelet function. It has been postulated that platelet abnormalities or alterations in blood viscosity in diabetics may contribute to diabetic retinopathy by causing focal capillary occlusion and focal areas of ischemia in the retina.

## OCULAR MANIFESTATIONS

The earliest stage of diabetic retinopathy is NPDR. In some patients, there is progression to proliferative retinopathy PDR. The incidence of more



**Fig. 6.22.1 Nonproliferative Diabetic Retinopathy With Microaneurysms.**

(A) Small dot hemorrhages, microaneurysms, hard (lipid) exudates, circinate retinopathy, an intraretinal microvascular abnormality, and macular edema. (B) Fluorescein angiography of the eye shown in A. Microaneurysms are seen as multiple dots of hyperfluorescence, but the dot hemorrhages do not fluoresce. The foveal avascular zone is minimally enlarged.

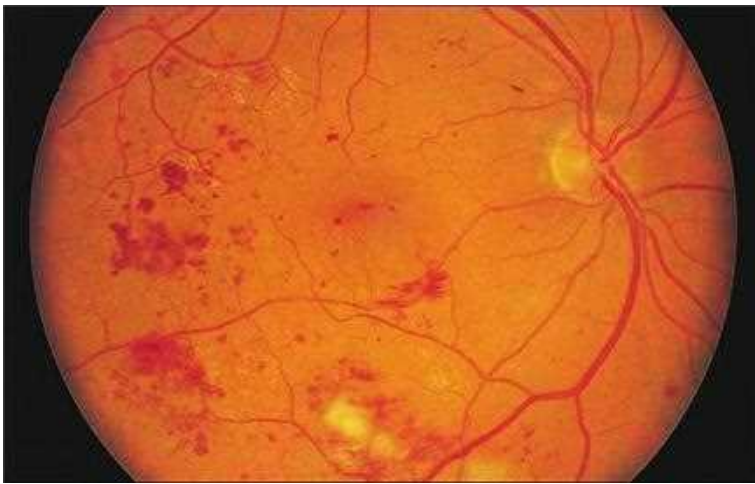
advanced levels of retinopathy increases based on duration of disease and glycemic control.

### Early Nonproliferative Diabetic Retinopathy

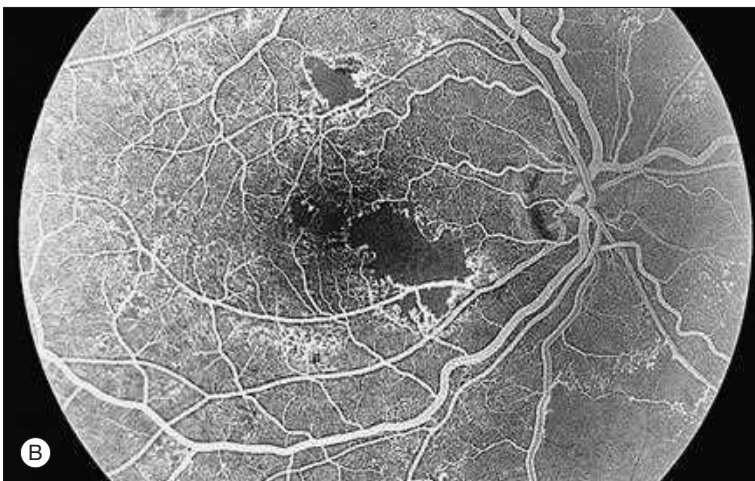
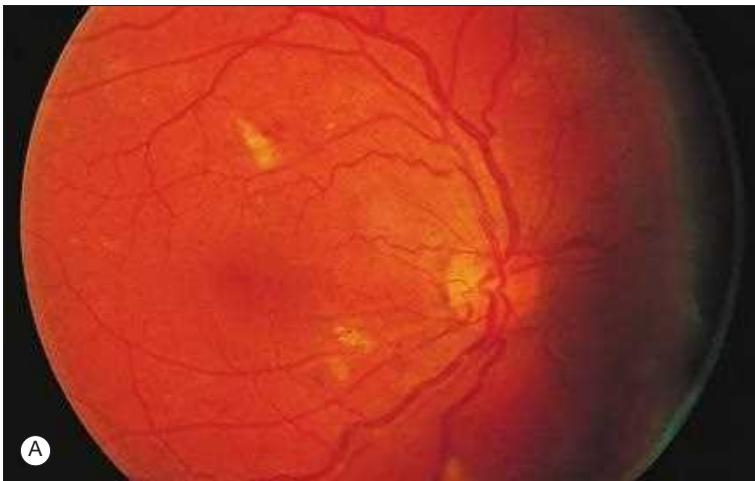
Microaneurysms are the first ophthalmoscopically detectable change in diabetic retinopathy and are considered the hallmark of NPDR (Fig. 6.22.1A). They are seen as small red dots in the middle retinal layers, typically in the macula. When the wall of a capillary or microaneurysm is weakened enough, it may rupture, giving rise to an intraretinal hemorrhage. If the hemorrhage is deep (i.e., in the inner nuclear layer or outer plexiform layer), it usually is round or oval ("dot or blot") (see Fig. 6.22.1A). It is very difficult to distinguish a small dot hemorrhage from a microaneurysm by ophthalmoscopy. Fluorescein angiography helps to distinguish patent (and not one filled with clotted blood) microaneurysms because they leak dye (see Fig. 6.22.1B). If the hemorrhage is superficial, in the nerve fiber layer, it takes a flame or splinter shape indistinguishable from a hemorrhage seen in hypertensive retinopathy (Figs. 6.22.2 and 6.22.3). Diabetics who have normal blood pressure may have multiple splinter hemorrhages. Nevertheless, the presence of numerous splinter hemorrhages in a diabetic patient should prompt a blood pressure check.

DME (see Fig. 6.22.1A) represents the leading cause of legal blindness in diabetics. The intercellular fluid comes from leaking microaneurysms or from diffuse capillary incompetence. Clinically, DME is best detected by slit-lamp biomicroscopy with a contact macular lens, although noncontact macular lenses can be used. The edema causes separation of cells, resulting in scattering of light by the multiple interfaces. This decreases the retina's translucency such that the normal retinal pigment epithelial and choroidal background pattern is blurred (see Fig. 6.22.1A). Pockets of fluid in the outer plexiform layer, if large enough, can be seen as cystoid





**Fig. 6.22.2 Nonproliferative Retinopathy With Some Blot Hemorrhages, Splinter Hemorrhages, and Cotton-Wool Spots.**

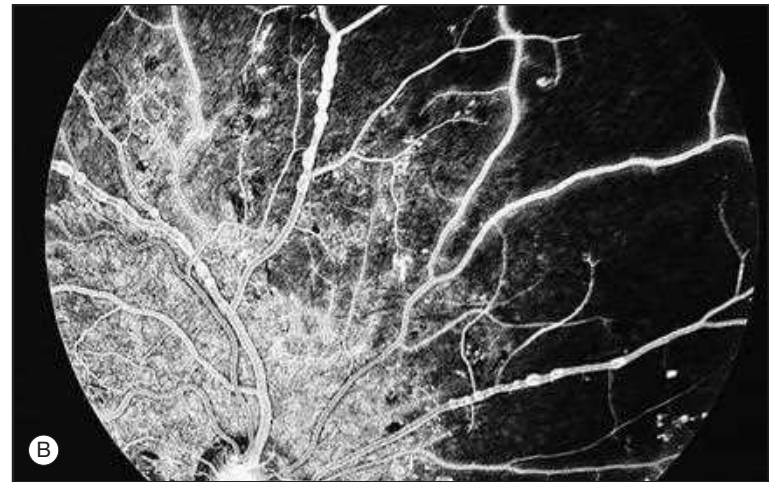


**Fig. 6.22.3 Nonproliferative Retinopathy.** (A) With soft exudates. (B) Fluorescein angiography shows capillary nonperfusion in the area of the superior cotton-wool spot and a larger area just inferonasal to the foveal avascular zone.

macular edema (CME). Usually CME is seen in eyes that have other signs of severe NPDR. In rare cases, CME is due to generalized diffuse leakage from the entire capillary network and can be seen in eyes with very few other signs of diabetic retinopathy.

If the leakage of fluid is severe enough, lipid may accumulate in the retina (see Fig. 6.22.1A); again, the outer plexiform layer is first to be affected. In some cases, lipid is scattered through the macula. In others, it accumulates in a ring around a group of leaking microaneurysms or around microaneurysms surrounding an area of capillary nonperfusion. This pattern is called circinate retinopathy (see Fig. 6.22.1A).

The application of optical coherence tomography (OCT) to management of DME has been very useful. The degree of DME and response to therapy can be quantified on OCT. Specifically, the central subfield thickness (CST)



**Fig. 6.22.4 Severe Nonproliferative Retinopathy.** (A) With cotton-wool spots, intraretinal microvascular abnormalities, and venous beading. (B) Fluorescein angiography shows severe capillary nonperfusion.

can be used to follow a patient's response to treatment of DME. In addition, the OCT presents qualitative information such as the presence of cysts, hard exudates, and degree of inner or outer retinal or external limiting membrane disruption and subretinal fluid. These findings are useful in following a patient's response to therapy.

In eyes treated with anti-VEGFs, the presence of disorganization of retinal inner layers (DRIL) has been associated with poorer visual acuity outcomes. The length of DRIL was associated with subsequent vision. The change in DRIL was associated with change in visual acuity (VA), with resolution of DRIL having the best VA. Early change in the extent of DRIL is inversely predictive of subsequent changes in visual acuity.<sup>26,27</sup>

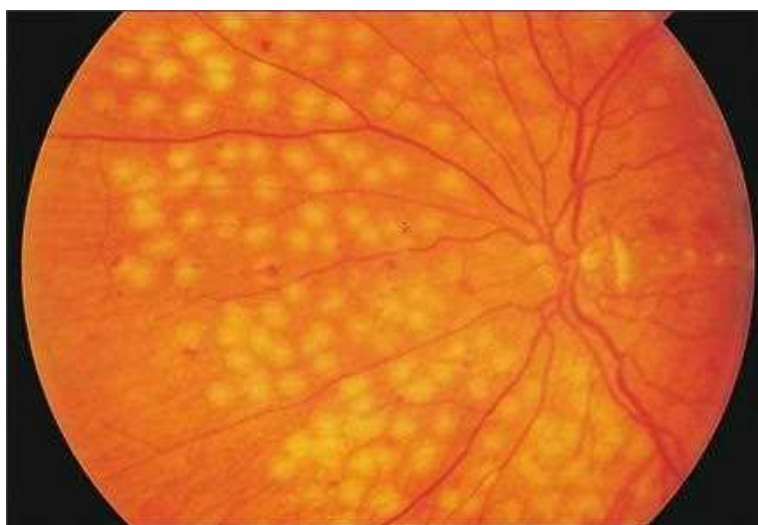
### Advanced Nonproliferative Diabetic Retinopathy

In advanced NPDR, signs of increasing inner retinal hypoxia appear, such as multiple retinal hemorrhages, cotton-wool spots (see Fig. 6.22.3), venous beading and vascular loops (Fig. 6.22.4), intraretinal microvascular abnormalities (IRMAs) (see Figs. 6.22.1A and 6.22.4), and large areas of capillary nonperfusion seen on fluorescein angiography.

Cotton-wool spots, also called soft exudates or nerve fiber infarcts, result from ischemia, not exudation. Local ischemia causes effective obstruction of axoplasmic flow in the normally transparent nerve fiber layer, and the subsequent swelling of the nerve fibers gives cotton-wool spots their characteristic white fluffy appearance. Fluorescein angiography shows lack of capillary perfusion in the area corresponding to a cotton-wool spot. Microaneurysms frequently surround the hypoxic area (see Fig. 6.22.3).

Venous beading (see Fig. 6.22.4) is an important sign of sluggish retinal circulation. Venous loops are nearly always adjacent to large areas of capillary nonperfusion. IRMAs are dilated capillaries that seem to function as collateral channels and are frequently difficult to differentiate from surface retinal neovascularization. Fluorescein dye, however, does not leak from IRMAs but leaks profusely from neovascularization. Capillary hypoperfusion often surrounds IRMA (see Fig. 6.22.4).





**Fig. 6.22.5** Approximately One-Half the Disc Area Shows Neovascularization of the Disc and Initial, Incomplete Panretinal Photocoagulation.

The ETDRS found that IRMAs, multiple retinal hemorrhages, venous beading and loops, widespread capillary nonperfusion, and widespread leakage on fluorescein angiography were all significant risk factors for the development of PDR. Interestingly, cotton-wool spots were not.<sup>28</sup>

### Proliferative Diabetic Retinopathy

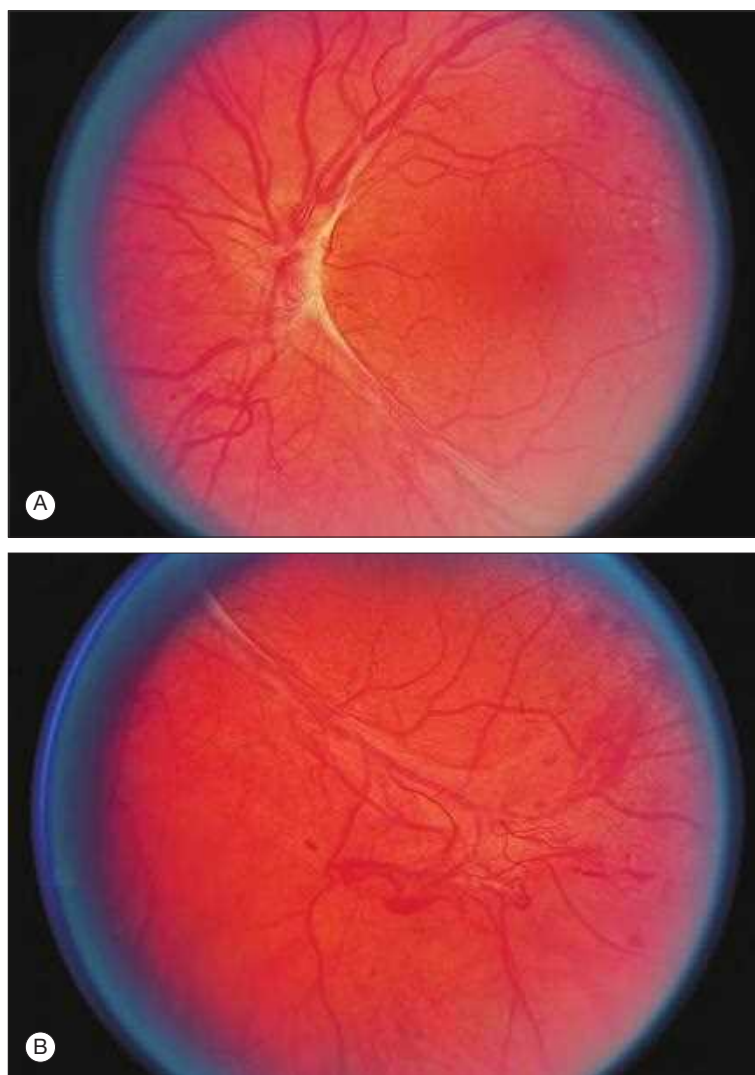
Although the macular edema, exudates, and capillary occlusions seen in NPDR often cause legal blindness, affected patients usually maintain at least ambulatory vision. PDR, on the other hand, may result in severe vitreous hemorrhage or retinal detachment, with hand-movements vision or worse. Approximately 50% of patients with very severe NPDR progress to PDR within 1 year.<sup>29</sup> Proliferative vessels usually arise from retinal veins and often begin as a collection of multiple fine vessels. When they arise on or within 1 disc diameter of the optic nerve they are referred to as NVD (neovascularization of the disc, Figs. 6.22.5 and 6.22.6). When they arise further than 1 disc diameter away, they are called NVE (neovascularization elsewhere) (see Fig. 6.22.6B). Unlike normal retinal vessels, NVD and NVE leak fluorescein into the vitreous.

Once the stimulus for growth of new vessels is present, the path of subsequent growth taken by neovascularization is along the route of least resistance. For example, the absence of a true internal limiting membrane on the disc could explain the prevalence of new vessels at that location. Also, neovascularization seems to grow more easily on a preformed connective tissue framework. Thus, a shallowly detached posterior vitreous face is a frequent site of growth of new vessels.

The new vessels usually progress through a stage of further proliferation, with associated connective tissue formation. As PDR progresses, the fibrous component becomes more prominent, with the fibrotic tissue being either vascular or avascular. The fibrovascular variety usually is found in association with vessels that extend into the vitreous cavity or with abnormal new vessels on the surface of the retina or disc. The avascular variety usually results from organization or thickening of the posterior hyaloid face. Vitreous traction is transmitted to the retina along these proliferations and may lead to traction retinal detachment.

NVE nearly always grows toward and into zones of retinal ischemia until posterior vitreous detachment occurs (see Fig. 6.22.6). Then the vessels are lifted into the vitreous cavity. The end stage is characterized by regression of the vascular tissue. Sometimes there may be contraction of the connective tissue components, development of subhyaloid bands, thickening of the posterior vitreous face, and the appearance of retinoschisis, retinal detachment, or formation of retinal breaks.

Posterior vitreous detachment in diabetics is characterized by a slow, overall shrinkage of the entire formed vitreous rather than by the formation of cavities caused by vitreous destruction. Davis et al.<sup>30</sup> have stressed the role of the contracting vitreous in the production of vitreous hemorrhage, retinal breaks, and retinal detachment. Neovascular vessels do not “grow” forward into the vitreous cavity but are pulled into the vitreous by the contracting vitreous to which they adhere. Confirmation of the importance of the vitreous in the development and progression of PDR comes from the long-term follow-up of eyes that have undergone successful vitrectomy in



**Fig. 6.22.6** Neovascularization. (A) Neovascularization of the disc with some fibrous proliferation. (B) Neovascularization elsewhere.

which neovascularization shrinks, fluorescein leakage decreases, and new areas of neovascularization rarely arise.

It has long been assumed that sudden vitreous contractions tear the fragile new vessels, causing vitreous hemorrhage. However, the majority of diabetic vitreous hemorrhages occur during sleep, possibly because of an increase in blood pressure secondary to early morning hypoglycemia or to rapid eye movement sleep. Because so few hemorrhages occur during exercise, it is not necessary to restrict the activity of patients with PDR. When a hemorrhage occurs, if the erythrocytes are behind the posterior vitreous face, they usually quickly settle to the bottom of the eye and are absorbed. However, when erythrocytes break into the vitreous body, they adhere to the gel, and clearing may take months or years.

A large superficial hemorrhage may separate the internal limiting membrane from the rest of the retina. Such hemorrhages usually are round or oval but also may be boat shaped. The blood may remain confined between the internal limiting membrane and the rest of the retina for weeks or months before breaking into the vitreous. Subinternal limiting membrane hemorrhages were formerly thought to occur between the internal limiting membrane and the cortical vitreous and were called subhyaloid or preretinal hemorrhages. It is now felt that true subhyaloid hemorrhages probably are quite rare. Tight subinternal limiting membrane hemorrhages are dangerous because they may progress rapidly to traction retinal detachment.

As the vitreous contracts, it may pull on the optic disc, causing traction striae involving the macular area or actually drag the macula itself, both of which contribute to decreased visual acuity.<sup>31</sup>

Two types of diabetic retinal detachments occur, those that are caused by traction alone (nonrhegmatogenous) and those caused by retinal break formation (rhegmatogenous). Characteristics of nonrhegmatogenous (traction) detachment in PDR include:

- The detached retina usually is confined to the posterior fundus and infrequently extends more than two thirds of the distance to the equator.

- The detached retina has a taut and shiny surface.
- The detached retina is concave toward the pupil.
- No shifting of subretinal fluid occurs.

Occasionally, a spontaneous decrease in the extent of a traction detachment may occur, but this is the exception rather than the rule. Traction on the retina also may cause focal areas of retinoschisis, which may be difficult to distinguish from full-thickness retinal detachment. In retinoschisis the elevated layer is thinner and more translucent.

When a detachment is rhegmatogenous, the borders of the elevated retina usually extend to the ora serrata. The retinal surface is dull and grayish and undulates because of retinal mobility due to shifting of subretinal fluid. Retinal breaks are usually in the posterior pole near areas of fibrovascular change. The breaks are oval in shape and appear to be partly the result of tangential traction from the proliferative tissue, as well as being due to vitreous traction. Determination of the location of retinal holes may be complicated by many factors, particularly poor dilatation of the pupil, lens opacity, increased vitreous turbidity, vitreous hemorrhage, intraretinal hemorrhage, and obscuration of the breaks by overlying proliferative tissue.

## Other Ocular Complications of Diabetes Mellitus

### Cornea

Corneal sensitivity is decreased in proportion to both the duration of the disease and the severity of the retinopathy.<sup>32</sup> Corneal abrasions are more common in people with diabetes, presumably because adhesion between the basement membrane of the corneal epithelium and the corneal stroma is not as firm as that found in normal corneas. Following vitrectomy, recurrent corneal erosion, striate keratopathy, and corneal edema are more common in diabetics than in nondiabetics.<sup>33</sup>

### Glaucoma

The relationship between diabetes and primary open-angle glaucoma is unclear. Some population-based studies have found an association<sup>34</sup> but others have not.<sup>35</sup>

Neovascularization of the iris (NVI) usually is seen only in diabetics who have PDR. PRP not only has protective value against NVI, it also is an effective treatment against established NVI.<sup>36</sup> If the media are clear, PRP should be performed prior to any other treatment for NVI, even in advanced cases.<sup>28</sup> If the media are too cloudy for PRP, transscleral laser or peripheral retinal cryoablation are alternative means of treatment (see later in this chapter). The presence of rubeotic glaucoma is a poor prognostic indicator for visual acuity and for life expectancy.<sup>37</sup> Anti-VEGF therapy is also used as an adjunctive treatment in eyes with NVI.

### Lens

The risk of cataract is 2–4 times greater in diabetics than in nondiabetics and may be 15–25 times greater in diabetics under 40 years old.<sup>38</sup>

Patients with diabetes mellitus who have no retinopathy have excellent results from cataract surgery, with 90%–95% having a final visual acuity of 20/40 or better, but chronic CME is about 14 times more common in diabetics than in nondiabetics.<sup>39</sup> The best-known predictor of postoperative success is the preoperative severity of retinopathy.<sup>40</sup> It was hoped that modern surgery, which leaves an intact posterior capsule, would protect the eye from NVI by reducing the diffusion of vasoproliferative factors into the anterior chamber, but several studies have shown that it does not. Furthermore, a neodymium-aluminum-garnet (Nd:YAG) laser capsulotomy does not increase the risk.<sup>32</sup> Other anterior segment complications that are more common in diabetics than in nondiabetics are pupillary block, posterior synechiae, pigmented precipitates on the implant, and severe iritis.<sup>39</sup>

Posterior segment complications of cataract surgery include macular edema, PDR,<sup>41</sup> vitreous hemorrhage,<sup>42</sup> and traction retinal detachment. Unlike prior reports, recent reports suggest that modern uncomplicated cataract surgery may not accelerate progression of diabetic retinopathy in type 2 diabetics with NPDR.<sup>43</sup> Caution should be observed when considering cataract surgery in patients who have diabetic retinopathy, but up to 70% of these patients can attain a final visual acuity of 20/40 or better.<sup>44</sup> In a pilot observational study of eyes with baseline DME at the time of cataract surgery, the DRCR showed that 32% improved four lines and 10% worsened at least two lines by week 16. The study was limited by small enrollment and concluded that it was unlikely that an adequate sample could be recruited within a reasonable time to pursue an interventional trial for eyes with DME in the setting of cataract surgery.<sup>45</sup> For patients without macular edema at the time of cataract surgery, the DRCR found

that preoperative noncentral DME or a history of DME treatment may increase the risk of developing central-involved DME 16 weeks after cataract extraction. In addition, visual outcomes were good, with over 85% achieving 20/40 or better visual acuity. However, this was achieved less often in eyes that developed central-involved ME (67%), although these eyes had a lower mean baseline VA (Snellen equivalent 20/63) than eyes that did not develop central-involved ME (Snellen equivalent 20/50).<sup>46</sup>

Cataract surgery in patients with active PDR often results in poorer postoperative visual outcome because of the high risk of both anterior and posterior segment complications. In one series, no patient with active PDR or preproliferative diabetic retinopathy achieved better than 20/80. Most experts recommend aggressive preoperative PRP.<sup>39,40</sup>

## Optic Neuropathy

As demonstrated by increased latency and decreased amplitude of the visual evoked potential, many diabetic patients without retinopathy have subclinical optic neuropathy. They have an increased risk for anterior ischemic optic neuropathy. In addition, diabetics are susceptible to diabetic papillopathy, which is characterized by acute disc edema without the pale swelling of anterior ischemic optic neuropathy. It is bilateral in one-half of cases and may not show an afferent pupillary defect.<sup>47</sup> Macular edema is a common concurrent finding and is the most common cause of failure of visual recovery in these patients.<sup>47</sup> Visual fields may be normal or show an enlarged blind spot or other nerve fiber defects. The prognosis is excellent, with most patients recovering to 20/50 or better.

## Cranial Neuropathy

Extraocular muscle palsies may occur in diabetics secondary to neuropathy involving the third, fourth, or sixth cranial nerves. The mechanism is believed to be a localized demyelination of the nerve secondary to focal ischemia. Pain may or may not be experienced, and not infrequently extraocular muscle palsy may be the initial clue to a latent diabetic condition. Recovery of extraocular muscle function in diabetic cranial nerve palsies generally takes place within 1–3 months.<sup>48</sup> When the third cranial nerve is involved, pupillary function is usually normal. This pupillary sparing in diabetic third cranial nerve palsy is an important diagnostic feature, helping to distinguish it from an intracranial tumor or aneurysm.

## DIAGNOSIS AND ANCILLARY TESTING

In nearly all instances, diabetic retinopathy is diagnosed easily via ophthalmoscopic examination. The hallmark lesions are microaneurysms, which usually develop in the posterior pole. Without microaneurysms, the diagnosis of diabetic retinopathy is in doubt. Fasting blood sugar testing, a glucose tolerance test, and HbA1C determinations all can be used to confirm the presence of systemic hyperglycemia.

Intravenous fluorescein angiography is a widely administered ancillary test and is helpful to assess the severity of diabetic retinopathy, to determine sites of leakage in macular edema, to judge the extent of capillary nonperfusion, and to confirm neovascularization. It is a useful preoperative test to evaluate the extent of retinopathy in patients who are to undergo cataract surgery and have media opacity. OCT angiography is being increasingly used as a noninvasive test in diabetic retinopathy to visualize capillary nonperfusion and neovascularization. OCT is widely used to assess and follow macular edema.

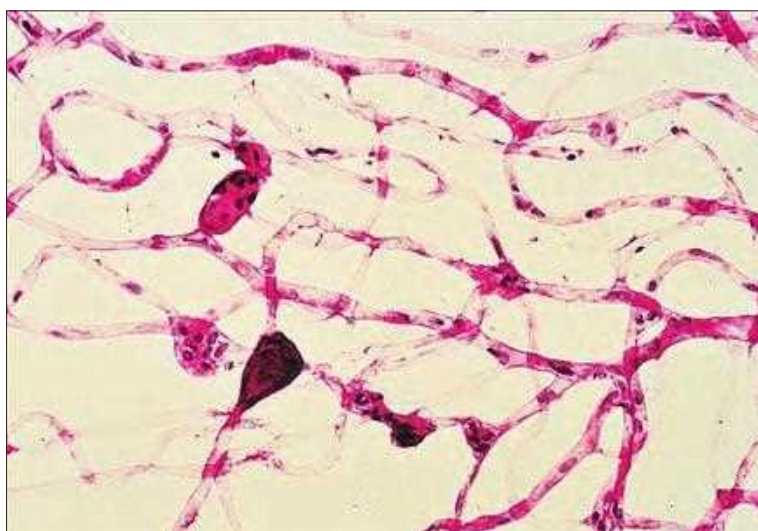
## DIFFERENTIAL DIAGNOSIS

The differential diagnosis is listed in [Box 6.22.1](#).

## PATHOLOGY

The earliest histopathological abnormalities in diabetic retinopathy are thickening of the capillary basement membrane and pericyte dropout. Microaneurysms begin as a dilatation in the capillary wall in areas where pericytes are absent; microaneurysms initially are thin walled. Later, endothelial cells proliferate and deposit layers of basement membrane material around themselves. Fibrin may accumulate within the aneurysm, and the lumen of the microaneurysm may become occluded ([Fig. 6.22.7](#)). In early cases, microaneurysms are present mostly on the venous side of the capillaries, but later they are also seen on the arterial side. Despite the multiple layers of basement membrane, they are permeable to water and large molecules, resulting in water and lipid accumulation in the retina. Because





**Fig. 6.22.7 Microaneurysms, Pericyte Dropout, and Acellular Capillaries Are Seen.**

### BOX 6.22.1 Differential Diagnosis of Diabetic Retinopathy

- Radiation retinopathy
- Hypertensive retinopathy
- Retinal venous obstruction (central retinal vein occlusion [CRVO], branch retinal vein occlusion [BRVO])
- The ocular ischemic syndrome
- Anemia
- Leukemia
- Coats' disease
- Idiopathic juxtafoveal retinal telangiectasia
- Sickle cell retinopathy

fluorescein passes easily through them, many more microaneurysms are seen on fluorescein angiography than on ophthalmoscopy (see Figs. 6.22.1 and 6.22.3).

## TREATMENT

### Medical Therapy

#### Antiplatelet Therapy

The ETDRS reported that aspirin 650 mg daily does not influence the progression of retinopathy, affect visual acuity, or influence the incidence of vitreous hemorrhages. However, there was a significant decrease in cardiovascular morbidity in the aspirin-treated group compared with the placebo cohort.<sup>49</sup> Clopidogrel and ticlopidine, like aspirin, inhibit adenosine diphosphate-induced platelet aggregation. They have been shown to decrease the risk of stroke in patients with transient ischemic attacks, but there is no clear evidence showing an impact on diabetic retinopathy.

#### Antihypertensive Agents

The Hypertension in Diabetes Study, part of the United Kingdom Prospective Diabetes Study (UKPDS), evaluated the effect of blood pressure control on the progression of diabetic retinopathy. Patients were treated with angiotensin-converting enzyme inhibitors (ACEIs) or beta-blockers to achieve “tight” control of blood pressure (<150/85 mm Hg) or “less tight” control (<180/105 mm Hg). The group with better blood pressure control had a 37% risk reduction in microvascular changes. There was no difference in effect between the two agents used. Lisinopril, an ACEI, has also been shown to decrease the progression of NPDR and PDR in normotensive diabetics. The patients in this study with the better glycemic control benefited more from lisinopril.<sup>50</sup>

#### Antiangiogenesis Agents

The discovery that VEGF plays a critical role in the initiation of diabetic neovascularization and an important role in DME has revolutionized management of these complications of diabetes. Several pharmacological inhibitors of angiogenesis have been shown to be beneficial in the therapy of center-involving DME.<sup>51–67</sup> These include:

- Pegaptanib sodium, a VEGF aptamer (Macugen, Eyetech Pharmaceuticals, NY).<sup>53–56</sup>
- Ranibizumab (Lucentis, Genentech).<sup>55–61</sup>
- Bevacizumab (Avastin, Genentech).<sup>63,64</sup>
- Aflibercept (Eylea, Regeneron).<sup>65–67</sup>

All four anti-VEGF agents improve visual acuity and promote normalization of the macular architecture in most eyes with DME. Because of their superior beneficial effect compared to laser and corticosteroids, with a relatively good safety profile, anti-VEGF therapy is now considered primary treatment of fovea-involving DME in most eyes.

The major problems with anti-VEGF therapy are cost and frequency of administration. In addition, the risk of endophthalmitis with anti-VEGF therapy in diabetics appears to be greater than with other ophthalmic conditions (e.g., neovascular age-related macular degeneration, retinal venous occlusion), with several studies suggesting the long-term incidence may approach 1%.<sup>51</sup> In current clinical practice, pegaptanib is not as widely used, as the other agents appear to be more efficacious.<sup>51,52</sup> The DRCR Protocol T compared the visual and anatomical outcomes of bevacizumab, ranibizumab, and aflibercept for treatment of diabetic macular edema in patients with 20/32–20/320 visual acuity.<sup>55</sup> All three drugs did result in some improvement in visual acuity and reduction of edema by OCT. There were 9–10 treatments given in the first year for all three drugs. Overall, mean change in visual acuity was best for aflibercept (13 letters) which was greater than ranibizumab (11 letters,  $p = 0.034$ ) or bevacizumab (10 letters,  $p < 0.001$ ). For visual acuities better than 20/50, there was no significant difference in the visual or anatomic outcomes. However, for visual acuities of 20/50 or worse, aflibercept resulted in a mean gain of 19 letters versus 14 letters for ranibizumab ( $p = 0.0031$ ) or 12 letters for bevacizumab ( $p < 0.001$ ). More eyes gained 15 or more letters with aflibercept (67%) than ranibizumab (50%,  $p < 0.001$ ) or bevacizumab (41%,  $p = 0.0078$ ). There were no significant differences between the drugs in terms of percentage of eyes that lost 10 or more letters or 15 or more letters from baseline. Both ranibizumab and aflibercept resulted in significantly greater reductions in mean CST than bevacizumab. No significant differences in safety were found among the three drugs.

The best dosing regimen for the anti-VEGF remains controversial. It is generally agreed that monthly injections are indicated until the fluid has resolved or until no further improvement occurs, but once that point has been reached, it remains unclear whether further “mandated” monthly injections or long-term monthly injections versus a switch to an as-needed protocol is best. For those clinicians choosing to combine anti-VEGF therapy with focal laser, the optimal timing of the laser and anti-VEGF therapy is not as yet determined.<sup>55–61</sup> However, most studies support delayed laser photocoagulation, usually at about 6 months after initiating anti-VEGF therapy. With respect to the role of anti-VEGF therapy combined with immediate or deferred focal laser, the DRCR Protocol J<sup>55,56</sup> showed that ranibizumab with deferred ( $\geq 24$  weeks) laser is more efficacious than focal laser alone, intravitreal ranibizumab plus prompt (within 3–10 days of injection) focal laser, triamcinolone acetate plus prompt laser, or sham plus prompt focal laser treatment. Eyes treated with ranibizumab plus either prompt or deferred focal laser had better visual acuity outcomes than eyes treated with triamcinolone plus prompt laser or sham plus prompt laser. Interestingly, reductions in OCT central subfield thickness were similar between the ranibizumab and triamcinolone groups, suggesting the visual benefits of intravitreal corticosteroids may be tempered by their side effects: cataract and elevated intraocular pressure (IOP). Indeed, for pseudophakic eyes, ranibizumab and triamcinolone groups had similar outcomes. The rate of endophthalmitis was 0.8% in the ranibizumab groups versus none in the corticosteroid group or laser alone eyes.<sup>55–57</sup>

#### Bevacizumab

Bevacizumab is in wide usage for treatment of DME. While not studied as rigorously as the other anti-VEGFs, the cost differential favors it so greatly, that for many clinicians it is the first line therapy. The best data on this drug comes from the DRCR Study Protocol T (see earlier).<sup>55</sup> In addition, the Bevacizumab or Laser Therapy (BOLT) Study<sup>63</sup> showed that bevacizumab had superior visual outcomes (20/50 Snellen equivalent) in the 80 enrolled patients compared to laser 54.8 (20/80) at 2 years. The mean change in visual acuity was a gain of 8.6 letters for bevacizumab versus a mean loss of 0.5 letters for laser arm eyes. Forty-nine percent of patients gained 10 or more letters ( $p = 0.001$ ), and 32% gained at least 15 letters ( $p = 0.004$ ) for bevacizumab versus 7% and 4% for laser eyes. The median number of treatments over 24 months was 13 for bevacizumab



and four for laser. A large retrospective study of bevacizumab for DME was performed by the Pan-American Collaborative Retina Study Group (PACORES).<sup>64</sup> This group showed that stability or improvement of visual acuity occurred with 1.25 mg or 2.5 mg bevacizumab. No difference was seen between the two doses. The mean vision gained was 2.4 lines at 24 months for both groups.

### Pegaptanib

Pegaptanib sodium (Macugen), a selective VEGF-165 aptamer, was the first anti-VEGF agent used in DME.<sup>51,52</sup> Although pegaptanib-treated eyes had slightly better visual acuity outcomes and reduction of retinal edema by OCT as compared with sham-treated eyes, the results were not clinically convincing enough to change the standard of care. In the phase 2 macular edema study, a small subset of eyes also had PDR. The PDR regressed during the period of active therapy but recurred at cessation of anti-VEGF treatment.<sup>53,54</sup> This drug's comparative efficacy has limited its use.

### Aflibercept

In the phase 3 VIVID and VISTA studies, 872 eyes with center-involved macular edema were randomized to receive intravitreal injection of aflibercept 2 mg every 4 weeks, 2 mg every 8 weeks after five monthly doses or macular laser.<sup>65</sup> The mean change in best-corrected visual acuity (BCVA) at week 52 from baseline was the primary endpoint. The primary endpoint was superior for aflibercept compared to laser controls at week 52 and sustained through week 100.<sup>66</sup> The results were similar for both dosing groups. The mean change in vision was a gain of 12.5 for 2 mg q4 and 10.7 for 2 mg q8 versus 0.2 letters for laser ( $p < 0.0001$ ) in VISTA, and 10.5 for 2 mg q4 and 10.7 for 2 mg q8 versus 1.2 letters for laser ( $p < 0.0001$ ) in VIVID. Eyes receiving aflibercept had more significant reductions in OCT thickness as compared with controls. Significantly more eyes also gained 15 or more letters from baseline in the aflibercept compared with the laser groups. An analysis of the mean visit-to-visit change in BCVA and central retinal thickness during the upload phase from the 2 mg q4 and the 2 mg q8 datasets showed continual functional and anatomical improvements after the fourth and fifth injections. This study suggests that intensive uploading is beneficial.<sup>67</sup>

### Additional Medical Therapies

Inhibition of protein kinase C, a compound critical in the cascade that activates VEGF expression, was not shown to be of benefit in the treatment or prevention of DME. An oral inhibitor of protein kinase C has been shown to suppress retinal neovascularization in animal models.<sup>68</sup> Recently, a protein kinase C inhibitor has been shown to reduce diabetes-induced hemodynamic abnormalities in patients with diabetic retinopathy and reduce the risk of vision loss in patients with macular edema. It delayed the progression of edema located more than 100  $\mu\text{m}$  from the foveal center to within 100  $\mu\text{m}$  of the foveal center (68% vs. 50%,  $p = 0.003$ ). Initial laser treatment for macular edema was 26% less frequent in eyes of ruboxistaurin-treated patients ( $p = 0.008$ ).<sup>69</sup> However there was no effect of ruboxistaurin on prevention of progression of diabetic retinopathy.<sup>70,71</sup>

In addition to anti-VEGF therapies, there are non-VEGF pathways that may be useful targets in the therapy of DME. One of these is the Tie 2 receptor pathway.<sup>72-74</sup> Inhibition of angiopoietin 2 (Ang2) is being investigated in combination with anti-VEGF therapies. The Boulevard Study is a phase 2 study that is comparing the efficacy of a bispecific antibody (Roche RG7716) to both VEGF and Ang2 with ranibizumab alone. The Ruby Study was a phase 2 study comparing the efficacy of a co-formulation of two drugs (aflibercept and nesvacumab) with aflibercept alone. The Boulevard Study has shown that the bispecific antibody achieved its primary endpoint of efficacy. Mean VA gain at 6 months was significantly improved for the bispecific antibody as compared with ranibizumab alone (3.6 letters difference,  $p = 0.03$ ); mean gain was 13.9 letters from baseline (written communication from Genentech.) The Ruby Study has shown no difference in the primary endpoint between the coformulated drug and aflibercept (written communication from Regeneron).

## Pharmacotherapy for Proliferative Diabetic Retinopathy

The use of anti-VEGF therapy for PDR initially was shown in the pegaptanib sodium for DME studies. In these studies, a few eyes with PDR were inadvertently included, and regression of the PDR occurred.<sup>53,54</sup> This led to specific studies evaluating the use of anti-VEGF for PDR. In a phase 1, prospective, randomized, controlled, open-label study, 20 active PDR patients

were randomly assigned to receive pegaptanib sodium (0.3 mg) every 6 weeks for 30 weeks or PRP laser. In the pegaptanib group, early regression was seen by week 3 (90%) with complete regression by week 12 that was maintained through week 36. In contrast, in the PRP group, 25% showed complete regression, 25% partial, and 50% showed persistent active PDR. Mean change in vision was +5.8 letters in pegaptanib-treated eyes and -6.0 letters in PRP-treated eyes.<sup>53</sup>

The DRCR Protocol S has compared anti-VEGF and PRP for eyes with PDR in a noninferiority study in 394 eyes.<sup>75</sup> Treatment with 0.5 mg ranibizumab (initially every 4 weeks for six injections unless no neovascularization at 4- or 5-month visit) was noninferior to PRP for visual acuity outcomes. Primary outcome was mean change in vision at 2 years compared to baseline. At 2 years, mean visual acuity improved 2.8 letters in the ranibizumab group versus 0.2 letters in the PRP group ( $p < 0.001$  for noninferiority). Both treatments were effective for controlling the PDR and in preventing NVI and visual loss. However, when improvements in visual acuity were evaluated, anti-VEGF was found to result in superior mean visual acuity over the course of 2 years when an area-under-the-curve analysis was performed. Greater numbers of eyes gained vision. Anti-VEGF also had superior visual field outcomes compared to laser. There was also a decreased need for vitrectomies and lower incidence of center-involved macular edema in the anti-VEGF eyes. PRP was rarely given for failure of anti-VEGF to control PDR. There was a lower amount of reduction in visual field.

An analysis of rate of progression of PDR (defined as first occurrence of vitreous hemorrhage, retinal detachment, anterior segment neovascularization, or neovascular glaucoma) showed that eyes treated with ranibizumab had lower rates (34% vs. 42%) of progression than eyes treated with PRP.<sup>76</sup> Incidentally, the risk of progression was higher for eyes receiving pattern scan laser than for eyes receiving conventional PRP (60% vs. 39%).

Despite these results, one needs to weigh other factors that may affect a patient's response to anti-VEGF therapy for PDR. If a patient is not likely to follow up and thus not likely to receive the needed anti-VEGF injections, one should probably not use anti-VEGF and instead proceed with PRP. In patients with PDR and DME, anti-VEGF is a reasonable choice.<sup>75</sup>

More recently, the RIDE and RISE studies have shown eyes treated with monthly ranibizumab were more likely to show improvement and less likely than sham eyes to show progression on the ETDRS retinopathy severity as graded on fundus photographs. These eyes were less likely to develop PDR.<sup>77</sup> Interestingly, patients with PDR had regression to NPDR levels. The DRCR showed that there was no difference in the rate of required pars plana vitrectomy 16 weeks later in eyes with vitreous hemorrhage given intravitreal ranibizumab versus sterile saline.<sup>78</sup>

### Corticosteroids

Even before clinical trials that investigated the long-term benefit of corticosteroids (triamcinolone acetonide) for DME, this treatment was in wide usage. In the short term, good visual results and improved OCT findings are seen in most eyes. However, with repeated injections over time, complications can occur frequently that limit the initial benefit. The DRCR network studies suggest that over 2 years of treatment, monotherapy with triamcinolone acetonide is not superior to laser photocoagulation for DME.<sup>79</sup> At 2 years, mean visual acuity was better in eyes treated exclusively with laser compared to eyes treated exclusively with either 1 mg triamcinolone ( $p = 0.02$ ) or 4 mg triamcinolone ( $p = 0.002$ ) groups.<sup>80</sup> As expected, intraocular pressure rise and cataract onset were greater in the triamcinolone group.

Since monotherapy with one agent is not how most patients are treated in the real world, subsequent studies looked at corticosteroids plus laser. As mentioned earlier, except perhaps in pseudophakic eyes, this combination is not recommended for primary treatment of DME if anti-VEGF agents are available.

There have been corticosteroids other than triamcinolone acetonide, evaluated for treatment of DME. A fluocinolone acetonide intravitreal insert was studied in the Famous Study.<sup>81</sup> The intravitreal inserts provide excellent sustained intraocular release of fluocinolone acetonide for one year or more. In a large trial, the FAME study, 29% of eyes receiving the 0.2  $\mu\text{g}$ /day fluocinolone implant gained three or more lines by year 2, versus 16% in the sham group ( $p = 0.002$ ).<sup>82</sup> Complications included elevation of IOP related events in 37% treated eyes versus 12% controls. Glaucoma surgery was required in 4.8% treated versus 0.5% controls. Cataract as an adverse event occurred in 82% of treated eyes, and 80% of treated eyes underwent cataract extraction over a period of 36 months versus corresponding data of 50% and 27% in the control group. Eyes with chronic DME had higher proportions of gain of 15 or more letters from baseline compared with

controls.<sup>83</sup> The study concluded that the fluocinolone implant is effective in eyes with chronic macular edema. The U.S. Food and Drug Administration (FDA) approval notes that this therapy is not to be used unless the eye has been previously treated with corticosteroids and has not had an elevation in IOP.

The dexamethasone intravitreal implant containing 700 µg dexamethasone (Ozurdex, Allergan, Irvine, CA) in a solid polymer drug delivery system that is also approved by the FDA for treatment of diabetic macular edema, in addition to macular edema from vein occlusions and uveitis. The MEAD study showed that 0.7 mg dexamethasone resulted in 22% treated eyes versus 12% sham eyes gaining 15 or more letters.<sup>84,85</sup> Also, dexamethasone-treated eyes had more significant reductions in CST on OCT (−112 µg versus −42 µg,  $p < 0.001$ ).

The BEVORDEX Study compared dexamethasone treated eyes and bevacizumab in a phase 2 study.<sup>86</sup> No significant differences were seen between the drugs for visual acuity or CST change by OCT at 24 months. However, 74% of dexamethasone-treated eyes versus 48% of bevacizumab-treated eyes had a rise in IOP of 5 mm Hg or more.

In vitrectomized eyes, the Champlain study showed that 55 vitrectomized eyes with treatment-resistant DME had statistically and clinically significant improvements in both visual acuity and vascular leakage with treatment. In fact, 30% gained 10 more letters.<sup>87</sup>

## Surgical Therapy

### Panretinal Photocoagulation

The Diabetic Retinopathy Study proved that both xenon arc and argon laser PRP significantly decrease the likelihood of progression of eyes with high-risk characteristics (HRC) to severe visual loss.<sup>88</sup> Eyes with HRC are defined as those with NVD greater than one fourth to one third of a disc area, those with any NVD and vitreous hemorrhage, or those with NVE greater than one-half the disc area and vitreous or preretinal hemorrhage.

The exact mechanism by which PRP works remains unknown. One hypothesis is that PRP decreases the production of vasoproliferative factors by eliminating areas of hypoxic retina. An alternative hypothesis suggests that by thinning the retina, PRP increases oxygenation of the remaining retina by allowing increased diffusion of oxygen from the choroid. Yet another hypothesis is that PRP leads to an increase in vaso-inhibitors by directly stimulating the retinal pigment epithelium to produce inhibitors of vasoproliferation.<sup>89</sup>

The goal of PRP is to arrest or to cause regression of the neovascularization. The recommended therapy is 1200–2000 burns that are 500 µm in diameter delivered through the Goldmann lens, or the equivalent number when using 200 µm burns delivered through the Rodenstock panfunduscope lens or Volk SuperQuad lens. The burns should be intense enough to lightly whiten the overlying retina using a duration of 0.1 second (see Fig. 6.22.5). There are newer lasers that deliver shorter bursts of laser energy that result in control of the neovascularization.

Some retinal specialists feel that there is no upper limit to the total number of burns and that treatment should be continued until regression occurs.<sup>90</sup> The only prospective, controlled study found that eyes that received supplementary PRP treatment had no improved outcome over those that received standard PRP only.<sup>91</sup> About two thirds of eyes with HRC that receive PRP have regression of their HRC by 3 months after treatment.

The ETDRS found that PRP significantly retards the development of HRC in eyes with very severe NPDR and macular edema.<sup>29</sup> After 7 years of follow-up, 25% of eyes that received PRP developed HRC as compared with 75% of eyes in which PRP was deferred until HRC developed. Nevertheless, the ETDRS concluded that treatment of severe NPDR and PDR short of HRC was not generally indicated for three reasons.

First, after 7 years of follow-up, 25% of the eyes assigned to deferral of PRP had not developed HRC. Second, when patients are closely monitored and PRP is given as soon as HRC develops, severe visual loss can be prevented. After 7 years of follow-up, 4.0% of eyes that did not receive PRP until HRC developed had a visual acuity of 5/200 or less, compared with 2.5% of eyes assigned to immediate PRP. The difference was neither clinically nor statistically significant. Third, PRP has significant complications. It often causes decreased visual acuity by increasing macular edema or by causing macular pucker.<sup>92,93</sup> Fortunately, the edema frequently regresses spontaneously over 6 months, but the visual field usually is moderately, but permanently, decreased. Color vision and dark adaptation, which often are already impaired, also are worsened by PRP.<sup>94</sup> However, if both eyes have severe NPDR, the ETDRS reported that PRP was not unreasonable, especially in patients who are unlikely to follow up closely.

Recently the pattern lasers have enabled semi-automated laser photocoagulation.<sup>95</sup> These lasers allow various patterns of laser spots to be given within a fraction of the time usually required when using traditional lasers. The duration of the laser application (usually 10–30 milliseconds) is also shorter than traditional lasers (100–300 milliseconds). Studies have shown that more laser spots are needed with increasing severity of PDR.<sup>96</sup> In a prospective study in which one eye was assigned to pattern laser single session and the other eye to multisection conventional PRP laser, control of PDR was achieved with less associated pain or complications.<sup>97</sup> However, applying the same number of spots used with traditional lasers does not achieve sustained regression of the lesions, probably because more laser spots are required to treat the same area of retina achieved with traditional lasers.<sup>98</sup>

### Peripheral Retinal Cryotherapy

Peripheral retinal cryotherapy is used to treat HRC in eyes with media too hazy for PRP. Reported benefits include resorption of vitreous hemorrhages and regression of NVD, NVE, and NVI. The main complication is the development or acceleration of traction retinal detachment in 25%–38% of eyes.<sup>99</sup> Therefore, this treatment should be avoided in patients with known traction retinal detachment, and all patients must be monitored carefully. In the current era of anti-VEGF therapy this option is mostly historical. This option is probably best reserved for those eyes with no visual potential and recalcitrant PDR that has been unresponsive to PRP or in which PRP cannot be applied. The DRCR Protocol AB will investigate the utility of anti-VEGF in eyes with vitreous hemorrhage compared to pars plana vitrectomy.

### Focal Laser for Macular Edema

Patz<sup>100</sup> was the first to show that argon laser photocoagulation decreases or stabilizes macular edema. Later, the ETDRS confirmed his results. The ETDRS<sup>29</sup> defined clinically significant macular edema as:

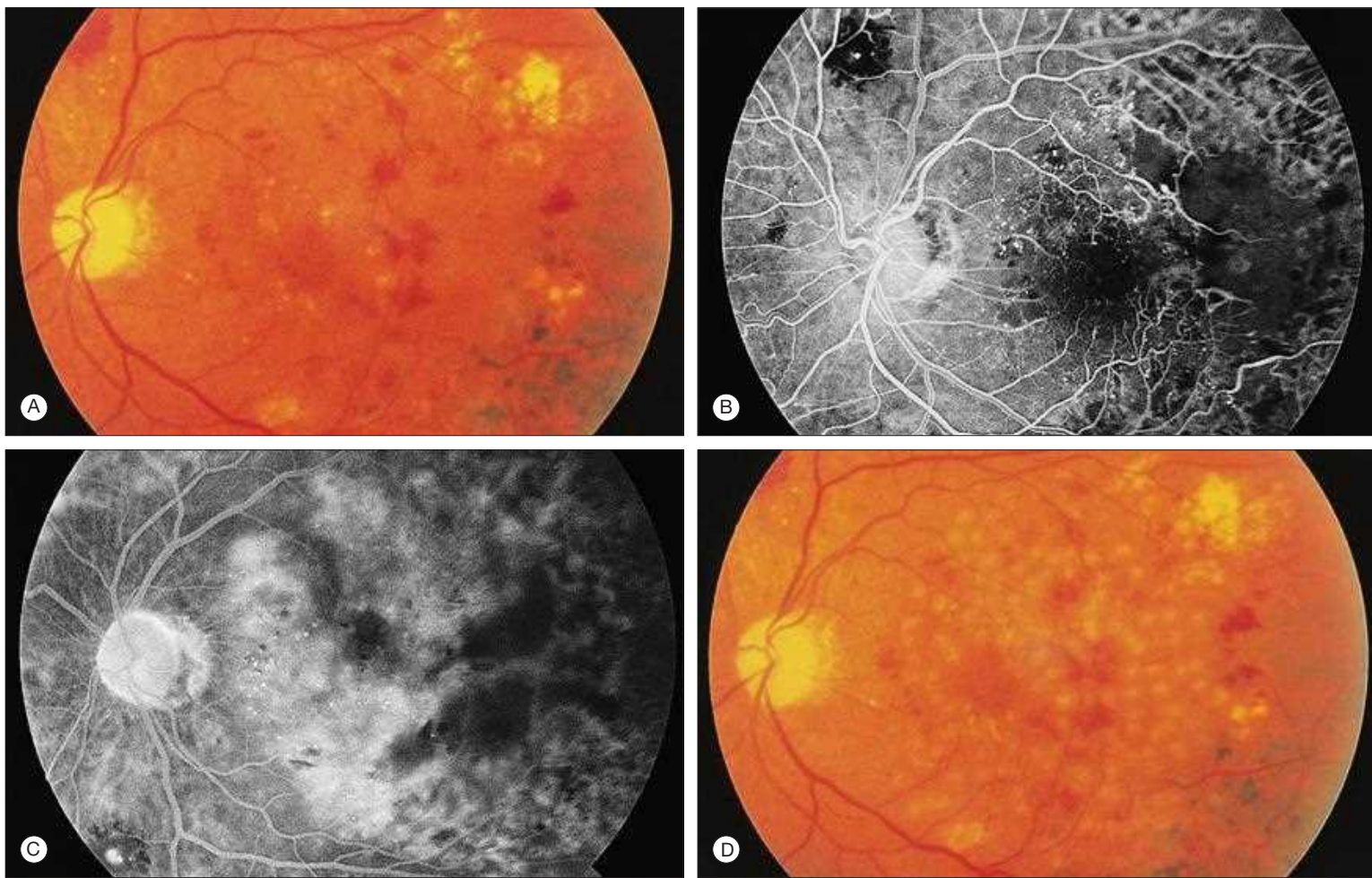
- Retinal thickening involving the center of the macula, or
- Hard exudates within 500 µm of the center of the macula (if associated with retinal thickening), and
- An area of macular edema greater than one disc area but within 1 disc diameter of the center of the macula.

In the era of spectral-domain optical coherence tomography (SD-OCT) imaging, intraretinal cysts are seen on SD-OCT imaging in eyes with relatively good visual acuity and no clinical thickening. There is no clinical trial to date that has addressed management of these “subclinical DME” eyes.

The ETDRS focal laser treatment strategy was to photocoagulate all leaking microaneurysms further than 500 µm from the center of the macula and to place a grid of 100–200 µm burns in areas of diffuse capillary leakage and in areas of capillary nonperfusion (Fig. 6.22.8). After 3 years of follow-up, 15% of eyes with clinically significant macular edema had doubling of the visual angle as opposed to 32% of untreated control eyes.<sup>101</sup> The ETDRS also showed that PRP should not be given to eyes with clinically significant macular edema unless HRC are present.<sup>29</sup> Patients with macular edema who have the best prognosis for improved vision have circinate retinopathy of recent duration or focal, well-defined leaking areas and good capillary perfusion surrounding the avascular zone of the retina. Patients with an especially poor prognosis have dense lipid exudate in the center of the foveola (Fig. 6.22.9). Other poor prognostic signs include diffuse edema with multiple leaking areas, extensive central capillary nonperfusion, increased blood pressure, and CME.<sup>101</sup> Nevertheless, the ETDRS found that even eyes with these adverse findings still benefited from treatment when compared with control eyes. Side effects of the focal laser include some loss of central vision, central scotomas, and decreased color vision. In addition, the retinal pigment epithelium (RPE) and retinal atrophy associated with the laser scars can enlarge over time and may encroach on fixation.<sup>102</sup> Following publication of the ETDRS, clinicians now use laser burns that are lighter and less intense to limit progressive laser scar expansion and the attendant visual side effects. Because of these side effects, investigators turned to pharmacological agents to treat DME. One of the first agents used was intravitreal triamcinolone acetate. However, as discussed earlier, the effect is transient and there is a high risk of cataract progression and secondary glaucoma.<sup>103</sup> Eyes with macular ischemia and better baseline vision may have less vision improvement with intraocular corticosteroids.<sup>103–104</sup> Anti-VEGF agents are more commonly employed due to their higher rates of efficacy and lower rates of complications.

Pattern laser results in barely visible 10 millisecond laser spots that reduce retinal edema with minimization of scar formation.<sup>95</sup> It will be





**Fig. 6.22.8 Macular Edema.** (A) In an eye previously treated with panretinal photocoagulation. (B) Midphase of fluorescein angiography showing microaneurysms, large areas of capillary nonperfusion, and slight enlargement of the foveal avascular zone. (C) Late phase of fluorescein angiography showing diffuse capillary leakage. (D) Grid pattern of focal macular photocoagulation in same eye.



**Fig. 6.22.9 Hard Exudate Plaque in the Center of the Macula.**

interesting to see whether combinations of pharmacotherapy and lighter application strategies can achieve durability with similar rates of visual efficacy as seen with anti-VEGF monotherapy and deferred argon laser. Micropulse lasers are also being studied for treatment of DME. High-density, subvisible, diode, micropulse lasers can achieve reduction of DME without laser-induced retinal damage.<sup>105–107</sup> A prospective, randomized, controlled, double-masked clinical trial has compared outcomes achieved with modified ETDRS focal/grid photocoagulation (42 patients), normal density subthreshold micropulse (39 patients), or high-density subthreshold micropulse (42 patients) in previously untreated DME eyes with baseline best corrected visual acuity worse than 20/40 and better than 20/400. All groups showed a significant progressive reduction of central macular thickness throughout the study ( $p < 0.001$ ). However, the visual acuity results were

best for the high-density subthreshold micropulse group (0.25 logMAR) and then the modified ETDRS group (0.08 logMAR). No improvement was found in the normal-density subthreshold micropulse group (0.03 logMAR). More research is needed in this area to further evaluate this new laser technique and to compare outcomes with anti-VEGF monotherapy of combination therapies.<sup>108</sup>

In summary, the Diabetic Retinopathy Study and the ETDRS conclusively proved that timely laser photocoagulation of diabetic retinopathy can reduce severe visual loss by 95%.<sup>109</sup> Such treatment makes sense not only from the humanitarian point of view, but also from a cost-effectiveness viewpoint. It has been estimated that ETDRS-style therapy saves \$250–500 million per year in the United States by enabling patients to avoid disability and welfare.<sup>110</sup> More recently, anti-VEGF therapies have raised our ability to improve visual acuity and hopefully will result in further avoidance of disability for our patients. Laser remains the treatment of choice for clinically significant DME that is *not* foveal involving.

### Vitrectomy in Diabetic Retinopathy

Vitrectomy plays a vital role in the management of severe complications of diabetic retinopathy. The major indications are nonclearing vitreous hemorrhage, macular-involving or macular-threatening traction retinal detachment, and combined traction-rhegmatogenous retinal detachment. Less common indications are macular edema with a thickened and taut posterior hyaloid, epiretinal membrane, severe preretinal macular hemorrhage, and neovascular glaucoma with cloudy media.<sup>111</sup>

To evaluate whether early vitrectomy (in the absence of vitreous hemorrhage) might improve the visual prognosis by eliminating the possibility of later traction macular detachment, the Diabetic Retinopathy Vitrectomy Study (DRVS) randomized 370 eyes with florid neovascularization and visual acuity of 20/400 or better to either early vitrectomy or to observation.<sup>112</sup> After 4 years of follow-up, approximately 50% of both groups had 20/60 or better, and approximately 20% of each group had light perception or worse. Thus the results indicate that such patients probably do not benefit from early vitrectomy. They should be observed closely so that vitrectomy, when indicated, can be undertaken promptly.



If a patient has a vitreous hemorrhage severe enough to cause a visual acuity of 5/200 or less, the chances of visual recovery within 1 year are only about 17%.<sup>113</sup> The DRVS randomized patients who had a visual acuity of 5/200 or less for more than 6 months into two groups: those who received an immediate vitrectomy and those whose vitrectomy was deferred for a further 6 months.<sup>113</sup> The goals of surgery were to release all anterior-posterior vitreous traction and to perform a complete PRP to reduce the incidence of recurrent hemorrhage. Of those who had deferred vitrectomy, 15% had a final visual acuity of 20/40 or better as opposed to 25% of those who had an immediate vitrectomy. In patients with type 1 diabetes, 12% of those who had a deferred vitrectomy had a final visual acuity of 20/40 or better, as opposed to 36% of those who had an immediate vitrectomy. The reason for this discrepancy is thought to be excessive growth of fibrovascular proliferation during the waiting period. For this reason, the DRVS concluded that strong consideration should be given to immediate vitrectomy, especially in type 1 diabetics (in type 2 diabetics, the final visual results were similar). Currently, with improved surgical techniques and tools, clinicians no longer defer surgery for diabetic vitrectomy. Patients with bilateral visual loss because of vitreous hemorrhage, rubeosis and hemorrhage, recurring hemorrhage, and known traction retinal detachment close to the macula should be offered early vitrectomy. If surgery is deferred, ultrasonography should be performed at regular intervals to make sure that traction retinal detachment is not developing behind the hemorrhage. In patients who have recurrent vitreous hemorrhage after vitrectomy, a simple outpatient air-liquid exchange may restore vision without the need for a repeat vitrectomy.<sup>114</sup>

Traction retinal detachments are usually a much greater challenge. In general, unless the macula becomes involved, observation is the best therapy for these patients, because in most cases the detachment does not progress into the macula. These patients should be counseled to seek immediate attention should macular vision suddenly be lost. The surgical objectives are to clear the media, to release all anterior-posterior traction, to release tangential traction via delamination or segmentation (cutting the fibrotic bridges between areas of tractional detachment), and to perform endophotocoagulation. The prognosis is best in patients who have small areas of traction. The prognosis is poorest in eyes with tabletop detachments, significant preoperative vitreous hemorrhage, no prior PRP, and advanced fibrovascular proliferation. If a lensectomy is required or if iatrogenic breaks are created, the results are poorer.<sup>115</sup> Approximately 60%–70% of patients have improved visual acuity and a final visual acuity of 20/800 or better, but 20%–35% have decreased vision after vitrectomy. Cases with severe peripheral fibrovascular proliferation also may require a scleral buckling procedure.<sup>116</sup> Repeated operations are required in about 10% of patients, most commonly for rhegmatogenous retinal detachment and recurrent vitreous hemorrhage.<sup>117</sup>

A possible cause of failure following an otherwise successful vitrectomy is NVI resulting in neovascular glaucoma. The risk is higher if there is preoperative NVI (33% versus 17%), if there is persistent retinal detachment after surgery, if the lens is removed during surgery, and if there is florid NVD. In eyes without these factors, the incidence of neovascular glaucoma is only about 2%. The pathogenesis of this complication is unknown. Some investigators believe that removal of the vitreous allows vasoproliferative factors produced in hypoxic retina to diffuse forward to the iris. Others believe that following vitrectomy increased oxygen diffusion occurs posteriorly out of the anterior chamber, thereby lowering its oxygen tension too far. Fortunately, if an eye does not develop iris neovascularization during the first 4–6 months after vitrectomy, it rarely does so later.<sup>118</sup> With the advent of anti-VEGF therapy, there is more hope for these eyes.

Another vision-threatening complication is neovascularization that originates from the anterior retina and extends along the anterior hyaloid to the posterior lens surface (anterior hyaloidal fibrovascular proliferation).<sup>119</sup> This is more common in young, phakic diabetics who have extensive capillary nonperfusion.

Vitrectomy for diffuse macular edema is controversial. Evidence indicates that patients with an abnormally taut posterior hyaloid are more likely to have visual improvement and reduction of edema as compared to patients with a posterior vitreous separation. Removal of the internal limiting membrane over the macula may be beneficial.<sup>120,121</sup>

## CONCLUSIONS

The prognosis for diabetic retinopathy used to be dismal. Timely laser photocoagulation as advocated by the Diabetic Retinopathy Study and the ETDRS reduced severe visual loss by 95%. Currently, anti-VEGF therapy can result in even better visual acuity outcomes for eyes with DME. The DRCR has shown that anti-VEGF therapy can also achieve control of PDR without loss of vision or visual field. We are thus on the threshold of a new treatment paradigm for diabetic retinopathy, that of primary pharmacotherapy. However, as in the past, these new treatments can only be offered if the patient presents and keeps follow-up appointments with their ophthalmologist. Even today, many diabetics still become legally blind because they do not present for timely ophthalmological examination and do not achieve excellent control of blood glucose levels and high blood pressure. Control of these systemic factors can significantly delay the onset and progression of retinopathy. Follow-up is even more important when primary pharmacotherapy is used to treat sight-threatening disease in lieu of laser. All of these issues must therefore be considered when planning therapy for diabetic retinopathy.

Although all agree that screening of asymptomatic diabetic patients is critical, the most cost-effective timing remains controversial. It generally is agreed that type 2 diabetics should be examined at the onset of their disease, then yearly thereafter. Type 1 diabetics do not have to be examined until 5 years into their disease course, but no sooner than puberty, then yearly thereafter. If retinopathy is detected, the frequency of examinations should be increased appropriately.

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# Ocular Ischemic Syndrome

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# 6.23

**Definition:** Ocular signs and symptoms secondary to severe, chronic arterial hypoperfusion.

## Key Features

- Visual loss.
- Blot retinal hemorrhages.
- Dilated, beaded retinal veins.
- Decreased ocular perfusion pressure.
- Ocular neovascularization.
- Severe ipsilateral or bilateral carotid artery obstruction.

## Associated Features

- Pain or ocular angina.
- Neovascular glaucoma.
- Mild anterior uveitis.
- Cherry-red spot in macula.
- Cotton-wool spots.
- Spontaneous pulsations of retinal arteries.
- Ischemic optic neuropathy.

## INTRODUCTION

Ocular ischemic syndrome (OIS) encompasses a spectrum of variable signs and symptoms arising from chronic ocular hypoperfusion, usually secondary to severe carotid artery obstruction. Additional names given to this condition include hypoperfusion retinopathy, hypotensive retinopathy, ischemic ocular inflammation,<sup>3</sup> and ischemic oculopathy.<sup>4</sup> In 1963 Kearns and Hollenhorst<sup>1</sup> introduced the term *venous stasis retinopathy* to first describe findings in patients with advanced carotid artery insufficiency. In order to avoid confusion, this term is best avoided, as it has been used by others when referring to nonischemic central retinal vein occlusion (CRVO),<sup>2</sup> an entirely different condition.

## EPIDEMIOLOGY AND PATHOGENESIS

OIS rarely develops before age 50, with a mean age of 65 years at presentation. Men are affected twice as often as women (reflecting the higher incidence of atherosclerotic cardiovascular disease in men) without racial predilection. Bilateral involvement occurs in approximately 20% of cases.<sup>5</sup> The incidence of the syndrome is estimated at 7.5 cases per million population annually, a figure that may be falsely low since the condition can often be clinically mistaken for other vascular diseases.<sup>6</sup>

Approximately 5% of patients who have hemodynamically significant atherosclerotic carotid artery disease develop OIS, with most cases generally showing 90% obstruction of the ipsilateral carotid artery system.<sup>5</sup> Patients with poor collateral circulation between the external and internal carotid systems are susceptible to developing OIS at even lesser degrees of occlusion, whereas those with well-developed collaterals may not develop the syndrome even with total occlusion of the internal carotid artery.<sup>1</sup> Uncommonly, in patients without carotid disease, isolated obstruction of the ipsilateral ophthalmic artery has been reported as a cause for OIS.<sup>12</sup>

The period and extent of the impaired blood flow necessary to develop this syndrome still is not clear. Color Doppler imaging of eyes with OIS has revealed decreased peak systolic flow velocities of the central retinal artery and reversal of flow within the ophthalmic artery. Reversal of the

ophthalmic artery flow represents collateralization to the external carotid artery system as a result of obstructions in the internal carotid artery system. This further contributes to hypoperfusion and subsequent ischemia of the optic nerve, choroid, retinal pigment epithelium, and outer segments of the photoreceptors, likely resulting in the visual loss seen in OIS.<sup>7,8</sup>

## OCULAR MANIFESTATIONS

### Symptoms

A history of transient vision loss is reported by 10%–15% of patients with OIS.<sup>23,25</sup> Decreased visual acuity is present in over 90% of affected patients at initial evaluation.<sup>5</sup> Loss of vision generally occurs gradually, over a period of weeks to months, but can occur abruptly. The severity is variable: 35% of affected eyes at the time of evaluation have a visual acuity of 20/40 (6/12) or better; 30% range from 20/50 (6/15) to 20/400 (6/120); in 35%, acuity is sufficient to count fingers or worse. The absence of light perception is an uncommon finding initially but may develop as a sequela of severe posterior segment ischemia frequently in combination with neovascular glaucoma.<sup>5</sup> Varying patterns of visual field loss, positive visual phenomena, and prolonged recovery of vision after exposure to bright lights are also associated symptoms.<sup>5,23,25</sup> A dull ache over the eye or brow, referred to by some authors as *ocular angina*, is reported in up to 40% of patients with OIS and can result from ischemia of the globe or elevated intraocular pressure (IOP) caused by neovascular glaucoma.<sup>5</sup>

### Anterior Segment

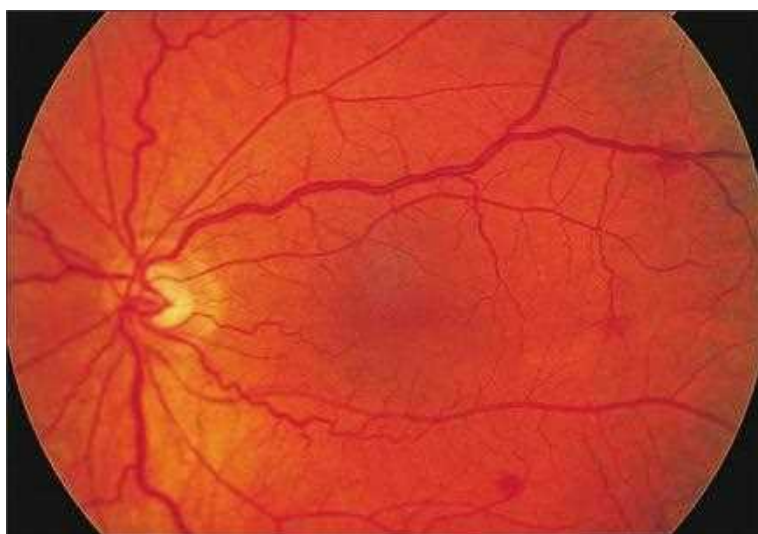
Anterior segment findings in OIS are common and rarely may be the sole ocular manifestation of carotid occlusive disease.<sup>5,24</sup> Anterior segment neovascularization in a nondiabetic patient without evidence of venous occlusive disease or other predisposing cause, is suggestive of OIS. Approximately two-thirds of eyes exhibit neovascularization of the iris at initial examination, with neovascular glaucoma seen in half of these eyes.<sup>5</sup> Despite complete angle closure by fibrovascular proliferation, some patients will demonstrate normal IOP due to decreased aqueous humor production as a result of impaired ciliary body perfusion from carotid occlusion. Anterior uveitis in eyes that have OIS has been well described.<sup>3</sup> Iritis, present in 20% of these eyes, is generally mild. Flare is a more prominent feature than the cellular response, and keratic precipitates are seen infrequently. The possibility of OIS must be considered in patients over 50 years of age who have new-onset iritis. Lens opacification, even formation of a mature cataract, may occur in the end stages of OIS.<sup>5</sup>

### Posterior Segment

Posterior segment signs are more frequent than those in the anterior segment and provide important clinical clues that support the diagnosis of OIS. Numerous changes can be seen in the fundus, including:

- Retinal arterial narrowing.
- Retinal venous dilation without tortuosity.
- Retinal hemorrhages and microaneurysms.
- Neovascularization of the optic disc or retina.
- Cherry-red spot.
- Cotton-wool spots.
- Spontaneous pulsations of the retinal arteries.

Retinal arterial narrowing and straightening, which are associated with areas of focal constriction, are commonly seen in eyes with OIS. Retinal veins may exhibit beading similar to that seen in diabetic retinopathy.



**Fig. 6.23.1 Retinal Vascular Changes in Ocular Ischemic Syndrome.** Narrowed retinal arteries; dilated, minimally tortuous retinal veins; and blot retinal hemorrhages are present in an eye that is affected by ocular ischemic syndrome.



**Fig. 6.23.2 Retinal Hemorrhages in Ocular Ischemic Syndrome.** Dot-and-blot hemorrhages, as well as microaneurysms, are seen commonly in the midperiphery of eyes that are affected by ocular ischemic syndrome.

Retinal veins are often dilated but not characteristically tortuous or only minimally so (Fig. 6.23.1). This latter feature may help to ophthalmoscopically differentiate OIS from CRVO, in which retinal veins are both dilated and often markedly tortuous.

Retinal hemorrhages are seen in 80% of affected eyes. Typically, these are deep retinal hemorrhages of the dot-and-blot variety, though hemorrhages from ruptured microaneurysms and less frequently nerve fiber layer hemorrhages can also be seen. Characteristically, hemorrhages are found in the midperiphery but can extend into the posterior pole (Fig. 6.23.2). Neovascularization, which ranges from mild to severe, may occur on the optic disc in more than one-third of patients who have OIS. Retinal neovascularization has been described in 8% of eyes.<sup>5</sup>

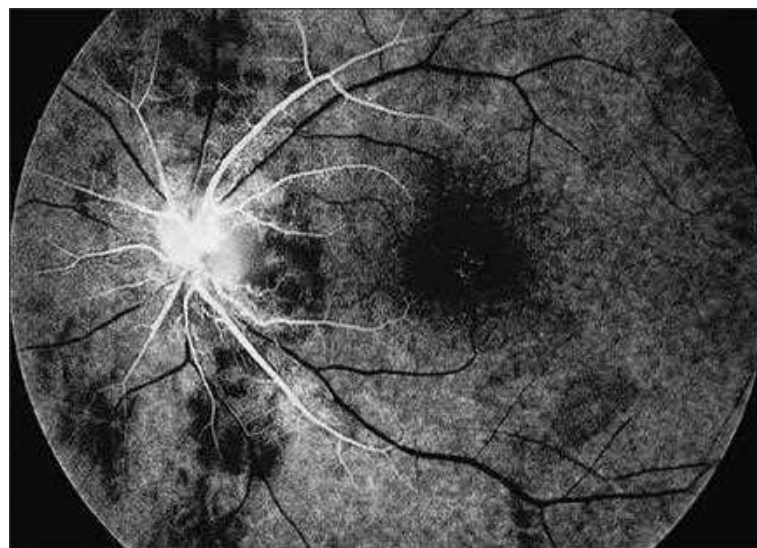
During examination, a cherry-red spot is seen in 12% of eyes with OIS.<sup>5</sup> This finding most commonly occurs as the IOP from neovascular glaucoma exceeds the central retinal artery's perfusion pressure. Cotton-wool spots and spontaneous pulsations of the retinal arteries are each found in 5% of eyes that have the syndrome.<sup>5</sup> They are typically multiple and occur predominantly in the peripapillary region. When not present spontaneously, retinal arterial pulsations can be elicited easily by minimal pressure on the globe, because of the severe diminution in ocular perfusion pressure. In contrast, eyes that have nonischemic CRVO require a normal amount of digital pressure to induce retinal arterial pulsations.<sup>9</sup> Though rarely performed currently, ocular plethysmography can be used to quantitatively assess diminished ocular perfusion pressure in OIS. Ischemic optic neuropathy, which presents with acute, pale swelling of the disc, has been infrequently reported in eyes affected by OIS.<sup>10</sup> Otherwise, the optic disc tends to be normal in appearance, unlike the disc edema seen with central retinal vein occlusion.

## DIAGNOSIS AND ANCILLARY TESTING

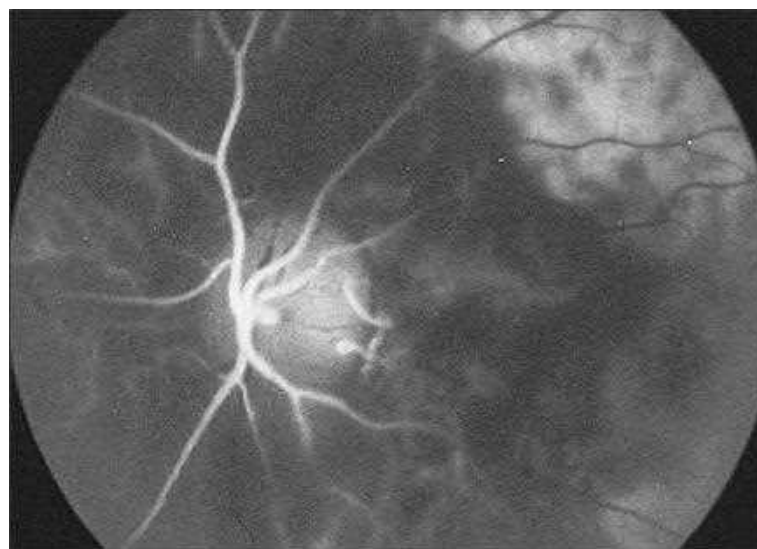
In addition to clinical examination, fluorescein angiography can help to establish the diagnosis of OIS. Ideally, a delay in arm-to-choroid and arm-to-retina circulation times is seen, but variation in the location and speed of injection may make these times difficult to assess. However, demonstration of a well-demarcated leading edge of fluorescein dye within a retinal artery is very unusual for a normal eye and suggests ocular hypoperfusion (Fig. 6.23.3). Patchy filling of the choroid that lasts more than 5 seconds is seen in about 60% of eyes with OIS (Fig. 6.23.4).<sup>5</sup>

Other findings on fluorescein angiography include an increased arteriovenous transit time, staining of the retinal vessels, macular edema, retinal capillary nonperfusion, and evidence of microaneurysms (especially in the periphery). The arteriovenous transit time exceeds 11 seconds in approximately 95% of affected eyes.<sup>5</sup> Late staining of retinal vessels, more prominent in arterioles than in venules, is present in about 85% of cases (Fig. 6.23.5).<sup>5</sup>

Electroretinography demonstrates a decrease in both the a-waves and b-waves in eyes that are affected by OIS, in contrast to the sparing of the a-wave found in central retinal artery occlusions.<sup>11</sup> The choroidal and outer retinal ischemia of eyes with global hypoperfusion accounts for this difference.

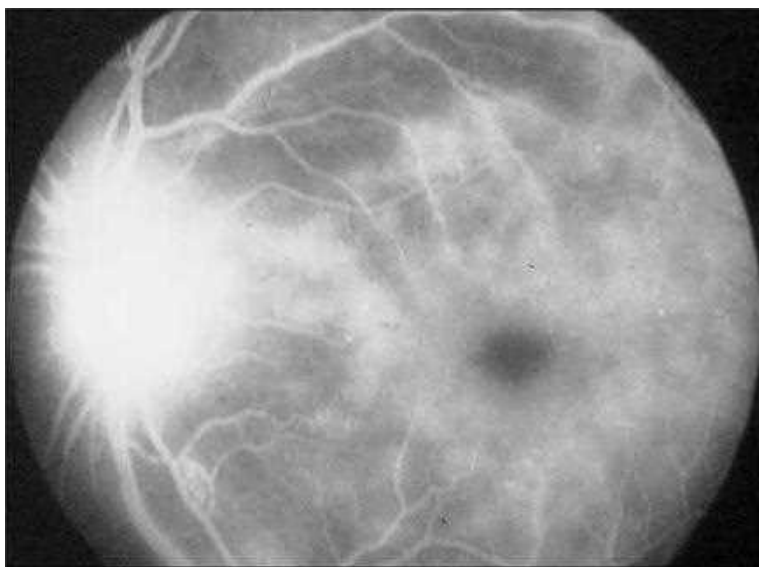


**Fig. 6.23.3 Fluorescein Angiography, Ocular Ischemic Syndrome.** A distinctly abnormal finding in a fluorescein angiogram of eyes that are affected by ocular ischemic syndrome is a well-demarcated leading edge of dye within the retinal arteries.



**Fig. 6.23.4 Patchy Choroidal Filling, Ocular Ischemic Syndrome.** Patchy choroidal filling that lasts more than 5 seconds occurs in about 60% of eyes affected by ocular ischemic syndrome.





**Fig. 6.23.5 Staining of Retinal Arteries, Ocular Ischemic Syndrome.** Prominent staining of retinal arteries, rather than venules, can help to differentiate an eye that has ocular ischemic syndrome from an eye that is affected by a nonischemic central retinal vein occlusion (which shows more prominent staining of the venules).

**TABLE 6.23.1 Features That Distinguish Ocular Ischemic Syndrome**

Feature	Ocular Ischemic Syndrome	Nonischemic Central Retinal Vein Occlusion	Diabetic Retinopathy
Laterality	80% unilateral	Unilateral	Bilateral
Age (years)	50–80	50–80	Variable
<b>Fundus Signs</b>			
Veins	Dilated, nontortuous	Dilated, tortuous	Dilated, beaded
Optic disc	Normal	Swollen	Normal
Retinal artery perfusion pressure	Decreased	Normal	Normal
Retinal hemorrhages	Mild	Mild to severe	Mild to moderate
Microaneurysms	Midperiphery	Variable	Posterior pole
Hard exudates	Absent unless in association with diabetes	Rare	Common
<b>Fluorescein Angiography</b>			
Choroidal filling	Delayed, patchy	Normal	Normal
Arteriovenous transit time	Prolonged	Prolonged	Normal
Retinal vessel staining	Prominent arterial staining	Prominent venous staining	Absent (usually)
Clinical signs and fluorescein angiography that help differentiate ocular ischemic syndrome from nonischemic central retinal vein occlusions or diabetic retinopathy.			

Color Doppler imaging is an excellent noninvasive means by which to assess the velocity of blood flow in the retrobulbar circulation. Diminution of blood flow velocities in the central retinal artery, choroidal vessels, and ophthalmic artery is typical. Reversal of flow in the ophthalmic artery is common also. Color Doppler imaging may be used to assess the carotid arteries simultaneously.

Carotid arteriography discloses generally a 90% or greater obstruction of the ipsilateral carotid artery in patients who have OIS.<sup>5</sup> Approximately 50% of eyes are associated with a 100% ipsilateral carotid artery stenosis, whereas in 10% there is a bilateral 100% carotid stenosis. If noninvasive carotid artery evaluation is unremarkable in an eye that shows signs suggestive of ocular ischemia, conventional carotid arteriography or digital subtraction angiography may be required to demonstrate possible chronic obstruction of the ophthalmic artery.<sup>11–13</sup> Rarely, cases of ocular ischemia may be induced by a more distal obstruction in the ophthalmic artery or even within the central retinal artery.

## DIFFERENTIAL DIAGNOSIS

Nonischemic CRVO and diabetic retinopathy are the conditions most likely to be confused with OIS. Various ocular signs help to differentiate these conditions (Table 6.23.1). One particularly useful differentiating feature is

a swollen optic disc, which typically is seen in nonischemic vein occlusions but not in OIS. Additionally, in eyes with CRVO the retinal veins will be dilated and tortuous, whereas in eyes with OIS there is venous dilation but only minimal or no tortuosity. Although microaneurysms may occur in both diabetic retinopathy and OIS, in diabetes they tend to involve the posterior pole preferentially. On rare occasions, giant cell arteritis may induce findings similar to those of OIS. In general, however, giant cell arteritis has a much more dramatic clinical picture, with ischemic optic neuropathy or retinal artery occlusion or both.

## SYSTEMIC ASSOCIATIONS

The atherosclerosis that affects the carotid artery sufficiently to cause OIS is generally widespread. Of patients who have OIS, 50% show evidence of ischemic heart disease and 25% have a history of previous cerebrovascular accidents.<sup>14</sup>

Additional risk factors for both atherosclerosis and arteriosclerosis are found in these patients, such as systemic arterial hypertension, which is found in two-thirds of patients who have OIS, and diabetes mellitus, which is observed in more than 50% of these patients.<sup>14</sup> An examination for hyperlipidemia should be undertaken unless the patient is also under therapy for this condition.

A 5-year mortality of 40% in patients who have OIS reflects the severity of their systemic vascular disease.<sup>14</sup> The main cause of death in these patients is ischemic heart disease, with stroke the second most common cause. Thus, referral for a cardiac evaluation should be considered if it has not been performed recently.

## PATHOLOGY

In the early stage of the OIS, the neural retina shows coagulative necrosis of its inner layers, which are supplied by the retinal arterioles. If the area of coagulative necrosis is small and localized, it appears clinically as a cotton-wool spot, a microinfarct of the nerve fiber layer. Histologically, the swollen end-bulbs of the infarcted nerve fiber layer superficially resemble cells, hence the term *cytoid body*. If the area of coagulative necrosis is extensive, it appears clinically as a gray neural retinal area, blotting out the background choroidal pattern. With complete coagulative necrosis of the posterior pole (e.g., after a central retinal artery occlusion), the red choroid shows through the central fovea as a cherry-red spot. The inner half of the neural retina becomes “homogenized” into a diffuse, relatively acellular zone. Generally, thick-walled retinal blood vessels are present.

## TREATMENT, COURSE, AND OUTCOME

Patients with mild OIS may maintain excellent vision, but the natural course of eyes that have more severe disease is quite poor.<sup>15</sup> Assessment of carotid artery function in patients with OIS is of utmost importance. The North American Symptomatic Carotid Endarterectomy Trial demonstrated that carotid endarterectomy was beneficial for patients with carotid stenosis of 70%–99% with a recent history of amaurosis fugax, a hemispheric transient ischemic attack, or a nondisabling stroke. The cumulative risk of ipsilateral stroke was 26% after 2 years for patients receiving antiplatelet treatment, whereas the cumulative risk of stroke was 9% 2 years after endarterectomy.<sup>16</sup> The benefit of endarterectomy was tempered by a 2.1% risk of severe stroke or death during the immediate postoperative period in the patients who underwent surgery versus 0.9% in the antiplatelet group. In symptomatic patients with carotid artery stenosis of 50%–69%, only a moderate reduction in risk of stroke was identified after carotid endarterectomy.<sup>17,18</sup>

Stabilization or improvement in vision has been reported in about 25% of eyes after endarterectomy.<sup>15</sup> Doppler color imaging has shown postoperative normalization of preoperative retrograde ophthalmic artery flow following endarterectomy.<sup>19</sup> Electroretinogram a-waves and b-waves can improve with increased amplitudes following endarterectomy.<sup>20</sup> Occasionally, in eyes that have ciliary body hypoperfusion, complete angle closure, and normal IOP, carotid endarterectomy has resulted in severe glaucoma immediately after surgery. In cases in which 100% obstruction and distal propagation of a thrombus has occurred, bypass procedures, such as superficial temporal artery to middle cerebral artery, have been attempted. Although the vision improves transiently in 20% of such eyes, it usually deteriorates within 1 year of surgery.<sup>15</sup> It is currently uncertain what role carotid artery stenting will play in the management of OIS.<sup>21</sup>

In cases that have iris neovascularization in which the anterior chamber angle is open, panretinal photocoagulation may induce regression of



the rubeosis. Unfortunately, the regression after laser therapy is not as prominent as that seen in patients who have iris neovascularization after CRVO.<sup>22</sup> Intravitreal injection of anti-VEGF agents such as bevacizumab has been shown effective in treating iris neovascularization secondary to OIS and should be considered in the management options.<sup>23,25</sup> Elevated IOP from neovascular glaucoma may require cyclodestructive therapies and/or filtering procedures.

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# Hemoglobinopathies

Michael D. Tibbetts, Allen C. Ho

# 6.24

**Definition:** A spectrum of ocular abnormalities, including peripheral “seafan” retinal neovascularization, which results from an inherited defect in the synthesis of the hemoglobin molecule.

## Key Features

- Macular ischemia.
- Retinal vascular peripheral nonperfusion.
- Retinal hemorrhages: “salmon patches,” “iridescent spots,” and “black sunbursts”.
- Peripheral retinal neovascularization: “seafans”.

## Associated Features

- Conjunctival “comma-shaped” capillaries.
- Iris atrophy and posterior synechiae.
- Sickie disc sign.
- Macular depression sign.
- Arteriovenous anastomoses.
- Vitreous hemorrhage.
- Retinal detachment.

## INTRODUCTION

Normal red blood cell hemoglobin comprises four polypeptide globin chains, each associated with a central heme ring (ferroprotoporphyrin).<sup>1</sup> The globin chains consist of two identical pairs of  $\alpha$  and  $\beta$  polypeptide chains. The sickle-cell hemoglobinopathies are characterized by a genetic error in  $\beta$ -chain synthesis, which results in abnormal function of the hemoglobin molecule. In conditions of ischemia and metabolic stress, the imperfect globin chains induce pathological alterations in red blood cell morphology. The altered red blood cells are labeled “sickle cells” because of their crescent shape.

Systemic and ocular sequelae are well described. Interestingly, the severity of systemic symptoms does not typically correlate with the severity of ocular manifestations. The most severe systemic complications are observed in sickle SS disease, whereas severe ocular features are most commonly noted in patients with sickle SC or sickle thalassemia (S-Thal) disease. In general, vision-threatening sequelae of the sickle hemoglobinopathies are secondary to ischemia or peripheral retinal neovascularization.

## EPIDEMIOLOGY AND PATHOGENESIS

Hemoglobinopathies can be characterized by electrophoresis and by the genetic mutations that lead to abnormal amino acid substitutions in the  $\beta$ -globin chain. Normal adult hemoglobin with two normal  $\alpha$  and  $\beta$  chains is termed hemoglobin A. Sickle hemoglobin, known as S, was initially described by Pauling and others in 1949 as a single point mutation that resulted in substitution of the amino acid valine for glutamic acid at the sixth position. The substitution of lysine for glutamic acid at this position results in the manufacture of hemoglobin C. The sickle hemoglobinopathies S and C are only two of many known mutations caused by qualitative errors in globin chain synthesis. Inadequate production of either normal or abnormal globin chains, a quantitative error in globin synthesis, is referred to as thalassemia or Thal.

Since these mutations are inherited, heterozygous or homozygous conditions exist. For example, normal hemoglobin comprises homozygous AA globin chains. Classic sickle cell anemia, or SS disease, usually arises when

parents who have sickle trait (AS) disease each pass on their single abnormal S globin chain mutation. In the United States, African-Americans comprise the majority of patients afflicted by the hemoglobinopathies, with sickle trait (Hb AS) affecting approximately 8% and sickle cell disease (SCD) diagnosed in approximately 0.15%.<sup>2</sup> If hemoglobin S is inherited from one parent and hemoglobin C from another, a double heterozygote form of hemoglobin is created known as sickle SC disease, which is nearly as prevalent as SS disease.<sup>2</sup>

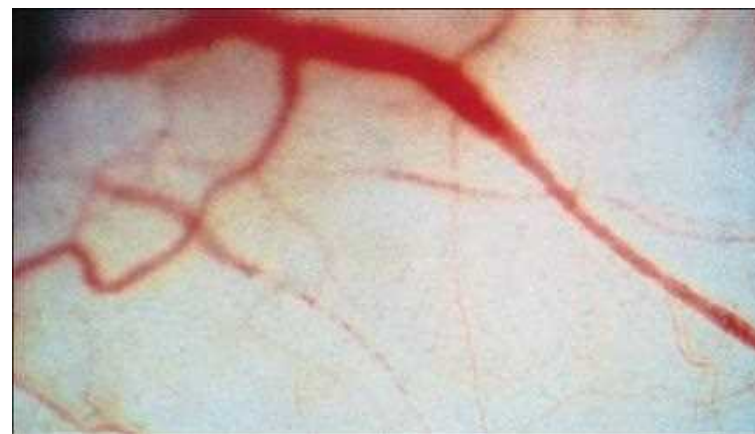
Normal hemoglobin confers pliability to the oval-shaped red blood cells, which allows them to pass easily through the microvasculature where they deliver oxygen. Sickle hemoglobins result in red blood cells with a crescentic, elongated shape, particularly under conditions of hypoxia or acidosis. This causes the blood cells to stack, which further exacerbates local ischemia. A vicious cycle of ischemia, red blood cell sickling, tissue hypoxia, and necrosis is set in motion.

Although sickle SS disease has the most severe systemic manifestations, hemoglobin SC and S-Thal have the most severe ocular manifestations with an earlier age of onset. The reasons for this discrepancy are likely multifactorial. The more severe anemia of SS disease is associated with lower red blood cell counts than those in hemoglobin SC and S-Thal disease. Relative anemia may decrease the viscosity of the remaining red blood cells, thereby causing less sludging in the circulation. Another theory posits that SS disease causes more frequent retinal infarction, whereas the less severe hemoglobinopathies such as SC disease cause more ischemia of the retinal tissues.<sup>3</sup> The retinal ischemia may increase the angiogenic response of vascular endothelial growth factor and stimulate neovascularization as opposed to the retinal necrosis induced by infarction.

Since many of the problems are time dependent, the overall prevalence of ocular complications of sickle disease is unknown. In a large cohort, 6% (49/783) of SS patients had proliferative sickle retinopathy (PSR) on initial examination compared with 32% (172/533) of SC patients.<sup>4</sup> Approximately 40%–43% of hemoglobin SC patients and 14%–20% of hemoglobin SS patients can be expected to develop PSR.<sup>5,6</sup>

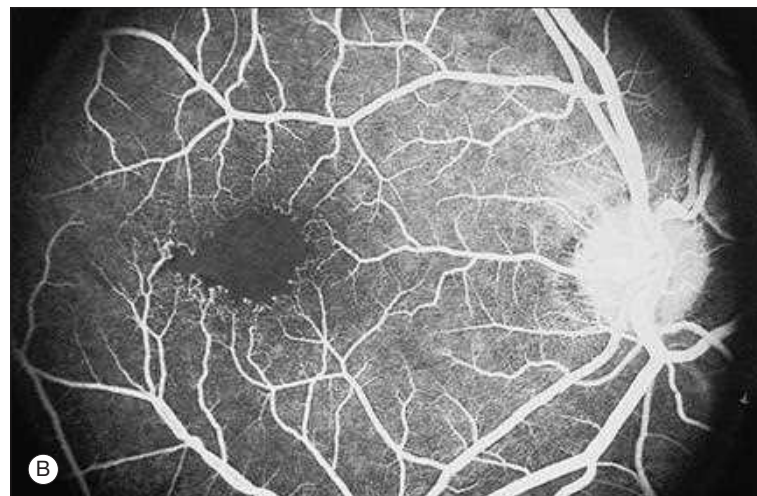
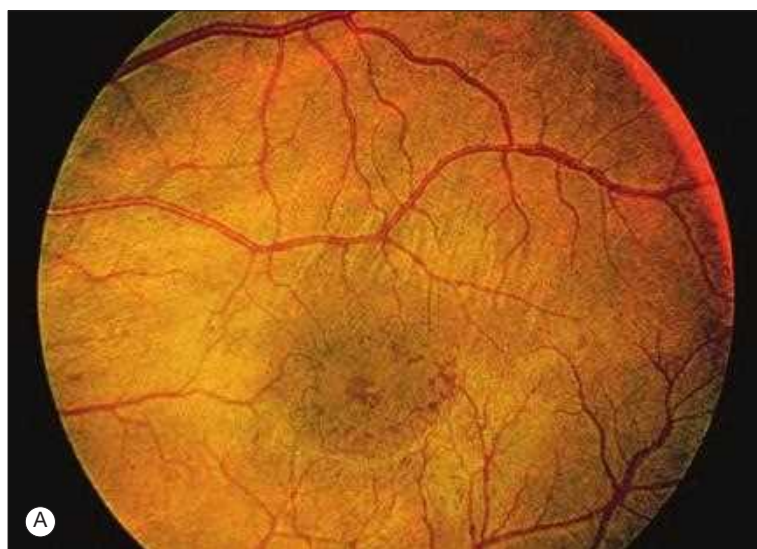
## OCULAR MANIFESTATIONS

Nearly all ocular or periocular structures can be affected by the sickle hemoglobinopathies. Classic anterior segment findings include conjunctival “comma-shaped” capillaries, which represent intravascular sludging of sickling red blood cells<sup>7</sup> (Fig. 6.24.1). Sectorial iris atrophy represents

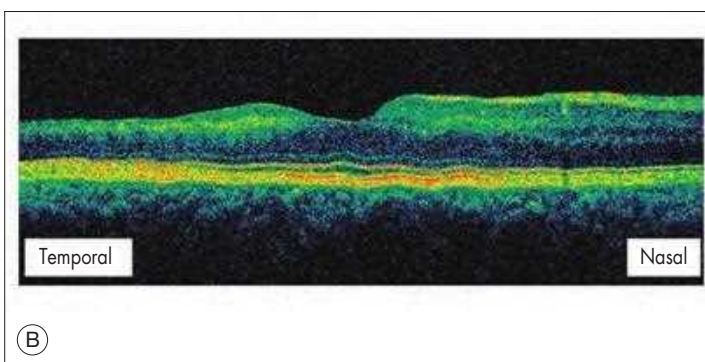
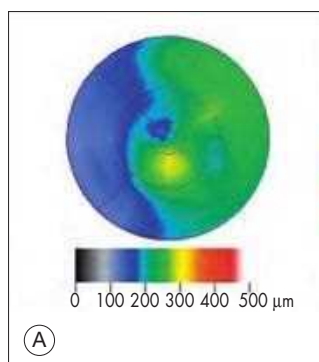


**Fig. 6.24.1** A Classic Anterior Segment Finding in Sickle Eye Disease Are Comma- or “S”-Shaped Conjunctival Capillaries. These vessels represent areas of red blood cell sickling or sludging within the capillary bed. (Courtesy William Tasman, MD.)





**Fig. 6.24.2 Sickle SC Disease.** (A) Macular ischemia with the macular depression sign and perifoveal vascular remodeling. (B) Fluorescein angiogram of the same patient demonstrating an irregular and moth-eaten perifoveal capillary network and vascular telangiectasia. (Courtesy William Tasman, MD.)



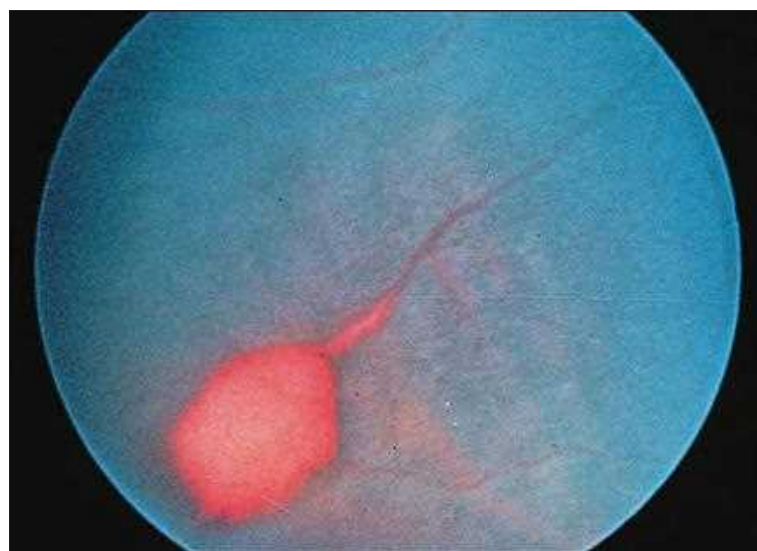
**Fig. 6.24.3 Optical Coherence Tomography of Macular Atrophy Secondary to Retinal Arteriolar Occlusion in a Patient With SS Disease.** (A) Macular map (6 mm diameter) digitally created from six standard-resolution optical coherence tomographic images demonstrating marked thinning of the temporal macula including the fovea. (B) Horizontal 6 mm high-resolution optical coherence tomographic macular image. Temporally, the inner retinal layers are atrophic, whereas the outer retinal layers remain normal thickness. (Courtesy Andre Witkin, MD.)

areas of anterior uveal ischemia. A mild anterior chamber cell and flare reaction may be observed secondary to incompetence of the blood–ocular barrier. The anterior segment manifestations generally do not pose significant risks for vision loss.

Posterior segment manifestations of sickle hemoglobinopathies may be observed in the vitreous body, optic disc, retina, and subretinal structures.<sup>8</sup> Vitreous hemorrhage secondary to peripheral retinal neovascularization may develop. The optic disc may demonstrate sludging red blood cells within prepapillary retinal capillaries, which appear as small dark spots or vascular lines on the optic disc head.<sup>9</sup> The “macular depression sign” represents atrophy and thinning of the inner retinal layers, which results in an oval depression of the bright central reflex and may be associated with a decrease in vision<sup>10</sup> (Fig. 6.24.2A). Optical coherence tomography (OCT) has confirmed this finding and demonstrated sparing of the photoreceptors and retinal pigment epithelium<sup>11,12</sup> (Fig. 6.24.3). OCT angiography also showed a correlation between retinal thickness measurements and vascular density of the fovea and parafoveal regions.<sup>13</sup> More debilitating macular ischemia can result in frank macular infarction with an enlarged foveal avascular zone secondary to multiple retinal arteriolar occlusions with an often insidious, progressive course.<sup>14–16</sup> Fluorescein angiography reveals irregularity in or enlargement of the foveal avascular zone, with adjacent areas of retinal capillary nonperfusion and retinal vascular remodeling (see Fig. 6.24.2B). Retinal arterial microaneurysms and cotton-wool spots may also be observed.

Retinal arteriolar sclerosis may be identified in areas in which there is diffuse capillary nonperfusion that reflects prior retinal vascular occlusion. Venous tortuosity is observed in as many as half of all patients who have SS disease and in one-third of patients who have SC disease but is not pathognomonic of sickle retinopathy. Angioid streaks are also described in association with SCD.

Other nonproliferative retinal findings are more characteristic of sickle hemoglobinopathies.<sup>17–19</sup> Salmon-colored retinal hemorrhages are preretinal or superficial intraretinal hemorrhages that occur adjacent to a retinal arteriole and are often found in the equatorial retina (Fig. 6.24.4). Histopathologically, they dissect into the vitreous cavity or into the subretinal space.<sup>20</sup> The salmon hue is attributed to an evolution of color changes—the



**Fig. 6.24.4 An Equatorial “Salmon Patch” Intraretinal Hemorrhage With Periarteriolar Hemorrhage.** These peripheral hemorrhages may lead to retinoschisis cavities lined with iridescent particles that comprise hemoglobin degradation products. The vision is 20/20 (6/6). (Courtesy William Tasman, MD.)

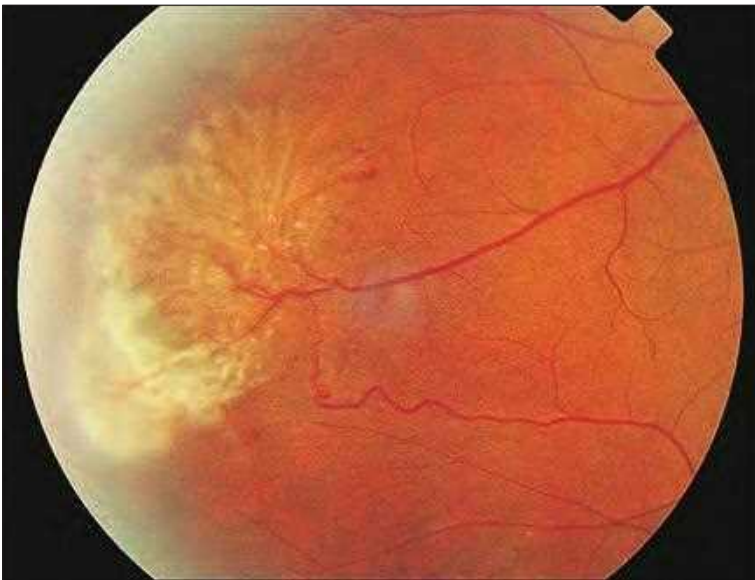
initial presentation is bright red. These hemorrhages result from the rupture of a medium-sized retinal arteriole due to ischemic vasculopathy. They usually resolve with few sequelae, although a retinoschisis cavity lined with iridescent refractile yellow particles may persist.

If the intraretinal hemorrhage dissects into the subneural retinal space and disturbs the retinal pigment epithelium, a black sunburst lesion may result (Fig. 6.24.5). These dark, irregularly shaped, spiculated or stellate lesions are the result of retinal pigment epithelial hyperplasia and intraretinal migration.<sup>20,21</sup> Since they are usually localized to the equatorial retina, the retinal pigment epithelium changes generally do not cause significant visual symptoms.





**Fig. 6.24.5 A Black “Sunburst” Retinal Lesion.** This is caused by a hemorrhage that dissected into the subneural retinal space and disrupted the retinal pigment epithelium, which culminated in pigmentary migration. Note the spiculated borders. (Courtesy William Tasman, MD.)



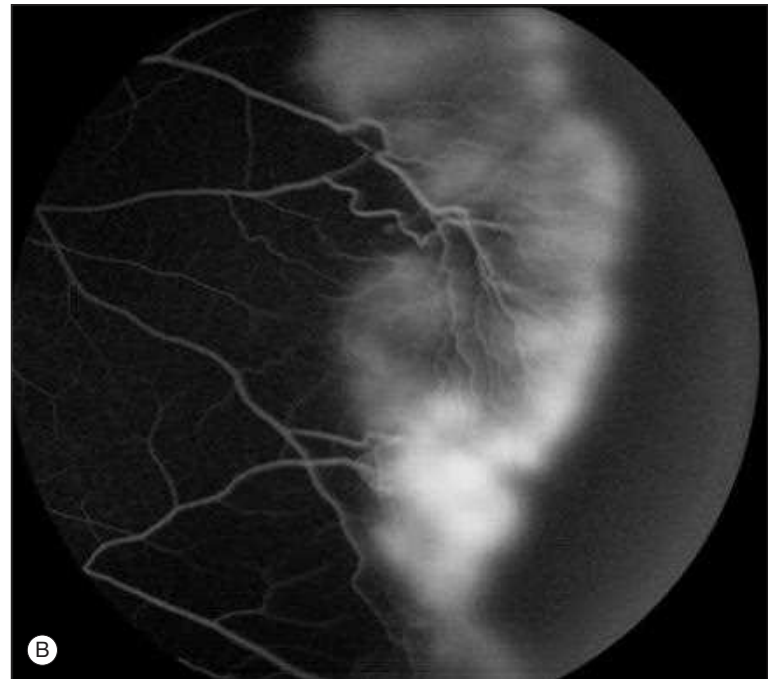
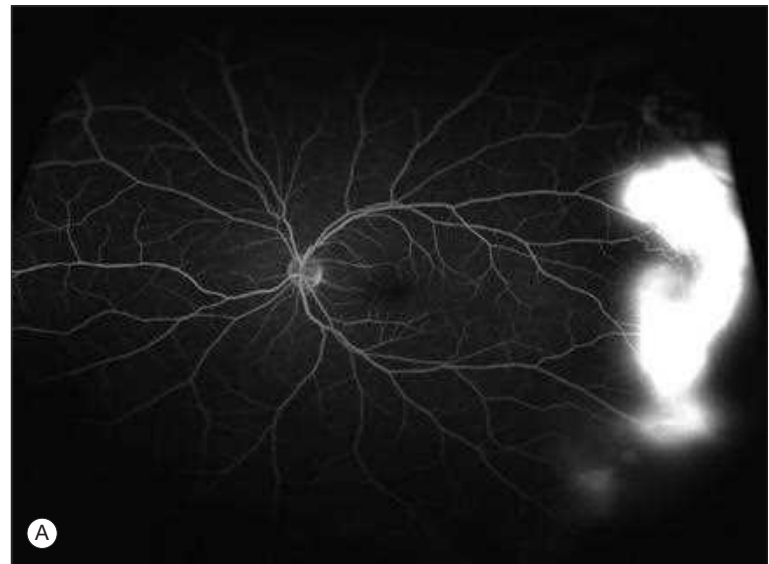
**Fig. 6.24.6 Peripheral Retina in a Sickle SC Patient.** Partially regressed peripheral retinal neovascularization at the junction of the perfused retina (to the right) and the nonperfused retina (to the far left).

PSR was classified into five stages by Goldberg<sup>18,22</sup>:

- Stage I: Peripheral arteriolar occlusions.
- Stage II: Arteriolar–venular anastomoses.
- Stage III: Neovascular proliferation.
- Stage IV: Vitreous hemorrhage.
- Stage V: Retinal detachment.

This progression of PSR typically occurs in the third or fourth decade of life, but the youngest case of PSR was reported in an 8-year-old patient with SC disease.<sup>23</sup> Peripheral retinal arteriolar occlusion can leave large areas of anterior retinal capillary nonperfusion, which is highlighted well by fluorescein angiography. Curiously, retinal venous occlusion is uncommon in patients who have SCD. Occluded arterioles initially appear dark red but subsequently evolve into “silver wire” vessels. Peripheral arteriolar–venular anastomoses evolve to shunt retinal arterial blood into retinal venules. These anastomoses can be best seen with fluorescein angiography at the junction of perfused and nonperfused retina, typically just peripheral to the equator.

Retinal neovascularization in a seafan configuration is the hallmark of PSR, extending from the border zone of perfused and nonperfused retina (see Fig. 6.24.5, Fig. 6.24.6). Initially, a seafan is supplied by one major feeding retinal arteriole and one major draining retinal venule. Over time,

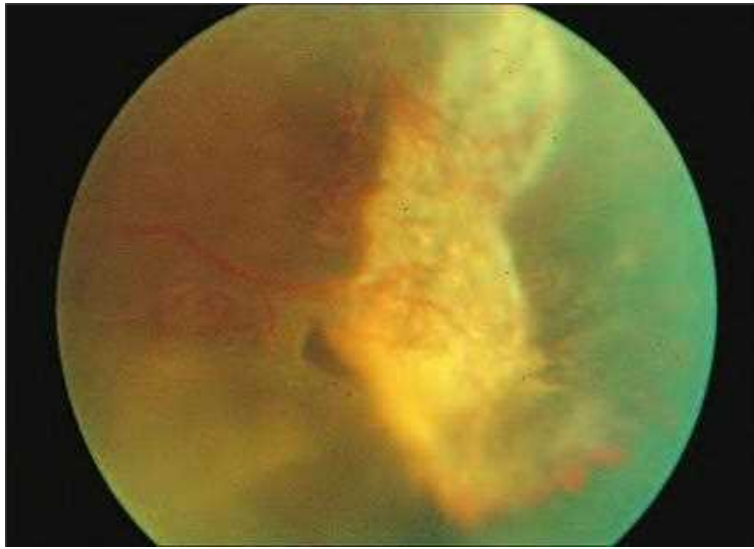


**Fig. 6.24.7 Fluorescein Angiography.** (A) Wide-field fluorescein angiography of proliferative sickle retinopathy (PSR) demonstrating extensive leakage of dye into the vitreous cavity from the sites of neovascularization. (B) Higher magnification fluorescein angiography of PSR demonstrating peripheral capillary nonperfusion (to the far right), retinal vascular remodeling, arteriovenous communications, and leakage of fluorescein dye into the vitreous cavity from the sites of neovascularization. (Courtesy Alok Bansal, MD.)

an arborization of the neovascular complex occurs. Seafans most commonly are observed in patients who have SC disease or S-Thal disease and are rare in the other hemoglobinopathies.<sup>18,22</sup> Fluorescein angiography demonstrates massive leakage of dye into the vitreous (Fig. 6.24.7). The seafans represent a progressive proliferative retinopathy, which exposes the patient to the risks of vitreous hemorrhage and retinal detachment. Seafans may spontaneously involute, resulting in areas of grayish white fibrovascular tissues that often have residual perfused retinal vessels at their base. About 40%–50% of seafans may undergo some degree of auto-infarction during their course.<sup>5</sup>

Vitreous hemorrhage is a common complication of retinal seafan formation. Patients with limited vitreous hemorrhage experience floaters, whereas those with dense vitreous hemorrhage have sudden severe vision loss. These hemorrhages may clear spontaneously with time or may persist to give ochre-colored vitreous membranes.

Retinal seafans may induce fibrovascular tissue on the surface of the retina that causes traction or rhegmatogenous retinal detachments (Fig. 6.24.8). Circumferential seafan involvement can cause peripheral tractional retinal detachment. In the areas of thin, nonperfused retina, atrophic, stretched retinal holes can develop to create combined traction and rhegmatogenous retinal detachments.



**Fig. 6.24.8 Traction-Rhegmatogenous Retinal Detachment.** A retinal tear has developed at the site of peripheral neovascularization and fibrosis, leading to a combined traction-rhegmatogenous retinal detachment. (Courtesy William Tasman, MD.)

## DIAGNOSIS

Most patients who present with the ophthalmic complications of sickle hemoglobinopathies are aware of their underlying red blood cell abnormality. Patients with SC and S-Thal disease who have minimal systemic manifestations can be completely unaware of their systemic diagnosis when the ocular complications flare. The characteristic history of hemoglobin SS patients—including multiple hospitalizations secondary to painful crises, chronic end-organ damage, multiple infections, and bony abnormalities—may not have been experienced with the other hemoglobinopathies.

Hemoglobin electrophoresis or DNA-based testing is necessary to characterize the abnormal globin chain type. A positive test for sickling, such as the solubility test (e.g., Sickledex), indicates the presence of hemoglobin S but does not distinguish between SS, AS, and double heterozygotes such as S-Thal and SC.<sup>1</sup>

Diagnosis of the ophthalmic manifestations of the sickle hemoglobinopathies is enhanced by careful examination of the conjunctiva, iris, anterior chamber, optic disc, and macula. Indirect ophthalmoscopy and peripheral retinal contact lens biomicroscopy are helpful to delineate retinal hemorrhages and proliferative changes. Fluorescein angiography characterizes macular perfusion and peripheral retinal perfusion. Early seafan formation is highlighted well by fluorescein leakage. Ultra-wide field imaging may be useful to assess peripheral nonperfusion and the stage of retinopathy (see Fig. 6.24.7).<sup>24</sup> Diagnostic ultrasonography can characterize posterior segment anatomy when a media opacity occurs, such as from vitreous hemorrhage or ochre membranes. OCT may demonstrate macular thinning with selective loss of the retinal ganglion cell and nerve fiber layer even in asymptomatic SCD patients.<sup>25</sup> OCT angiography may show abnormalities in the parafoveal vascular system that is more common in patients with SC disease and proliferative retinopathy.<sup>13</sup>

## DIFFERENTIAL DIAGNOSIS

Other causes of macular ischemia and peripheral retinal neovascularization, vitreous hemorrhage, and neural retinal detachment are listed in Box 6.24.1.

## SYSTEMIC ASSOCIATIONS

Patients who have classic sickle SS disease manifest a variety of systemic abnormalities, which include anemia, bone marrow infarcts, bony sclerosis (e.g., vertebral “fishmouthing”), aseptic necrosis of the femoral head, ischemia to visceral organs, shortness of breath caused by pulmonary infarcts, and an increase in susceptibility to bacterial infections, particularly salmonellosis caused by reticuloendothelial cell dysfunction. Other hemoglobinopathies result in less severe systemic disease with a mild anemia as the only manifestation.

### BOX 6.24.1 Differential Diagnosis of Hemoglobinopathies

#### Other Causes of Macular Ischemia

- Diabetic retinopathy
- Retinal vascular obstruction
- Embolic phenomena such as talc retinopathy

#### Other Causes of Peripheral Retinal Neovascularization, Vitreous Hemorrhage, and Retinal Detachment

- Proliferative diabetic retinopathy
- Retinal vein obstruction
- The ocular ischemic syndrome
- Sarcoidosis
- Pars planitis
- Retinopathy of prematurity
- Familial exudative vitreoretinopathy
- Eales' disease

## TREATMENT

Advances in treatment have reduced the morbidity and increased the life expectancy of patients with SCD over the last 40 years.<sup>26</sup> Most notably, hydroxyurea therapy has been shown to reduce morbidity and mortality by boosting levels of fetal hemoglobin (HbF).<sup>27</sup> In addition, stem cell transplantation in both children and adults with severe disease can reverse the sickle cell phenotype, and gene therapy is under active investigation.<sup>28,29</sup>

For the ocular manifestations of SCD, treatment efforts focus on altering the course of PSR to reduce the chance of vitreous hemorrhage and retinal detachment.<sup>17</sup> Cryotherapy, diathermy, xenon arc photocoagulation, and argon laser photocoagulation all have been employed to treat peripheral retinal neovascularization. Cryotherapy has been used to treat peripheral retinal neovascularization in the presence of vitreous hemorrhage when the neovascular proliferation is only partially visualized and when vitreous hemorrhage precludes treatment with laser photocoagulation. In recent years, cryotherapy has largely been abandoned because of the significant complication rate.

Various methods of laser photocoagulation effectively induce regression of peripheral neovascularization.<sup>30–34</sup> Feeder-vessel laser photocoagulation requires intensive treatment with high energy but is more likely to be complicated by chorioretinal or choriovitreal neovascularization, retinal detachment, and vitreous hemorrhage.<sup>35</sup> Scatter laser photocoagulation of areas that surround seafan proliferation and associated areas of ischemic retina can induce lesion regression. The rationale is to ablate areas of ischemic retina that are stimulating neovascular proliferation. This hypothesis is supported by studies demonstrating hypoxia-inducible factor 1 $\alpha$  and vascular endothelial growth factor (VEGF) were strongly expressed in retinal cells within avascular (nonperfused) retina in patients with proliferative sickle cell retinopathy.<sup>36</sup> Scatter laser photocoagulation can be performed as a localized treatment confined to areas anterior to the patent neovascular fronds or in a 360° peripheral, circumferential retinal scatter technique to the anterior retina.<sup>30,33,35</sup> The rationale of the 360° scatter treatment is to induce regression of existing peripheral retinal neovascularization and to prevent the formation of any future neovascularization. These techniques can be performed with light to moderate intensity burns approximately 500  $\mu$ m in diameter placed approximately one burn width apart. Scatter laser photocoagulation, either localized or circumferential, is the treatment of choice to prevent complications secondary to peripheral seafan proliferation.

Vitreous hemorrhage secondary to PSR may be followed for up to 6 months to await spontaneous clearing. If areas of retinal neovascularization can be identified through the vitreous hemorrhage, the associated anterior retina should be treated with scatter laser photocoagulation. When the retina is not well visualized, it is important to follow these eyes with ultrasonography, although a minority of patients progress to retinal detachment.

Anti-vascular endothelial growth factor (VEGF) agents have gained increasing roles in the management of many retinal vascular diseases, but their utility in SCD has not been fully investigated.<sup>2</sup> Case reports have described the regression of retinal neovascularization and resolution of vitreous hemorrhage following intravitreal injection of bevacizumab or ranibizumab.<sup>37,38</sup> However, there are no large-scale studies to assess the long-term effects and incidence of complications.



Surgery on patients who have sickle hemoglobinopathies is fraught with ocular and systemic pitfalls. Systemically, a preoperative workup to assess the severity of anemia, hemoglobin electrophoretic status, and overall systemic condition is critical. Intraoperative and postoperative systemic complications include thromboembolic events such as pulmonary or cerebral embolism. Prophylactic exchange transfusions to increase levels of hemoglobin A may reduce the rate of anterior segment ischemia and optic nerve and macular infarcts. However, studies suggest that exchange transfusions are not needed with modern vitreoretinal surgical techniques.<sup>39</sup>

Adequate hydration and supplemental oxygen often are administered during the perioperative periods. If possible, surgery should be performed under monitored local anesthesia. Vasoconstrictive agents, such as epinephrine in the anesthetic block and pupillary dilating agents, should be avoided. Many advocate lowered intraocular pressure (IOP) to both maximize intraocular perfusion and avoid hemoconcentration. Single doses of carbonic anhydrase inhibitors or intravenous mannitol may be administered to lower IOP but should not be used repetitively.

Anterior segment ischemia does not usually occur if care is taken to avoid elevations of IOP and if the anterior ciliary circulation is not violated.<sup>40</sup> The possibility of anterior segment ischemia is reduced by avoiding treatments in the horizontal meridians, which harbor the long posterior ciliary arteries and avoiding transection of the horizontal and vertical rectus muscles. With current vitrectomy instrumentation, fluctuations in IOP during vitrectomy surgery are less common. An ultrasound to elucidate the intraocular anatomy is important in cases of vitreous hemorrhage. The peripheral vitreous may be firmly attached to shallow areas of traction retinal detachment at the sites of fibrovascular proliferation and may not be well visualized intraoperatively.

In cases of combined traction-rhegmatogenous retinal detachment, the surgical goals include the release of areas of traction that elevate the retina as well as the removal of fibrovascular proliferation. Once the retina is flat, scatter endolaser photocoagulation is performed. Postoperatively, the patient's IOP must be monitored closely, particularly if intraocular gas is used.

Patients with sickle hemoglobinopathies who develop postoperative or posttraumatic hyphema are at risk for posterior segment ischemia or infarction even at mildly elevated IOPs. Low oxygen tension and high ascorbic acid levels in the anterior chamber promote sickling of red blood cells, which then can obstruct the trabecular meshwork and lead to a greater elevation of IOP. Aggressive lowering of IOP to less than 25 mm Hg is indicated, with some authors recommending early paracentesis to reduce the IOP in acute situations.

## COURSE AND OUTCOME

The course for patients who have ocular complications secondary to sickle hemoglobinopathies is variable.<sup>26,41,42</sup> Untreated, the incidence of blindness

from PSR is about 12%.<sup>5</sup> Advancements in systemic therapy as well as modern laser and vitrectomy techniques have reduced the risk of vision loss.<sup>43,44</sup> Patients who require intraocular surgery for vitreous hemorrhage or retinal detachment have a higher risk of systemic and postoperative ocular complications, including anterior segment ischemia and optic disc or macular infarction. Patients whose PSR is rendered quiescent with laser photocoagulation may enjoy excellent vision in the long term. In one study of long-term follow-up following laser photocoagulation, only 4% of treated eyes had a repeat vitreous hemorrhage versus 66% of untreated eyes, and severe visual loss in both groups was rare.<sup>42</sup>

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# Coats' Disease and Retinal Telangiectasia

*Ferhina S. Ali, Diana V. Do, Julia A. Haller*

# 6.25



**IN THIS CHAPTER**  
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**Definition:** A localized, congenital, retinal vascular disorder consisting of abnormal telangiectatic segments of blood vessels that result in leakage.

## Key Features

- Retinal telangiectasia.
- Retinal capillary nonperfusion.
- Dilated intercapillary spaces.
- Lipid exudate.
- Subretinal fluid.

## Associated Features

- Usually unilateral.
- Male predominance.
- Fibrovascular macular scars.
- Leukokoria.
- Rare systemic associations, especially muscular dystrophies.

## INTRODUCTION

Retinal telangiectasia is found in a wide range of ocular disease processes. Most retinal telangiectases are acquired secondary to local or systemic conditions such as branch retinal vein occlusion and diabetic retinopathy. Primary retinal telangiectasia is found in Coats' disease, Leber's miliary aneurysms, idiopathic juxtafoveal telangiectasia, and other angiomatous diseases.

## EPIDEMIOLOGY

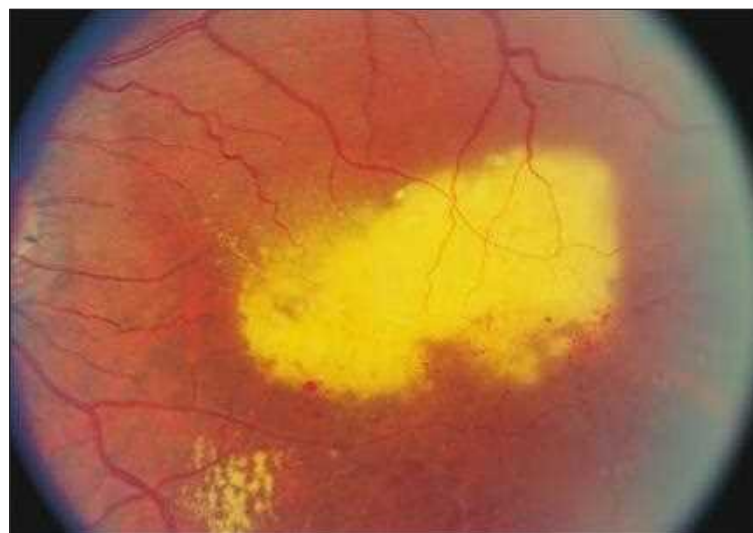
Coats' disease, described by Coats<sup>1</sup> in 1908, affects men three times as often as women, has no reported racial or ethnic predilection, and is usually unilateral, although as many as 10% to 15% of cases may be bilateral. The average age at diagnosis is 8–16 years, although the disease has been described in patients as young as 4 months. Approximately two-thirds of juvenile cases present before age 10 years. Coats' disease can also be diagnosed in adulthood.

Although it does not appear to be inherited, recent reports implicate genetic mutations in the development of Coats' disease. Cremers and associates found that 55% of cases with retinitis pigmentosa and Coats'-like exudative vasculopathy contained a mutation in the *CRB1* gene.<sup>2,3</sup> Several reports implicate a deficiency of norrin, a retinal protein, in the pathogenesis of Coats' disease.<sup>4,5</sup> Analysis of archival tissue from nine enucleated eyes from males with unilateral Coats' disease revealed a mutation in the *NDP* gene on chromosome Xp11.2 in one subject. Berger and coworkers<sup>6,7</sup> developed a mutant mouse line with the Norrie's disease model and demonstrated abnormalities of the retinal vessels, including telangiectasia, bulb-like dilatations, and underdevelopment of the capillary bed. He and colleagues reported elevated intraocular levels of vascular endothelial growth factor (VEGF) in four eyes with Coats' disease.<sup>8</sup>

## OCULAR MANIFESTATIONS

Coats' disease is characterized by discrete zones of alteration in the retinal vascular structure with aneurysmal dilatation, capillary dropout, and leakage. Vision may decrease as a result of leakage from the abnormal vascular channels that are formed, with consequent edema, lipid deposition, and exudative retinal detachment. The typical fundus picture of Coats' disease is one of retinal vascular abnormalities associated with localized lipid deposition and varying degrees of subneural retinal exudate (Fig. 6.25.1). Vessels may appear sheathed and telangiectatic, and they may have aneurysms that are grape like, clustered, or lightbulb shaped. Often the vessels are adjacent to areas that lack normal capillaries (Fig. 6.25.2). The severity of vascular malformation parallels the degree of surrounding neural retinal thickening, exudation, hemorrhage, and destruction of small vessels. Aberrant arteriovenous communicating channels are frequently present, and occasionally true retinal neovascularization occurs. Leakage from the abnormal vascular bed produces a cloudy subretinal exudate that gravitates toward the posterior pole. As the serous component of the exudate is resorbed by retinal vessels, the lipid-rich yellowish component is left beneath and within the outer neural retinal layers.<sup>9</sup> Over long periods, this yellow exudate may stimulate the ingrowth of blood vessels and fibrous scar tissue (Fig. 6.25.3). The vascular abnormalities occur more commonly superotemporally; they also are found in the macular and paramacular areas. On average, two quadrants of retina are found to be affected at the initial diagnosis in older patients, but young patients may have more serious disease and more extensive retinal involvement. In more advanced and severe cases of Coats' disease, exudative retinal detachment develops (Fig. 6.25.4).<sup>10</sup>

The clinical course is variable but generally progressive. Acute exacerbations of the disease may be interspersed with more quiescent stages. Spontaneous remissions have been reported, with spontaneous occlusion of the vessels and resorption of the exudate, but these are the exception. Secondary complications include neovascularization, vitreous hemorrhage,

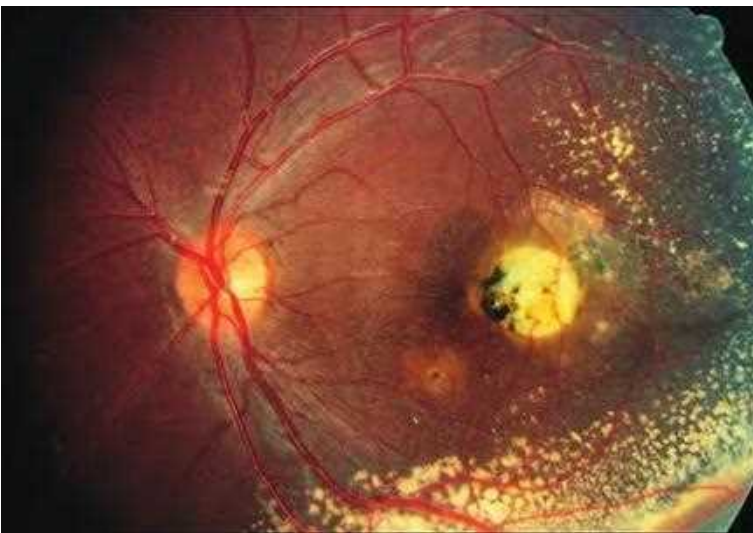


**Fig. 6.25.1 Coats' Disease.** Note the typical vascular abnormalities with aneurysmal dilatation, telangiectasia, exudation, and severe lipid deposition in the macula.

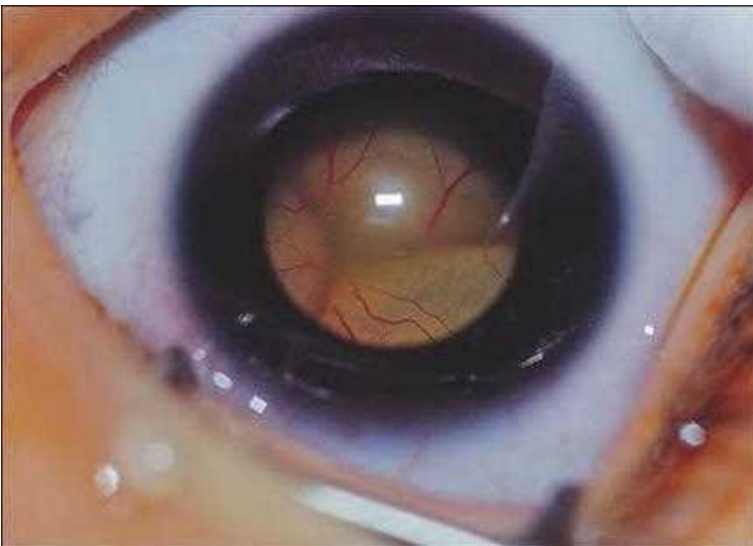




**Fig. 6.25.2 Vessels May Appear Sheathed, Dilated, and Telangiectatic or Feature Grape-Like Bunches of Aneurysms.** Vascular changes that are saccular and lightbulb shaped may be seen as well.



**Fig. 6.25.3 Long-Standing Submacular Exudate.** This may stimulate ingrowth of blood vessels or fibrous tissue, with retinal pigment epithelium migration and hyperplasia and the formation of fibrous scars.



**Fig. 6.25.4 In Children, Coats' Disease May Present as Leukokoria With Advanced Lipid Deposition and Exudative Retinal Detachment.** In this eye, the anterior chamber is shallowed slightly, and the retina is immediately behind the lens.



**Fig. 6.25.5 Fluorescein Angiography of Coats' Disease.** In this eye, extensive vascular changes are seen to extend temporally from the macula, with zones of telangiectasia and aneurysm formation adjacent to a large area of capillary nonperfusion. Beading of the blood vessel walls and anomalous vascular communicating channels are present.

cataract, rubeosis iridis, and neovascular glaucoma, with phthisis bulbi in severe cases.<sup>11,12,13</sup>

## DIAGNOSIS

In children, Coats' disease is typically diagnosed as a result of the recognition of poor vision, strabismus, or leukokoria. In patients with leukokoria, a white pupillary reflex on photographs may be the initially noted abnormality. In these cases, the disease is usually advanced, with extensive lipid deposition and retinal detachment (see Fig. 6.25.4). In adults, the most common presenting complaint with Coats' disease is poor vision.

In advanced cases of Coats' disease, rubeosis iridis, angle-closure glaucoma, and cataract may be present. The diagnosis is confirmed ophthalmoscopically when the typical vascular abnormalities are seen in association with lipid deposition and subretinal exudate. The retinal vascular abnormalities occur in small clusters and include kinked, looped, tortuous, and sheathed vessels of varied and irregular caliber.

## ANCILLARY TESTING

Fluorescein angiography is a useful tool for delineating the nature and extent of the vascular abnormalities present in this disease. Most commonly, numerous areas of telangiectasia and micro- and macroaneurysm formation are seen, with beading of blood vessel walls and anomalous vascular communicating channels (Fig. 6.25.5). Early and persistent dye leakage documents the source of exudation and hemorrhage.<sup>9,14,15</sup> The microvasculature may be diffusely absent, with areas of complete capillary nonperfusion.

Optical coherence tomography (OCT) may also be a useful tool to monitor macular edema associated with Coats' disease. When present, abnormal macular thickness on OCT can be quantitatively determined before and after treatment with laser or pharmacological therapy to gauge the response to a particular therapy. OCT angiography reveals an abnormal foveal avascular zone in the superficial capillary plexus.<sup>16</sup>

## DIFFERENTIAL DIAGNOSIS

The severe juvenile form of Coats' disease, which presents with exudative retinal detachment, must be differentiated from other diseases that cause leukokoria in childhood, including retinoblastoma, retinopathy of prematurity, retinal detachment, persistent hyperplastic primary vitreous, congenital cataract, toxocariasis, incontinentia pigmenti, Norrie's disease, and familial exudative vitreoretinopathy. Gass<sup>9</sup> has pointed out that telangiectatic vessels may appear on the surface of both retinoblastomas and Coats' disease lesions. In retinoblastoma, these dilated vessels are continuous with the large vascular trunks that extend into the tumor; in Coats' disease, the dilated vessels do not extend into the subretinal mass.<sup>9</sup>

Ultrasonography is a convenient, noninvasive test that may distinguish between Coats' disease and retinoblastoma and other entities. The

retinal detachment in Coats' disease typically is exudative, with an absence of the calcifications seen in retinoblastoma. Computed tomography (CT) may help characterize intraocular morphology, quantify subretinal densities, detect calcium, and identify vascularity within the subretinal space through the use of contrast enhancement. Also, CT may help detect other abnormalities within the orbit or intracranial space. Examination of subretinal fluid is used rarely, but it confirms the diagnosis of Coats' disease on the basis of cholesterol crystals and pigment-laden macrophages in the absence of tumor cells.<sup>11</sup>

Less severe stages of Coats' disease, especially in adults, must be differentiated from other disorders that produce vascular changes and exudation. These include inflammatory disorders such as Eales' disease, vasculitis, and collagen vascular disease. Tumors accompanied by exudation may mimic Coats' disease, as may diabetic vasculopathy with lipid deposition, branch retinal vein occlusion with vascular remodeling and edema, rhegmatogenous retinal detachment, radiation retinopathy, idiopathic juxtafoveal telangiectasia, von Hippel disease, angiomas of retina, exophytic capillary hemangioma, and sickle cell retinopathy. In these cases, a thorough review of the systems and medical and family histories usually help differentiate primary from secondary disorders.<sup>11,9,10</sup>

## Idiopathic Juxtafoveal Retinal Telangiectasia

Idiopathic juxtafoveal retinal telangiectasia is a group of disorders initially described by Gass and Oyakawa<sup>17</sup> in 1982. The disease is characterized by onset in adulthood and presentation with mild blurring of central acuity caused by exudate from ectatic retinal capillaries in the juxtafoveal region of one or both eyes. They divided these patients into four categories: groups 1A, 1B, 2, and 3.<sup>17,9</sup>

### Group 1A

Group 1A disease consists of unilateral congenital parafoveal telangiectasia, which typically occurs in men and affects only one eye. Retinal vascular abnormalities are present in a small area, one to two disc areas in diameter, in the temporal half of the macula. Onset of symptoms—with visual loss in the 20/40 (6/12) or better range—typically develops at a mean age of 40 years. Photocoagulation of areas of leakage may help restore acuity.

### Group 1B

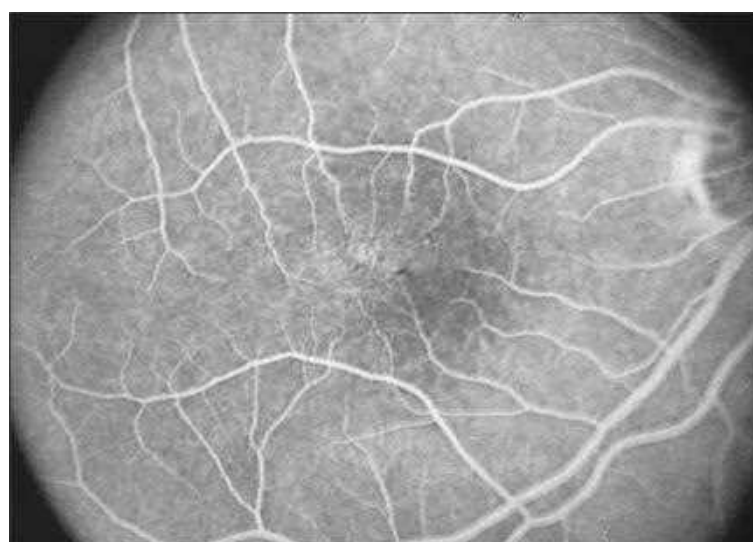
Group 1B disease consists of unilateral idiopathic parafoveal telangiectasia, usually found in middle-aged men who have blurring caused by a tiny area of capillary telangiectasia confined to one clock hour at the edge of the foveal avascular zone. Vision is usually 20/25 (6/7) or better. Photocoagulation usually is not considered for these eyes because of the proximity of the leakage to the fovea and the good prognosis without treatment. The lesion may be acquired or may simply be a very small focus of congenital telangiectasia.

### Group 2

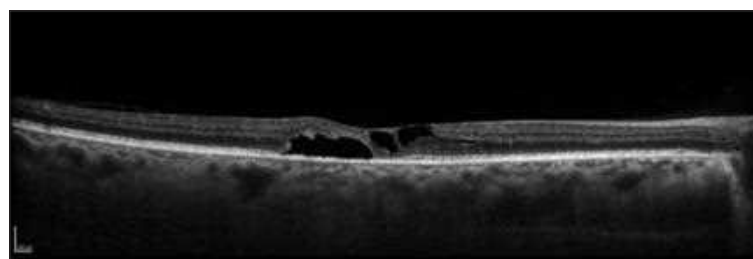
Group 2 disease consists of bilateral, acquired, idiopathic parafoveal telangiectasia. This variant affects patients in the fifth and sixth decades; mild blurring of vision occurs in one or both eyes. The patients typically have small, symmetrical areas of capillary dilatation, usually the size of one disc area or less, in both eyes. The vascular changes may be temporal only or may include all or part of the parafoveal nasal retina too. No lipid is deposited, and minimal serous exudation is present. A hallmark is the characteristic gray appearance of the lesions on biomicroscopic examination with occasional glistening white dots in the superficial retina. Red-free photography often highlights these findings best (Figs. 6.25.6 and 6.25.7). These patients also commonly have right-angled retinal venules that drain the capillary abnormalities and are present in the deep or outer retinal layers. Retinal pigment epithelial hyperplasia eventually tends to develop along these venules. In these patients, slow loss of visual acuity over many years is produced by atrophy of the central fovea; patients also may develop subretinal neovascularization, hemorrhagic macular detachment, and retinohoroidal anastomosis.

### Group 3

Bilateral idiopathic perifoveal telangiectasia with capillary occlusion is a rare variant in which adults experience loss of vision because of progressive obliteration of the capillary network, which begins with telangiectasia. The capillaries' aneurysmal malformations are more marked than in the other, milder forms of the disease; no leakage occurs from the capillary bed.



**Fig. 6.25.6 Bilateral Idiopathic Parafoveal Telangiectasia Can Often Best Be Demonstrated With Red-Free Photography.** This eye features capillary abnormalities present for virtually 360° in the parafoveal area. Early transit of the eye demonstrates a plexus of capillary abnormalities ringing the fovea.



**Fig. 6.25.7 Optical Coherence Tomography Findings in Idiopathic Parafoveal Telangiectasia.**

Yannuzzi et al. proposed an updated classification.<sup>18</sup> Broadly classified into Type 1, or unilateral aneurysmal dilation predominantly in men, and Type 2 perifoveal telangiectasia, bilateral telangiectasia limited to the perifoveal area without visible aneurysms but associated with subretinal neovascularization, readily identifiable on OCT angiography.<sup>19</sup>

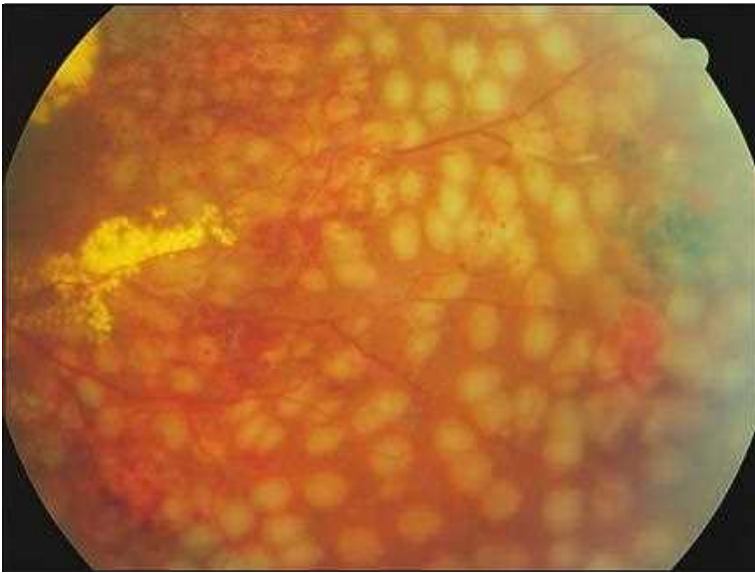
## The MacTel Project

An international research collaboration comprising more than 30 centers, the MacTel Project, was initiated in 2005 to better understand disease pathogenesis, epidemiology, and potential treatments of idiopathic macular telangiectasia type 2. The MacTel Project found a prevalence of diabetes mellitus of 28% and hypertension of 52% in MacTel type 2, suggesting a vasculopathic etiology of the disease.<sup>20</sup> The project has also identified a genetic susceptibility locus for the disease using gene mapping, but precise genetics of the disease remains unknown.<sup>21</sup> Given the potential for neurodegenerative etiology for type 2 macular telangiectasia, the MacTel Project is investigating the benefits of intraocular delivery of ciliary neurotrophic factor as a treatment for this disease.<sup>22</sup>

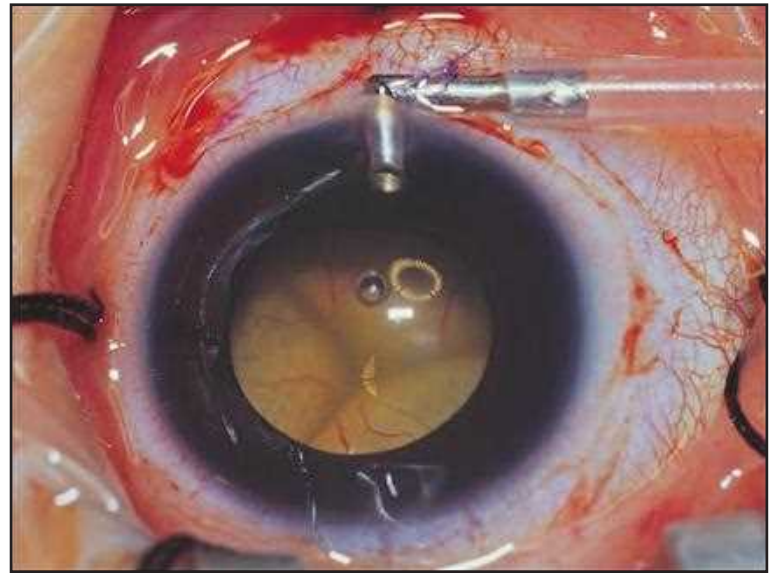
## Potential Treatments for Idiopathic Juxtafoveal Retinal Telangiectasia

Several treatment modalities have been explored for group 2 parafoveal telangiectasia. Laser photocoagulation to leaking parafoveal vessels has not been demonstrated to stop the vascular leakage or improve visual acuity.<sup>23</sup> Although intravitreal triamcinolone has been shown to reduce retinal leakage, visual acuity outcomes are variable, and corticosteroid-related adverse events may be limitations with longer follow-up duration.<sup>24</sup> Retrospective and prospective studies of intravitreal injections of anti-VEGF agents such as bevacizumab and ranibizumab have resulted in decreased retinal leakage but not improved vision.<sup>25–30</sup> Therefore VEGF inhibition is not routinely recommended for parafoveal telangiectasia without secondary choroidal neovascularization. If choroidal neovascularization develops, intravitreal anti-VEGF therapy is the most effective therapy available to regress the neovascular tissue.<sup>26</sup>





**Fig. 6.25.8 Initial Photocoagulation of the Eye Shown in Fig. 6.25.5.** Large, medium-intensity spots have been placed on leaking aneurysms, sparing the foveal avascular zone at first. More peripherally, photocoagulation covers temporal aneurysms and is also placed in a scatter pattern in zones of nonperfusion.



**Fig. 6.25.9 Technique Used for Drainage of Subretinal Fluid in Eyes With Extensive Exudative Detachment.** The pediatric infusion cannula is sutured into the anterior chamber through a limbal stab incision with a single Vicryl suture. This is placed in a convenient quadrant so that the eye can be rotated and a posterior draining sclerotomy fashioned. The infusion runs into the anterior chamber and around intact lens zonules, keeping the eye formed as voluminous quantities of thick, yellow subretinal fluid are drained; this subretinal fluid is speckled with cholesterol and lipid deposits.

## SYSTEMIC ASSOCIATIONS

Isolated case reports have described a number of other diseases that occurred simultaneously in patients with Coats' disease. In many cases, it is doubtful that an actual causal association exists. Gass<sup>9</sup> described a patient who had a facial angioma and typical retinal telangiectasia and another who had bilateral retinal disease and progressive facial hemiatrophy. Bilateral telangiectasia and Coats' syndrome have been reported in multiple family members who have facioscapulohumeral muscular dystrophy and deafness. No definite connection has been made between other systemic or ocular conditions and Coats' disease. The adult form of the disease has been described as frequently associated with hypercholesterolemia, although such an association does not occur in the juvenile form.<sup>31,32</sup>

## TREATMENT

The major goal of treatment in Coats' disease is to preserve or improve visual acuity or, when this is impossible, to preserve the anatomical integrity of the eye. Intervention is contemplated when exudation is central and/or extensive and progressive. In severe, untreated cases, total retinal detachment, iris neovascularization with glaucoma, and phthisis bulbi can result. Treatment of Coats' disease is directed toward closure of the abnormal, leaking retinal vessels to allow resorption of exudate. In many cases, the visual results are poor even with successful treatment, especially when the macula is involved initially in the exudative process.<sup>12,31,33–35</sup>

Laser photocoagulation is the treatment of choice in mild to moderate cases of exudation from Coats' disease. Fluorescein angiographic guidance allows precise, localized treatment of the leaking aneurysms and vessels. Lesions that leak are treated directly with relatively large (200–500  $\mu$ m) applications of moderate-intensity light (Fig. 6.25.8).<sup>11</sup> Scatter photocoagulation to areas of extensive nonperfusion are of unproven value but may lessen the chance of secondary neovascularization. Peripheral lesions may be treated with the indirect laser, which may need to be done under general anesthesia in children.

Where subretinal fluid is present, cryotherapy, as opposed to laser, to the anomalous vessels is recommended using a single freeze or freeze-refreeze technique. If the retina is highly elevated, it may be necessary to drain subretinal fluid to flatten the retina and allow sufficient freeze to reach the retinal vessels. In these cases, the retina is flattened, the eye reformed, and cryotherapy or laser applied (Fig. 6.25.9) (Video 6.25.1). Subretinal pigmentation and fibrosis usually ensue and follow the lipid resolution. If this involves the macula, visual return is commensurately poor.<sup>11</sup>

Another approach to eyes with significant retinal detachment is to perform a scleral buckling procedure.<sup>31</sup> Harris<sup>34</sup> reported that a scleral buckle sometimes aids the application of postoperative photocoagulation, because it can be oriented beneath the abnormal vessels, and anomalies at the apex of the buckle can be treated effectively. Siliodor et al.<sup>33</sup> reported

a series of 13 children who had blind eyes and bullous exudative detachments followed either after no treatment or after surgery that involved intraocular infusion, drainage of subretinal fluid, and cryotherapy on one or more occasions. Of the six untreated eyes, four developed painful neovascular glaucoma and underwent enucleation. The seven treated with surgery all remained cosmetically acceptable and comfortable; none developed neovascular glaucoma.

In selected cases of Coats' disease with intravitreal proliferation and traction detachment, vitreous surgery may improve the clinical course. Machemer and Williams<sup>36</sup> reported successful results with surgical removal of vitreal and preretinal membranes and destruction of leaking vessels in a small series of patients.

Repeated therapeutic laser or cryotherapy treatments are typically required in eyes that have Coats' disease. Exudate typically begins to resorb within six weeks of treatment if the abnormal vasculature has been eliminated. Depending on the amount of lipid accumulation, in many cases, it takes months to more than a year for complete resolution. Recurrence of exudate after initially successful treatment signals the development of new abnormal leaking vessels; these must be searched out meticulously. Contact lens biomicroscopy with a three-mirror lens sometimes is a useful adjunct to indirect ophthalmoscopy in these cases, as is wide field fluorescein angiography. Recurrences may occur years after initially successful treatment, so it is particularly important to follow juvenile patients who may develop significant problems if not followed carefully. Egerer et al.<sup>31</sup> recommended that all patients who have Coats' disease should be examined at least twice a year to catch any early recurrent problems that may develop in a small percentage of these patients.

Intravitreal triamcinolone has been reported to give short-term benefit in select cases of Coats' disease. Othman and colleagues combined intravitreal triamcinolone with either laser photocoagulation or cryotherapy in 15 eyes and found that treatment resulted in reabsorption of subretinal fluid and macular exudates.<sup>37</sup> Other published reports demonstrate improvement in visual acuity and decrease in retinal thickness after intravitreal triamcinolone.<sup>38</sup> More recently, pharmacological therapy with intravitreal inhibitors of VEGF have been reported to have biological activity in Coats' disease.<sup>39–43</sup> Ramasubramanian and Shields reported a retrospective analysis of eight patients with Coats' disease with partial or near total exudative retinal detachment.<sup>40</sup> Treatment with laser photocoagulation and/or cryotherapy plus additional intravitreal bevacizumab (1.25 mg/0.05 ml) with a mean follow-up period of 8.5 months resulted in resolution of retinopathy and subretinal fluid. Vitreous fibrosis in four patients at month five with a traction retinal detachment in three patients was possibly related to the use of intravitreal bevacizumab. Caution is advised when using anti-VEGF therapy for patients with Coats' disease.



## COMPLICATIONS OF TREATMENT

Complications of photocoagulation and cryotherapy for Coats' disease include inflammation, hemorrhage, chorioretinal anastomosis formation, and retinal, chorioretinal, and subretinal fibrosis. Macular distortion secondary to epiretinal membrane formation and contraction has been reported following photocoagulation for Coats' disease and may occur even if the disease is untreated. Gass<sup>9</sup> reported one adult patient who developed total retinal detachment and proliferative vitreoretinopathy after cryotherapy for peripheral retinal telangiectasia that was discovered late in life; the eye initially had 20/20 (6/6) acuity.

With intraocular surgical intervention, additional risks include cataract formation, choroidal hemorrhage, retinal detachment, endophthalmitis, glaucoma, and phthisis.

Intravitreal triamcinolone has been associated with elevated intraocular pressure and cataract progression. Anti-VEGF agents have been associated with retinal fibrosis evolving into traction retinal detachment in case reports.<sup>40</sup> Careful monitoring of patients after administration of pharmacological therapies is advised.

## COURSE AND OUTCOME

The clinical course in Coats' disease is variable, but it is usually progressive. Continued exudation from abnormal vascular channels produces a gradual accumulation of lipid and serous retinal detachment. The downhill course is more rapid in eyes with more extensive vascular abnormalities. Acute exacerbations of the disease may occur with intervening periods of relative stability. The end stage of the exudative process, seen in eyes with severe Coats' disease and particularly in young patients who have an early onset of symptoms, is total retinal detachment, which may be followed by rubeosis iridis, neovascular glaucoma, and eventually phthisis bulbi.

Shields and colleagues conducted a large retrospective review of 150 patients with Coats' disease to determine risk factors for poor visual outcome and enucleation.<sup>44</sup> Risk factors predictive of poor visual outcome (20/200 or worse) were postequatorial, diffuse, or superior location of the telangiectasis and exudation, failed resolution of subretinal fluid after treatment, and presence of retinal macrocysts. Significant risk factors for enucleation included elevated intraocular pressure and iris neovascularization.

The ultimate prognosis for eyes with Coats' disease can be measured in terms of two endpoints: visual acuity and anatomical stability. Unfortunately, central visual acuity is frequently poor in eyes with Coats' disease, because the disease is not diagnosed and treated until after significant macular lipid deposition is present. Even with good treatment and resolution of the macular deposits, significant subretinal fibrosis and macular impairment are present.

Visual acuity results may be quite good in patients who have very mild vascular anomalies that do not require treatment or are discovered and treated before the macula is involved by the exudative process. It is difficult to estimate the frequency with which this situation develops in the general population, because reported series discuss only more severe cases referred to tertiary treatment centers, and the disease is rare enough to have avoided scrutiny in population-based studies.

Eyes with severe exudation and retinal detachment rarely retain vision better than 20/400 (6/120), and many see much worse than this. Nevertheless, successful treatment of leaking vascular channels may salvage some vision, and this has the advantage of stabilizing the eye anatomically. Occasionally an eye may be saved structurally without light perception.

The prognosis for retaining anatomical integrity of the globe is much better. Most eyes with Coats' disease, however, can be saved, be cosmetically acceptable, grow and develop otherwise normally, and in many cases have useful vision. Amblyopia therapy, strabismus surgery, and other types of ancillary rehabilitation may be useful and should not be neglected as part of the total treatment of these patients.

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## Radiation Retinopathy and Papillopathy

## 6.26

Ahmet Kaan Gündüz, Carol L. Shields

**Definition:** A slowly progressive occlusive vasculopathy affecting the retina, choroid, and optic nerve, with a delayed onset after irradiation.

**Key Features**

- Retinal microaneurysms.
- Retinal hemorrhages.
- Retinal telangiectatic vessels.
- Retinal hard exudates.
- Macular edema.
- Cotton-wool spots.
- Optic disc swelling.

**Associated Features**

- Retinal neovascularization.
- Disc neovascularization.
- Vitreous hemorrhage.
- Iris neovascularization.
- Optic atrophy.
- Occlusive choroidal vasculopathy.
- Polypoidal choroidal vasculopathy.

**RADIATION RETINOPATHY**

Radiation retinopathy (RR) is characterized by a slowly progressive occlusive vasculopathy with a delayed onset after irradiation.<sup>1</sup> Radiation retinopathy was first described in 1933 by Stallard, who noted retinal exudation, retinal hemorrhage, retinal pigment epithelial changes, and optic disc edema in patients treated with radon seeds for retinal tumors.<sup>2</sup> In 1935, Moore expanded on the initial observations made by Stallard.<sup>3</sup>

RR has been documented after both plaque radiotherapy (also termed *brachytherapy*) and external beam radiotherapy (EBRT) (also termed *teletherapy*) following treatment of intraocular tumors. RR can also develop after EBRT of orbital, paranasal sinus, and intracranial tumors, as well as thyroid ophthalmopathy and orbital inflammation.<sup>1,4</sup> In recent years, a better understanding of the biological effects of ionizing radiation, development of techniques enabling more accurate focusing of radiation to target tissues, and earlier diagnosis and treatment have helped decrease the risk of vision loss resulting from RR.

**Pathology and Pathogenesis**

Histopathological studies of the eyes with RR confirm the predominantly vascular nature of damage produced by radiation therapy. There is an unequivocal loss of endothelial cells with relative sparing of the pericytes.<sup>1,4,5</sup> This is in contrast to diabetic retinopathy, where the target cell is the pericyte instead of endothelial cells.<sup>5</sup>

Radiation basically has two side effects on tissues.<sup>5,6</sup> First, radiation directly damages the endothelial cell DNA. The endothelial cells undergoing mitosis and proliferating at the time of radiation are most vulnerable and eventually succumb to death. As a result of this insult, the remaining endothelial cells migrate and divide in an effort to compensate for the damaged segments. However, if the damage is extensive, there is a relative endothelial cell deficiency, leading to a vasculopathy characterized by vascular leakage, platelet aggregation, and activation of the clotting cascade. Second, the indirect effect of radiation involves creation of free radicals (OH) from water contained within the cell cytoplasm. Free radicals are

highly reactive and induce further DNA damage.<sup>6</sup> The differential sensitivity between endothelial cells and pericytes is the result of direct exposure of endothelial cells to high oxygen and iron found in blood, which generates some of the free radicals.<sup>1,6</sup> Cell damage usually starts on the arterial side of the circulation, where free radical generation is greater because of higher oxygen tension.<sup>1,6</sup> Small retinal vessels are involved first, leading to capillary closure. Larger retinal vessels and choroidal vessels can also be affected later in the course of the disease.

**Clinical Features**

RR is suspected when there is a history of radiation exposure and ocular examination reveals the characteristic fundus findings. RR has a clinical course similar to diabetic retinopathy.<sup>1,7-9</sup> Therefore, it is prudent to classify RR as nonproliferative radiation retinopathy (NPRR), proliferative radiation retinopathy (PRR), and radiation maculopathy (RM) similar to the classification in diabetic retinopathy.<sup>7</sup> In NPRR, retinal capillary changes, retinal edema, retinal hemorrhages, microaneurysms, telangiectatic vessels, hard exudates, vascular sheathing, and cotton-wool spots are evident. When these nonproliferative changes are present within 3 mm of the foveola, the condition is referred to as RM (Fig. 6.26.1). With the development of widespread areas of capillary nonperfusion, retinal and disc neovascularization develop, leading to PRR. If untreated, PRR can result in vitreous hemorrhage, iris neovascularization, and neovascular glaucoma.

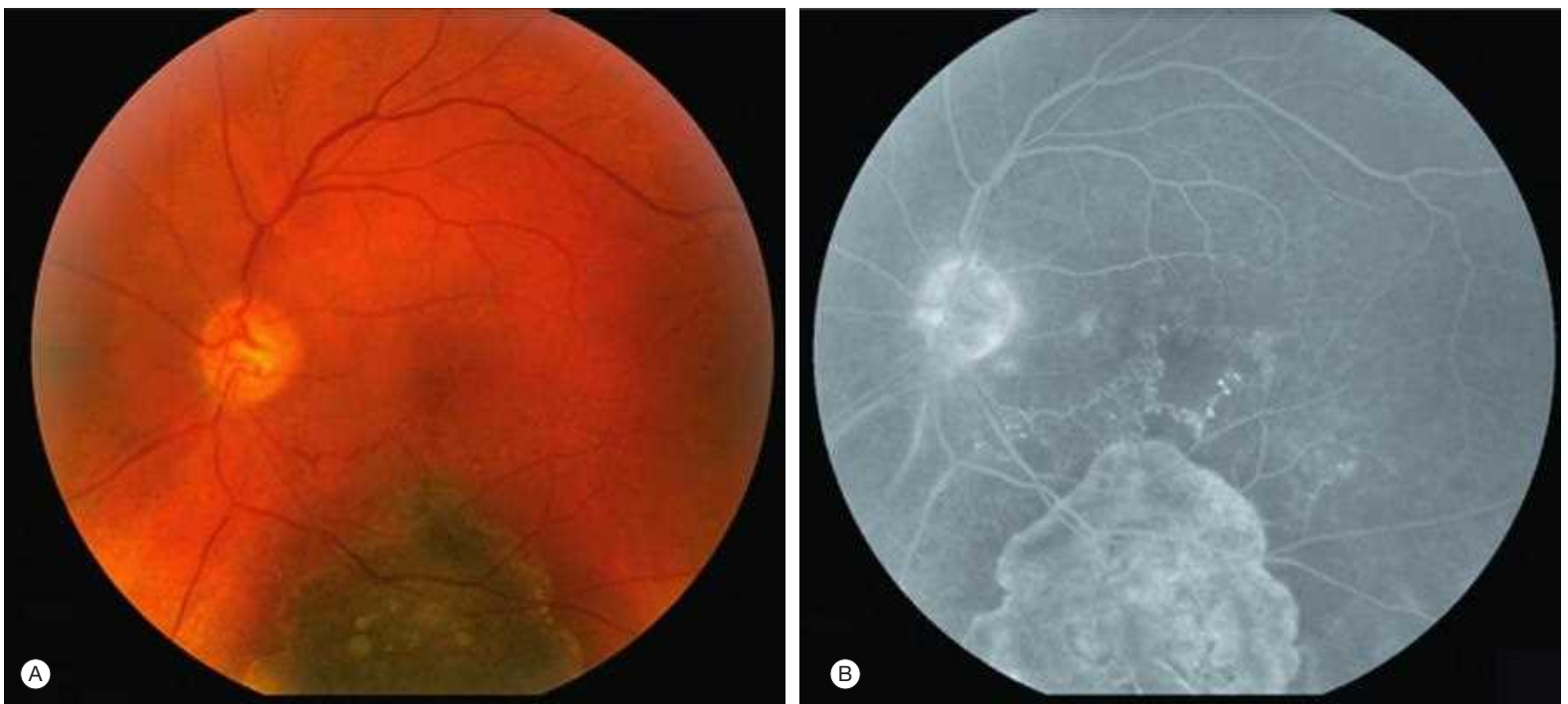
Other manifestations of radiation effects on the posterior globe include radiation choroidopathy, including closure of choroidal vessels, leading to choroidal atrophy, polypoidal choroidal vasculopathy, and choroidal infarction.<sup>7</sup> Radiation-related retinal pigment epitheliopathy is another effect that manifests with mottling of the retinal pigment epithelium (RPE), hyperplasia, and eventual atrophy. The term RR is most often used in the literature to broadly encompass all fundus changes, including NPRR, PRR, and RM, as well as radiation choroidopathy and RPE changes.

RR can develop as early as one month to over 15 years after radiation exposure. However, it most commonly occurs between six months and three years.<sup>4</sup> Gündüz et al. reported that 5% of the 1300 patients treated with plaque radiotherapy had NPRR at 1 year and 42% at 5 years.<sup>7</sup> More serious PRR developed in 1% at 1 year and 8% at 5 years.<sup>7</sup> The Collaborative Ocular Melanoma Study (COMS) confirmed these clinical observations and assessed histopathological evidence of RR in enucleated eyes following plaque radiotherapy for melanoma. The authors of that study found that 55% of eyes had evidence of microvascular abnormalities related to RR.<sup>10</sup> Sagoo et al. found that for juxtapapillary melanoma (posterior margin within 1 mm of the optic disc), the risks of RR and RM were higher at 75% and 65%, respectively, after plaque radiotherapy.<sup>11</sup> These studies were based on ophthalmoscopic observations and done mostly before the availability of optical coherence tomography (OCT). Using OCT, Horgan et al. found an increased incidence of macular edema in 40% of eyes by 1 year and in 61% by 2 years after plaque radiotherapy for choroidal melanoma.<sup>12</sup> For proton beam radiation treatment of juxtapapillary and parapapillary melanomas, those located <1 disc diameter from the optic disc, the 5-year rate of RM was 60%.<sup>13</sup> A more recent study evaluating ciliary body as well as choroidal melanomas treated with proton beam irradiation found a 5-year RR rate of 85%.<sup>14</sup>

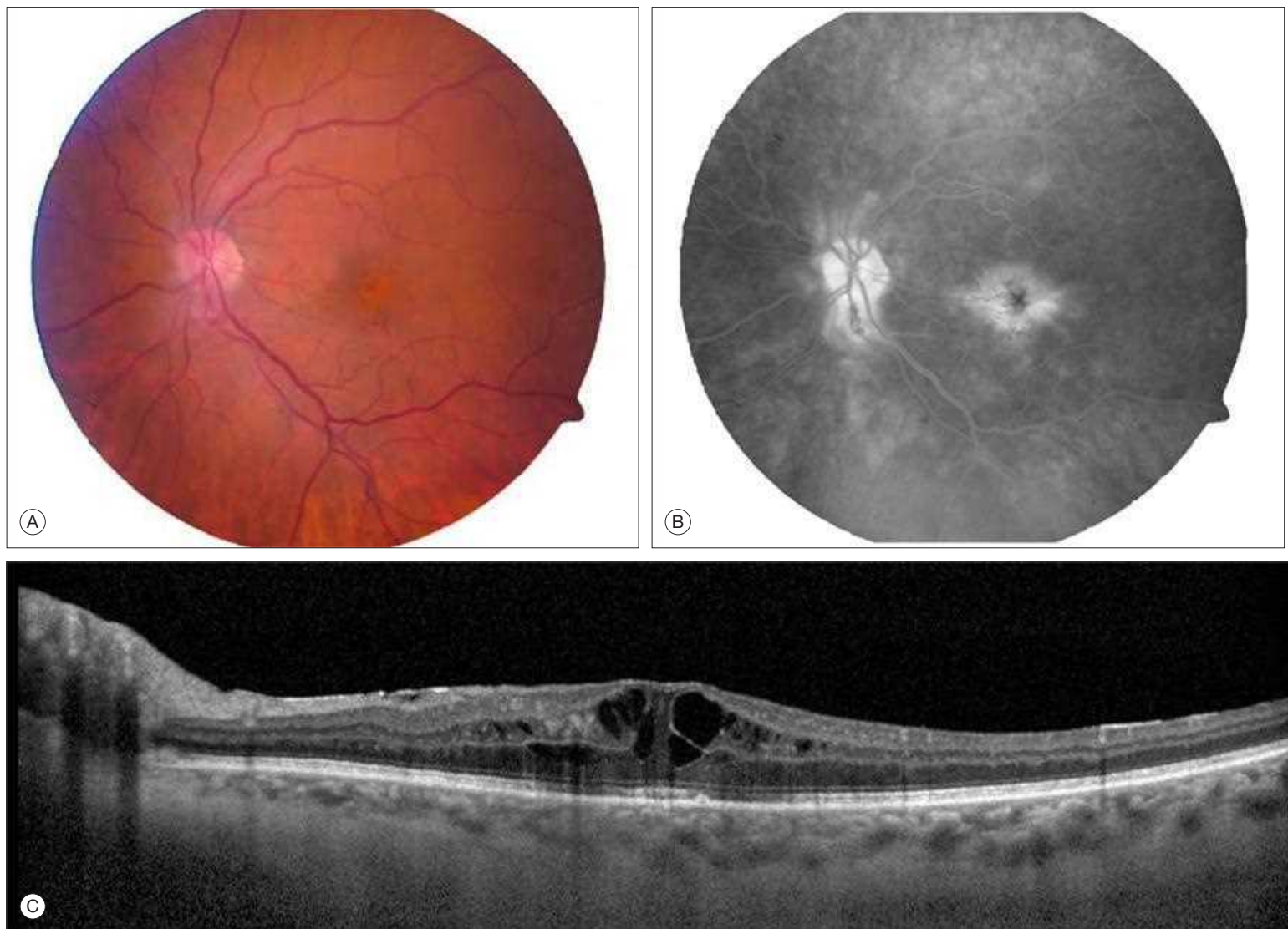
**Diagnostic Studies**

Fluorescein angiography (FA), OCT, and OCT angiography (OCTA) are diagnostic studies that are most helpful in the evaluation of eyes with RR. FA can demonstrate microvascular changes, capillary dropout, retinal nonperfusion, retinal and disc neovascularization, and macular edema<sup>7-9</sup> (see Fig. 6.26.1; Fig. 6.26.2). It is especially useful in classifying RM as





**Fig. 6.26.1** Radiation maculopathy following plaque radiotherapy for choroidal melanoma (A) showing regressed melanoma inferiorly and retinal telangiectasia, microaneurysms, and exudation in the inferior macula. On fluorescein angiography (B), macular telangiectasia, microaneurysms, and nonperfusion are found. Staining of the optic disc implies radiation-related damage.



**Fig. 6.26.2** Radiation maculopathy with retinal telangiectasia and hemorrhage (A), fluorescein angiographic petaloid staining (B), and optical coherence tomographic outer plexiform cystoid edema (C).

ischemic versus nonischemic. In eyes with ischemic maculopathy, there is little chance for visual improvement with currently available treatment methods. Eyes with nonischemic maculopathy are amenable to treatment, as discussed below.

Using FA, radiation-related macular edema is classified into diffuse, focal, and mixed types based on the pattern of dye leakage. This classification is useful if grid or focal laser treatments are to be applied. Indocyanine green angiography (ICGA) can demonstrate areas of choroidal hypoperfusion; however, this method of angiography is not routinely used in the evaluation of RR.

OCT is a noninvasive procedure that has the advantages of providing quantitative measurement of macular edema. OCT is an important modality in evaluating presymptomatic radiation-induced macular edema (see Fig. 6.26.2). A study by Horgan et al. found that OCT detected evidence of macular edema approximately 5 months earlier than in the case of clinically detected RM.<sup>12</sup> The median visual acuity at the time of OCT-evident macular edema was 20/40. Horgan et al. proposed a five-grade scale for radiation macular edema based on OCT findings:

Grade 1 – noncystoid edema extrafoveal.

Grade 2 – cystoid edema extrafoveal.

Grade 3 – noncystoid edema foveolar.

Grade 4 – cystoid edema foveolar.

Grade 5 – cystoid edema foveolar severe, simulating serous retinal detachment.

Increasing grade of macular edema was found to be associated with worse visual acuity. With the introduction of spectral domain OCT (SD-OCT) technology, better central foveal thickness measurements and superior visualization of the retinal layers became possible.

As a further step in diagnosis of RM, OCTA has come into use. OCTA is a noninvasive technology that can visualize both the superficial and deep capillary plexuses of the retina as well as choroidal vasculature in a noninvasive manner without injection of dye. In contrast, FA can visualize only the superficial retinal plexus and requires dye injection.<sup>15,16</sup> OCTA can demonstrate enlargement of the foveal avascular zone and reduction in parafoveal capillary density of both superficial and deep capillary plexuses as well as parafoveal nonperfusion, capillary dropout, microaneurysms and telangiectasia in eyes with choroidal melanoma after plaque radiotherapy, even in the absence of clinical and SD-OCT evidence of radiation maculopathy.<sup>15,16</sup> The deeper capillary plexus and choroidal vasculature may be affected more because radiation is delivered from the scleral side in plaque radiotherapy (Figs. 6.26.3 and 6.26.4). Therefore OCTA is currently the most sensitive method for detection of early RM and probably for assessment of its severity as well.

Electroretinography (ERG) studies are rarely used in the evaluation of RR and RM. ERG reflects the mass response of retina and may demonstrate decreased amplitudes in widespread RR.

## Risk Factors

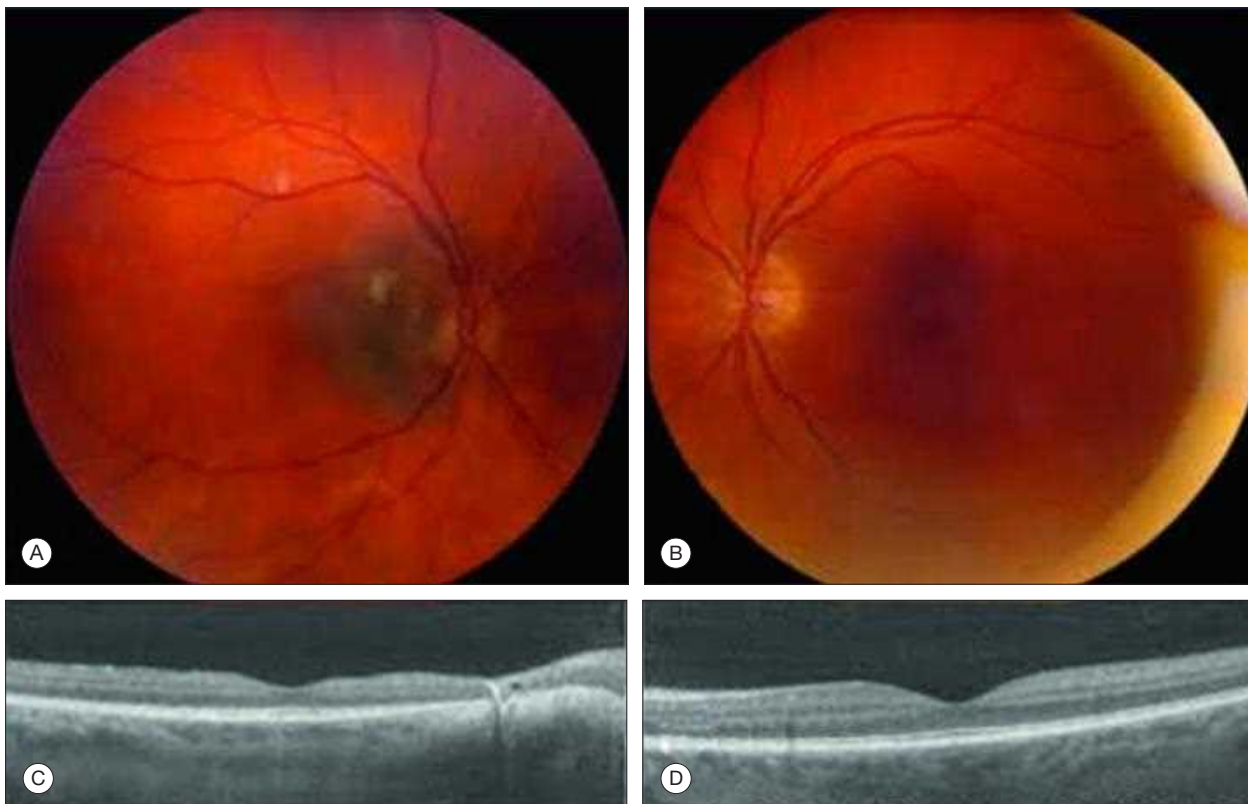
### Brachytherapy

Tumor type, thickness, location, radioisotope type, and radiation parameters are important factors to consider in the development of RR following brachytherapy. With plaque radiotherapy, the risk of RR is related to total radiation dose. Total radiation dose is, in turn, related to tumor type. In the treatment of posterior uveal (ciliary body and choroidal) melanoma, therapeutic apical tumor doses range from 80 to 100 Gy, whereas in circumscribed choroidal hemangioma the apical dose is only approximately 20–25 Gy.

Total radiation doses that result in 5% and 50% complication rates at 5 years are defined as tissue tolerance doses—TD<sub>5</sub> and TD<sub>50</sub>. The retina has a TD<sub>5</sub> value of 45 Gy and a TD<sub>50</sub> value of 60 Gy.<sup>17</sup> First, with the therapeutic apical doses used for uveal melanoma, the retina and the macula are inevitably exposed to radiation doses in excess of the normal tissue tolerance doses discussed above. Therefore, RR is seen more often after brachytherapy for choroidal melanoma than that for similar-sized choroidal hemangioma because of the higher radiation dose used in the treatment for melanoma. Second, tumor thickness >4 mm has also been associated with a greater risk of RM.<sup>18</sup> The spillover radiation dose delivered to the surrounding retina is greater with increasing tumor thickness. Third, tumor location is a factor in the development of visually significant RM. Brown et al. found that RM did not develop if the fovea received a dose of ≤50 Gy in brachytherapy.<sup>8</sup> A subsequent study by Gündüz et al. validated this finding.<sup>7</sup> With brachytherapy for peripheral tumors, the fovea receives a smaller radiation dose, and the risk for RM is less. A number of radioactive isotopes, including cobalt-60, iridium-192, ruthenium-106, iodine-125, and palladium-103, have been used in ocular brachytherapy. Of these, the use of cobalt-60 and iridium-192 has been almost totally abandoned because of the higher energy and marked radiation side effects of these radioisotopes. Radiation parameters including tumor apex dose >90 Gy, apex dose rate >75 cGy/hr, and base dose rate >260 cGy/hr were found to lead to RR on a univariate model in one study.<sup>7</sup> Coexisting morbidities, including diabetes mellitus, and concurrent chemotherapy increase the risk of RR in both teletherapy and brachytherapy.<sup>4</sup>

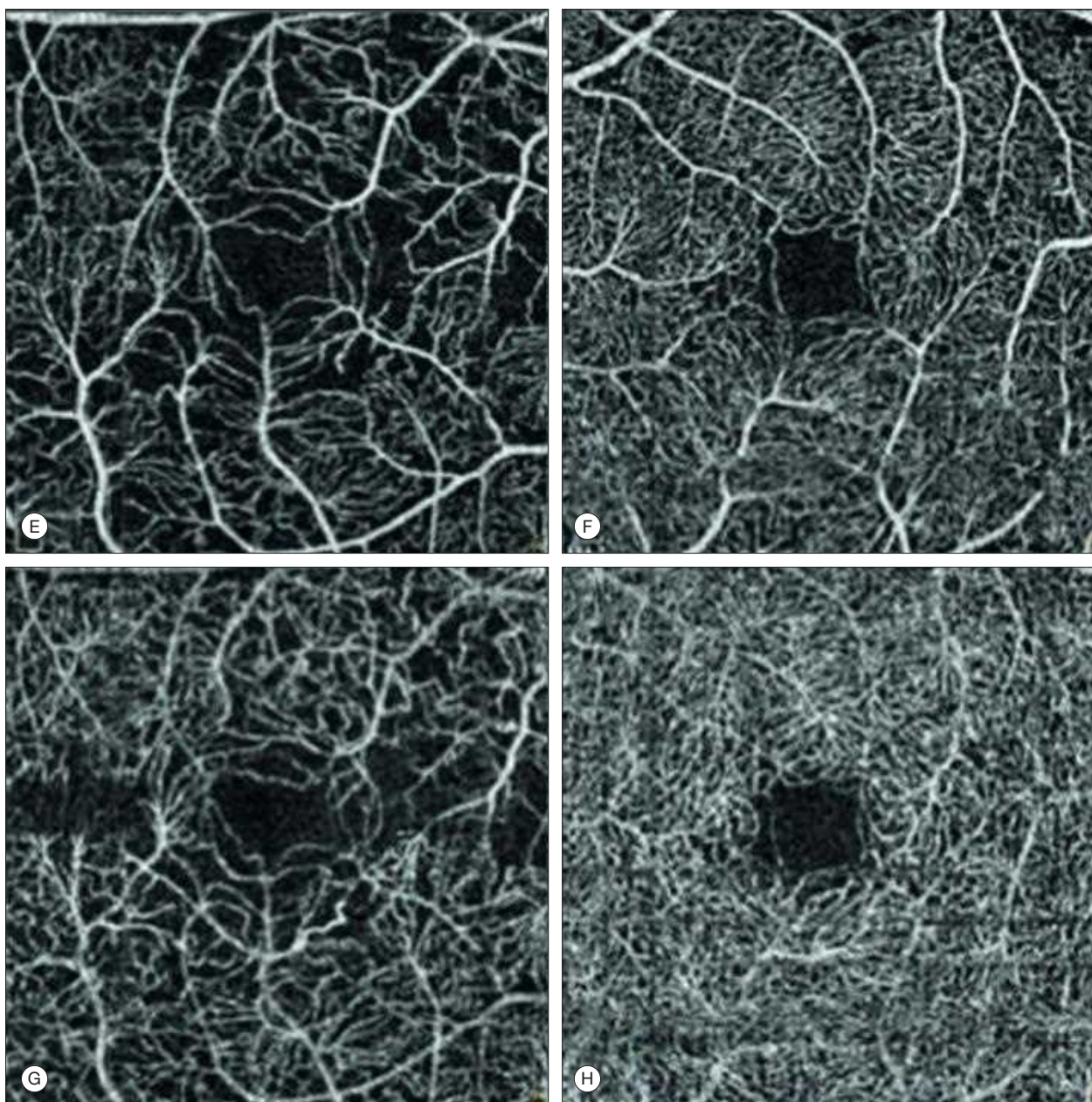
### Teletherapy

Total radiation dose, fractionation, field design, and type and rate of administration are factors that affect the development of RR after EBRT. RR has



**Fig. 6.26.3** Mild radiation maculopathy after plaque radiotherapy. Color fundus photographs show temporally located small, biopsy-proven irradiated juxtapapillary choroidal melanoma in the right eye (A) and normal fellow eye (B). Note the nerve fiber layer infarctions in the papillomacular region and superior macular region of the right eye (A). Spectral-domain optical coherence tomography (SD-OCT) of the right eye after irradiation shows regular foveal contour and normal central macular thickness with no evidence of intraretinal edema or subretinal fluid (C). There is retinal thinning in the papillomacular region from previous subretinal fluid and the vertical bright line through the retina marks the site of needle biopsy (C). Normal SD-OCT findings in the left eye (D).





**Fig. 6.26.3, cont'd** Optical coherence tomography angiography (OCTA; 3-mm scan) of the superficial capillary plexus shows decreased capillary density and widening of the foveal avascular zone (FAZ) in the irradiated right eye (E) compared with the normal fellow eye (F). OCTA (3-mm scan) of deep capillary plexus shows similar findings, including decreased capillary density and widening of the FAZ in the irradiated right eye (G) compared with the normal fellow eye (H).

been seen following EBRT doses ranging from 15 to 60 Gy. However, RR usually occurs with doses  $>45$  Gy. Hyperfractionation is associated with a decreased incidence of RR,<sup>19</sup> and patients who received fractions of  $<1.9$  Gy are unlikely to develop RR, as found in one study.<sup>19</sup> When the treatment site is closer to the eye, the incidence of RR is higher. With respect to proton beam radiotherapy of posterior uveal melanoma, the risk factors for development of RR include posterior tumor margin  $<3$  mm to fovea and optic nerve, larger tumor base diameter, and increased tumor thickness, as reported in one study.<sup>14</sup>

## Differential Diagnosis

RR can be clinically indistinguishable from changes seen in patients with diabetic retinopathy. Other conditions that need to be considered in the top differential diagnosis include branch retinal vein occlusion, central retinal vein occlusion, hypertensive retinopathy, Coats' disease, and perifoveal telangiectasia.

## Treatment

Prevention, if possible, is better than treatment. Unfortunately, RR is an inevitable side effect of radiotherapy, and complete prevention is not possible. However, a number of strategies have been developed to decrease the dose of radiation and hence the risk of development of RR because once macular ischemia develops, vision loss is irreversible.

## Reducing the Dose of Radiation

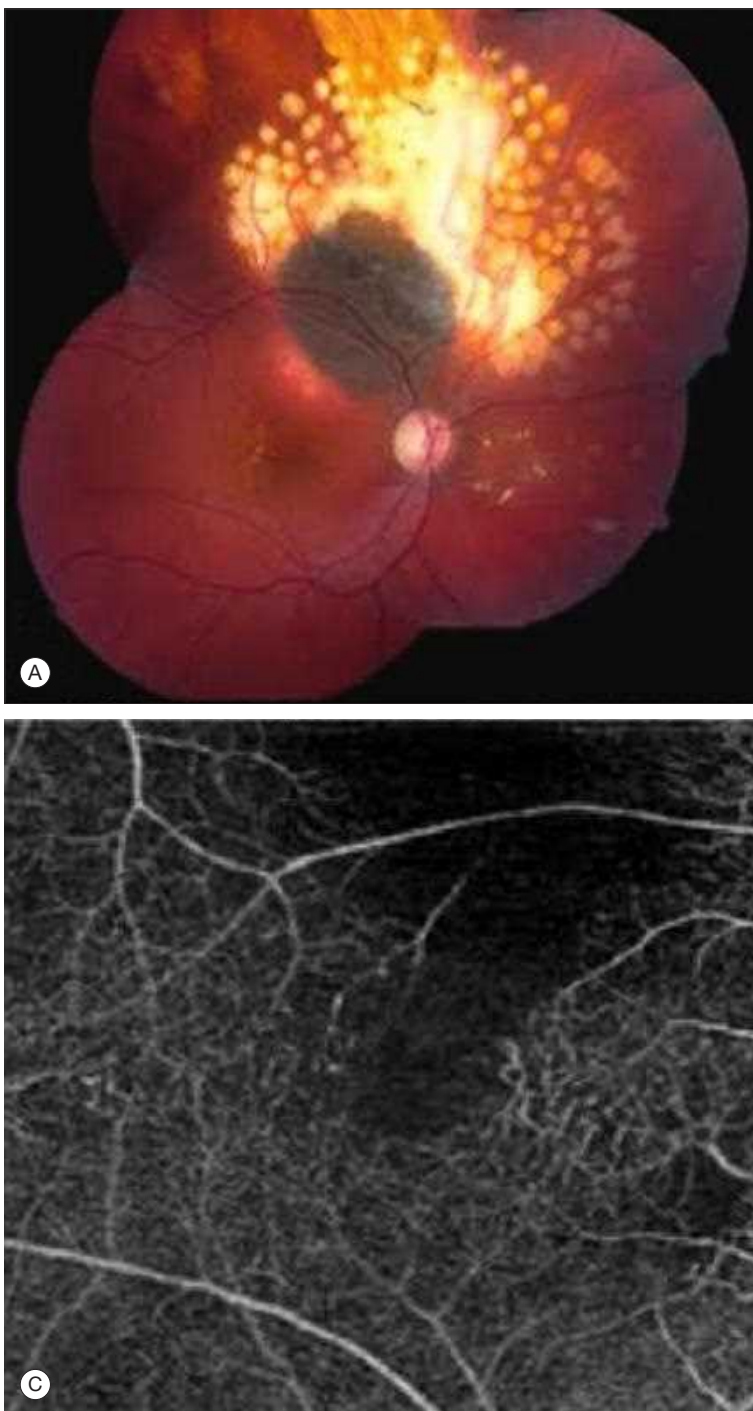
For brachytherapy, the use of collimating plaques as well as eccentric positioning of the plaques so that the posterior plaque edge is aligned with the posterior tumor margin may help decrease the radiation dose to the macula. Further measures include de-escalating (lowering) the apex tumor dose (to 63 Gy) in an effort to reduce the total radiation dose to macula<sup>20</sup> and filling the vitreous cavity with silicone oil to attenuate intraocular radiation.<sup>21</sup> For teletherapy, appropriate shielding of the ocular structures during EBRT can minimize radiation exposure. As previously mentioned, hyperfractionation of EBRT has been associated with decreased incidence of RR.

## Laser Photocoagulation

Focal/grid macular laser photocoagulation has been used to treat RM, sector scatter and panretinal laser for severe NPRR and PRR, and circumferential laser around the tumor to prevent or delay RM and RR. Focal/grid macular laser photocoagulation has been used to treat RM with variable success. Studies by Kinyoun et al. and Hykin et al. demonstrated a benefit in visual acuity following treatment.<sup>9,22</sup> However, the effect was not sustained with longer follow-up in the study by Hykin et al.<sup>22</sup>

Sector scatter and panretinal laser photocoagulation has been widely used to treat NPRR and PRR after plaque radiotherapy (Fig. 6.26.5). Bianciotto et al. reported that 66% of eyes that underwent panretinal photocoagulation had complete resolution of PRR.<sup>23</sup> In a study by Finger et al., eyes with choroidal melanoma treated by plaque radiotherapy received





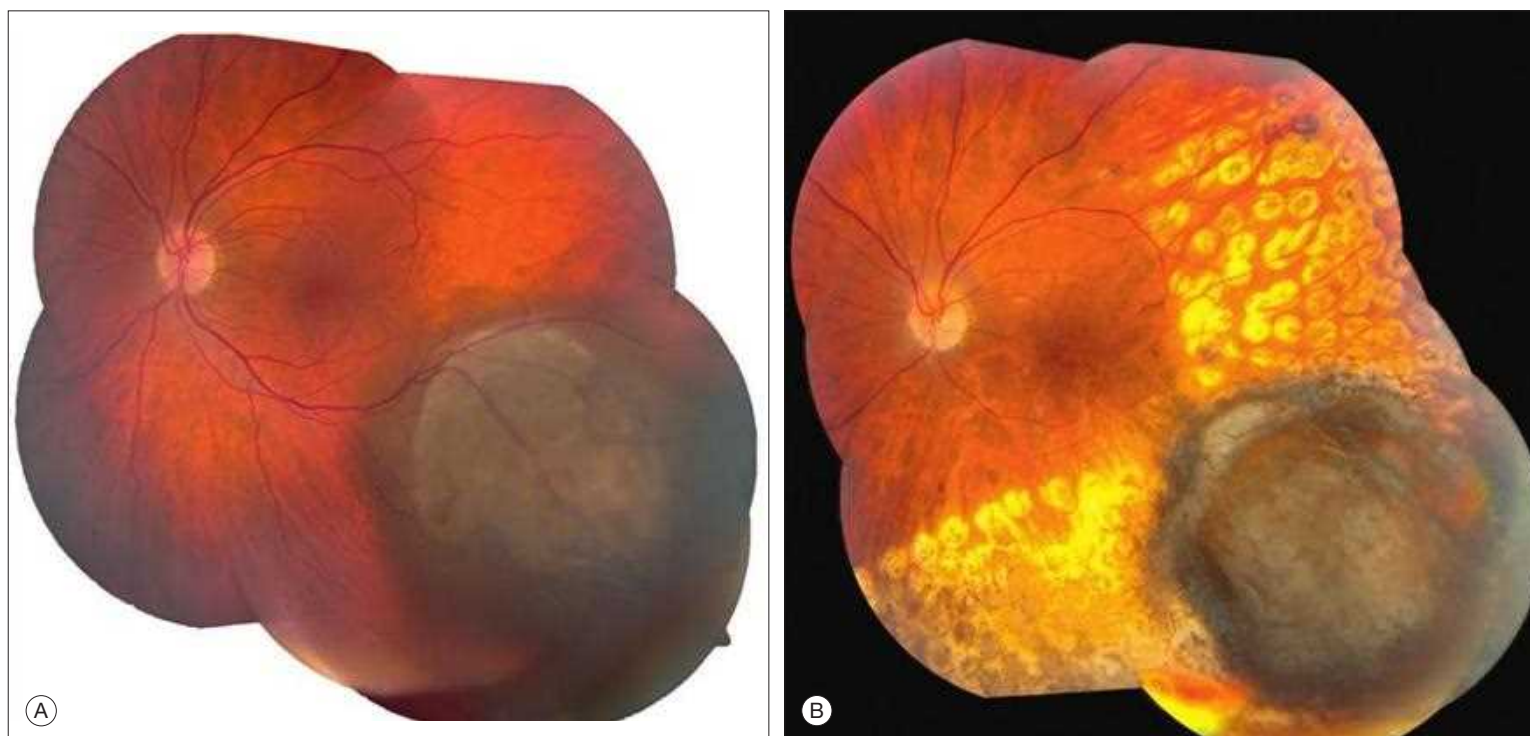
**Fig 6.26.4** Severe radiation maculopathy after plaque radiotherapy for biopsy-proven choroidal melanoma. Composite color fundus photograph shows juxtapapillary melanoma located superotemporal to the optic disc, sector laser photocoagulation scars, choroidal atrophy from plaque irradiation, and radiation maculopathy and retinopathy (A). Optical coherence tomography angiography (OCTA; 6-mm scan) of the superficial capillary plexus shows widening of the foveal avascular zone (FAZ), reduced capillary density, microaneurysms, and nonperfusion superiorly (B). OCTA (6-mm scan) of deep capillary plexus shows similar findings, including widening of the FAZ, reduced capillary density, and microaneurysms, but more pronounced macular nonperfusion superiorly (C). Deep capillary plexus is affected more compared with the superficial plexus because radiation is delivered from the scleral side in plaque radiotherapy producing more severe damage in the choroid and outer retina.

sector scatter laser photocoagulation at the first sign of retinopathy, proliferative or nonproliferative.<sup>24</sup> With plaque brachytherapy, an area of ischemia develops in and 2–3 mm surrounding the location of the plaque. Treating this area and any further areas of intraretinal microangiopathy or neovascularization with scatter laser photocoagulation caused regression of retinopathy in 64% of eyes. In the same study, a subset of eyes were treated prophylactically with scatter laser photocoagulation without clinical evidence of RR, and none lost more than three lines of vision at final follow-up.<sup>24</sup> Materin et al. similarly used prophylactic circumferential sector laser photocoagulation and sub-Tenon's membrane triamcinolone injection in eyes with choroidal melanoma managed by plaque radiotherapy and concluded that this treatment combination was safe and effective to decrease the occurrence of RM.<sup>25</sup>

### Intravitreal Anti-Vascular Endothelial Growth Factor Agents

Uveal melanomas produce high levels of vascular endothelial growth factor (VEGF) in vitreous and humor aqueous and that larger tumors are associated with higher levels of VEGF.<sup>26</sup> Therefore, trace macular edema may even be present before treatment. Several small case series and retrospective

reports examined the use of intravitreal bevacizumab (anti-VEGF agent) in the treatment of RM utilizing time-domain OCT (TD-OCT). Many of these studies demonstrated a reduction in macular edema following intravitreal bevacizumab.<sup>27</sup> However, sustained decrease in macular edema often required multiple injections, and visual acuity was not found to improve significantly. More recent studies concentrated on early SD-OCT diagnosis and prompt treatment of RM. In one such report, 50% of the patients had stable or improved vision at 3 years with repeated intravitreal anti-VEGF treatment.<sup>28</sup> As a further step, Shah et al. studied the prophylactic effect of anti-VEGF therapy on RM. Those authors reported that patients receiving intravitreal bevacizumab injections every 4 months (a total of 7 injections) after plaque radiotherapy for uveal melanoma demonstrated OCT-evident macular edema and vision loss less frequently at the end of 2 years compared with controls who did not receive treatment.<sup>29</sup> This study showed that prophylactic periodic anti-VEGF therapy leads to long-term stabilization of radiation vasculopathy. Other anti-VEGF agents, including ranibizumab and aflibercept, can also be used for the treatment of RM. Finger et al. found that continuous anti-VEGF therapy with either bevacizumab or ranibizumab was well-tolerated with no RPE atrophy and preserved vision in 80% of patients with RM over a 10-year period.<sup>30</sup> The situation may be similar to exudative age-related macular degeneration where continuous



**Fig. 6.26.5** Medium-sized choroidal melanoma at the inferotemporal equator of the left eye (A) before treatment. After plaque radiotherapy (B), the melanoma has regressed and radiation maculopathy with nerve fiber layer infarcts in the macular region is noted. Sector panretinal photocoagulation was performed for proliferative radiation retinopathy, leaving minimal vitreous hemorrhage near the melanoma scar.

fixed-interval dosing of intravitreal anti-VEGF therapy seems to provide better vision stabilization or improvement status compared to as-needed regimens.<sup>31</sup> Finger et al. also pointed out that higher doses of anti-VEGF (2.5 mg versus 1.25 mg for bevacizumab and 2.0 mg versus 0.5 mg for ranibizumab) and shorter injection intervals may be used in refractory RM cases.<sup>30</sup> Tachyphylaxis or resistance to one anti-VEGF agent after an initial responsive phase may occur and requires switching to another anti-VEGF agent. Intravitreal anti-VEGF therapy also appears effective in reducing radiation-related neovascularization and vitreous hemorrhage in addition to RM, and therefore it may have a disease-modifying activity in these circumstances.<sup>32</sup>

### Corticosteroids

Triamcinolone acetonide is thought to downregulate various cytokines and decrease capillary permeability. It is used to treat macular edema secondary to various retinal pathologies and has similarly been used to treat RM. One study found that intravitreal triamcinolone acetonide (4 mg/0.1 mL) does transiently reduce macular edema and improve visual acuity.<sup>33</sup> A randomized controlled trial assessed the efficacy of periocular triamcinolone (40 mg) given at the time of plaque application, 4 months and 8 months later in preventing radiation maculopathy.<sup>34</sup> At the 18-month follow-up, eyes treated with periocular triamcinolone demonstrated less evidence of macular edema on OCT and less vision loss compared with the control group. The study reported similar rates of elevated intraocular pressure and cataract progression between the two groups.<sup>34</sup> Patients with severe, massive cystoid edema that prove to be refractory to three sequential injections of anti-VEGF agents may also benefit from consolidation with intravitreal triamcinolone.<sup>35</sup> Although triamcinolone may decrease macular edema, permanent inner segment ellipsoid band changes may limit visual recovery. Use of intravitreal dexamethasone implant has also been reported in RM.<sup>36</sup>

### Other Treatments

There are case reports of successful treatment of RR using photodynamic therapy as well as hyperbaric oxygen and oral pentoxifylline.<sup>37–39</sup> Advanced PRR complicated by vitreous hemorrhage and/or tractional retinal detachment may require pars plana vitrectomy for removing blood and reattaching the retina.<sup>40</sup>

### Prognosis

Mild NPRR, characterized by subtle capillary dropout and occasional microaneurysms may not significantly affect vision and could remain

stable for years. Patients with advanced RM and PRR can present with markedly decreased vision. In the COMS, it was estimated that 43% of patients would have a visual acuity of 20/200 or less 3 years after plaque radiotherapy.<sup>41</sup> In an analysis of 1106 eyes with uveal melanoma treated with plaque radiotherapy, Shields et al. found loss of visual acuity ( $\geq 5$  Snellen lines) in 33% of eyes at 5 years and 69% at 10 years.<sup>42</sup> A later analysis by the same group for 354 large melanomas (tumor thickness  $> 8$  mm), revealed visual acuity of 20/200 or worse in 57% of the eyes by 5 years and 89% by 10 years.<sup>43</sup>

## RADIATION PAPILLOPATHY

Radiation papillopathy (RP) or radiation optic neuropathy, similar to RR, may be seen after both brachytherapy and teletherapy. Interestingly, almost all patients who suffer from acute RP have accompanying RR, especially RM.

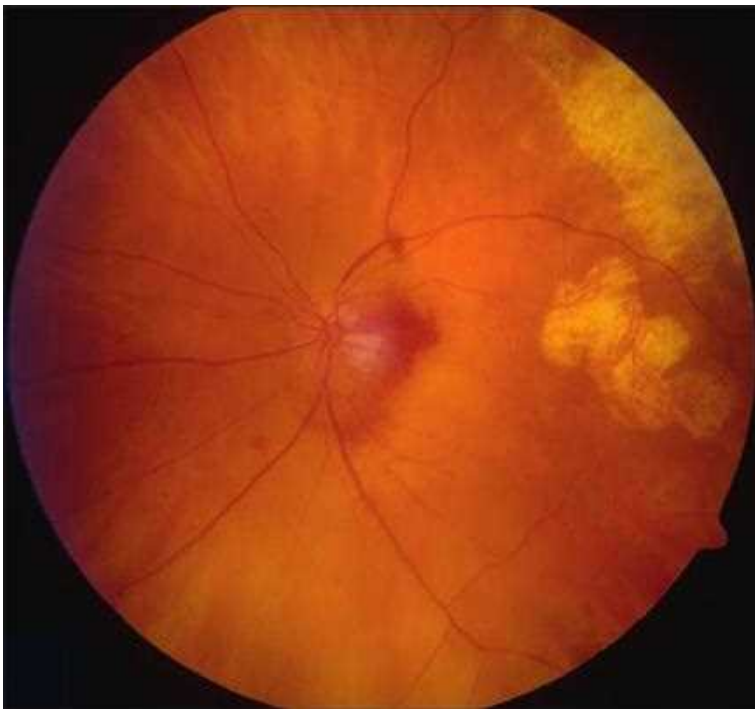
### Pathology and Pathogenesis

Radiation injury includes both vascular and neuropathic effects.<sup>4</sup> The creation of radiation-induced free radicals affects both the vascular endothelial cells and neuroglial cells. The induction of genetic mutations in glial cells by ionizing radiation can lead to demyelination and necrotic degeneration.<sup>4</sup> Comorbidities, including diabetes mellitus, and concurrent chemotherapy are risk factors that increase the severity of disease. The dose of radiation and latent period for the development of RP are similar to those for RR. RP usually develops with optic disc doses above 60 Gy and fraction size  $> 2$  Gy.<sup>44</sup>

### Clinical Features

RP presents with disc hyperemia, disc swelling, peripapillary edema, hard exudates, hemorrhage, and nerve fiber layer infarcts in the acute phase (Figs. 6.26.6 and 6.26.7). Rarely, RP can present with a central retinal vein occlusion secondary to disc edema. Optic nerve head swelling can persist for weeks or months but eventually leads to optic atrophy. This pattern of presentation simulates an anterior ischemic optic neuropathy. However, other rare cases of radiation optic nerve damage may simulate posterior ischemic optic neuropathy. These cases present with decreased visual acuity and relatively normal appearance of the fundus in the early stages, with optic atrophy developing later. This latter presentation usually occurs after teletherapy of the eye or adjacent structures. Because the optic nerve is confined within the scleral canal and dura, RP-associated exudative





**Fig. 6.26.6** Radiation papillopathy following plaque radiotherapy for choroidal melanoma showing disc edema, telangiectasia, and hemorrhage. Note the adjacent retinopathy with vascular thinning and dilation along the superotemporal vessels.

vasculopathy and edema occur within a confined space and lead to a visually devastating course. Some cases of RP may be associated with disc neovascularization that apparently arises from regional ischemia.<sup>45</sup>

## Diagnostic Studies

FA demonstrates that the optic disc and surrounding retinal areas are hypofluorescent in the early phase. In the late phase, there is usually leakage over the optic nerve. These findings can be explained on the basis of vascular incompetence leading to capillary closure and leakage. Preliminary data show that OCT can be used in the diagnosis and follow-up of patients with RP with features of optic disc swelling, increased optic disc thickness, and decreased peripapillary retinal thickness.<sup>46</sup> OCTA may show abnormal vessels on the optic disc. Decreased amplitudes and increased latency can be seen on flash visual evoked potential testing.

## Differential Diagnosis

RP should be differentiated from all causes of optic nerve swelling including nonarteritic optic neuropathy, arteritic (giant cell) optic neuropathy, optic neuritis, tumor invasion of the optic nerve, and papilledema.

## Treatment

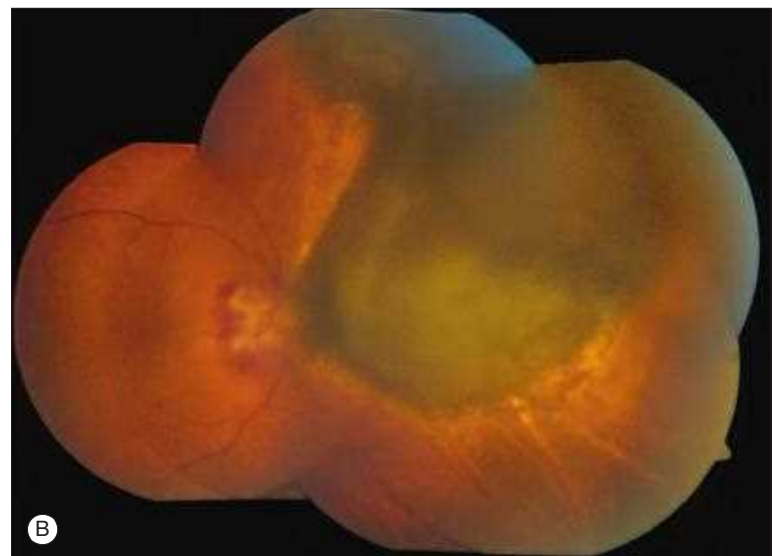
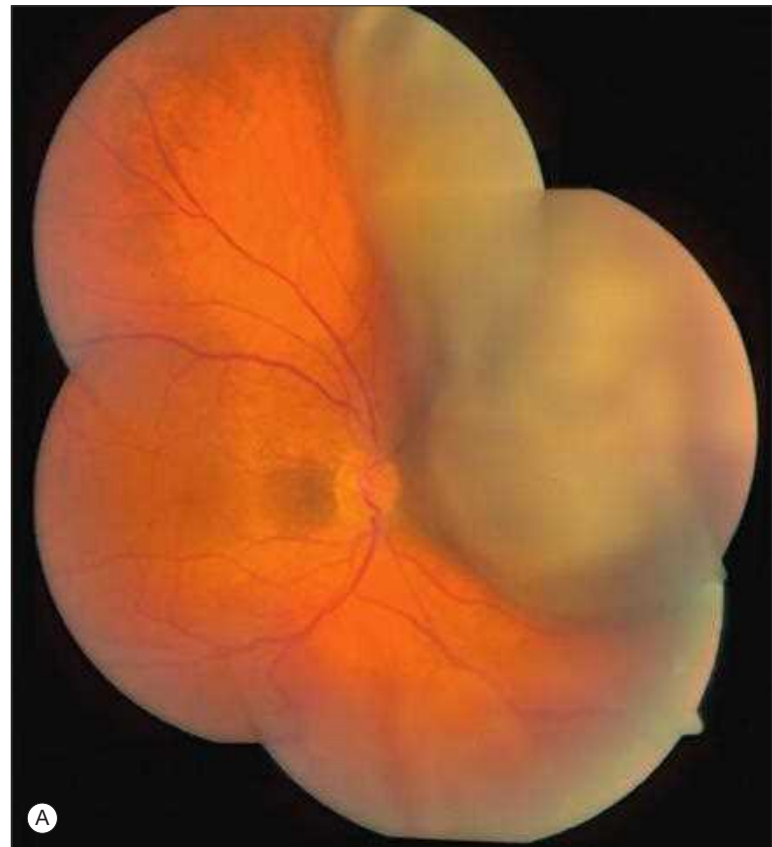
There is no proven effective treatment for RP. It is usually managed with only observation. In rare cases, oral corticosteroids may be helpful to decrease pain and degree of visual loss resulting from RP. Shields et al. used intravitreal injection of 4 mg/1 mL triamcinolone acetonide, given 4 months apart, to treat acute RP.<sup>47</sup> Those authors concluded that intravitreal triamcinolone acetonide was effective in the short term to save and, in some cases, modestly improve vision. Finger and Chin reported that intravitreal injections of bevacizumab (1.25 mg/0.05 mL) given every 6–8 weeks lead to improved vision and reduced hemorrhage and disc edema in RP.<sup>45</sup>

## Prognosis

RP generally has a poor visual outcome. Vision loss is characteristically severe with hand motions to no light perception. However, there are examples of spontaneous improvement in vision in some cases.<sup>48</sup>

## SUMMARY

RR and RP may develop after radiation exposure of any type and have characteristic fundusoscopic features. FA, OCT, and OCTA are currently the



**Fig. 6.26.7** Large-sized choroidal melanoma in the nasal quadrant of the right eye (A) before treatment. After plaque radiotherapy (B), the melanoma has regressed and radiation papillopathy with disc edema and hemorrhage is noted.

most helpful studies that aid in early diagnosis, treatment planning, and subsequent follow-up. For RR treatment, laser photocoagulation and intravitreal injections of anti-VEGF medications or triamcinolone acetonide are used. Prophylactic treatment before development of RR and RM leads to better prognosis for vision. Intravitreal injections of the above drugs can also be used for RP, although in most cases little benefit in visual acuity has been demonstrated.

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# Proliferative Retinopathies

Jeevan R. Mathura, Jr., Srilaxmi Bearely, Lee M. Jampol

6.27

**Definition:** A heterogeneous group of disorders with preretinal and optic disc neovascularization.

## Key Features

- Retinal new blood vessels.
- Optic disc new blood vessels.

## Associated Features

- Retinal ischemia.
- Retinal capillary nonperfusion.
- Posterior segment inflammation.
- Neoplasia.
- Vitreous hemorrhage and fibrous proliferation.
- Retinal detachment.

## INTRODUCTION

Proliferative retinopathies are diseases associated with preretinal or disc neovascularization (NV).<sup>1</sup> They can be divided into two major categories (Box 6.27.1),<sup>2-6</sup> each with its own subset of hereditary disorders:

- Systemic diseases.
- Localized retinal vascular and ocular inflammatory diseases.

In this chapter, retinal angiogenesis is reviewed, after which an approach for the management of a patient who has posterior segment NV of unknown cause is suggested. Finally, specific entities with retinal NV are described.

## RETINAL ANGIOGENESIS

Evidence suggests that the orderly development and maintenance of the normal retinal vasculature requires the balance of proangiogenic and antiangiogenic factors. Ischemia, inflammation, or neoplasia may upset this balance, resulting in pathological new blood vessel formation (Fig. 6.27.1).<sup>7</sup> Posterior segment NV involves the local upregulation of proangiogenic cytokines.

Animal studies have demonstrated that upregulated vascular endothelial growth factor (VEGF) is an important stimulant for pathological ocular NV. In experimental models, increased expression of VEGF stimulates NV, whereas antagonists of VEGF signaling inhibit NV.<sup>8</sup>

VEGF has been shown to be upregulated by hypoxia. Hypoxia-inducible factor (HIF) is a promoter for VEGF. Hypoxia suppresses ubiquitination of HIF1 $\alpha$ , which results in increased levels of VEGF.<sup>9</sup> Levels of VEGF are elevated in the retina and vitreous of patients and animals with ischemic retinopathies.<sup>10</sup> VEGF antagonists, such as bevacizumab<sup>11</sup> and ranibizumab,<sup>12</sup> have been shown to cause regression of new vessels. Aflibercept, an antagonist of VEGF and placental growth factor (PGF), is being investigated and now widely used for this indication.<sup>13</sup> This potentially could demonstrate increased efficacy as PGF may be important in the development of proliferative retinopathies.<sup>14</sup>

NV has the potential to cause loss of vision because the new vessels are fragile and rupture easily. Patients may develop vitreous hemorrhage, fibrovascular scarring, epiretinal membranes (ERMs), and retinal traction, which can lead to both rhegmatogenous and tractional retinal detachments (TRDs). Early detection of NV and appropriate treatment may minimize the risks of these complications.

## BOX 6.27.1 Retinal Neovascularization

### Systemic Diseases

- Diabetes mellitus
- Hyperviscosity syndromes
- Aortic arch syndromes and ocular ischemic syndromes
- Carotid-cavernous fistula
- Multiple sclerosis
- Retinal vasculitis
- Systemic lupus erythematosus
- Arteriolitis with SS-A autoantibody
- Acute multifocal hemorrhagic vasculitis
- Vasculitis resulting from infection
- Vasculitis resulting from Behçet's disease
- Sarcoidosis
- Coagulopathies

### Systemic Diseases With a Strong Hereditary Component

- Sickling hemoglobinopathies
- SC, SS, S $\beta$ -thalassemia, SO Arab
- Other hemoglobinopathies
- AC and C- $\beta$  thalassemia
- Small-vessel hyalinosis
- Incontinentia pigmenti
- Familial telangiectasia, spondyloepiphyseal dysplasia, hypothyroidism, neovascularization, and tractional retinal detachment

### Retinal Vascular and Ocular Inflammatory Diseases

- Eales' disease
- Retinal artery or vein occlusion
- Frosted branch angiitis<sup>2</sup>
- Idiopathic retinal vasculitis, aneurysms, and neuroretinitis<sup>3</sup>
- Retinal embolization (e.g., talc)
- Retinopathy of prematurity
- Encircling buckling operation
- Uveitis, including pars planitis
- Acute retinal necrosis
- Birdshot retinochoroidopathy
- Long-standing retinal detachment
- Choroidal melanoma, choroidal hemangioma
- Cocaine abuse
- Optic nerve aplasia,<sup>4</sup> myelinated nerve fiber layer<sup>5</sup>
- Radiation retinopathy<sup>6</sup>

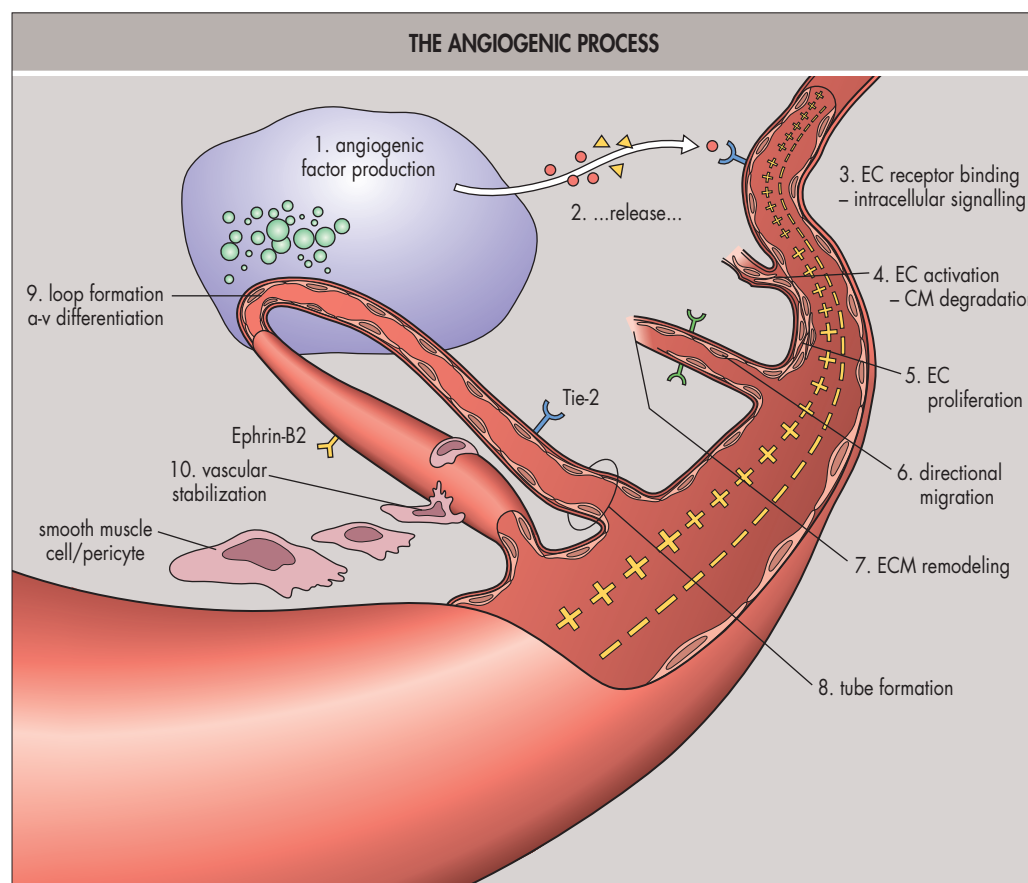
### Retinal Diseases With a Strong Hereditary Component

- Familial exudative vitreoretinopathy
- Inherited retinal venous beading
- Retinoschisis
- Retinitis pigmentosa
- Autosomal dominant vitreoretinopathies

## OVERVIEW OF DIAGNOSING NEOVASCULARIZATION

If the cause of retinal NV is unknown, the physician should obtain a detailed medical, family, birth, and social histories. Diabetes, retinopathy of prematurity (ROP), talc retinopathy, and familial (autosomal dominant, recessive, or X-linked) exudative vitreoretinopathy (FEVR) all are diagnoses that a thorough history will help to uncover. Furthermore, with a detailed review of systems and a family history, disorders can be grouped quickly





**Fig. 6.27.1 Sequence of Events in Angiogenesis.**

Ischemic tissue makes and releases angiogenic factors, which bind to specific receptors on vascular endothelial cells (ECs). This binding activates the ECs, which then proliferate and directionally migrate through remodeled extracellular matrix. These migrating ECs form tubes and then loops, which eventually become stabilized by smooth muscle cells and pericytes.

into one of the categories outlined in [Box 6.27.1](#). Finally, laboratory tests can be directed toward specific disorders suggested by the history and examination. For example, a suspected diagnosis of a hemoglobinopathy may be confirmed by hemoglobin electrophoresis.

Retinal NV can be visualized during ophthalmoscopy and on fundus photography as new vessels above the surface of the retina. In addition to imaging TRDs and ERMs, optical coherence tomography (OCT) can detect retinal NV seen as abnormal tissue in the vitreous, attached to the retina or optic nerve.<sup>15</sup> Fluorescein angiography (FA) is helpful not only for identifying retinal NV but also for delineating areas of ischemia as indicated by capillary nonperfusion. OCT angiography (OCTA) can detect flow in preretinal and optic disc NV and also areas of capillary nonperfusion.<sup>16</sup> This can be performed without the intravenous dye injection needed for FA; however, a smaller field is visualized.

## OVERVIEW OF TREATING NEOVASCULARIZATION

Treatment is given to prevent complications, such as vitreous hemorrhage and retinal detachment. In addition to treatment of the underlying systemic condition, the neovascular tissue itself should be treated by photocoagulation, anti-VEGF therapy, anti-inflammatory therapy, cryotherapy, or vitreoretinal surgery, alone or in combination.

The rationale of treatment is to alter ischemic or inflammatory tissues so that the neovascular stimulus is suppressed,<sup>17</sup> this is usually accomplished by laser in the range of 532–577 nm to create retinal burns. In general, laser spots are scattered about 1–2 burn-widths apart in areas of the retina thought to be ischemic. The power and duration settings on the laser are adjusted so that the laser burn appears as a moderate-intensity, gray-white lesion.

If the retinal ischemic process seems to affect the entire retina diffusely, such as in diabetes mellitus, scatter photocoagulation should be placed throughout the peripheral retina (panretinal photocoagulation). Local scatter laser directed to areas of capillary nonperfusion is indicated for some conditions, such as sickle cell retinopathy,<sup>18</sup> incontinentia pigmenti,<sup>19</sup> retinal vein occlusion,<sup>20</sup> and ROP.<sup>21</sup> Direct treatment of vessels flat on the retina that feed or drain neovascular tissue (feeder-vessel coagulation) is effective. However, such treatment has a greater incidence of complications, which include retinal tears or breaks in Bruch's membrane,

compared with scatter treatment. Direct treatment of elevated neovascular tissue is not effective.

When hemorrhages or dense cataracts are present, red or diode laser may be used because these wavelengths penetrate such media better, or the cataract may be removed.

Cryotherapy may be useful if neovascular tissue cannot be treated with laser (e.g., because of a media opacity or the treatment area is very anterior). Similar to the laser, it is applied to peripheral ischemic retina and affects the neovascular tissue indirectly. Alternatively, vitreoretinal surgery is indicated for long-standing vitreous hemorrhage, for repair of rhegmatogenous or tractional retinal detachment, and when epiretinal membrane removal is needed. Removal of the posterior vitreous face also removes the scaffolding for further NV. Furthermore, vitrectomy may remove angiogenic factors affecting the retinal vasculature.

The use of intravitreal injections of anti-VEGF is efficacious, alone or in combination with other modalities, especially if media opacity is present. Treatment with anti-VEGF alone, however, may require visits for injections up to every 4 weeks.<sup>12</sup>

Anti-VEGF treatment has been shown to be efficacious for pediatric proliferative retinal diseases and may require only one injection, but these indications are not standard of care at this time.<sup>22–24</sup>

## ENTITIES ASSOCIATED WITH RETINAL NEOVASCULARIZATION

### Systemic Diseases

#### Diabetes Mellitus

The vast majority of NV from diabetes occurs posterior to the equator ([Fig. 6.27.2](#)). A program of tight blood sugar control helps to prevent the development of neovascularization. (For a more detailed description of diabetic retinopathy, see Chapter 6.22.)

#### Hyperviscosity Syndromes

Patients with certain diseases, such as chronic myelogenous leukemia,<sup>25</sup> essential thrombocytosis, or polycythemia vera, may exhibit dramatic elevations in their leukocyte, platelet, or red blood cell counts, respectively. These elevations increase blood viscosity, which may produce sludging of blood in the peripheral retina. The consequences of this abnormal flow



**Fig. 6.27.2 Diabetes Mellitus.** Large areas of retinal neovascularization seen in a patient who has long-standing insulin-dependent diabetes mellitus.

include venular dilation, perivenous sheathing, capillary dropout, and microaneurysm formation. NV develops at the border of perfused and nonperfused retina.<sup>26</sup>

### Aortic Arch Syndromes and Ocular Ischemic Syndromes

Patients with atherosclerosis that involves the carotid artery or aortic arch, arteritis (e.g., Takayasu's disease), or syphilitic aortic involvement may develop iris, disc, or peripheral retinal NV.<sup>27</sup> Extensive narrowing of the large arteries that supply the eye causes ischemia and subsequent NV. Although both cryotherapy and scatter photocoagulation are helpful, they are less successful in these syndromes than in others, perhaps because the vasoproliferative stimulus is so intense and diffuse within the eye (see Chapter 6.23). Interventions, such as carotid endarterectomy, may improve perfusion to the retina resulting in regression of the neovascularization.<sup>28</sup>

### Carotid–Cavernous Fistula

In a carotid–cavernous fistula, carotid arterial blood enters the cavernous sinus venous system directly, bypassing the eye, and consequent ischemia may stimulate retinal NV.<sup>29</sup>

### Multiple Sclerosis

Patients with multiple sclerosis may develop uveitis, peripheral retinal venous inflammatory sheathing (Rucker's sign), or arteriolar sheathing, which occurs less frequently. If the vasculitis affects perfusion, ischemia and NV may ensue.<sup>30</sup>

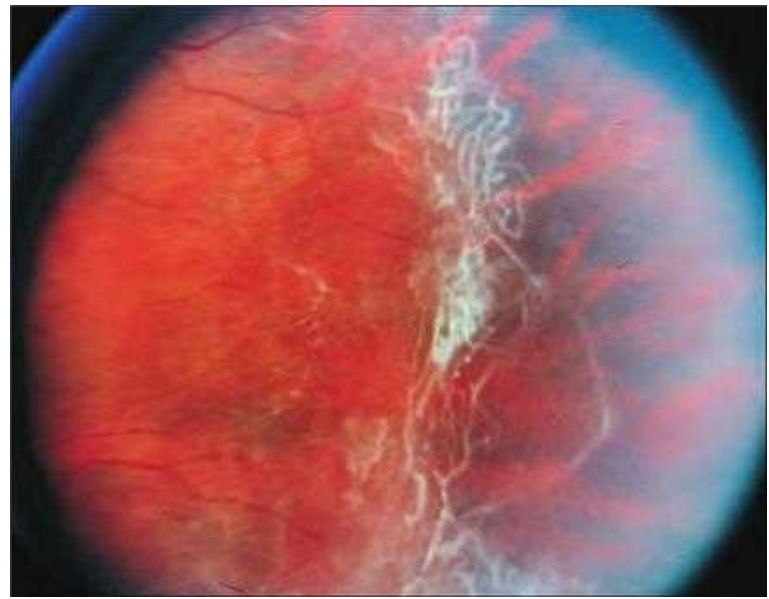
### Retinal Vasculitis

NV may result from ocular inflammation. The neovascular signal may be from ischemia, as blood flow is impaired, or induced by the inflammatory response. Specific vasculitic entities that cause retinal neovascularization include systemic lupus erythematosus (SLE),<sup>31</sup> arteriolitis with SS-A autoantibody, acute multifocal hemorrhagic vasculitis, and vasculitis that occurs with infection (e.g., herpesviruses, *Toxoplasma*, and cytomegalovirus<sup>32</sup>).

In SLE, vascular proliferation may occur despite normal antinuclear antibody (ANA) or complement levels. Patients who have a constellation of findings that resemble SLE and whose blood studies are ANA negative and SS-A autoantibody positive also may develop proliferative changes. Patients affected by acute multifocal hemorrhagic vasculitis have decreased visual acuity, retinal hemorrhages, posterior retinal infiltrates, vitritis, and papillitis, and they also may develop retinal NV.<sup>33</sup> Treatment of the underlying vasculitis with anti-inflammatory agents or immune suppression may be beneficial.

### Sarcoidosis

Sarcoidosis is an idiopathic granulomatous disorder that affects multiple organ systems. The ocular manifestations are disparate and include uveitis with periphlebitis. Inflammation may stimulate NV either by the direct liberation of an angiogenic stimulus or indirectly by blocking blood flow, which results in ischemia.<sup>34</sup>



**Fig. 6.27.3 Incontinentia Pigmenti.** The peripheral retina of a patient who has incontinentia pigmenti demonstrates somewhat elevated vessels with white vessel walls. The majority of these vessels show nonperfusion. The more posterior retina was perfused, and the anterior retina was ischemic.

## Systemic Diseases That Have a Strong Hereditary Component

### Hemoglobinopathies

In sickling hemoglobinopathies, erythrocytes can assume the shape of an elongated crescent or sickle. Point mutations result in amino acid substitutions within the hemoglobin molecule that change its tertiary structure under conditions of low oxygen tension, acidosis, or hypercapnia. These abnormally shaped erythrocytes become trapped in precapillary arterioles or capillaries and disrupt circulation. Common tissues affected are those of the spleen, bones, lungs, and eyes. These diseases are highly prevalent among people of Mediterranean, African, Indian, and Saudi Arabian ancestries.

Sickling of erythrocytes and changes of the vascular endothelium in the retinal periphery result in capillary nonperfusion. Ischemic signals lead to peripheral NV that takes the shape of a sea fan, a type of coral.<sup>35</sup> Although the term *sea fan* is associated with sickle cell retinopathy most commonly, almost any type of peripheral retinal NV may assume this configuration. Investigations of angiogenic factors in proliferative sickle cell retinopathy have demonstrated VEGF and basic fibroblast growth factor to be associated with sea fan formations.<sup>36</sup>

The likelihood of NV depends on the type of hemoglobinopathy. For example, patients who have hemoglobin SC disease are 10 times more likely to develop peripheral NV compared with patients affected by hemoglobin SS disease. This difference may be partly secondary to the higher hematocrit and blood viscosity in hemoglobin SC disease.

Loss of vision can occur if fragile neovascular tissue hemorrhages into the vitreous. With repeated hemorrhages and vitreous degeneration, fibrovascular elements of the vitreous may exert traction on the retina, and tractional or rhegmatogenous retinal detachment may ensue. Fibrovascular proliferation or nonvascular epiretinal membranes that affect the macula can degrade vision by the formation of macular pucker or macular holes. Hemoglobinopathies other than sickle cell disease, such as AC and C- $\beta$  thalassemia, rarely may cause peripheral retinal NV.

### Incontinentia Pigmenti

Incontinentia pigmenti is a rare X-linked dominant disorder that tends to be lethal for male fetuses in utero, so nearly all affected patients are female. Patients have dermatological, neurological, dental, and ophthalmological findings.

One third of patients with incontinentia pigmenti have ophthalmological findings, including cataracts, strabismus, optic atrophy, and foveal hypoplasia. The peripheral retinal vasculature often is poorly developed (Fig. 6.27.3), and at the junction of normal and abnormal vasculature, arteriovenous anastomoses, microvascular anomalies, and neovascularization may develop.<sup>37</sup> Vitreous hemorrhage, retinal tears, and retinal detachment may ensue. Although a predilection for peripheral involvement of

vascular changes is well established, the posterior pole can be affected by similar findings. NV has been treated effectively in some cases by using cryopexy or laser.

## Retinal Vascular and Ocular Inflammatory Diseases

### Eales' Disease

Strictly defined, Eales' disease is an exclusively bilateral disorder of young (20–45 years old), otherwise healthy adults most commonly noted in developing countries (especially India). These patients have periphlebitis and develop peripheral retinal capillary nonperfusion, often superotemporally. The etiology remains unknown. Hypersensitivity to tuberculin protein has been reported; however, no clear relationship to tuberculosis has been found. The designation of Eales' disease sometimes is used for any patient who has peripheral NV and no clinical or laboratory features that identify another specific entity.

The principle that neovascularization occurs at the border of perfused and nonperfused retina applies to Eales' disease.<sup>38</sup> Scatter photocoagulation of ischemic retina has been shown to cause regression of neovascular tissue, presumably by a modulation of the ischemic signal for NV. Direct feeder-vessel treatment also has been used. The phlebitis responds to systemic or ocular corticosteroid therapy. Overall, the visual prognosis in Eales' disease is good, although patients may develop complications, such as vitreous hemorrhage, tractional or rhegmatogenous retinal detachment, rubeosis irides, secondary glaucoma, or cataract.

### Retinal Vein Occlusion

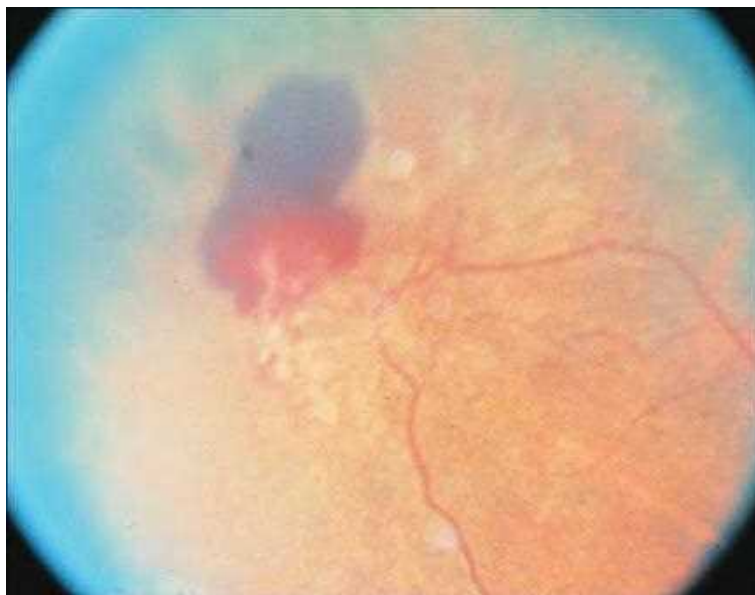
Retinal neovascularization can occur with branch retinal vein occlusion.<sup>39</sup> Complications include vitreous hemorrhage, epiretinal membranes, and tractional or rhegmatogenous retinal detachments (see Chapter 6.20: Venous Occlusive Disease of the Retina).

### Retinal Embolization

Drug abusers who intravenously inject chopped pills that contain talc may develop retinal NV.<sup>40</sup> The talc reaches the ocular arterial system after passage through capillaries or collaterals in the pulmonary vascular system. The talc wedges in smaller-caliber arterioles, such as those found in the macula and retinal periphery. Ischemia and neovascularization may ensue (Fig. 6.274).

### Retinopathy of Prematurity

ROP affects the peripheral vasculature of the retina. Normal vascularization of the retina commences at 4 months' gestation and usually is completed by 9 months. In some instances of low birth weight, prematurity, and supplemental administration of oxygen, the normal process of vascularization is interrupted. How this occurs is poorly understood, but it is



**Fig. 6.274 Talc Retinopathy.** An area of sea fan neovascularization with a small overlying vitreous hemorrhage is shown in an intravenous drug abuser. Talc retinopathy is demonstrated elsewhere in the fundus.

thought that hyperoxia from supplemental oxygen may further interrupt normal vascular development and that hypoxia associated with maturing avascular retina may result in liberation of angiogenic stimuli. Some infants progress to NV and its complications, which include tractional, exudative, or rhegmatogenous retinal detachment (see Chapter 6.21: Retinopathy of Prematurity).<sup>41</sup>

The presence of risk factors for ROP must trigger careful examination and follow-up. Treatment helps preserve an attached macula (see Chapter 6.21).

### Uveitis

Some patients with uveitis, especially intermediate uveitis and pars planitis, develop NV of the disc or peripheral retina. Uveitic NV appears to be determined by the severity of inflammation and presence of retinal nonperfusion (see Part 7: Uveitis and Other Intraocular Inflammations).<sup>42</sup>

### Acute Retinal Necrosis

Both herpes simplex and herpes zoster cause the acute retinal necrosis syndrome, with findings that include anterior uveitis, vitritis, retinal vasculitis, necrotizing retinitis, and retinal detachment. The inflammation and ischemia may stimulate vascular proliferation (see Part 7: Uveitis and Other Intraocular Inflammations).<sup>43</sup>

### Birdshot Chorioretinopathy

Birdshot chorioretinopathy is characterized by white lesions in the choroid, and by vitritis, papillitis, and macular edema. Closure of peripheral retinal vessels may lead to vasoproliferation (see Part 7: Uveitis and Other Intraocular Inflammations).<sup>44</sup>

### Long-Standing Retinal Detachment

Retinal ischemia in a patient who has a prolonged retinal detachment may result from disruption of either the retinal or choroidal supply of oxygen or nutrients to the retina. The NV may appear angiomatous or may take the shape of a sea fan. Surgical repair of a rhegmatogenous detachment can cause regression of the neovascularization.<sup>45</sup>

### Choroidal Melanoma and Hemangioma

Choroidal melanoma<sup>46</sup> and hemangioma,<sup>47</sup> perhaps by the release of a tumor angiogenic factor or secondary to retinal detachment over the tumor, can promote neovascularization that overlies the tumor. Treatment of a choroidal melanoma with radiation or scatter photocoagulation can cause regression of the neovascularization. (Ocular tumors are covered in Part 8.)

## Hereditary Retinal Diseases

### Familial Exudative Vitreoretinopathy

FEVR is a group of vascular disorders of the peripheral retina with findings on retinal examination that are very similar to those of ROP. However, FEVR differs from ROP in that patients usually are born at full term, have normal birth weight, and have not had supplemental oxygenation. In addition, a positive family history often is found. A demarcation line that separates vascular retina from avascular retina may occur in the retinal periphery. Peripheral retinal vessels assume a characteristic straightened course.

Presumably, an ischemic signal from the avascular retina stimulates NV. These vessels may leak, form intraretinal or subretinal exudates, and result in exudative retinal detachment. Some eyes develop cicatricial changes, which include straightened retinal vessels, foveal ectopia, meridional folds, or tractional or rhegmatogenous retinal detachment. Other complications include cataract, band keratopathy, rubeosis iridis, neovascular glaucoma and, in some eyes, phthisis bulbi.<sup>48</sup> As in ROP, treatment depends on early recognition.

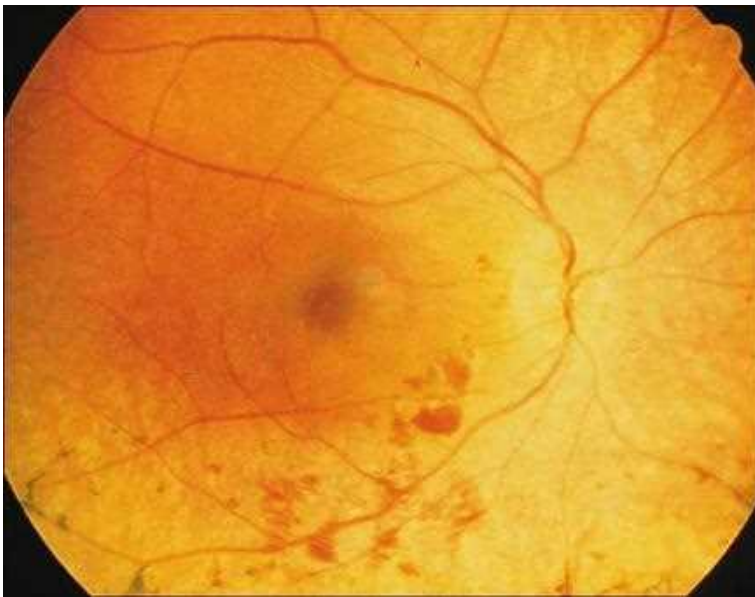
### Inherited Retinal Venous Beading

This rare entity has an autosomal dominant inheritance pattern. Findings include venous beading, microaneurysms, hemorrhages, exudates, NV, and vitreous hemorrhage.<sup>49</sup>

### Retinoschisis

Patients who have X-linked (juvenile) retinoschisis, degenerative retinoschisis, or acquired retinoschisis with shaken baby syndrome<sup>50</sup> can develop retinal NV. In X-linked retinoschisis, whitish deposits may be seen at the point where peripheral vessels appear to be occluded. Consequent to vascular occlusion, ischemia may promote NV.<sup>51</sup>





**Fig. 6.27.5 Retinitis Pigmentosa.** This fundus view demonstrates neovascularization of the disc, neovascularization elsewhere, and a small vitreous hemorrhage in a patient who has autosomal dominant retinitis pigmentosa.

### Retinitis Pigmentosa

Patients with retinitis pigmentosa can have neovascularization of the disc and retina (Fig. 6.27.5).<sup>52</sup> The pathogenesis of the NV is unknown but may be related to the inflammation seen in this disorder. These patients have diffuse loss of retinal pigment epithelial cells, so laser photocoagulation burns are difficult to create. Treatment of the neovascularization may not

be necessary in these patients as it may spontaneously regress (see Chapter 6.14: Progressive and “Stationary” Inherited Retinal Degenerations).

### Autosomal Dominant Vitreoretinopathy

Autosomal dominant vitreoretinopathy is a rare disorder that manifests as abnormal peripheral chorioretinal pigmentation with a characteristic sharp demarcation near the equator. Patients also may manifest cataract, macular edema, retinal NV, vitreous hemorrhage, and selective b-wave reduction on electroretinography.<sup>53</sup> This entity has been shown to be caused by specific mutations in the BEST1 gene.<sup>54</sup>

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## Retinal Arterial Macroaneurysms

6.28

Ivy Zhu, William F. Mieler, Clement C. Chow

**Definition:** Localized fusiform or saccular dilatation of a retinal arterial vessel within the first three orders of bifurcation.

**Key Features**

- Retinal hemorrhage (subretinal, intraretinal, preretinal, and vitreous).
- Macular edema and lipid exudation.

**Associated Features**

- Leaking, telangiectatic vessels in the capillary bed that surrounds the macroaneurysm.
- May be associated with occlusion of retinal artery or vein.

**INTRODUCTION**

Although aneurysms of the retinal arteries have been noted since the early 1900s, Robertson in 1973 was the first to coin the term “macroaneurysm” to describe a distinct clinical entity that consisted of an acquired focal dilatation of a retinal artery within the first three orders of bifurcation.<sup>1</sup> Macroaneurysms are saccular or fusiform in shape and vary from 100–250 microns in diameter; this differentiates them readily from capillary microaneurysms, which are usually <100 microns in diameter. Retinal arterial macroaneurysms (RAMs) can be further differentiated from the vessel dilatations seen in Coats’ disease, in which multiple saccular outpouchings of predominantly the venous and capillary systems are associated with congenital retinal telangiectasias and lipid exudation and primarily found in young males.

RAMs typically arise, enlarge, and then eventually thrombose, fibrose, and involute. Although the clinical course is most often benign, significant visual morbidity may result from macular hemorrhage, exudate, or edema, or from the development of a vitreous hemorrhage. Thus a typical categorization of RAMs, first provided by Lavin et al., is (1) hemorrhagic—where hemorrhage is the dominant finding, measures >1 disc diameter, and causes loss of visual acuity; (2) exudative—where exudates are the dominant finding, measures >1 cup diameter, and causes loss of visual acuity; and (3) quiescent—where hemorrhage and/or exudate, if it exists, spares the macula and does not lead to loss in visual acuity.<sup>2</sup>

**EPIDEMIOLOGY AND PATHOGENESIS**

The prevalence of RAMs ranges from 0.01% to 0.07%.<sup>3,4</sup> Most patients with RAMs are over age 60 years,<sup>5–9</sup> and RAMs occur predominantly in females (60%–100%).<sup>5–10</sup> Macroaneurysms typically present in one eye, with bilaterality in <10%.<sup>11</sup> The most consistent association is with systemic hypertension—a large controlled study reported it in 79% of patients with RAMs.<sup>9</sup> Less commonly, RAMs may be part of a known syndrome, such as idiopathic retinal vasculitis, aneurysms, and neuroretinitis (IRVAN) syndrome, or inherited as seen in familial retinal arterial macroaneurysms (FRAMs).<sup>12–14</sup>

The exact pathogenesis of a macroaneurysm is unknown, but several theories exist. Some compare RAMs to cerebral arterial aneurysms, which are generally 100–300 microns in diameter, are also more common in women, and occur in patients age >50 years with a history of hypertension.<sup>1,2,15</sup> Chronic hypertension, along with the replacement of arterial smooth muscle by collagen in aging, may effect a focal dilatation of the arterial wall in an area of weakness or prior damage. Lavin et al. postulated that macroaneurysms are detected more frequently at arteriovenous

crossings because at these locations the arterial and venous walls are in contact without an adventitial layer, which results in an area of limited structural support.<sup>2</sup> Other investigators have noted the development of macroaneurysms at the sites of previously detected emboli.<sup>7,16</sup> They hypothesized that focal arterial damage secondary to embolization can lead to aneurysm formation. However, Gass proposed that the focal, yellow arterial plaques, often present at these sites of previously reported emboli, are most likely atheromas.<sup>17</sup>

There may be differences between the RAMs that lead to hemorrhagic complications and those that result in lipid exudation.<sup>8</sup> Saccular or “blowout” aneurysms are more prone to bleed, possibly as a result of a thin, stretched aneurysmal sac. These develop closer to the optic nerve head, where perfusion pressures are higher.<sup>2</sup> Additionally, systolic blood pressures above 200 mm Hg are more common in patients who have bleeding macroaneurysms. Fusiform dilatations, however, are more prone to exudation and to be associated with venous occlusions.<sup>2,8</sup> It is also possible that the cause of those aneurysms that eventually lead to hemorrhagic complications is more dependent on hypertension and vessel wall damage, while the cause of those that lead to exudation is more contingent on local vascular factors.

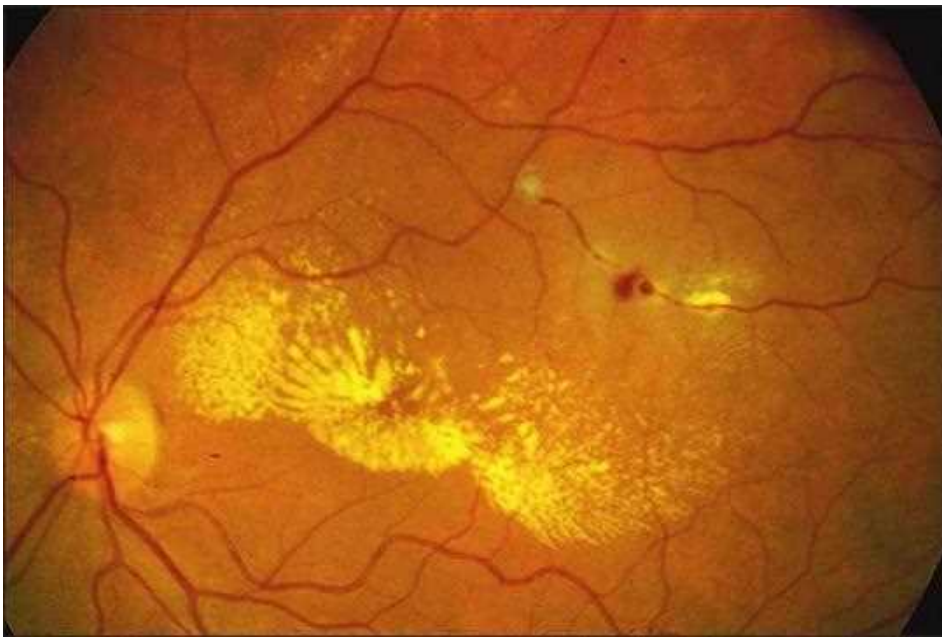
**OCULAR MANIFESTATIONS**

Hemorrhagic macroaneurysms can result in acute loss of vision with evidence of subretinal, intraretinal, or preretinal hemorrhage on ocular examination (Fig. 6.28.1). Subretinal hemorrhage may be toxic to the retina, and fibrin clot retraction in the submacular space can lead to permanent structural change, affecting central vision. Often the hemorrhage obscures the site of the aneurysm, but the presence of a localized preretinal and subretinal hemorrhage over a major retinal artery should suggest the possibility of its presence. A nonclearing vitreous hemorrhage without evidence of retinal tear or posterior vitreous detachment may be the result of a macroaneurysm. Because bleeding tends to thrombose the aneurysm, once the hemorrhage has cleared, detection may be difficult. The involved artery often retains a focal tortuosity or “Z”-shaped kink at the location of the



**Fig. 6.28.1 Hemorrhagic Macroaneurysm.** Surrounding hemorrhage in the retinal and subretinal space surrounding the artery.





**Fig. 6.28.2 Exudative Macroaneurysm.** Note the extensive leakage from the macroaneurysm located along the superotemporal arcade, with marked lipid exudation that extends into the central macula

previously ruptured aneurysm, which lends indirect evidence in support of the diagnosis.

Patients may present with a more gradual decline in vision secondary to serous fluid and lipid accumulation in the macula (Fig. 6.28.2). Exudative macroaneurysms are most often located on the temporal vascular arcades. In one series, 94.7% of macroaneurysms were in the temporal retina, with an equal distribution between superotemporal and inferotemporal locations.<sup>18</sup> Rarely, macroaneurysms may occur on the optic nerve head, cilio-retinal artery, and nasal vessels.<sup>19,20</sup> They frequently demonstrate a circinate lipid pattern (see Fig. 6.28.2).

Macroaneurysms discovered on routine examination may have only a small (or absent) cuff of hemorrhage and lipid exudation associated with them. Up to 10% of macroaneurysms may be pulsatile on presentation; although some investigators maintain that this shortly precedes rupture, most believe it is of no prognostic significance.<sup>11</sup> Marked, chronic foveal exudate can cause structural and permanent changes and may therefore indicate poor visual outcomes.

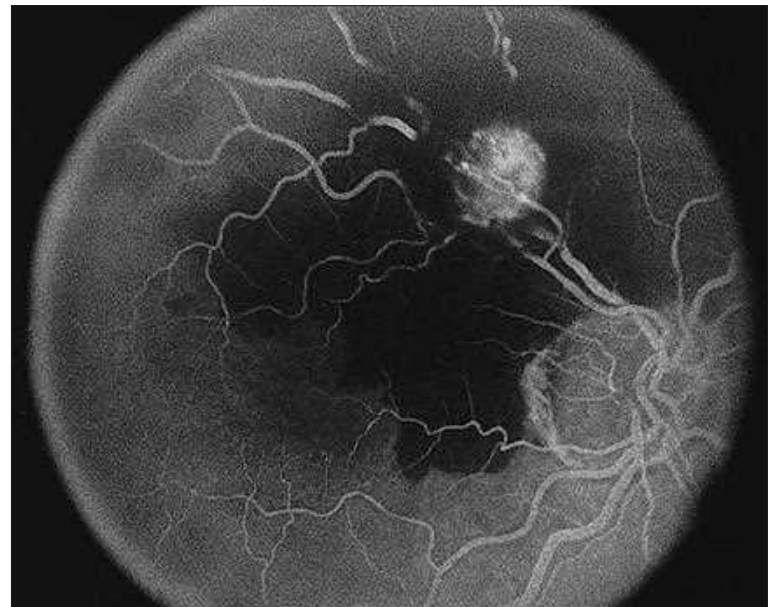
Macroaneurysms may be associated with retinal vein occlusions, often in the artery that serves the vascular territory of the occluded vein.<sup>9</sup> Distal arterial narrowing and arterial occlusion of the involved vessel are common and have been reported to occur in 26% and 8% of cases, respectively.<sup>9</sup> Macular hole formation after macroaneurysm rupture has also been reported.<sup>21–23</sup> In addition, one report documents the development of retinal macroaneurysms in a 62-year-old patient who had a history of congenital arteriovenous communications.<sup>24</sup>

## DIAGNOSIS AND ANCILLARY TESTING

Fluorescein angiography (FA) may reveal the macroaneurysm, usually demonstrating immediate, complete filling of the aneurysm (Fig. 6.28.3). In some cases, irregular and incomplete filling may be associated with partial thrombosis, and a faint shell of fluorescence may be displayed with a completely involuted macroaneurysm.<sup>11</sup> Leakage from the wall of the aneurysm is common in active lesions. Evidence of arteriolar narrowing usually is present proximal and distal to the macroaneurysm.<sup>16</sup> In many cases, microvascular abnormalities surround the aneurysm, including a wider capillary-free zone, capillary dilatation, capillary nonperfusion, microaneurysms, and intra-arterial collateral vessels<sup>16,18</sup> (Fig. 6.28.4).

In cases with dense hemorrhage where FA does not provide definitive evidence of a RAM, indocyanine green angiography (ICGA) can be a useful adjunct.<sup>25</sup> Because the absorption and emission spectra are in the near-infrared range, the dye can better penetrate through dense hemorrhages, revealing structures that may otherwise be obscured. Additionally, in treatment of a macroaneurysm, the ICG dye may leak less than fluorescein, thus providing well-defined images.<sup>25</sup>

There has been an increase in the role of optical coherence tomography (OCT) in the assessment and treatment of RAMs. Traditionally, it has been used to assess for the presence of macular edema and serous detachment, as well as to monitor response to treatment.<sup>26</sup> In eyes with untreated, active RAMs, OCT shows a round inner retinal lesion, which has a thick



**Fig. 6.28.3 Hemorrhagic Macroaneurysm.** Fluorescein angiography demonstrating complete early filling of the macroaneurysm with fluorescein dye, and surrounding blockage from the hemorrhage.

hyperreflective wall with a dark lumen<sup>27</sup> (Fig. 6.28.5). After laser photocoagulation, OCT shows hyperreflectivity in the lumen of the macroaneurysms, indicating thrombus formation.<sup>27</sup> Superficial retinal hemorrhage, intraretinal lipids, and intraretinal edema predominantly involving the outer retinal layers can also be seen associated with macroaneurysms.<sup>27,28</sup>

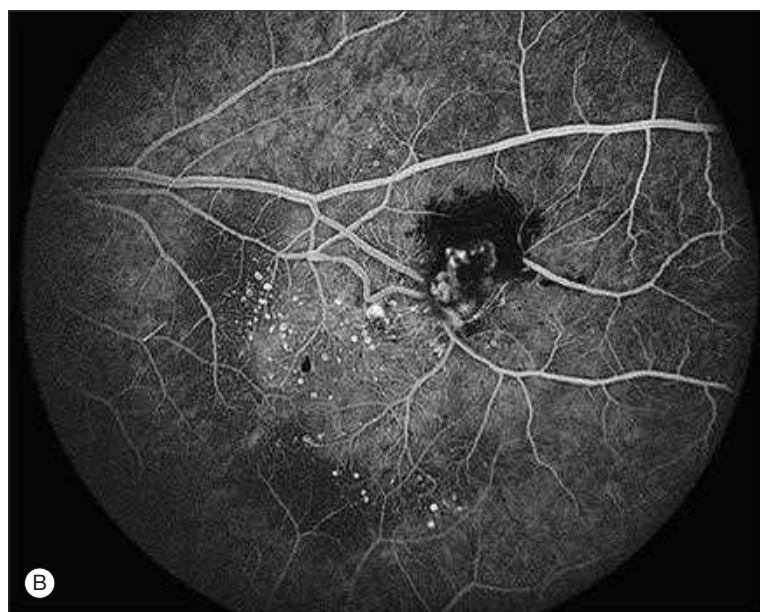
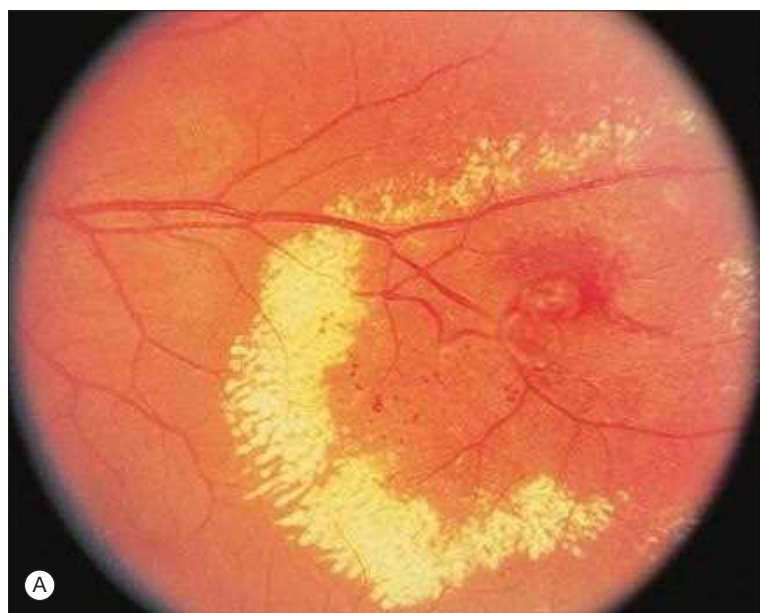
OCTA may provide a noninvasive alternative for high-resolution visualization of these lesions before and after laser treatment. In a case series of three patients with RAMs, OCTA (with or without traditional OCT) was able to localize the depth of the lesion and provide dynamic information on blood flow in different retinal layers.<sup>29</sup>

## DIFFERENTIAL DIAGNOSIS

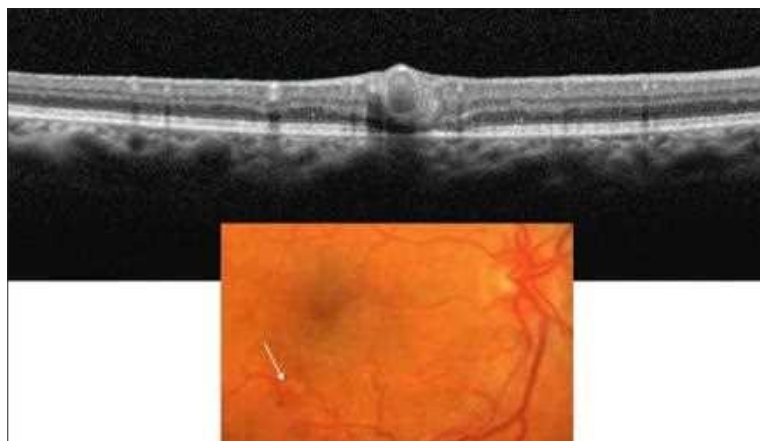
Large-capillary aneurysms secondary to retinal venous obstruction may simulate RAMs.<sup>30,31</sup> In the Branch Vein Occlusion Study,<sup>32</sup> four types of aneurysms were found in the area of the vein occlusion: arterial, capillary, venous, and associated with collaterals. Other similar-appearing conditions include:

- Retinal telangiectasia of Coats' disease<sup>10</sup> (Fig. 6.28.6).
- Capillary hemangiomas of the retina.<sup>33</sup>
- Acquired nonfamilial angiomas, along with vasoproliferative tumors.<sup>34,35</sup>
- Choroidal neovascular membrane from age-related macular degeneration (Fig. 6.28.7); IRVAN (idiopathic retinal vasculitis, aneurysms, and

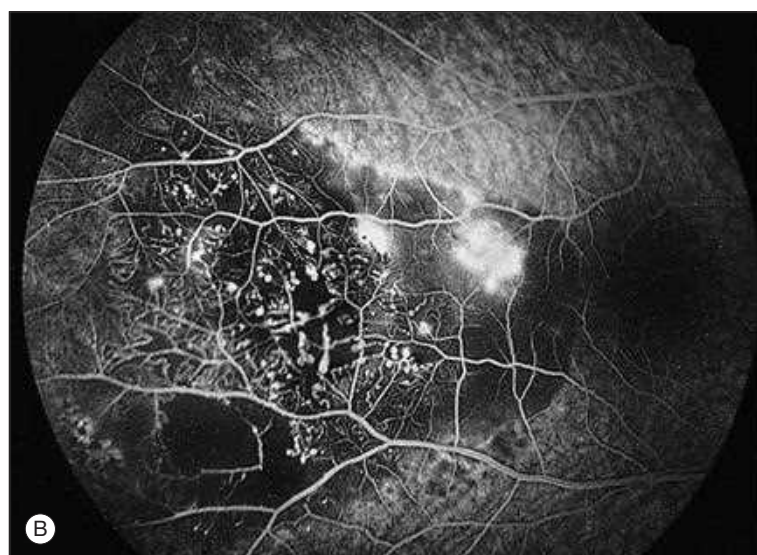
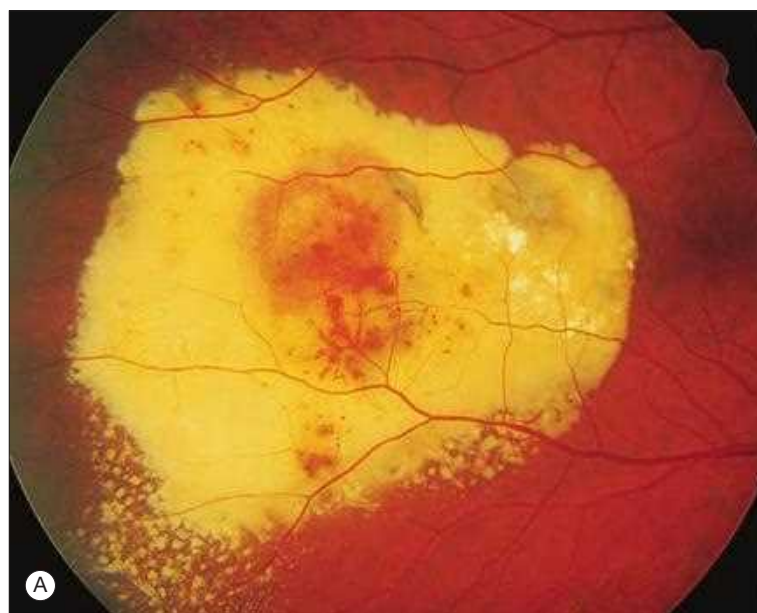




**Fig. 6.28.4 Macroaneurysm With Surrounding Dilated, Telangiectatic Capillary Bed.** (A) A large bilobed macroaneurysm with surrounding circinate lipid. (B) Fluorescein angiography demonstrates dilated, tortuous capillaries and microaneurysms surrounding the macroaneurysm. (Courtesy Susan Fowell, MD.)



**Fig. 6.28.5** Spectral-domain optical coherence tomography (SD-OCT) scan of a macroaneurysm, located inferotemporal to the macula reveals a round inner retinal lesion.



**Fig. 6.28.6 Retinal Telangiectasis (Coats' Disease).** (A) Classic appearance of Coats' disease with massive lipid exudation and resultant exudative retinal detachment. (B) Fluorescein angiography documents large telangiectatic vessels and numerous leaking aneurysms.

neuroretinitis) syndrome (Fig. 6.28.8)<sup>12,15,36,37</sup>; familial retinal artery macroaneurysms (FRAMs).<sup>13,14</sup>

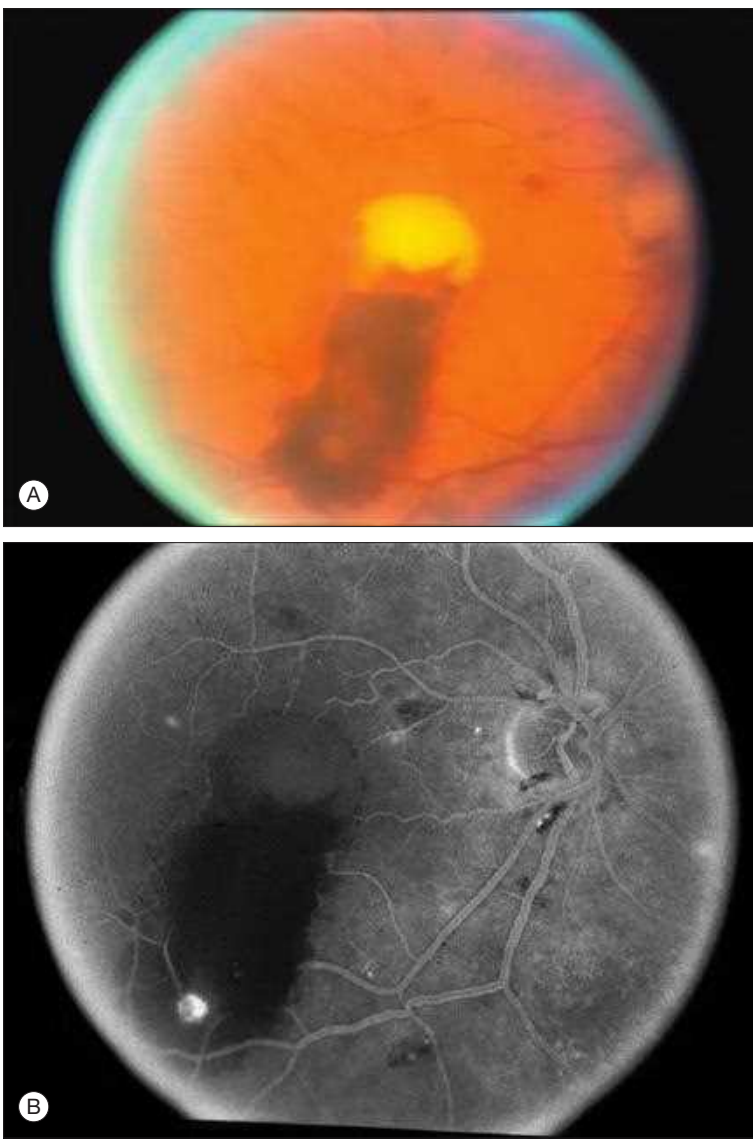
## SYSTEMIC ASSOCIATIONS

The only consistent systemic association with RAMs is systemic arterial hypertension. In a case-control series, 79% of patients with macroaneurysms were found to have hypertension compared with 55% of controls—a statistically significant difference.<sup>9</sup> The evaluation of a patient with a macroaneurysm but no previous history of hypertension should include a workup for hypertension and possibly an additional cardiac workup.<sup>18</sup>

## PATHOLOGY

Gold et al. described a pathological specimen from a patient with a single macroaneurysm and a large ring of circinate lipid in the macula.<sup>38</sup> The macroaneurysm was located at an arteriovenous crossing, surrounded by dilated capillaries and a heterogeneous accumulation of collagen, hemosiderin, and lipid, with a paramacular deposition of lipid and proteinaceous exudate in the outer plexiform layer. It was proposed that the dilated capillary network surrounding the macroaneurysm was the source of serous and lipid exudation into the macula. Other reports of ruptured aneurysms have shown evidence of a break in the artery covered by a dense fibrin-platelet clot that contains blood, exudate, lipid-laden macrophages, hemosiderin, and fibroglial reaction products in amounts that vary among patients (Fig. 6.28.9).<sup>39</sup>



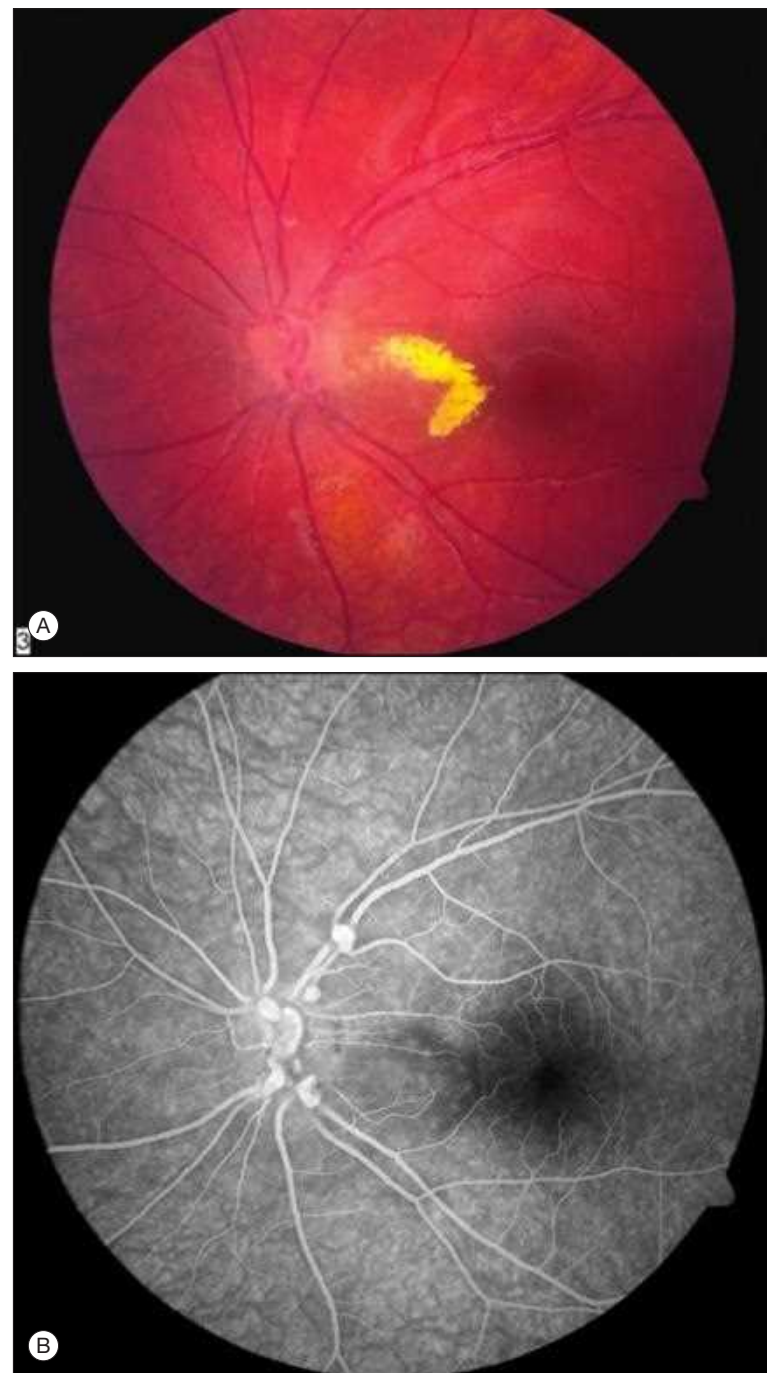


**Fig. 6.28.7 Macular Hemorrhage, Simulating Age-Related Macular Degeneration.** (A) Subretinal and subretinal pigment epithelium (RPE) hemorrhage in the macula and coursing inferiorly. (B) Fluorescein angiography reveals the source of the hemorrhage to be a retinal arterial macroaneurysm.

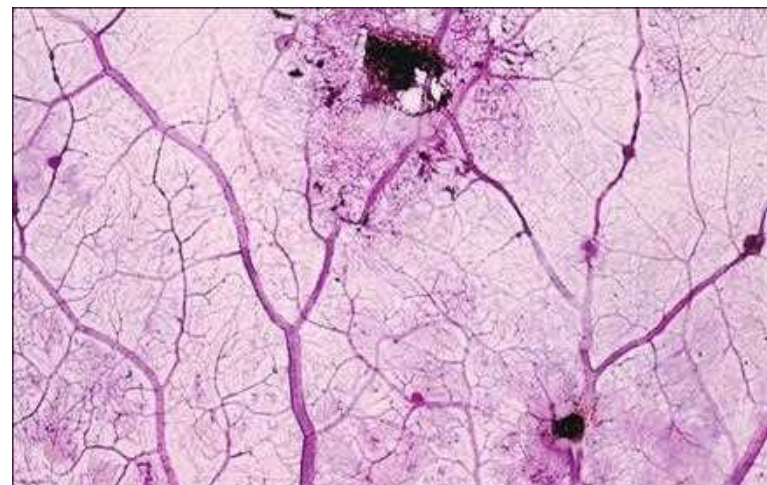
## TREATMENT, COURSE, AND OUTCOME

Hemorrhagic macroaneurysms, especially those that cause vitreous or pre-retinal hemorrhage, tend to thrombose, and ultimately, the visual outcome for patients with these macroaneurysms is better than for those with exudative macroaneurysms, which lead to development of macular edema.<sup>5,6,8,13,40</sup>

Treatments using the xenon arc,<sup>7,8</sup> argon,<sup>2,13,41</sup> and dye yellow<sup>42,44</sup> lasers, both directly at and around the macroaneurysm, have been described, although a laser approach remains controversial. Some investigators believe that patients who have exudative macroaneurysms and significant macular involvement should undergo photocoagulation treatment, either directly to the lesion<sup>7,8,43,44</sup> (Fig. 6.28.10) or to the surrounding capillary bed<sup>13,40</sup> in an effort to close the macroaneurysm and the leaking perianeurysmal vessels. The rationale is that the poorest visual outcomes are observed when macular edema and lipid are allowed to remain for many months. However, no prospective trial of laser treatment for RAMs has been performed, and the several small, uncontrolled clinical series have demonstrated mixed results. Multiple investigators have found no visual benefit to using laser therapy compared with observation, and some have even reported a greater risk for visual decrease with laser therapy.<sup>8,15,41</sup> In contrast, Joondeph et al. reported improvement in visual acuity in 8 of 12 cases with use of the dye yellow laser.<sup>44</sup> Meyer et al. reported that eyes with hemorrhagic RAMs treated with laser compared with controls had greater improvement in visual acuity, whereas there was no difference between the treatment and observation groups in eyes with exudative RAMs.<sup>45</sup> A larger case series of 49 eyes with RAMs showed comparable final visual acuity after 3 years in patients who were untreated, treated with laser, or treated surgically.<sup>46</sup> However, the authors suggested that the equivocal

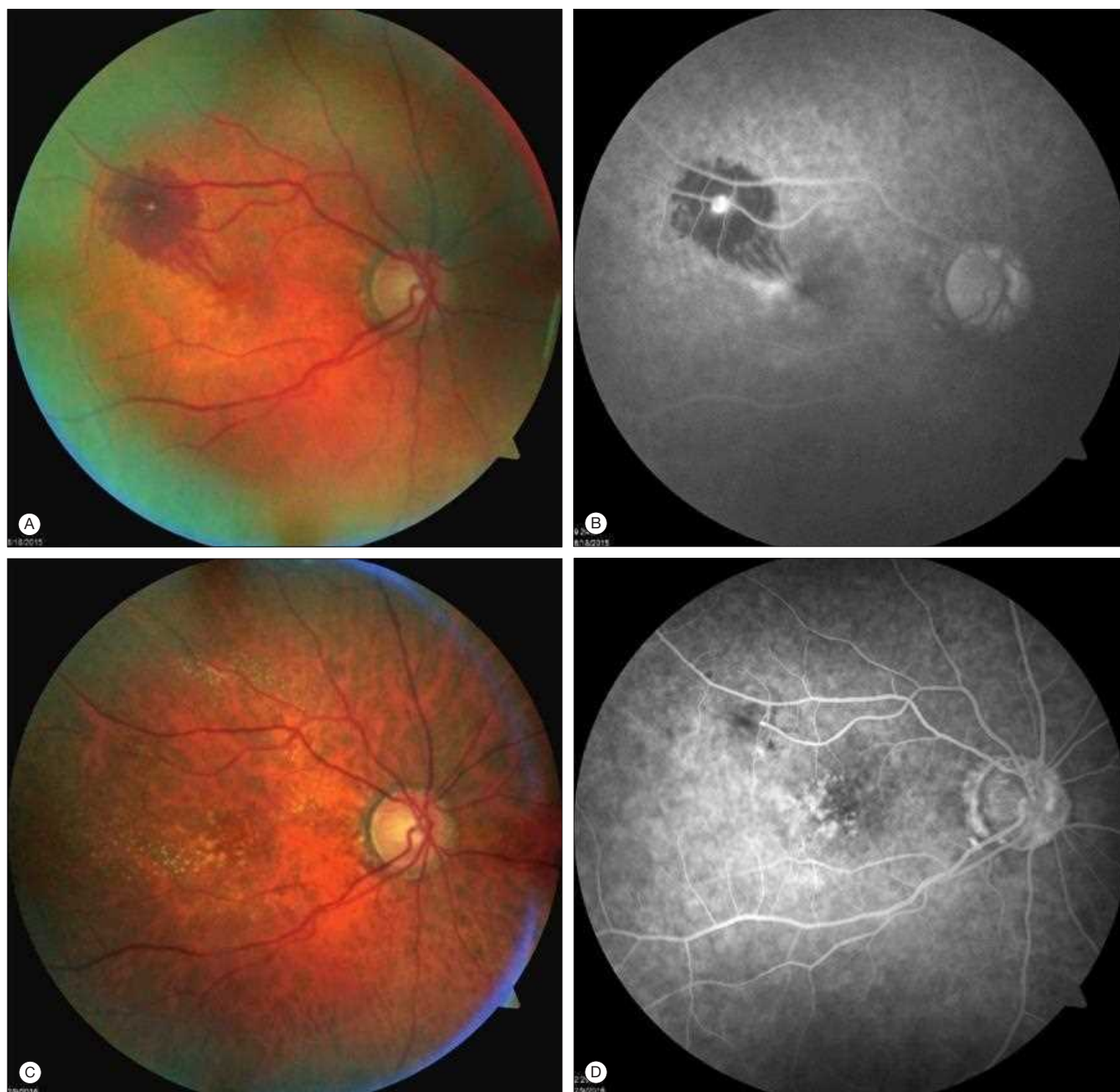


**Fig. 6.28.8 Idiopathic Retinal Vasculitis and Neuroretinitis (IRVAN) Syndrome.** (A) Numerous arterial dilatations on the first order retinal vessels. (B) Fluorescein angiography highlights the arterial dilatations.



**Fig. 6.28.9 Histopathology of a Retinal Arteriolar Macroaneurysm.** Periodic acid-Schiff-stained trypsin-digest preparation. (Courtesy Streeten BW. In: Yanoff M, Fine BS. Ocular pathology, 4th ed. London, UK: Mosby; 1995.)





**Fig. 6.28.10 Hemorrhagic, Mildly Exudative Macroaneurysm.** (A) Superotemporal macroaneurysm, surrounded by hemorrhage, and mild macular edema. (B) Fluorescein angiography shows leakage from the macroaneurysm, and late leakage in the macula as well. (C) Focal laser ablation of the macroaneurysm, combined with an intravitreal injection of bevacizumab. (D) Fluorescein angiography shows occlusion of the superotemporal artery, although still with mild macular edema.

outcomes resulted from individualized disease management, with more severe cases undergoing more invasive treatment. Laser surgery has been associated with an increased threat of arteriolar occlusion, which theoretically may be amplified when using the dye yellow laser.<sup>9,42</sup> Other complications include enlargement of laser scar, choroidal neovascularization, and subretinal fibrosis. Subthreshold laser treatment has been proposed as an alternative to minimize the adverse effects of conventional laser by reducing the duration of laser exposure and by using a subvisible clinical endpoint.<sup>47,48</sup> In a randomized trial, Battaglia et al. compared the effects of subthreshold (810 nm infrared diode laser) and conventional laser (647 nm krypton laser) treatment in 25 patients with symptomatic RAMs associated with macular edema.<sup>47</sup> Both groups achieved similar outcomes with significantly improved visual acuity (from 20/100–20/40), resolution of macular edema, and improved OCT retinal thickness at the 1-year follow-up. Three eyes (23%) in the conventional laser group developed symptomatic epiretinal membrane, whereas the subthreshold group

had no complications. However, until definitive studies are performed to elucidate the role of laser, it should be reserved for select exudative macroaneurysms that threaten the fovea with the progressive accumulation of lipid. When employing conventional laser, argon green, or dye yellow lasers, long-duration burns (0.2–0.5 seconds) and large spot sizes (500 mm diameter) can be used. With subthreshold laser, an infrared diode laser can be used with high power (1400 mW) and short duration (0.3 seconds with duty cycle of 15%).<sup>47</sup>

Intravitreal anti-vascular endothelial growth factor (anti-VEGF) agents, including bevacizumab, ranibizumab, and aflibercept, have also been used off-label to treat macular edema and/or hemorrhages secondary to RAMs (see Fig. 6.28.10).<sup>49–53</sup> A prospective interventional case series of 37 patients showed a statistically significant improvement in visual acuity (20/80–20/25) and central subfield thickness (520–214  $\mu$ m) after 3 monthly intravitreal bevacizumab injections.<sup>53</sup> However, a retrospective case series of 23 eyes, which compared bevacizumab injection with observation,

showed no statistically significant difference in visual acuity or central macular thickness after 3 months, although more rapid improvement was noted in the treatment arm.<sup>54</sup> There are also favorable reports of the use of intravitreal ranibizumab<sup>55-57</sup> and aflibercept.<sup>58</sup> A randomized controlled trial is required to further elucidate the indications for use, beneficial effects, and recommended treatment schedule of anti-VEGF agents, especially because spontaneous improvement is common.

The neodymium:yttrium–aluminum–garnet laser (Nd:YAG) has been employed in the treatment of dense premacular hemorrhage.<sup>59,60</sup> Nd:YAG photodisruption creates a focal opening in the anterior surface of the preretinal hemorrhage, allowing drainage into the vitreous cavity. In a study of six eyes with preretinal hemorrhage secondary to macroaneurysm formation, all eyes showed improvement of vision within 1 week of Nd:YAG photodisruption.<sup>59</sup> In a retrospective review of 21 eyes with premacular hemorrhage secondary to various causes, visual improvement resulted within 1 month of Nd:YAG photodisruption in 16 eyes.<sup>60</sup> However, seven patients required additional vitrectomy for nonclearing vitreous hemorrhage and complications, including macular hole and retinal detachment. The macular hole occurred in an eye with premacular subhyaloid hemorrhage of only 1 disc diameter. The authors postulated that the small size of the hemorrhage did not provide a sufficient dampening effect for the laser burst, and they subsequently recommended that laser drainage be used only if the hemorrhage is beyond 3 disc diameters in size.<sup>60</sup> This treatment modality can be used for rapid visual recovery but most likely results in a visual outcome no better than that with the natural course of the disease. Furthermore, complications from laser photocoagulation can include hemorrhage, epiretinal membrane formation, retinal toxicity, and arterial occlusion leading to retinal ischemia.<sup>61-63</sup> Long-term studies are needed to better define the risks and benefits of laser photodisruption, especially for hemorrhage associated with RAMs.

Pars plana vitrectomy with the use of tissue plasminogen activator (t-PA) has been advocated for the removal of dense, thick subretinal hemorrhage.<sup>64-69</sup> Patients with submacular hemorrhage secondary to RAM have had generally favorable visual outcomes with this technique.<sup>64,65,67-69</sup> However, McCabe et al., in their retrospective review of 41 cases with macular hemorrhage secondary to RAMs, found that patients managed with observation alone had good visual outcomes that were comparable with those of patients managed surgically.<sup>70</sup> Oie and Emi reported that surgical removal of the macroaneurysm along with the hemorrhage might be of use in cases where it is still felt that surgery is indicated to remove the subretinal hemorrhage.<sup>71</sup> In support of this theory, Koinzer et al. in a case series of 49 patients found that although patients treated with observation, laser, and vitrectomy had similar outcomes at 3 years, patients who underwent surgery initially presented with poorer vision.<sup>46</sup> They suggested that intervention should be determined by the severity of the initial presentation and that surgical management may be appropriate in cases of subretinal hemorrhage threatening the macula.

Investigators have also successfully treated submacular hemorrhage by using pneumatic displacement both with and without adjunct intravitreal t-PA.<sup>72-76</sup> Pneumatic displacement consists of pretreatment with intravitreal t-PA followed by injection of perfluoropropane or sulfur hexafluoride gas and prone positioning for at least 24 hours to compress the macula directly and displace the submacular hemorrhage inferiorly. Because retinal toxic

effects of t-PA have been observed in animal studies, investigators recommend avoiding intravitreal injections of t-PA in concentrations >25 µg/0.1 mL.<sup>72</sup> Likewise, caution was advised in the use of intravitreal t-PA injection in patients with RAMs because of a possible increased risk of vitreous hemorrhage. In one study, Mizutani et al. reported vitreous hemorrhage in all four patients pretreated with t-PA.<sup>75</sup> With concerns of t-PA toxicity, Ohji et al. reported a series of five patients treated with perfluoropropane gas followed by prone positioning, without pretreatment with t-PA.<sup>74</sup> Vision improved, and blood was displaced from the fovea partially or completely in all five patients. Nevertheless, Ohji et al. speculated that solid blood clots present >1 week may not be displaced with gas compression alone.<sup>74</sup>

Several risk factors indicative of a poor visual outcome have been identified in a report by Yang et al., including the presence of foveal exudates and subfoveal hemorrhage.<sup>77</sup> Still, even in the presence of subfoveal hemorrhage, a number of these patients will do well without specific treatment other than observation.<sup>70</sup> Ultimately, the preferred treatment for patients with macular hemorrhage secondary to RAM remains controversial and is often determined on a case by case basis.

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# Age-Related Macular Degeneration

Miin Roh, Ivana K. Kim

# 6.29

**Definition:** A common, chronic, progressive degenerative disorder of the macula that affects older individuals and features loss of central vision as a result of abnormalities in the photoreceptor/retinal pigment epithelium/Bruch's membrane/choroidal complex often resulting in geographic atrophy and/or neovascularization.

## Key Features

- Age >50 years.
- Bilateral.
- Drusen.
- Hyperpigmentation of the retinal pigment epithelium (RPE).
- Hypopigmentation of the RPE.
- Geographic atrophy.
- Detachment of the retinal pigment epithelium.
- Macular choroidal neovascularization.

## Associated Features

- Subretinal fluid.
- Intraretinal fluid.
- Subretinal hemorrhage.
- Intraretinal or inner retinal hemorrhage.
- Lipid exudation.
- Subretinal fibrosis (disciform scarring).
- Specific genetic risk alleles, particularly in genes controlling the complement system.

## INTRODUCTION

Age-related macular degeneration (AMD) is the leading cause of irreversible visual impairment among older adults worldwide affecting 30–50 million individuals.<sup>1–5</sup> Loss of visual acuity typically results from progressive degeneration of the photoreceptors, retinal pigment epithelium (RPE), and choriocapillaris, although the earliest manifestation of the disease appears histopathologically as abnormalities within Bruch's membrane. The advanced form of the disease is characterized by choroidal neovascularization (CNV), geographic atrophy (GA; atrophy of the RPE, choriocapillaris, and photoreceptors), or both. The disease nearly always begins as the non-neovascular or dry form of AMD and may progress to GA or the neovascular (wet) form in one or both eyes. When neovascularization occurs, there is accumulation of fluid, hemorrhage, and lipid exudation within the macula that can culminate in fibrosis referred to as a *disciform scar*. It is controversial whether the wet and dry forms of AMD represent two distinct disease entities or end-stage manifestations of the same disease.<sup>6</sup> Once advanced AMD develops in one eye, there is an increased likelihood of having GA or neovascularization in the fellow eye. A simplified severity scale based on fundus appearance was established to assess the risk of converting to advanced AMD.<sup>7</sup> Large drusen, any pigment changes, and the disease state of the fellow eye were particularly predictive for developing advanced AMD. The cause of AMD is multifactorial and influenced by age, ethnic background, and a combination of environmental and genetic factors.<sup>5,8</sup> There is no cure; however, vitamin supplementation, good nutrition, and cessation of smoking can slow the progression of the dry form of AMD,<sup>9,10</sup> and drugs that inhibit vascular endothelial growth factor-A (VEGF-A) have been successful in treating the wet form of AMD.<sup>11–16</sup>

## EPIDEMIOLOGY

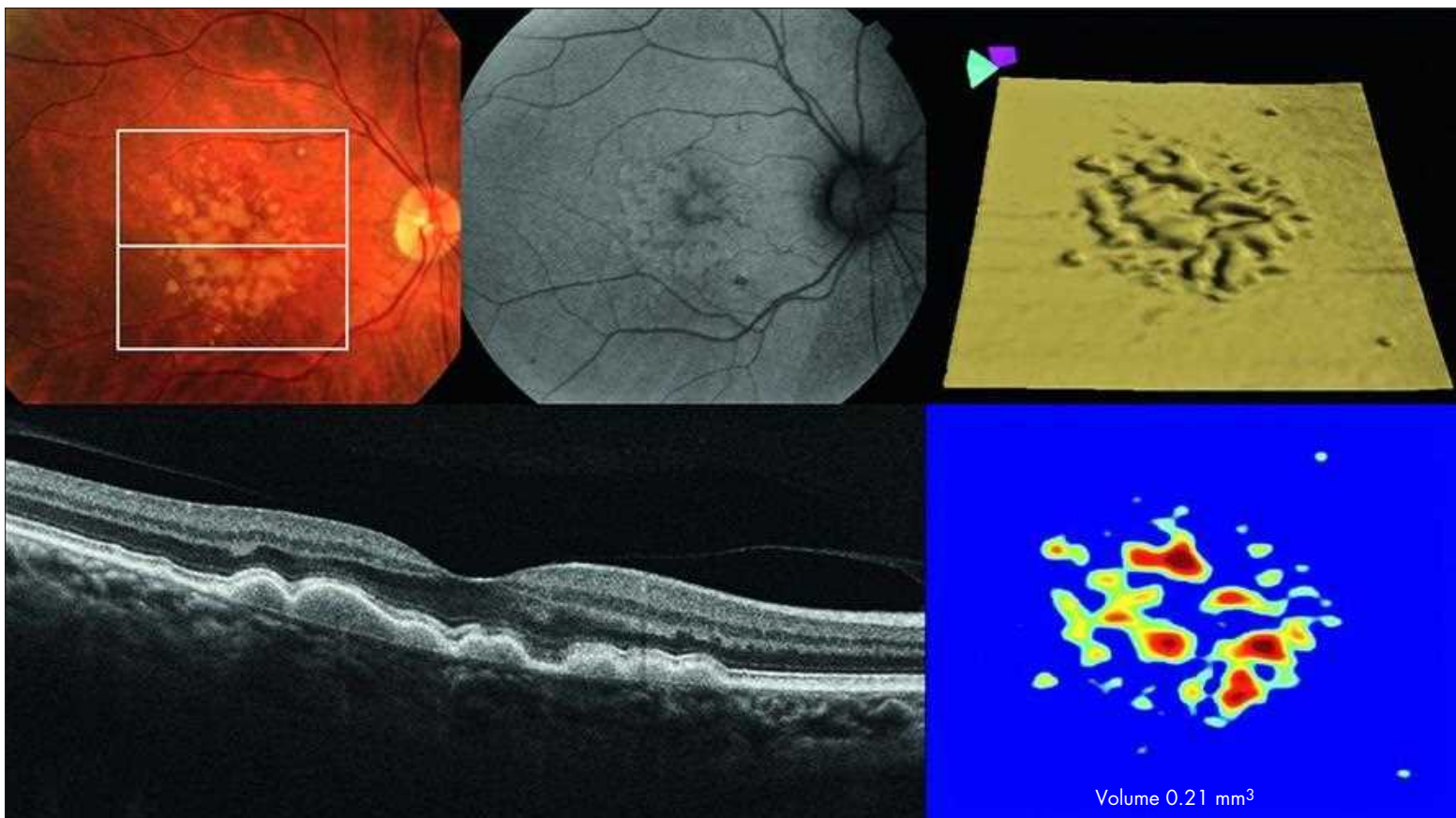
Many studies have reported the prevalence of AMD in a variety of populations by using varying definitions.<sup>4</sup> The World Health Organization (WHO) estimated in 2002 that 8.7% of the world's blindness was caused by AMD, with 14 million people being blinded or severely visually impaired because of it. Most of the affected individuals live in developed countries. In general, advanced AMD is rare before age 55 years and more common in persons 75 years of age and older. The prevalence of neovascular AMD and GA appears to vary in different ethnic and racial groups throughout the world. Advanced AMD can be classified broadly into two types: dry and wet AMD. Although dry AMD accounts for the majority of all diagnosed cases, wet AMD is responsible for the majority of the severe vision loss and usually occurs over weeks to months.<sup>17</sup> Although neovascularization has been the most common cause of severe vision loss, GA, the most advanced form of dry AMD, can cause significant loss of vision as well, and this form of blindness, which evolves slowly over years, will become even more common as a result of successful anti-VEGF therapy and as the population ages.<sup>3,4</sup> The prevalence of advanced AMD increases with each decade after age 50 years, with the highest prevalence found among those age >80 years.<sup>3</sup> In 2000, advanced AMD affected more than 1.75 million people in the United States, with that number expected to rise to 3 million by 2020 as the “baby boom” population ages.<sup>3</sup>

## PATHOGENESIS

Insights into the pathogenesis have come through the evaluation of histopathological specimens and genetic association studies in different populations. Early in the disease process, lipids are deposited in Bruch's membrane, possibly from failure of the RPE to process the cellular debris associated with outer segment turnover. These deposits are known as *basal linear deposits* and *basal laminar deposits*. Only later in the disease process are drusen visible. The appearance of drusen is the earliest visible clinical sign of AMD.

Analysis of typical drusen that elevate the RPE reveals that they contain lipid, amyloid, complement factors, and additional cellular components.<sup>18,19</sup> The appearance of drusen is preceded by or concomitant with the thickening of the Bruch's membrane collagenous layers, degeneration of elastin and collagen within Bruch's membrane with calcification of Bruch's membrane, increased levels of advanced glycation end products, and accumulation of lipids as well as exogenous proteins.<sup>20</sup> These changes may serve as a hydrophobic barrier to impede the passage of fluid and nutrients between the choroid and the outer retina, resulting in relative ischemia. Subsequent ingrowth of neovascularization from the choriocapillaris may then occur through fractures in Bruch's membrane.<sup>21</sup>

Family history is an established determinant of risk as best shown from twin studies.<sup>8</sup> In studies of monozygotic twins with AMD and common environmental as well as dietary influences, the fundus appearance and degree of visual loss were strikingly similar (89%–100%). Clinical concordance in dizygotic twins reared in a shared environment was markedly less but still substantial (46%), consistent with typical siblings. The importance of heredity was confirmed when polymorphisms within genes encoding complement factor H, human high-temperature requirement A-1 (HTRA1), complement C2, CFB, and C3 were shown to be predictors of risk for AMD.<sup>22–27</sup> Although it is unknown precisely how genetic variation in the complement cascade predisposes patients to AMD, evidence suggests that dysregulation of the innate complement pathway leads to aberrant inflammatory responses, resulting in the accumulation of debris within Bruch's membrane. Many components of the activated complement cascade, such as C3a and C5a, were previously identified in drusen.<sup>28,29</sup> However, the mechanism whereby the complement pathways initially



**Fig. 6.29.1 Right Eye of a 69-Year-Old Woman With Intermediate Age-Related Macular Degeneration (AMD), Showing Soft Drusen.** (Top left) Color fundus photograph showing the superimposed location of the spectral-domain optical coherence tomography (SD-OCT) dataset indicated by the *white square*. (Top middle) Fundus autofluorescence. (Top right) Retinal pigment epithelium (RPE) segmentation map. (Bottom left) Foveal horizontal B-scan corresponding to the *white line* on the color fundus photograph. (Bottom right) RPE elevation map.

become activated remains to be elucidated. It has recently been demonstrated that the risk of bilateral GA is associated with CFH (complement factor H), whereas HTRA1 attributes more risk to the risk of bilateral CNV. Furthermore, C3 has been shown to confer more risk for GA than CNV.<sup>26</sup> The identification of these genes confirms the genetic component of AMD that and inflammation plays an important role. However, AMD in different ethnic groups may or may not be associated with the same genetic loci or polymorphisms.

The most important environmental risk factors are smoking and obesity.<sup>30</sup> Other risk factors for the development of AMD have been identified despite a limited understanding of the exact pathophysiology. Various researchers implicate atherosclerosis, oxidative damage, phototoxicity, and diet.<sup>4</sup> Evidence of light exposure as a cause of AMD is inconclusive with only a few clinical studies showing a positive association between sun exposure and late AMD.<sup>31,32</sup> However, several case-control studies failed to show an association between sunlight exposure and AMD.<sup>33,34</sup>

## OCULAR MANIFESTATIONS

### Dry AMD

#### *Drusen and Focal Hyperpigmentation of the RPE*

Drusen are one of the earliest signs of AMD. Clinically, typical drusen appear as focal, whitish yellow excrescences deep to the retina. Generally, they cluster in the posterior pole but can appear anywhere in the fundus. Drusen in an extramacular location are of no known visual consequence. Typical drusen deposits are located between the RPE and Bruch's membrane and vary widely in number, size, shape, and distribution. Most drusen are 20–100  $\mu\text{m}$  in diameter and are characterized as hard or soft as well as small ( $<63 \mu\text{m}$ ), intermediate ( $>63 \mu\text{m}$  but  $<125 \mu\text{m}$ ), or large ( $\geq 125 \mu\text{m}$ ).<sup>7,35</sup>

Hard drusen, which appear as round, discrete yellow-white spots, measure  $<63 \mu\text{m}$ . These drusen are commonly identified in many populations; they are not age related and do not carry an increased risk for the development of neovascularization, with approximately 80% of the general population age  $>30$  years manifesting at least one. In contrast, soft drusen

are ill defined, with nondiscrete borders, measuring  $\geq 63 \mu\text{m}$  (Fig. 6.29.1). Different population-based studies and clinical trials have indicated that large, soft, confluent drusen are age related and associated, with a higher risk for development of advanced AMD with the development of neovascularization.<sup>7,32,36</sup> After the age of 70 years, 26% of individuals have large or soft drusen, and 17% have confluent drusen.<sup>37</sup>

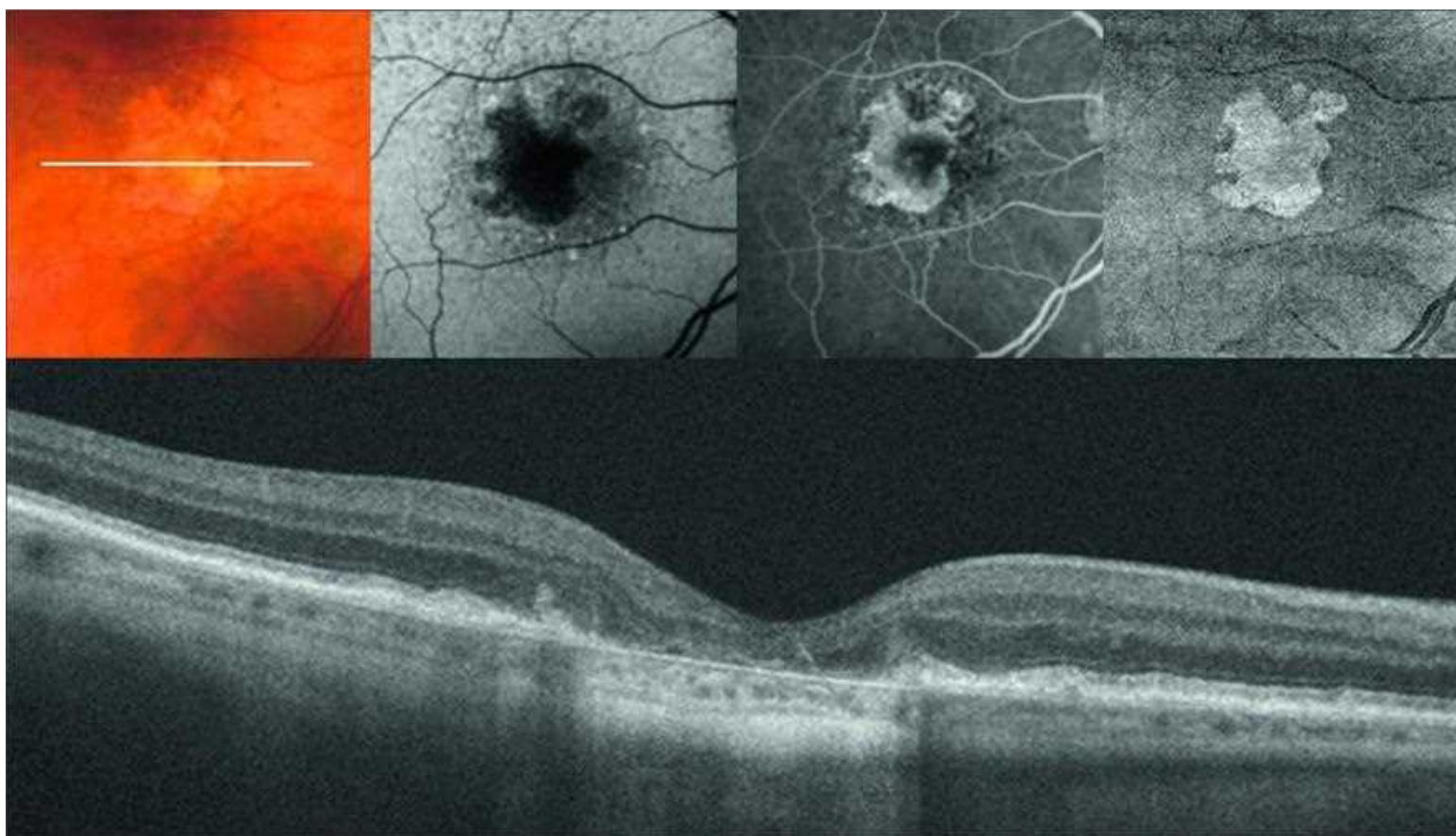
Reticular pseudo-drusen, which appear as yellow faint interlacing network, were first identified on blue-light fundus photography,<sup>38</sup> and recent Optos ultra-wide field imaging showed that reticular pseudo-drusen were found in 11% of the AREDS2 cohort.<sup>39</sup> Reticular pseudo-drusen were initially shown to be associated with a high risk of progression to neovascular AMD<sup>40–42</sup> but subsequently found to be equally associated with development of atrophic AMD in a recent epidemiological study.<sup>41,43,44</sup> Although their origin is unclear, the original histopathology localized reticular pseudo-drusen to changes in the choroid with loss of choroidal vessels accompanied by fibrous replacement of choroidal stroma in a reticular pattern.<sup>40</sup> More recent studies have identified them as subretinal deposits above the RPE.<sup>45,46</sup> For the most part, drusen alone do not cause severe visual acuity loss but can be associated with complaints of light adaptation, mild metamorphopsia, loss of reading speed, and impaired contrast sensitivity.

Focal hyperpigmentation of the RPE is another important clinical feature of nonneovascular AMD. The risk of developing soft drusen and GA increases in its presence.<sup>47</sup>

#### *Geographic Atrophy*

GA is clinically seen as one or more well-delineated areas of hypopigmentation or depigmentation because of absence or severe attenuation of the underlying RPE (Fig. 6.29.2). The larger, deep choroidal vessels are more readily visualized through the atrophic patches that also lack photoreceptors and choriocapillaris. These areas are usually small (less than a disc area) and may surround the fovea in a petaloid pattern, and they typically coalesce over time or manifest as one large central lesion up to 7 mm in diameter. If the foveal center is spared, good visual acuity may be preserved, although reading vision may remain poor because of a constricted central visual field. Many eyes that have GA also exhibit drusen. In fact, most cases of GA occur in a pattern corresponding to the regression of





**Fig. 6.29.2 Right Eye of an 84-Year-Old Woman With Advanced Age-Related Macular Degeneration (AMD), Showing Geographic Atrophy.** (Top from left to right) Color fundus photograph, fundus autofluorescence, late phase fluorescein angiography, and optical coherence tomography (OCT) fundus image. (Bottom) Foveal horizontal B-scan corresponding to the *white line* on the color fundus photograph.

prior, significant drusen. Visual acuity loss from dry AMD is generally caused by GA involving the foveal region.<sup>48-51</sup>

## Neovascular AMD

Neovascular or wet AMD is characterized by the presence of neovascularization within the macula. This neovascularization may result from the ingrowth of neovascularization from the choriocapillaris under the macular region, which is typical CNV, or may arise predominantly within the retina and is known as *retinal angiomatous proliferation* (RAP). In the advanced forms of neovascular AMD, it is not unusual to see retinal–choroidal anastomoses, a communication between retinal and choroidal circulations.

Patients often report a sudden worsening of their central vision, often with distortion. The clinical manifestations of neovascular AMD can include the following: subretinal fluid; intraretinal fluid; retinal, subretinal, or sub-RPE hemorrhage; lipid exudates; gray or yellow-green discoloration or plaque-like membrane; RPE detachment; RPE tear (Figs. 6.29.3, 6.29.4 and 6.29.5). In end-stage disease, the neovascularization results in a fibrovascular or atrophic macular scar and subsequent permanent damage to the central vision.

### Detachment of the RPE

A retinal pigment epithelial detachment (PED) may be caused by serous fluid, fibrovascular tissue, hemorrhage, or the coalescence of drusen beneath the RPE. Each has a unique clinical appearance and exhibits specific fluorescence patterns on angiography. Fibrovascular PED represents a type of occult CNV described later. Hemorrhagic PED manifests as a dark elevation of the RPE because of underlying blood, showing blocked fluorescence throughout all phases of angiography. Serous PED appears as a dome-shaped detachment of the RPE, exhibiting bright, diffuse hyperfluorescence with progressive pooling in a fixed space. Drusenoid PEDs, caused by coalescence of drusen, show staining, often with fading fluorescence in the late phase and an absence of leakage.<sup>52</sup>

## DIAGNOSIS AND ANCILLARY TESTING

Clinical examination is usually sufficient to establish a diagnosis of AMD, although subtle macular abnormalities are best detected with the help of

ancillary tests, such as fundus autofluorescence (FAF), optical coherence tomography (OCT), fluorescein angiography (FA), indocyanine green angiography (ICGA), and optical coherence tomography angiography (OCTA).

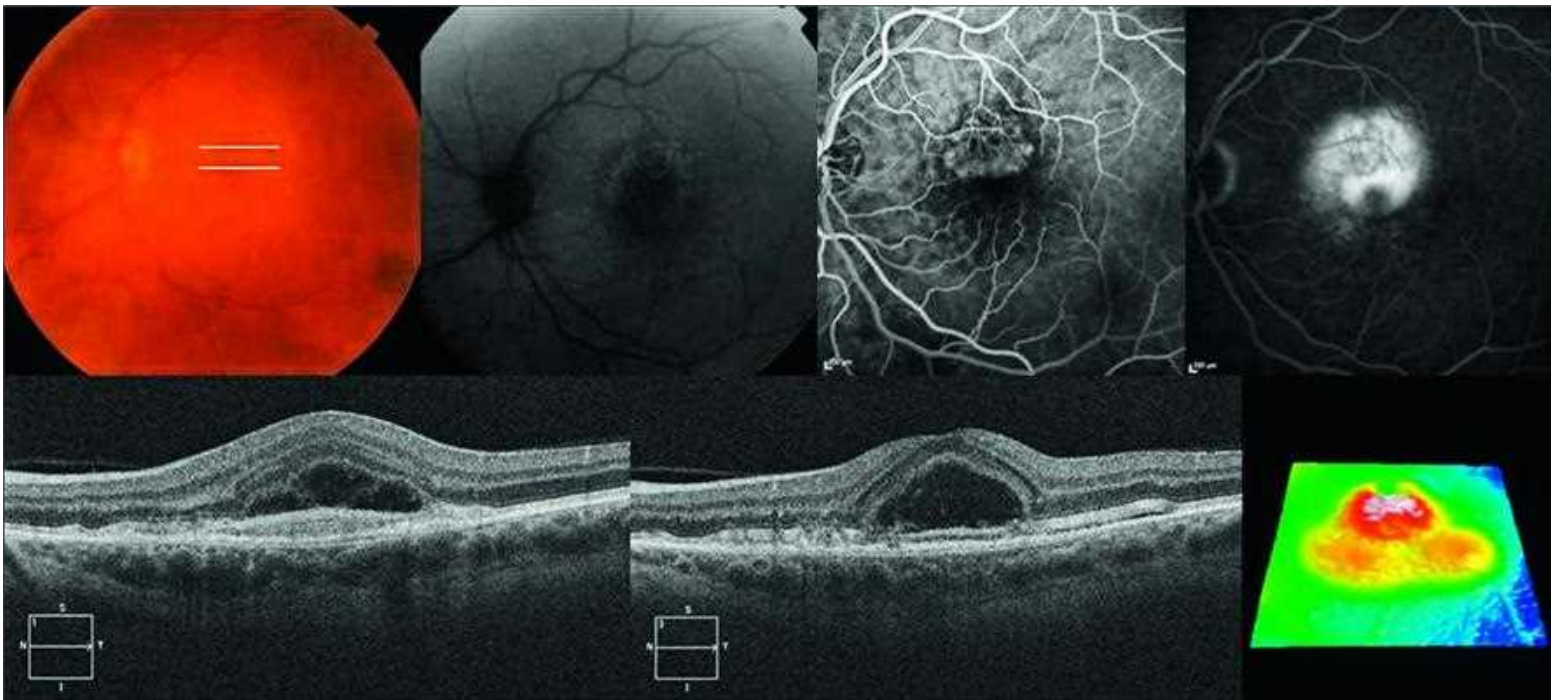
## Fundus Autofluorescence

FAF represents an imaging modality capable of reflecting the morphological changes associated with the metabolism of lipofuscin. It allows for noninvasive, topographical, in vivo imaging of intrinsic fluorophores in the macula. Depending on the instrument, FAF imaging is obtained using an excitation wavelength ranging from 488 nm to 585 nm and an emission bandwidth of 500–700 nm. Areas of GA exhibit very low to extinguished FAF signals (dark) as a result of loss of RPE and lipofuscin, which leads to a region with a high-contrast transition between the area of atrophy and the perilesional retina (see Fig. 6.29.2). In addition, various patterns of perilesional FAF changes may be predictive of disease progression.<sup>53-56</sup>

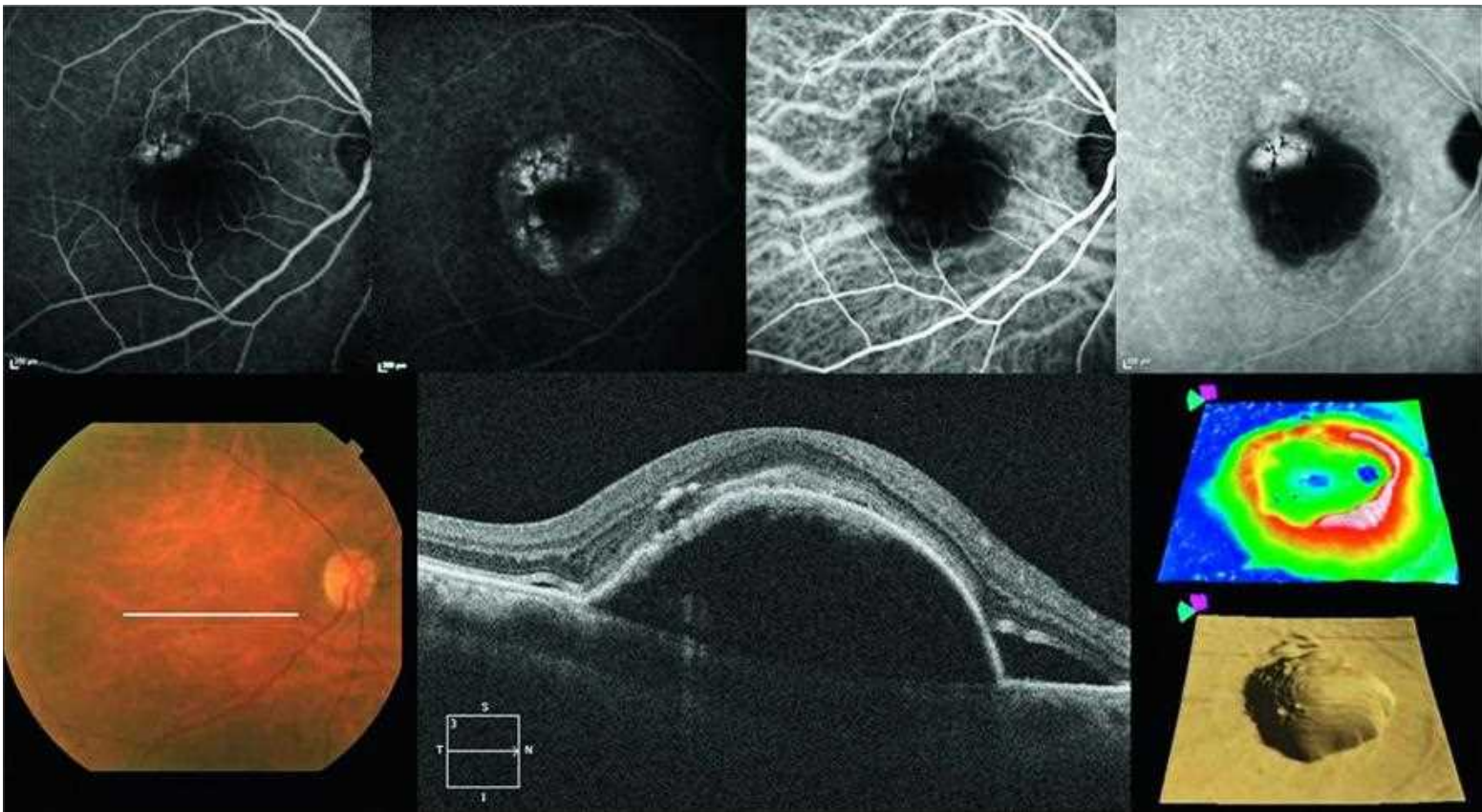
## Optical Coherence Tomography

OCT may be a useful ancillary test in any stage of AMD. In patients with dry AMD, the high-definition averaged B-scans are useful to assess the ultra-structure of drusen and to examine adjacent retinal layers that can be compromised by the disease process. The acquisition of raster scans comprising a large number of lower-density B-scans combined with the use of segmentation algorithms results in the ability to generate maps of the internal limiting membrane and the RPE, which provides information on the RPE geometry and therefore a unique perspective of drusen. Currently, segmentation algorithms can be applied to the data set and provide the actual volume and area of drusen (see Fig. 6.29.1).<sup>57,58</sup> The progression of early AMD to severe forms, such as GA, can be monitored by using OCT. The loss of RPE and photoreceptors are easily observed in the B-scans (see Fig. 6.29.2). The area of GA can be measured by using the OCT fundus image (OFI) and the sub-RPE slab OFI.<sup>59,60</sup> The OFI represents a virtual fundus image resulting from the en face summation of the reflected light from each A-scan. This en face OFI identifies GA as a bright area resulting from the increased penetration of light into the choroid where atrophy has occurred in the macula (see Fig. 6.29.2; Figs. 6.29.6 and 6.29.7), whereas





**Fig. 6.29.3** Left Eye of a 75-Year-Old Man With Advanced Age-Related Macular Degeneration (AMD), Showing Classic Choroidal Neovascularization. (Top from left to right) Color fundus photograph, fundus autofluorescence, early phase fluorescein angiography, and late phase fluorescein angiography. (Bottom from left to right) Optical coherence tomography (OCT) B-scan imaging the choroidal neovascularization, corresponding to the *top white line* on the color fundus photograph, foveal horizontal B-scan corresponding to the *bottom white line* on the color fundus photograph and retinal thickness map, showing an increase in the central retinal thickness.



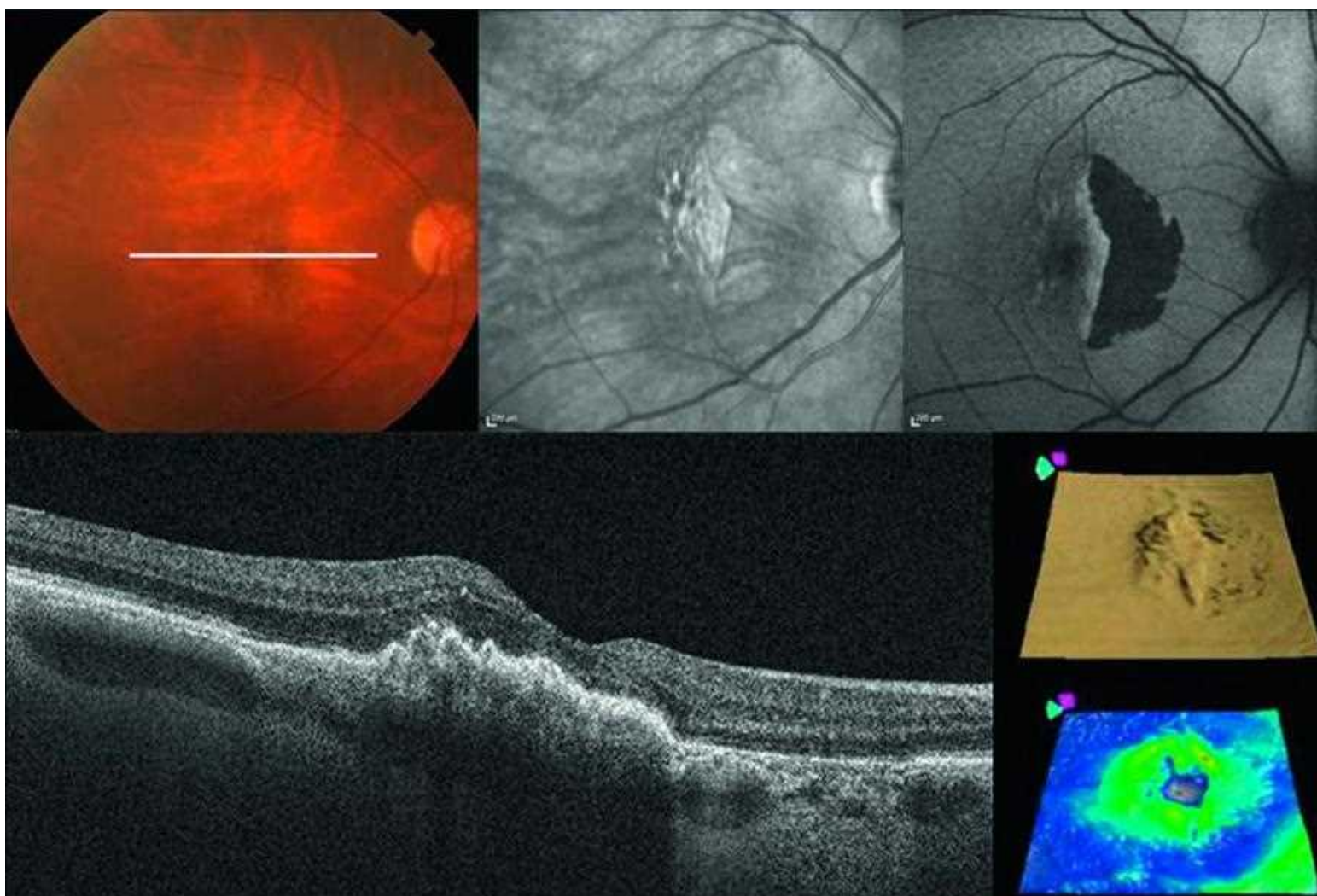
**Fig. 6.29.4** Right Eye of a 78-Year-Old Woman With Advanced Age-Related Macular Degeneration (AMD), Showing Occult Choroidal Neovascularization With Retinal Pigment Epithelial Detachment (PED). (Top from left to right) Early-phase fluorescein angiography (FA), late-phase FA, early-phase indocyanine green angiography (ICGA), and late-phase ICGA. (Bottom left) Color fundus photograph. (Bottom middle) Foveal horizontal optical coherence tomography (OCT) B-scan, corresponding to the *white line* on the color fundus photograph. (Bottom right) Retinal thickness map and retinal pigment epithelium (RPE) segmentation map.

the sub-RPE slab OFI is the summation of the reflected light from beneath the RPE.

OCT is more widely used in wet AMD by physicians. High-definition B-scans can be used to identify some of the wet AMD features, such as the presence of intraretinal or subretinal fluid, presence of retinal PEDs, which can be classified in serous (vascularized and nonvascularized), fibrovascular, and hemorrhagic PEDs. The macular fluid can be identified by

examining B-scans and by reviewing retinal thickness maps, which calculate the retinal thickness between the internal limiting membrane and the RPE (see Fig. 6.29.3). Since the advent of drugs that inhibit VEGF, one of the strategies for monitoring eyes with wet AMD has been to use OCT to determine whether the treatment is effective in resolving the macular fluid. The effect of anti-VEGF therapy can then be assessed on the basis of the qualitative appearance of B-scans and the qualitative as well as quantitative





**Fig. 6.29.5** Right Eye of a 78-Year-Old Woman With Advanced Age-Related Macular Degeneration (AMD), Showing Choroidal Neovascularization With a Retinal Pigment Epithelium (RPE) Tear. (Top left) Color fundus photograph. (Top middle) Infrared image. (Top right) Fundus autofluorescence. (Bottom left) Foveal horizontal optical coherence tomography (OCT) B-scan, corresponding to the *white line* on the color fundus photography. (Bottom right) RPE segmentation map and retinal thickness map.

changes in retinal thickness maps (Fig. 6.29.8). In addition, the same algorithm used to measure drusen can also be used to reproducibly measure the area and volume of PEDs, thus monitoring the natural history and the treatment effect in wet AMD patients.<sup>61</sup>

OCT also allows the physician to distinguish between causes of visual acuity loss that may not be directly associated with AMD, such as a subtle epiretinal membrane or vitreomacular traction.

## Fluorescein Angiography

FA is usually performed to confirm the presence of CNV and identifies the characteristics of a lesion, including the location and type of abnormal vessels, which may be helpful in serving as a baseline examination for future studies to decide whether treatment has been effective.

On the basis of angiographic patterns of fluorescence, the neovascular lesion may be categorized as type 1 (occult), type 2 (classic), or type 3 (retinomatous angiomatous proliferation). *Type 1* CNV refers to new blood vessels that proliferate underneath the RPE and is also called *occult* CNV. Occult CNV is recognized angiographically by one of two patterns: fibrovascular PED or late leakage from an undetermined source. Fibrovascular PED is characterized by an area of irregular elevation of the RPE (which is neither as bright nor as discrete as in classic CNV), often with stippled hyperfluorescence present in the midphase of the angiogram and leakage or staining by the late phase (see Fig. 6.29.4). Late leakage from an undetermined source usually appears as speckled hyperfluorescence with dye pooled in the subretinal space in the late phase, and the source of the leakage does not correspond to classic CNV or a fibrovascular PED in the early or midphase portion of the angiogram. In *type 2* CNV, new blood vessels are between the neurosensory retina and RPE. Type 2 or classic CNV is characterized by bright, often “lacy,” early hyperfluorescence exhibiting prominent leakage in the late phase (see Fig. 6.29.3). *Type 3* CNV or

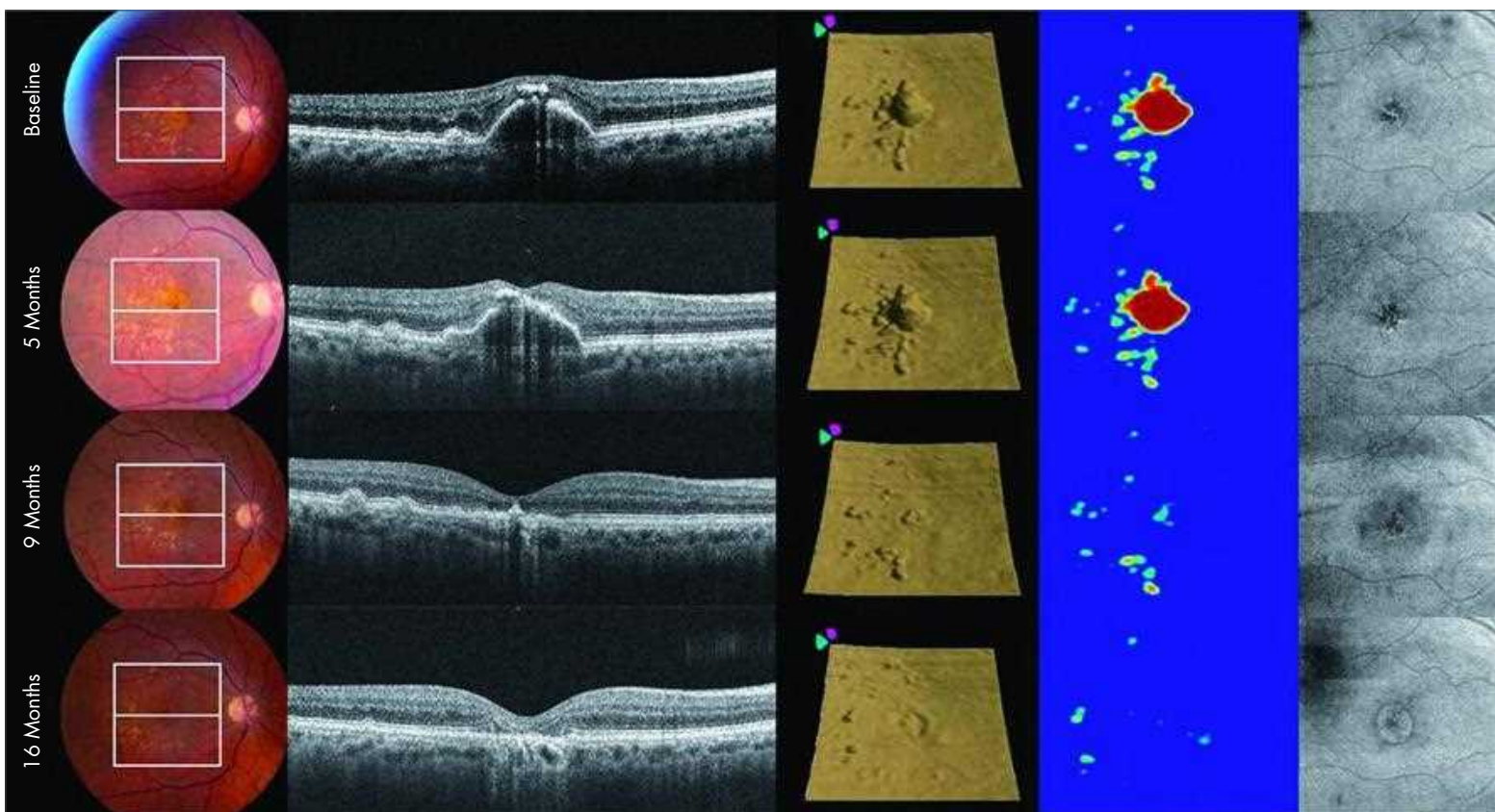
RAP forms new blood vessels within or below the sensory retina beginning with capillary proliferation, formation of intraretinal neovascularization, and retinal–retinal anastomoses. This retinal neovascularization then extends beneath the neurosensory retina to become subretinal neovascularization (SRN). With time, SRN may merge with the choroidal circulation beneath the RPE to form retinal–choroidal anastomosis.<sup>62</sup> Angiograms are also evaluated for the presence of hemorrhage, blocked fluorescence that does not correspond to hemorrhage, or serous detachment of the RPE. Neovascularization within the area of the serous detachment may not be identifiable because of intense hyperfluorescence.

## Indocyanine Green Angiography

ICGA has been used to diagnose and guide treatment in patients with AMD. The ICG dye binds to plasma proteins, limiting leakage from choroidal vessels, thus delineating the choroidal circulation better compared with FA. The appearance of CNV based on ICGA may be categorized into three types: focal hot spots, plaques, and a combination of the two (see Fig. 6.29.4). Laser treatment based on ICGA findings has been advocated, but the data remain anecdotal and unproven in any prospective study.<sup>63,64</sup> ICGA is particularly useful in identifying polypoidal choroidal vasculopathy (PCV), a variant of exudative AMD characterized by orange-red nodules and serosanguinous pigment epithelial detachments on ophthalmoscopy. ICGA demonstrates polyps and branching vascular networks in this condition that are often difficult to detect on FA<sup>65–69</sup> (Fig. 6.29.9).

## Optical Coherence Tomography Angiography

Optical coherence tomography angiography (OCTA) is a noninvasive method to visualize blood flow using various algorithms.<sup>70</sup> The motion contrast between the rapidly repeated OCT B scans is used to generate



**Fig. 6.29.6 Right Eye of a 78-Year-Old Man With a Drusenoid Retinal Pigment Epithelial Detachment (DPED) That Collapsed and Formed Geographic Atrophy (GA).** (Top row) Color fundus image, foveal horizontal B-scan, RPE segmentation map, RPE elevation map, and the OCT fundus image at baseline. (Second row) Five months of follow-up. (Third row) 9 months of follow-up. (Bottom row) 16 months of follow-up. Retinal pigment epithelium (RPE) segmentation map (third column) and RPE elevation map (fourth column) show the DPED volume at baseline ( $0.24 \text{ mm}^3$ ) and 5 months ( $0.26 \text{ mm}^3$ ). A collapse of the DPED was observed after nine months of follow-up with development of GA, as seen on the OFI at the 16 month visit (bottom right). The B-scan of the five-month visit shows breakdown of the RPE, with an increased light penetration preceding the collapse of the DPED and the formation of GA.

three-dimensional and depth-resolved images of individual vascular plexuses and segment the inner retina, outer retina, and choriocapillaries without the use of intravenous contrast dye.<sup>71-76</sup> There are several reports<sup>77-79</sup> suggesting that the OCTA is highly sensitive in detecting neovascular complex according to the location of the lesion and can provide depth, area, and flow of CNV.<sup>80</sup> However, signal attenuation from the RPE, media opacity, and retinal hemorrhage still limits precise visualization, and inaccurate segmentation slab design among different instruments is also a major limiting factor in detecting retinal/choroidal vascular abnormalities.<sup>81</sup> The use of a swept source laser centered at a longer wavelength of 1050 nm for OCTA may allow for deeper tissue penetration and better visualization of choroidal vascular pathology.<sup>76</sup> Unlike FA or ICGA, OCTA does not detect dye leakage, which is beneficial for imaging the fenestrated choriocapillaris but is limited in applications where alterations in vascular permeability are markers of disease.

## DIFFERENTIAL DIAGNOSIS

Individuals affected by AMD are typically older adults and have drusen present in the involved or fellow eye. The differential diagnosis of dry AMD includes other conditions that affect the RPE and choriocapillaris (Box 6.29.1). CNV has been described in a variety of ophthalmic conditions (Box 6.29.2), including pathological myopia, inflammatory conditions, choroidal ruptures, ocular histoplasmosis syndrome, and angioid streaks. When CNV is detected, it is important to determine whether AMD is the cause because other causes of CNV may carry different prognoses, which affects counseling and treatment decisions.<sup>66,82,83</sup>

Other causes of subretinal hemorrhage must be ruled out, including retinal arterial macroaneurysm (which usually shows fluorescein leakage from the aneurysm centered along a retinal arteriole). Other causes of subretinal fluid also need to be considered, most commonly central serous chorioretinopathy, particularly the chronic recurrent form that can be seen in older patients. FA, ICGA, FAF, and enhanced-depth OCT imaging are usually helpful in diagnosing central serous chorioretinopathy.<sup>66,84,85</sup>

### BOX 6.29.1 Differential Diagnosis for Dry Age-Related Macular Degeneration

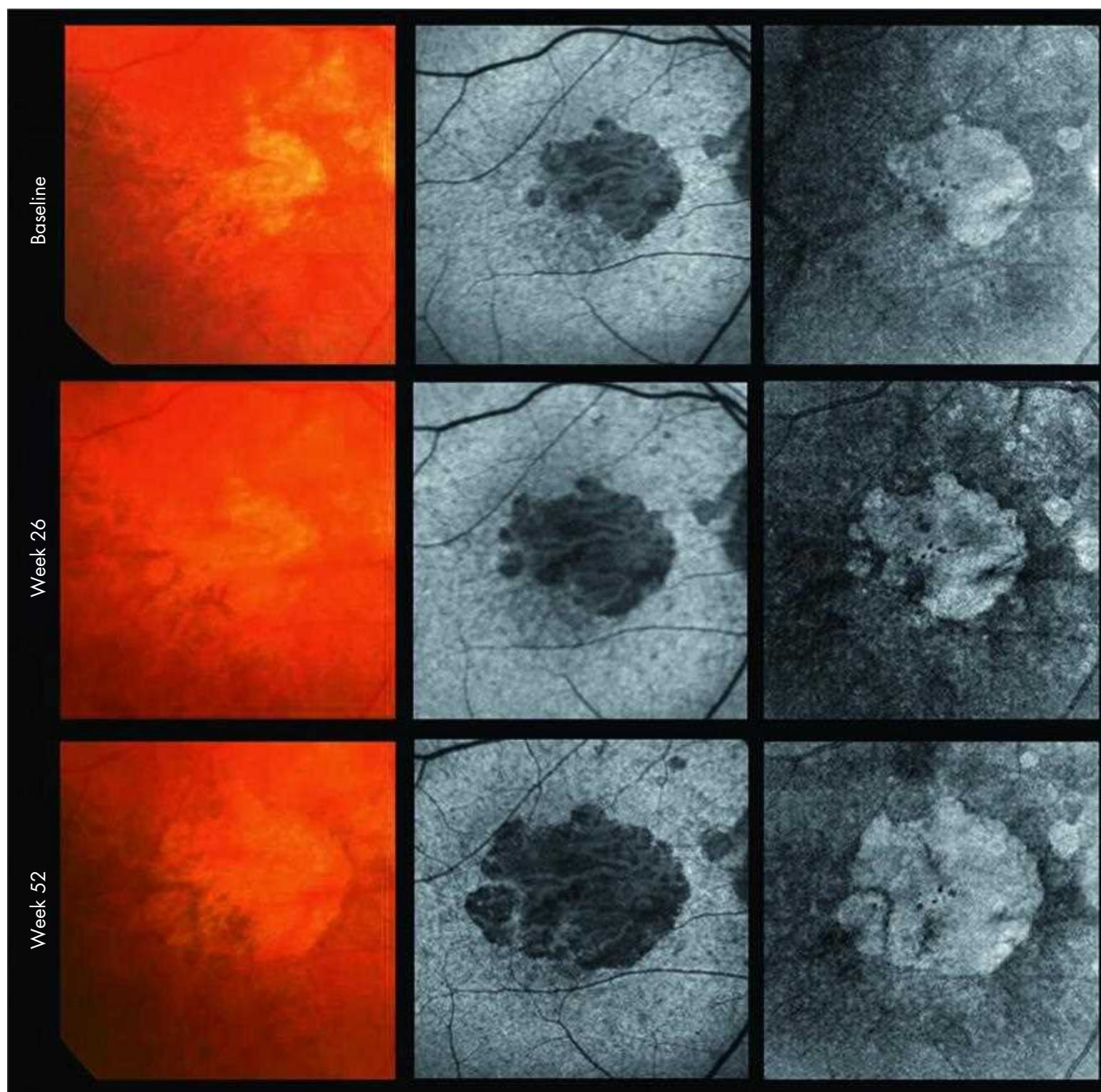
- Hereditary diseases
- Pattern dystrophy
- Stargardt disease
- Best disease
- Angioid streaks
- Central serous chorioretinopathy
- Macular telangiectasia type II
- Multifocal choroiditis
- Acute posterior multifocal placoid pigment epitheliopathy
- Toxic lesions
- Chloroquine
- Phenothiazines
- Canthaxanthin
- Cuticular drusen with or without a vitelliform lesion
- Adult vitelliform dystrophy

## PATHOLOGY

Histopathologically, drusen appear as focal areas of eosinophilic material between the basement membrane of the RPE and Bruch's membrane.<sup>20</sup> They stain positively with periodic acid-Schiff stain. Soft drusen are larger and represent a detachment of the thickened inner aspect of Bruch's membrane along with the RPE. Generally, minimal photoreceptor degeneration overlies drusen.

Bruch's membrane is a five-layered structure in which the basement membrane of the RPE represents the innermost layer.<sup>86,87</sup> The outermost layer is a second basement membrane associated with the endothelium of the choriocapillaris. A zone of elastin is sandwiched on both sides by the inner and outer collagenous layers. An age-related change is the



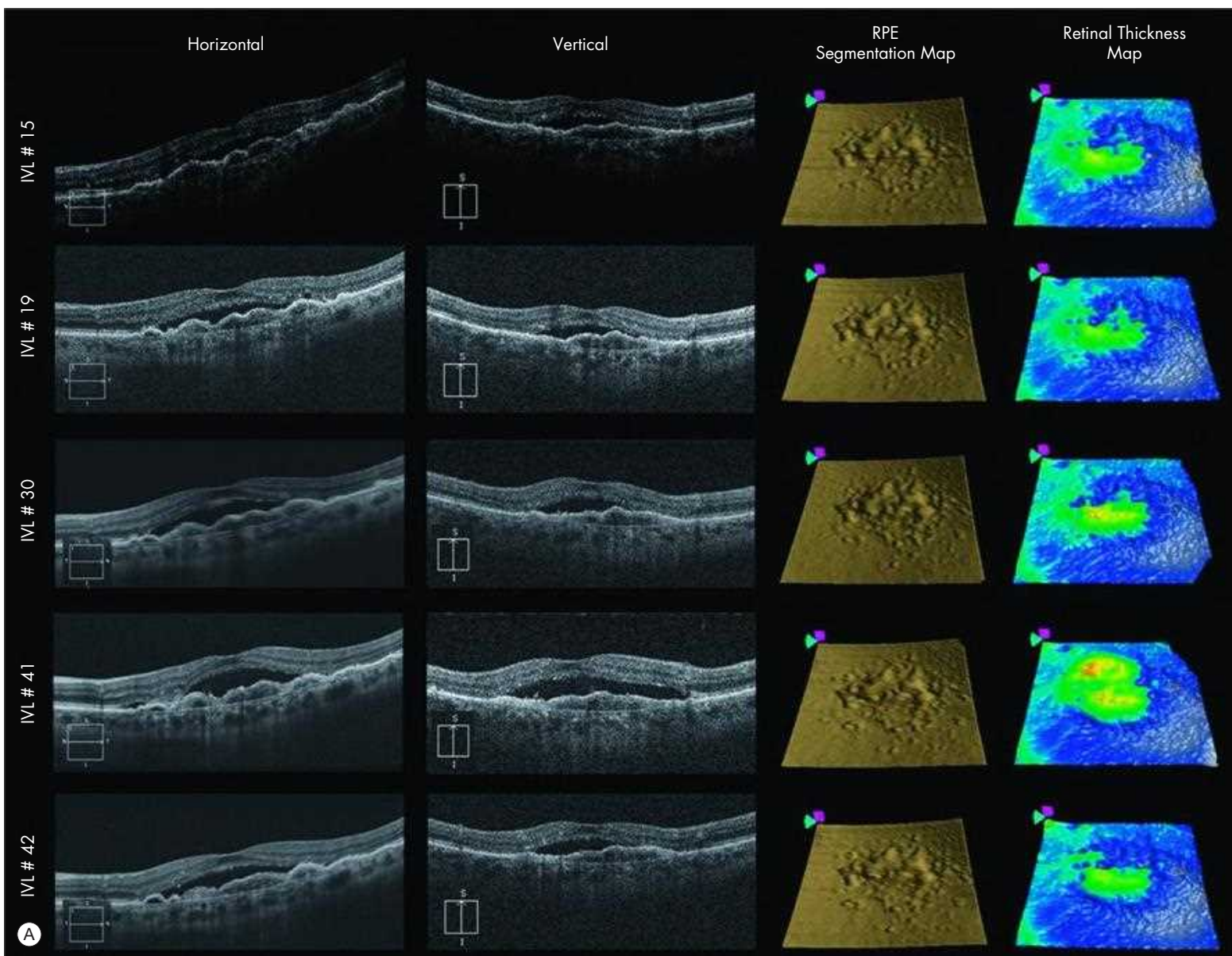


**Fig. 6.29.7 Right Eye of a 79-Year-Old Man With Geographic Atrophy Growing in Area Over a 12-Month Period.** (Top row) Baseline. (Middle row) Week 26. (Bottom row) Week 52 images. (Left column) Color fundus images. (Middle column) Heidelberg autofluorescence. (Right column) Optical coherence tomography (OCT) fundus image.

#### BOX 6.29.2 Partial List of Common Ophthalmic Conditions Associated With Choroidal Neovascularization

- Age-related macular degeneration
- Angioid streaks
- Best disease
- Choroidal osteoma
- Fundus flavimaculatus
- Idiopathic causes
- Multifocal choroiditis
- Ocular histoplasmosis syndrome
- Optic disc drusen
- Optic nerve head pits
- Pathological (progressive) myopia
- Pattern dystrophies
- Photocoagulation
- Sarcoidosis
- Serpiginous or geographic choroiditis
- Toxoplasmic retinochoroiditis
- Traumatic choroidal rupture
- Polypoidal choroidal vasculopathy





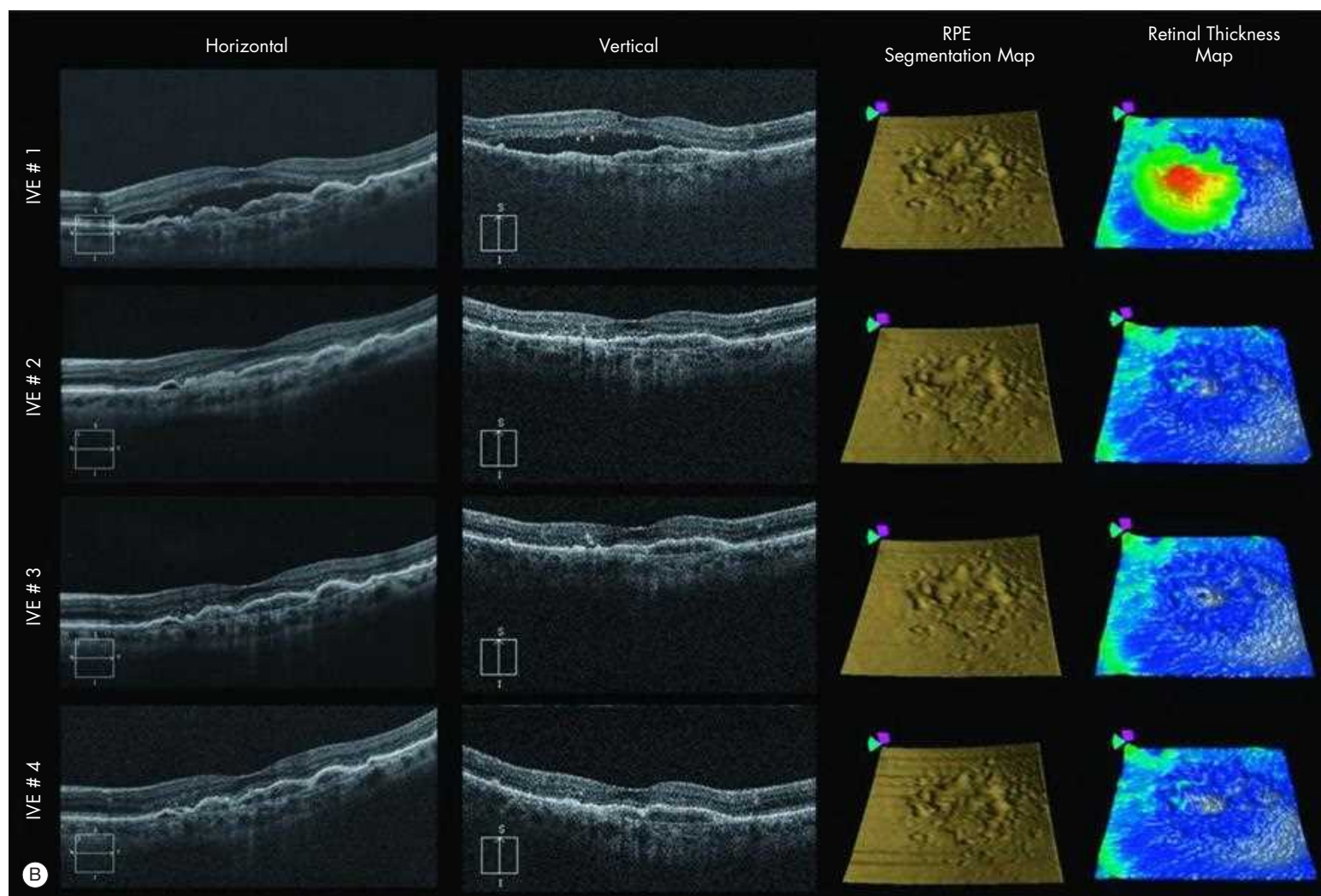
**Fig. 6.29.8** Optical coherence tomography (OCT)–guided therapy with treat and extend strategy using anti-vascular endothelial growth factor (VEGF) for the treatment of neovascular age-related macular degeneration (AMD). Patient presented a poor response to ranibizumab with good results after switching to aflibercept. (A) 15th through 42nd ranibizumab injections: OCT images after ranibizumab injection in an eye with neovascular AMD. Horizontal (first column on left) and vertical (second column) OCT scans, retinal pigment epithelium (RPE) segmentation map (third column) and retinal thickness map (fourth column on right) of the left eye are shown before injection of ranibizumab nos. 15, 19, 30, 41, and 42.

appearance of basal laminar deposits, which represent type IV collagen, between the RPE cell surface and the basement membrane. Progressive thickening of this inner part of Bruch's membrane is associated with RPE degeneration. Eosinophilic deposits that coalesce between the RPE basement membrane and the inner collagenous zone of Bruch's membrane are called basal linear deposits. It is difficult to differentiate these two types of deposits with the use of light microscopy. One hypothesis suggests that the material accumulates from damaged RPE cells. Aging also results in increased lipid deposition in Bruch's membrane.<sup>21</sup> Bruch's membrane often shows areas of calcification and fragmentation as well, and these changes are found more commonly in eyes that harbor CNV caused by AMD. The choriocapillaris shows thickened and hyalinized vascular walls, whereas the larger choroidal vessels appear normal. Loss of the RPE in GA is accompanied by loss of the overlying photoreceptors, and the underlying choriocapillaris is also generally hyalinized.

CNV represents new blood vessel ingrowth from the choriocapillaris through a degenerated Bruch's membrane. The earliest histopathological form of CNV consists of fine vessels within Bruch's membrane.<sup>21</sup> Occasionally, a low-grade granulomatous inflammation accompanies CNV. Even when CNV is first noted clinically, the histopathology shows a prominent fibrotic component. The fibrotic component may be associated with hyperplasia or metaplasia of the RPE, overlying retinal atrophy, and cystoid macular edema. Hemosiderin from previous hemorrhage may be seen.

## NATURAL HISTORY AND PROGNOSIS

Early macular degeneration can progress to late manifestations with accompanying vision loss. The risk of progression is highly variable and depends on the severity and extent of the features of early macular degeneration. Drusen and the drusenoid PEDs may progress following different growth patterns. They can increase in volume and area, develop GA (see Fig. 6.29.6) or CNV, remain stable or decrease without any apparent anatomical defect in the macula.<sup>58,88,89</sup> In the course of 5 years, up to 5% of patients with early AMD can progress to late AMD, and the rate increases to nearly 15% in 15 years.<sup>33,90</sup> The Age-Related Eye Disease Study (AREDS) quantified this risk and showed that people with small drusen in both eyes have a very low risk of progression—between 0.4% and 3.0% in 5 years.<sup>7</sup> Hard drusen is a common finding and is not associated with AMD progression. However, soft drusen and RPE changes are associated with a risk of 6.5% and 71%, respectively, for progression to late AMD in a 5-year period.<sup>91</sup> If large drusen and pigmentary abnormalities are present in both eyes, this risk increases to around 47.3%.<sup>7</sup> Several reports support the dynamic nature of drusen with spontaneous resorption of some drusen, as well as the formation of new drusen, and both these activities can occur simultaneously in the same macula.<sup>58,92,93</sup> Regression of soft macular drusen has been described in clinical and histopathological studies.<sup>94-99</sup> Gass first noted that drusen could fade and disappear, leaving only an irregular mottling of the



**Fig. 6.29.8, cont'd (B)** 1st through 4th aflibercept injections: OCT images before aflibercept injection in an eye with neovascular AMD. Horizontal (first column on left) and vertical (second column) OCT scans, RPE segmentation map (third column) and retinal thickness map (fourth column on right) of the left eye are shown before injection of aflibercept no. 1, 2, 3, and 4 with good response and resolution of the persistent subretinal fluid.

RPE but that visual acuity may not be affected. He also observed that most cases of GA occurred after the fading of drusen or the collapse of a serous detachment of the RPE, resulting in degeneration and atrophy of the RPE and photoreceptors (see Fig. 6.29.6).<sup>94</sup> These observations were supported by large population-based studies, in which it was noted that some patients showed drusen regression without any residual defects.<sup>97-99</sup>

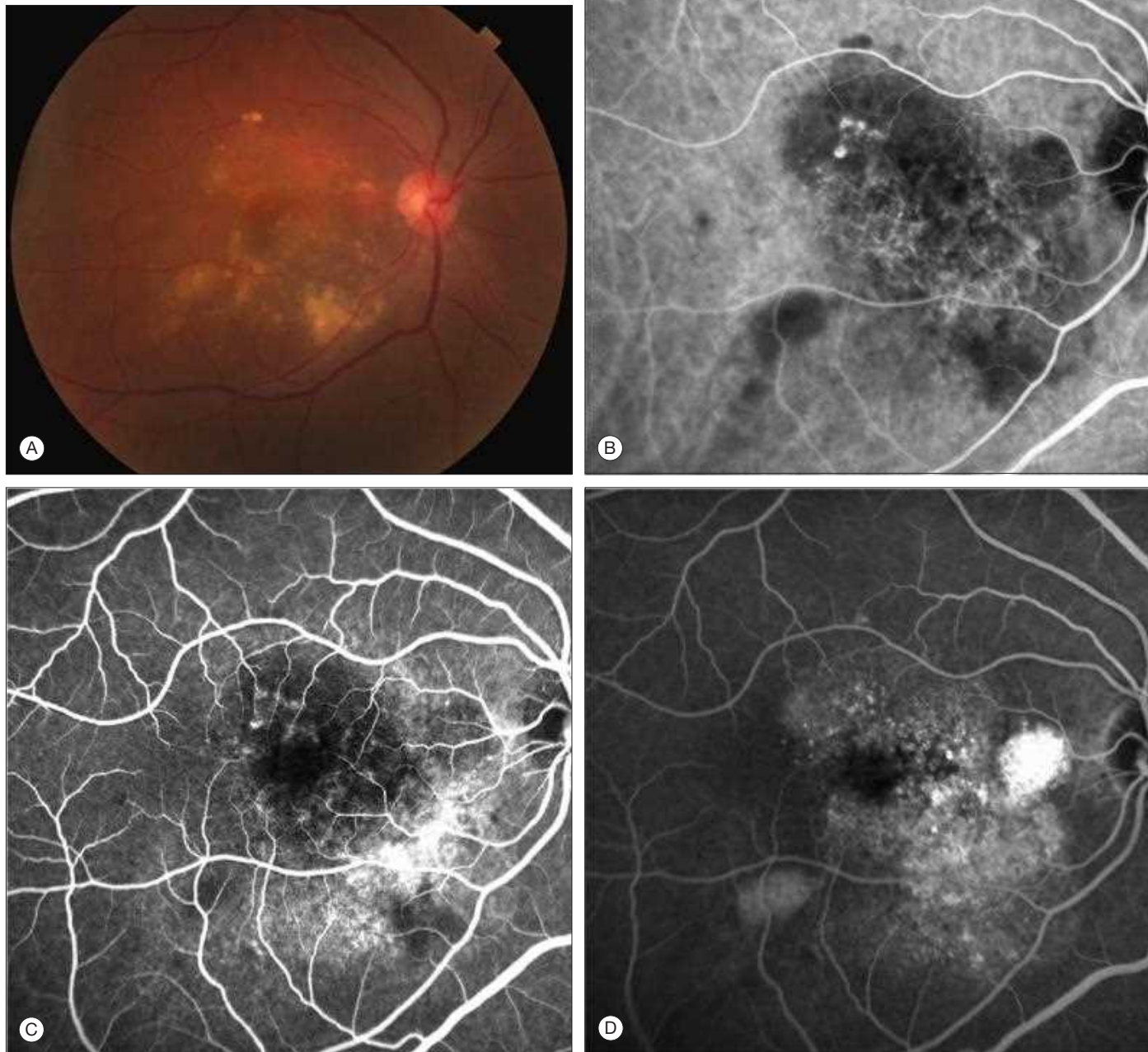
GA initially develops as focal areas of depigmentation. Eventually, these coalesce or expand to involve the central macula causing progressive worsening of vision to legal blindness. From the onset of GA, the mean time to legal blindness is 5–9 years (see Fig. 6.29.7).<sup>95,100</sup> Neovascular complications have more of an acute onset with sudden development of central blurring and distortion. If left untreated, the area of neovascularization expands rapidly and a large fibrous scar develops in the macula. A meta-analysis of data from several controlled clinical trials showed that within 3 years of the onset of neovascularization, more than half of untreated eyes will have vision of 20/200 or worse.<sup>101</sup> More than 90% of patients with wet AMD treated with anti-VEGF intravitreal injections will maintain stable vision and one third will have vision improvement.<sup>11,12</sup> Wet AMD is often bilateral, and the risk of a fellow eye being affected is 30% in a 6-year period.<sup>102</sup> The Macular Photocoagulation Study (MPS) reported that the 5-year risk of neovascularization in fellow eyes of individuals with unilateral neovascular AMD was 10% in those without large drusen and 30%–46% in those with large drusen.<sup>103</sup> These risk estimates have been confirmed by the more recent AREDS.<sup>104</sup> The MPS and AREDS showed that in patients with unilateral neovascular AMD, the 5-year risk of developing neovascularization in fellow eyes that manifest both soft drusen and focal hyperpigmentary changes was >50%.<sup>103,104</sup>

## TREATMENT AND PREVENTION

### Dry AMD

Currently, there is no proven therapy that stops the progression of dry AMD. Vitamin supplementation, dietary modification, and cessation of smoking are the current recommendations thought to slow the progression of visual acuity loss in dry AMD.<sup>105</sup> The AREDS (Age-Related Eye Disease Study) study was the first large, prospective trial to show a benefit of antioxidant and zinc supplementation on the progression of AMD and the associated vision loss.<sup>9,106</sup> In these studies, a combination of oral supplementation of vitamin C (500 mg), vitamin E (400 IU), beta-carotene (15 mg), zinc oxide (80 mg), and cupric oxide (2 mg) was beneficial in patients at high risk of developing advanced stages of AMD, lowering the risk by about 25%. The relative risk of vision loss of  $\geq 3$  lines was reduced by 19% in patients taking the supplementation. The high-risk group included patients with advanced AMD in one eye and those with intermediate dry AMD, defined as extensive intermediate-size drusen ( $\geq 63$   $\mu\text{m}$  but  $<125$   $\mu\text{m}$ ), at least one large druse ( $\geq 125$   $\mu\text{m}$ ), or noncentral GA in one or both eyes. Cases of advanced AMD were defined as having any evidence of neovascularization (photocoagulation or other treatment for CNV, hemorrhage under the retina or RPE, or subretinal fibrosis), central GA, or nondrusenoid PED, including serous RPE detachment. Other studies with oral supplementation have demonstrated an increased risk of lung cancer in smokers who take beta-carotene.<sup>107</sup> For this reason, it is recommended that smokers should be offered a form of AREDS vitamin supplementation without beta-carotene. The AREDS 2 study revealed no additional





**Fig. 6.29.9 Right Eye of a 66-Year-Old Female With Polypoidal Choroidal Vasculopathy (PCV).** (A) Color fundus image. (B) Indocyanine green angiography showing polyps. (C–D) Early-phase fluorescein angiography and late-phase fluorescein angiography.

benefit of adding lutein and zeaxanthin (carotenoids), and omega-3 long-chain polyunsaturated fatty acids (docosahexaenoic acid eicosapentaenoic acid) to the original AREDS formula in reducing the risk of AMD progression.<sup>108</sup>

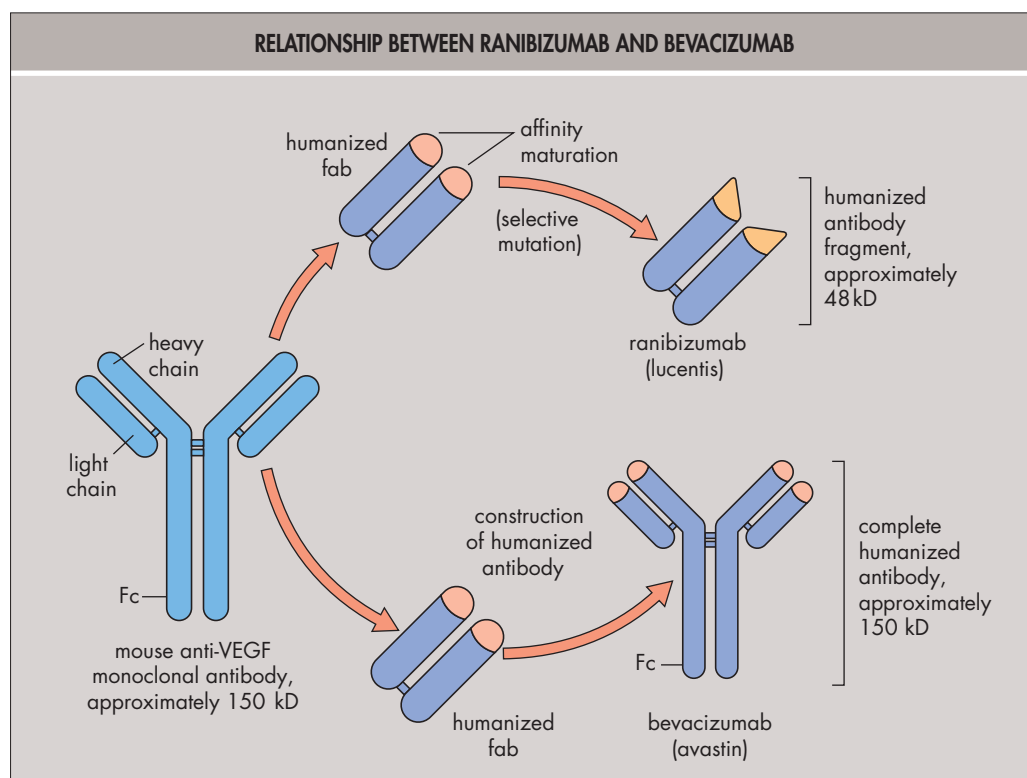
On the basis of the multifactorial pathogenesis of AMD, various strategies have been proposed to treat the nonexudative form of AMD, but these strategies have had limited success to date. Given the genetic association between complement pathway polymorphisms and the risk of AMD, numerous trials of anticomplement drugs have been conducted. Early investigations with a systemic C5 inhibitor (eculizumab) did not show any benefit in reducing GA progression or drusen volume.<sup>109</sup> In phase III studies, the anti-factor D antibody lampalizumab failed to slow the enlargement of GA.<sup>110</sup> A phase IIb/III study for GA with the visual cycle modulator emixustat did not show any difference in lesion growth rate compared with placebo.<sup>111</sup> A small pilot study with high-dose atorvastatin showed promising results with resolution of drusenoid pigment epithelial detachment in patients with high-risk dry AMD.<sup>112</sup> In addition, neuroprotective agents, as well as cell-based and gene therapies,<sup>113–115</sup> are under investigation.

## Neovascular AMD

Several treatments for neovascular AMD have been extensively studied in large, prospective, randomized trials. These include thermal laser photocoagulation,<sup>116–120</sup> photodynamic therapy (PDT) with verteporfin (Visudyne; Novartis Ophthalmics and QLT Inc.), and anti-VEGF drugs, including pegaptanib sodium (Macugen; Eyetech/OSI), bevacizumab (off-label, Avastin; Genentech, South San Francisco), ranibizumab (Lucentis; Genentech, South San Francisco), and aflibercept (Eylea; Regeneron, Tarrytown, NY). Currently, the standard of care for the treatment of neovascular AMD involves the intravitreal injection of bevacizumab or ranibizumab or aflibercept.

## Verteporfin Photodynamic Therapy

PDT uses low-energy light to activate an intravenously injected photosensitizing agent and induce closure of a neovascular complex.<sup>121,122</sup> The goal of PDT is to specifically target neovascular tissue while sparing surrounding and overlying retinal structures.<sup>123</sup>



**Fig. 6.29.10 Relationship Between Ranibizumab and Bevacizumab.** (Redrawn with permission from Steinbrook R. The price of sight: ranibizumab, bevacizumab, and the treatment of macular degeneration. *N Engl J Med* 2006;355:1409–12.)

Two large, prospective trials evaluated verteporfin PDT for the treatment of subfoveal CNV caused by AMD: the Treatment of AMD with Photodynamic Therapy (TAP) study and the Verteporfin in Photodynamic Therapy (VIP) study. At 24 months, the TAP study demonstrated lower rates of moderate vision loss in patients with predominantly classic CNV treated with verteporfin PDT (47%) compared with placebo (62%).<sup>124,125</sup> At 24 months, the VIP study, which included mostly patients with occult CNV but without classic CNV, identified a statistically significant benefit, with 54% in the verteporfin group experiencing moderate vision loss compared with 67% in the placebo group. However, 4% of verteporfin-treated eyes experienced acute severe visual acuity decrease, defined as a loss of  $\geq 20$  letters within 7 days of treatment. Causes of severe visual acuity decrease included hemorrhage, neurosensory detachment, and idiopathic visual acuity loss, which was most likely caused by choroidal infarction.<sup>126</sup>

Attempts to optimize visual acuity outcomes have explored delayed light application in the Verteporfin with Altered Light in Occult CNV (VALIO) study<sup>127</sup> and reduced fluence in the Verteporfin in Minimally Classic CNV (VIM) study.<sup>128</sup> However, no added benefit was observed. Another option pioneered by Spaide<sup>129</sup> was to combine PDT with intravitreal triamcinolone acetonide in the hope of improving visual acuity outcomes with PDT and decreasing the treatment burden.

## Anti-VEGF Therapies

VEGF-A stimulates both angiogenesis and increased vascular permeability and is the major angiogenic factor implicated in the pathogenesis of exudative eye diseases.<sup>130</sup> In humans, four major isoforms of VEGF-A have been identified as a result of alternative RNA splicing (VEGF<sub>121</sub>, VEGF<sub>165</sub>, VEGF<sub>189</sub>, and VEGF<sub>206</sub>), and at least five minor isoforms exist as well (VEGF<sub>145</sub>, VEGF<sub>148</sub>, VEGF<sub>162</sub>, VEGF<sub>165b</sub>, VEGF<sub>183</sub>). The larger VEGF-A isoforms can be cleaved by plasmin and metalloproteinases to produce the diffusible, biologically active, cleavage products VEGF<sub>110</sub> and VEGF<sub>113</sub>, respectively.<sup>131,132</sup> Although VEGF<sub>165</sub> is the most prevalent form of VEGF, all the aforementioned isoforms and proteolytic products are biologically active, with VEGF<sub>121</sub> being the most common isoform in the early stages of experimental CNV in animal models.<sup>133</sup> The consistent correlation between pathological neovascularization in the eye and the expression of VEGF-A provided strong evidence to suggest that inhibition of VEGF-A in the eye could be a viable treatment strategy for the treatment of exudative ocular diseases.<sup>134</sup>

### Pegaptanib Sodium

Pegaptanib sodium (Macugen; Eyetech/Valeant Pharmaceuticals) was the first VEGF-A inhibitor approved by the U.S. Food and Drug Administration (FDA) in 2004 for the treatment of neovascular AMD. Pegaptanib is

an RNA aptamer that binds and inhibits VEGF<sub>165</sub> and larger isoforms of VEGF-A, much like an antibody would bind an antigen.

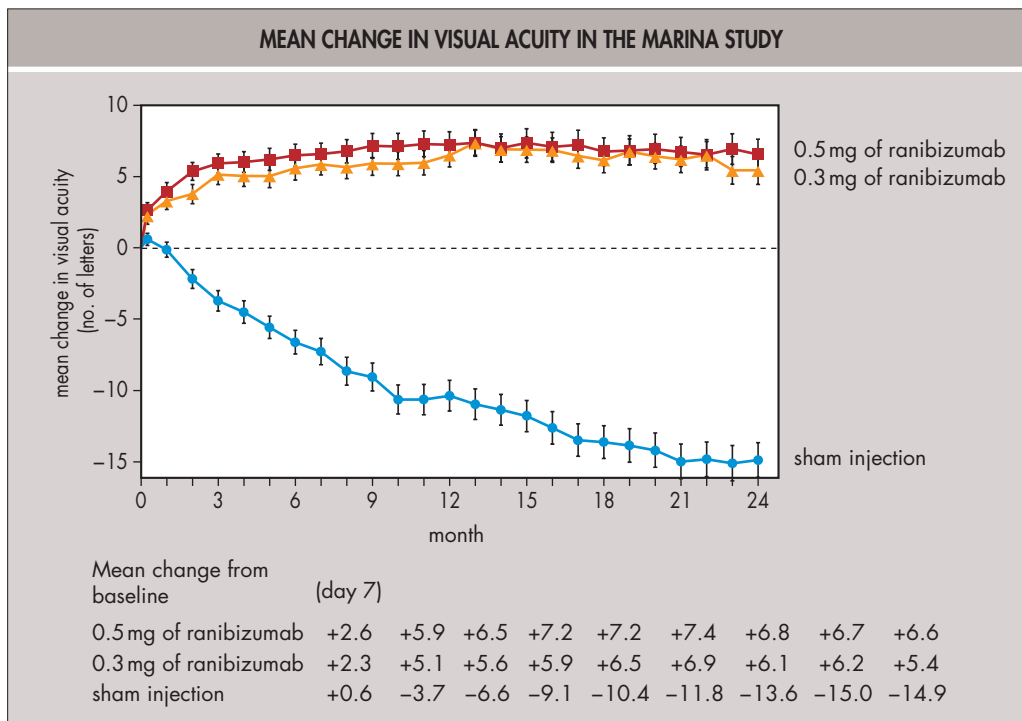
Two concurrent phase II/III multicenter, randomized, double-blind, sham-controlled, 2-year studies led to FDA approval in 2004. These pivotal clinical trials were known as the VEGF Inhibition Study in Ocular Neovascularization (VISION) trials. In these trials, patients with neovascular AMD were randomized to receive intravitreal injections of pegaptanib sodium (0.3, 1.0, or 3.0 mg) or sham injection at six-week intervals for 48 weeks.<sup>135,136</sup> At 1 year, in 70% of patients treated with 0.3 mg pegaptanib loss of 15 letters was prevented, compared with 55% in the control group ( $P < 0.001$ ). However, only 6% of pegaptanib-treated patients gained at least 15 letters of visual acuity. The 2-year results demonstrated that patients treated with 0.3 mg pegaptanib for 2 years were more likely to maintain visual acuity compared with patients who received usual care for 2 years or who stopped pegaptanib sodium treatment after 1 year.<sup>136</sup>

### Ranibizumab

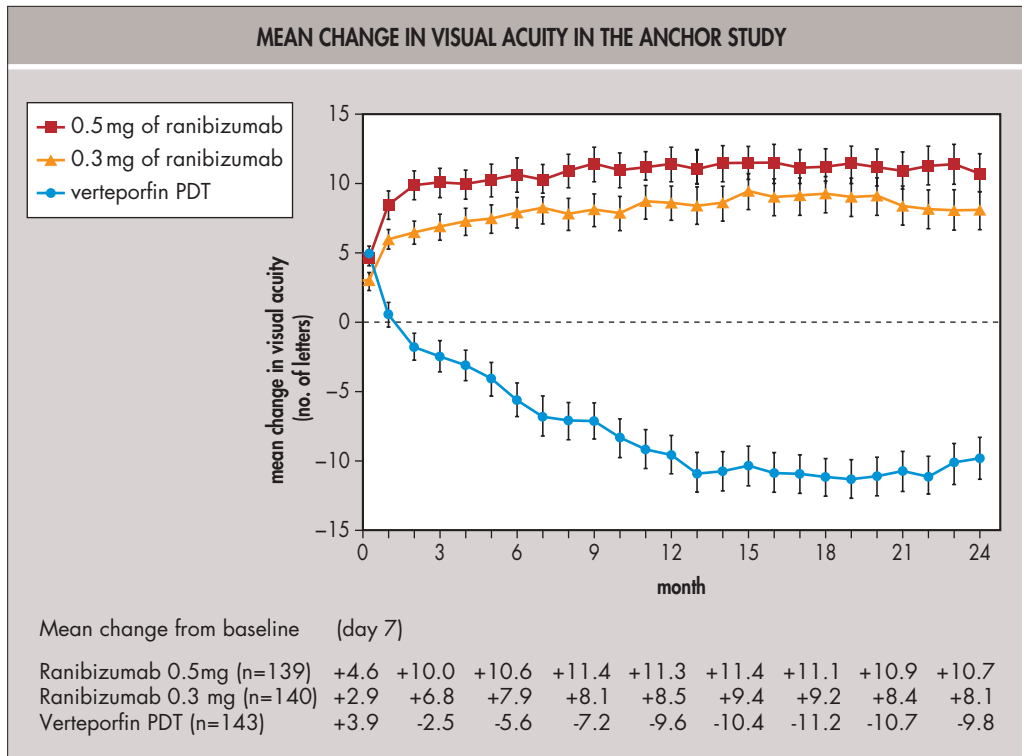
Ranibizumab is the antigen-binding fragment (Fab) of a monoclonal humanized antibody that binds and inhibits all the aforementioned biologically active forms of VEGF-A (Fig. 6.29.10).<sup>137</sup>

Ranibizumab is administered as an intravitreal injection and received FDA approval in 2006 on the basis of two pivotal phase III trials known as MARINA (Minimally Classic/Occult Trial of the Anti-VEGF Antibody Ranibizumab in the Treatment of Neovascular AMD) and ANCHOR (Anti-VEGF Antibody Ranibizumab for the Treatment of Predominantly Classic Choroidal Neovascularization in AMD). The MARINA trial was a randomized, double-masked, sham-controlled, 2-year study of monthly intravitreal ranibizumab (0.3 or 0.5 mg) in minimally classic or occult CNV secondary to AMD.<sup>12</sup> At 2 years, in 92% and 90% of treated patients (0.3 and 0.5 mg, respectively) a 15-letter loss was prevented compared with 53% in the control group ( $P < 0.001$ ). The mean increase in visual acuity was 5.4 and 6.6 letters for the 0.3 mg and 0.5 mg groups, respectively, while the sham-injected group experienced loss of 14.9 letters for a difference of  $>20$  letters between the sham and treated groups ( $P < 0.001$ ) (Fig. 6.29.11). Visual acuity improvement of at least 15 letters was observed in 26% and 33% of treated patients (0.3 and 0.5 mg, respectively) compared with 4% of sham-injected patients ( $P < 0.001$ ). A treatment benefit was observed in the ranibizumab-treated group compared with the sham group regardless of the patient's gender, age, lesion type, lesion size, or duration of disease.<sup>138</sup> Moreover, the beneficial visual acuity outcomes were associated with improvements in both angiographic and OCT measures.<sup>139</sup>

ANCHOR was a multicenter, randomized, double-masked, 2-year study comparing monthly intravitreal ranibizumab (0.3 or 0.5 mg) with verteporfin PDT in patients with predominantly classic CNV secondary to AMD. At 2 years, in 90% and 89.9% of treated patients (0.3 and 0.5 mg, respectively)



**Fig. 6.29.11 Mean Change from Baseline in Visual Acuity at 12 and 24 Months in the MARINA Study.** (Redrawn with permission from Rosenfeld PJ, Brown DM, Heier JS, et al. Ranibizumab for neovascular age-related macular degeneration. *N Engl J Med* 2006;355:1419–31.)



**Fig. 6.29.12 Mean Change from Baseline in Visual Acuity at 12 and 24 Months in the ANCHOR Study.** (From Brown DM, Michels M, Kaiser PK, et al. Ranibizumab versus verteporfin photodynamic therapy for neovascular age-related macular degeneration: two-year results of the ANCHOR study. *Ophthalmology* 2009 Jan;116(1):57–65.e5.)

a 15-letter loss was prevented compared with 65.7% in the control group ( $P < 0.001$ ). The mean increase in visual acuity was 8.1 and 10.7 letters for the 0.3 mg and 0.5 mg groups, respectively, while the PDT-treated group lost 9.8 letters ( $P < 0.001$ ) (Fig. 6.29.12). Visual acuity improvements of at least 15 letters were observed in 34.3% and 41% of treated patients (0.3 and 0.5 mg, respectively) compared with 6.3% of PDT-treated controls ( $P < 0.001$ ).<sup>14</sup>

### Bevacizumab

Bevacizumab is a full-length humanized monoclonal antibody that binds and inhibits all the biologically active forms of VEGF-A (see Fig. 6.29.10). In 2004, the FDA approved bevacizumab for the treatment of metastatic colorectal cancer. At that time, a study was initiated to explore the off-label use of intravenous bevacizumab for the treatment of neovascular AMD. This study, known as the Systemic Avastin Therapy for Neovascular AMD (SANA) Study, showed that systemic bevacizumab could reduce leakage from CNV and significantly improve vision and decrease OCT central

retinal thickness in patients with neovascular AMD.<sup>140,141</sup> A mild elevation of mean systolic and diastolic blood pressures by 3 weeks (+11 mm Hg,  $P \equiv 0.004$ ; +8 mm Hg,  $P < 0.001$ ) was the only reported adverse event.

In May 2005, the first patient was treated with an intravitreal dose of bevacizumab, and the response appeared identical to the responses previously observed with systemic bevacizumab and intravitreal ranibizumab.<sup>142</sup> Since that initial case was reported, subsequent retrospective and prospective studies have reported significant improvement in mean visual acuity and reduced OCT central retinal thickness in patients with neovascular AMD following monthly or OCT-guided intravitreal bevacizumab at doses ranging from 1.25 to 2.5 mg.<sup>143-165</sup>

### Ranibizumab Versus Bevacizumab

To better assess bevacizumab's safety and efficacy compared with ranibizumab, the National Eye Institute sponsored the Comparison of Age-Related Macular Degeneration Treatments Trial (CATT). The CATT study compared bevacizumab with ranibizumab in neovascular AMD

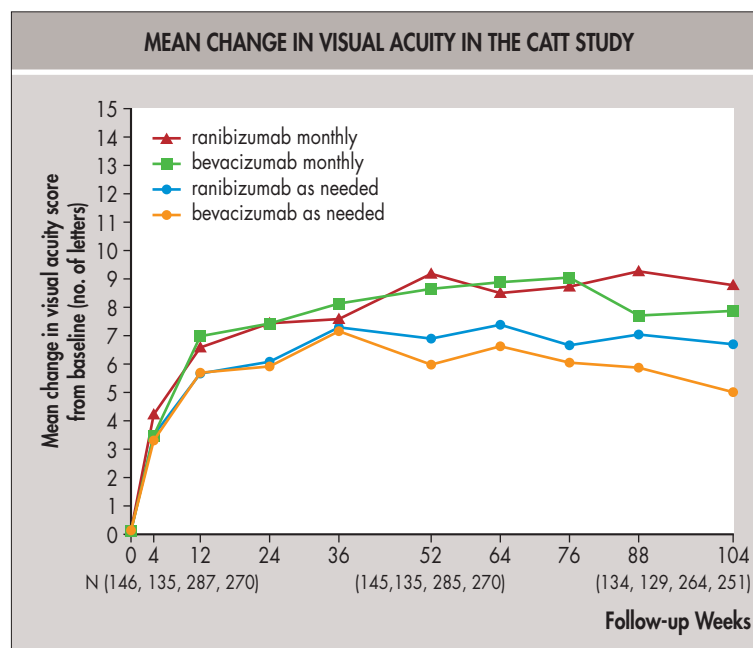


patients with all major lesion subtypes on either a monthly or “as needed” injection schedule with monthly evaluation. At 1 year, bevacizumab and ranibizumab were equivalent when administered monthly, with an increase of 8.0 and 8.5 letters, respectively. Bevacizumab administered as needed was equivalent to ranibizumab as needed, with an improvement of 5.9 and 6.8 letters, respectively. The proportion of patients who gained at least 15 letters at the end of the first year did not differ significantly among the groups, ranging from 24.9% in the ranibizumab-as-needed group to 34.2% in the ranibizumab-monthly group ( $P = 0.09$ ). In the second year of the CATT trial, patients receiving monthly treatment were randomly reassigned to the as-needed or the monthly treatment group. For both drugs, the visual outcomes at 2 years were slightly better for those maintained on monthly treatment for 2 years compared with those receiving as-needed treatment for both years or only the second year (Fig. 6.29.13). In a period of 1 year, there were no differences between the groups with regard to rates of death, myocardial infarction, and stroke.<sup>13,16</sup>

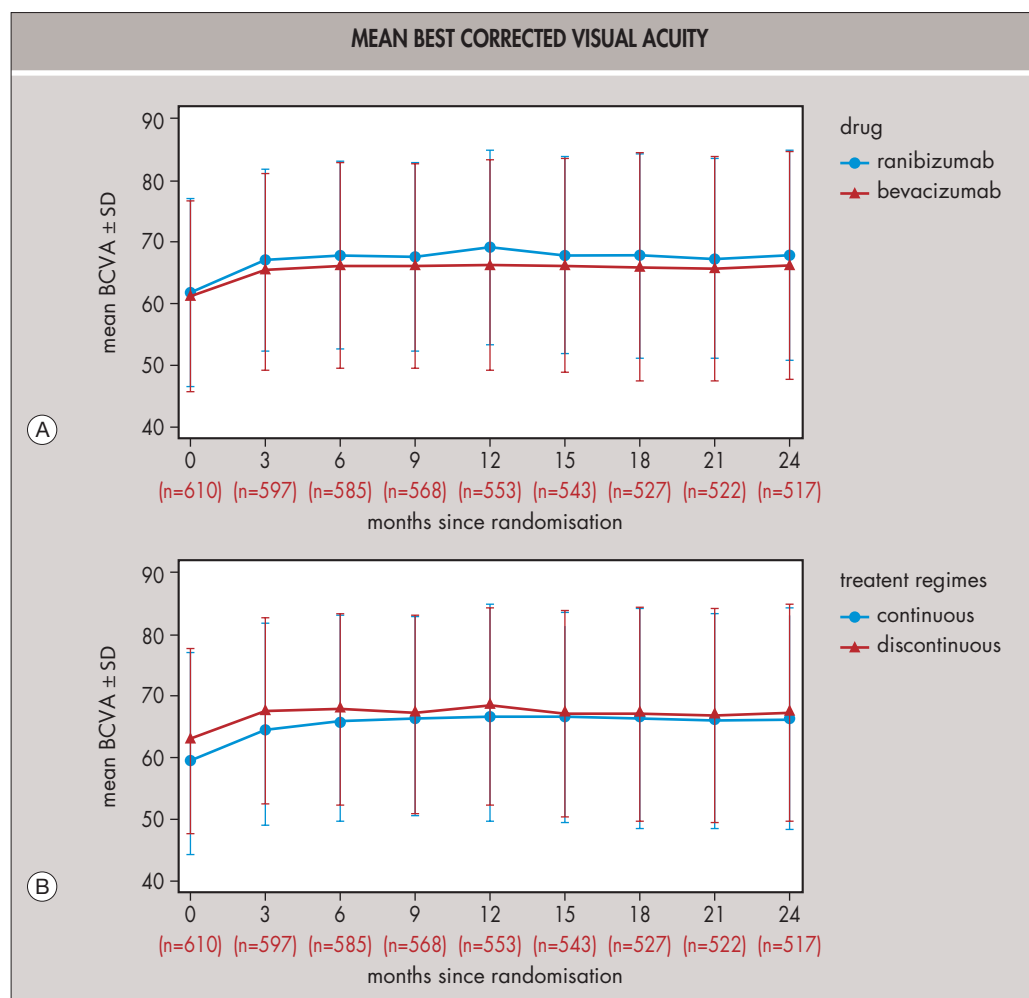
In the United Kingdom, the Alternative Treatments to Inhibit VEGF in Age-Related Choroidal Neovascularization (IVAN) randomized trial also compared both drugs given on a monthly or as-needed basis. One difference from the CATT trial was that all patients received three consecutive monthly injections to start the trial and three consecutive monthly injections whenever retreatment was required in the as-needed groups. The analyses were inconclusive when comparing the change in visual acuity between both drugs, but the outcomes would have been equivalent if IVAN had used the same noninferiority endpoints as CATT. IVAN did show equivalence when comparing monthly to as-needed treatments at 1 year (Fig. 6.29.14). The serum VEGF level was lower with bevacizumab ( $P < 0.0001$ ) and higher with discontinuous treatment ( $P = 0.004$ ); however, the clinical importance of this finding remains unclear. Regarding safety profiles, arteriothrombotic events and heart failures occurred more often with ranibizumab than with bevacizumab ( $P = 0.03$ ); however, these events occurred in <2% of patients.<sup>15</sup> After 2 years,<sup>166</sup> comparison by drug was inconclusive, using the preset of noninferiority of 3.5 letter limit ( $P = 0.26$ ). Continuous and discontinuous treatments were equivalent for distance VA ( $P = 0.18$ ). Other smaller clinical trials comparing both drugs have been conducted in the United States and Switzerland and showed similar results.<sup>167,168</sup>

## Aflibercept

Aflibercept, a fusion protein containing VEGF receptor ligand-binding domains and the Fc region of immunoglobulin G1 (IgG1), has been studied both as an intravenous and intravitreal drug (Fig. 6.29.15). A phase I/II study using aflibercept intravenously showed efficacy, but the higher dose of 3.0 mg caused dose-limiting toxicities, which included hypertension and proteinuria.<sup>169</sup> Phase III studies (VEGF Trap-Eye: Investigation of



**Fig. 6.29.13 Mean Change from Baseline in Visual Acuity at 12 and 24 Months in the CATT Study.** (From Martin DF, Maguire MG, Fine SL, et al. Ranibizumab and bevacizumab for treatment of neovascular age-related macular degeneration: two-year results. *Ophthalmology* 2012 Jul;119(7):1388–98.)



**Fig. 6.29.14 Mean Best Corrected Visual Acuity Through 24 Months in the IVAN Study.** (From Chakravarthy U, Harding SP, Rogers CA, et al. A randomised controlled trial to assess the clinical effectiveness and cost-effectiveness of alternative treatments to Inhibit VEGF in Age-related choroidal Neovascularisation (IVAN). *Health Technol Assess* 2015 Oct;19(78):1–298.)

Efficacy and Safety in Wet AMD [VIEW] 1 and 2) compared 0.5 or 2.0 mg of intravitreal aflibercept administered monthly for 3 consecutive months, followed by the same doses every 4 weeks or 2 mg every 8 weeks compared with ranibizumab 0.5 mg every 4 weeks. Patients were followed up for 24 months. VIEW 1 was conducted in the United States and Canada and showed that 95%–96% of the patients treated with aflibercept maintained visual acuity compared with 94% in the ranibizumab group. The mean visual acuity improvement from baseline was greater in patients receiving aflibercept 2 mg monthly compared with ranibizumab (10.9 versus 8.1 letters;  $P < 0.01$ ). In VIEW 2, conducted in Europe, Asia Pacific, Japan, and Latin America, 96% of patients in each aflibercept group achieved maintenance of vision compared with 94% in the ranibizumab group. There was no statistically significant difference between the mean change in visual acuity of all groups in VIEW 2 (Fig. 6.29.16).<sup>170</sup> The treatment has shown to be safe and well tolerated in all aflibercept studies.<sup>170-172</sup> In the second year

of VIEW 1 and VIEW 2, patients were followed up monthly with a PRN (Pro ReNata) protocol, but with a maximum interval of 12 weeks between injections. When analyzing VIEW 1 and 2 together, the results obtained in the first year persisted through the second year, with no statistically significant difference between the mean changes in visual acuity and stability of vision in all groups.<sup>170,171</sup>

## Anti-VEGF Treatment Regimens

Intravitreal ranibizumab was the first FDA-approved treatment for neovascular AMD that improved visual acuity outcomes in most patients and prevented the leakage and growth of neovascularization in all the major angiographic forms of CNV. Although these results were impressive, they were achieved by performing monthly intravitreal injections. In an attempt to decrease the burden of monthly injections, alternative dosing strategies were pursued (Fig. 6.29.17).

In the Phase IIIb, Multicenter, Randomized, Double-Masked, Sham Injection-Controlled Study of the Efficacy and Safety of Ranibizumab (PIER) study, patients were randomized to receive either the 0.3 or 0.5 mg dose of ranibizumab or a sham injection. They were treated monthly for 3 consecutive months followed by a treatment every 3 months thereafter. At 2 years, mean visual acuity had decreased an average of 2.2 and 2.3 letters from baseline and only 15% and 8.2% of patients treated gained at least 15 letters (in 0.3 mg and 0.5 mg, respectively).<sup>173</sup> Although these results were better than those in the sham-injected control group, these outcomes were not as good as the visual acuity outcomes of monthly dosing observed in the MARINA and ANCHOR studies.

The EXCITE (Efficacy and Safety of Ranibizumab in patients with Subfoveal CNV secondary to AMD) study was designed to compare monthly regimens with quarterly regimens.<sup>174</sup> The monthly group maintained the initial gains in visual acuity with a final improvement of 8.3 EDTRS letters at 12 months. The quarterly groups had visual acuity improvement at the end of the first 3 months, with a subsequent decline in visual acuity over 12 months of follow-up, showing a gain of 4.9 and 3.8 letters in the 0.3 mg and the 0.5 mg quarterly groups, respectively.

An individualized dosing strategy utilizing OCT was investigated in a study known as PrONTO (Prospective OCT Imaging of Patients with Neovascular AMD Treated with Intracocular Ranibizumab). This phase I/II study enrolled 40 patients and explored whether dosing that was based on the presence of fluid in the macula as detected by OCT could result in fewer injections but achieve visual acuity outcomes similar to the results obtained with monthly dosing.<sup>175</sup> The study design mandated three consecutive monthly injections with intravitreal ranibizumab (0.5 mg). Then, from month 3 through month 24, patients were examined monthly with OCT and additional injections were performed only if certain OCT-based criteria were fulfilled. After 1 year, the mean improvement in visual acuity from baseline was 9.3 letters ( $P < 0.001$ ), and at 2 years, it was 11.1 letters

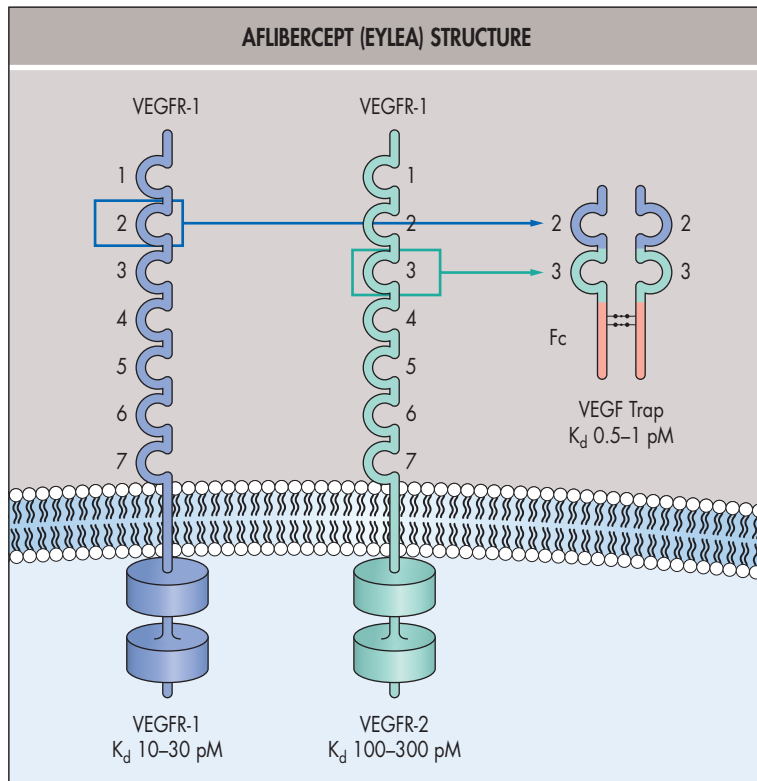


Fig. 6.29.15 Aflibercept Structure.

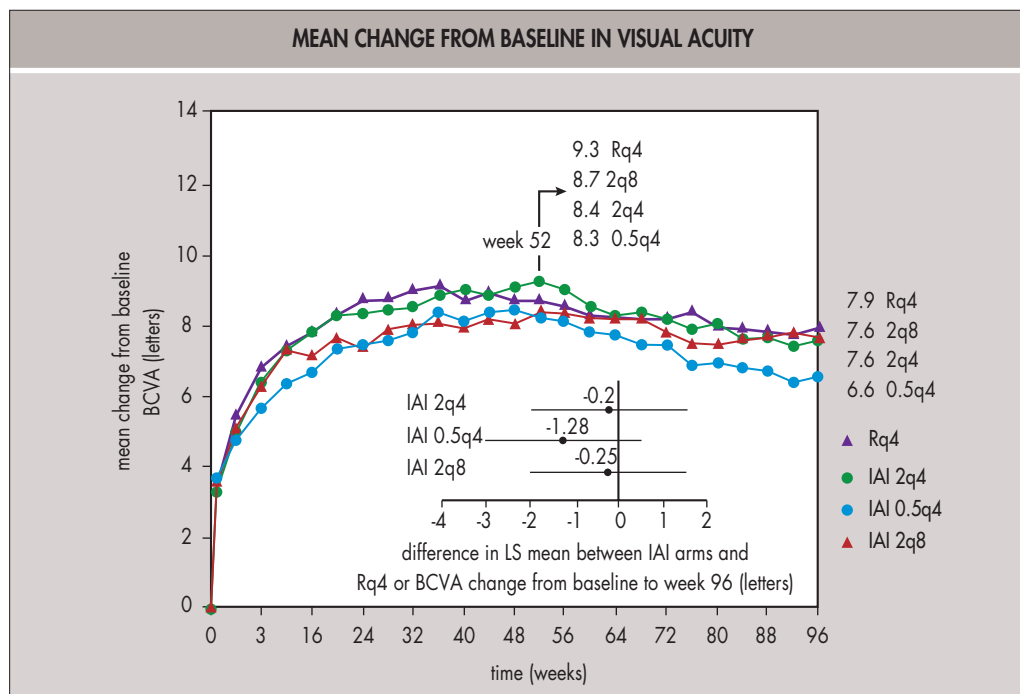


Fig. 6.29.16 Mean Change from Baseline in Visual Acuity at 24 Months in the VIEW 1 and VIEW 2 Studies. (From Schmidt-Erfurth U, Kaiser P, Korobelnick JF, et al. Intravitreal aflibercept injection for neovascular age-related macular degeneration. *Ophthalmology* 2014;121:193–201.)

( $P < 0.001$ ). More than one third of eyes (35%) in PrONTO gained at least 15 letters of visual acuity at 1 year and 43% gained at least 15 letters at 2 years. These visual acuity outcomes were comparable with the outcomes in the MARINA and ANCHOR trials. Moreover, these visual acuity outcomes were achieved with an average of 5.6 of a maximum of 13 monthly injections the first year and 9.9 injections out of a maximum of 25 monthly injections over 2 years.<sup>176</sup>

Another OCT-based retreatment strategy known as “treat and extend” has been widely adopted, with the goal of reducing the number of injections and as well as the number of visits while maintaining optimal visual results.<sup>177,178</sup> In this approach, in the absence of signs of exudation based on OCT and clinical examination, injections intervals are gradually extended, typically up to a maximum of 12 weeks. In the LUCAS (Lucentis Compared

to Avastin Study) trial, the treatment interval was extended by 2 weeks at a time, up to a maximum interval of 12 weeks.<sup>179</sup> After 24 months of follow-up, visual results with bevacizumab were equivalent to those with ranibizumab, with 7.4 and 6.6 letters gained with a mean of 18.2 injections for bevacizumab and 16.0 injections for ranibizumab ( $P < 0.001$ ).<sup>180</sup>

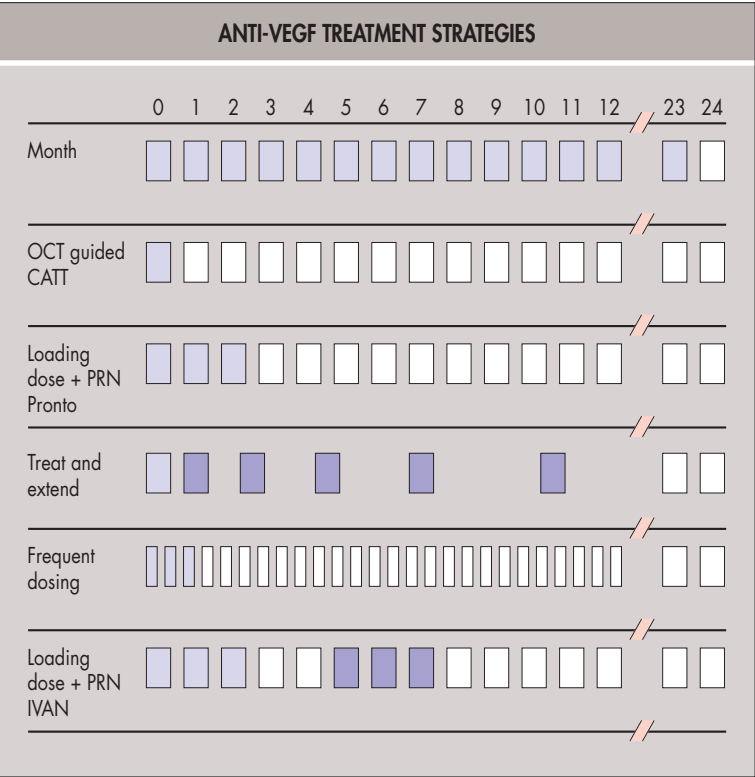
To determine if a higher dose of ranibizumab could provide similar or improved visual outcomes with less frequent treatment, the HARBOR trial (Study of Ranibizumab Administered Monthly or on an As-needed Basis in Patients with Subfoveal Neovascular Age-related Macular Degeneration) randomized 1098 patients into four groups: 0.5 mg versus 2.0 mg and monthly versus as-needed dosing following three monthly injections. After 24 months of follow-up, the mean improvement in visual acuity was similar among all treatment groups (+9.1, +8.0, +7.9, and +7.6 letters for the 0.5 mg monthly, 2.0 mg monthly, 0.5 mg as-needed, 2.0 mg as-needed groups, respectively) (see Fig. 6.29.18). The average number of injections in year 2 was 5.6 for the as-needed groups and 4.3 for the 0.5 mg and 2.0 mg groups, respectively. The higher dose of ranibizumab was not proven to provide additional efficacy or durability, but the study provided additional confirmation that OCT-guided treatment with the 0.5 mg dose can achieve the expected visual results with fewer injections.<sup>181</sup>

### Combination Therapies

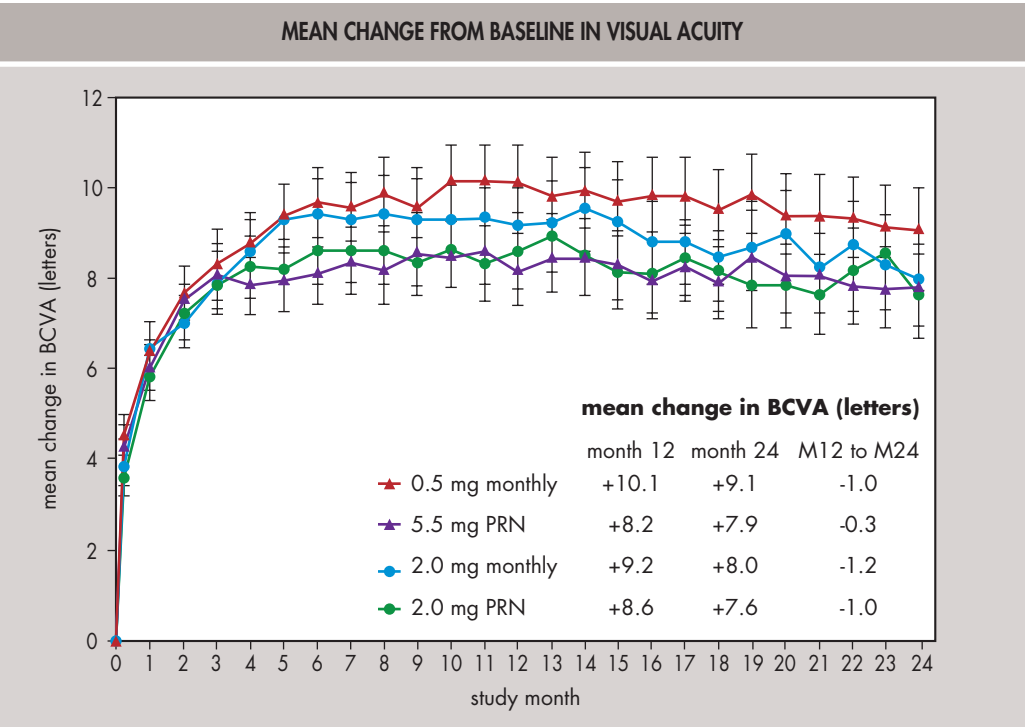
#### Anti-VEGF Therapy Plus PDT

The combination of anti-VEGF injections and PDT has been explored as a means of reducing injection frequency. The MONT BLANC study compared the efficacy and safety of standard-fluence PDT with as-needed ranibizumab versus as-needed ranibizumab as monotherapy,<sup>182</sup> and the DENALI study compared monthly ranibizumab monotherapy versus as-needed ranibizumab combined with reduced-fluence or standard-fluence PDT.<sup>183</sup> Both studies showed comparable results between monotherapy and combination therapy.<sup>182,183</sup> Moreover the MONT BLANC study did not show that combination therapy significantly reduced the number of ranibizumab injections in 1 year.<sup>182</sup> The verteporfin and bevacizumab (VIA) study<sup>184</sup> was a very small randomized double-masked clinical trial comparing bevacizumab combined with reduced-fluence PDT (25 J/cm<sup>2</sup> and 12 J/cm<sup>2</sup>) versus bevacizumab alone. The investigators found that the combination of bevacizumab with PDT significantly reduced the frequency of bevacizumab retreatment through 6 months.

Although superior functional or anatomical results have not been proven with combination PDT and anti-VEGF therapy in typical neovascular AMD, it does appear that this combination therapy is more efficacious for the polypoidal choroidal vasculopathy. The EVEREST study showed that PDT alone or in combination with ranibizumab was more effective at inducing complete polyp regression at 6 months.<sup>185</sup> One-year results of the EVEREST 2 study further demonstrated that combination therapy

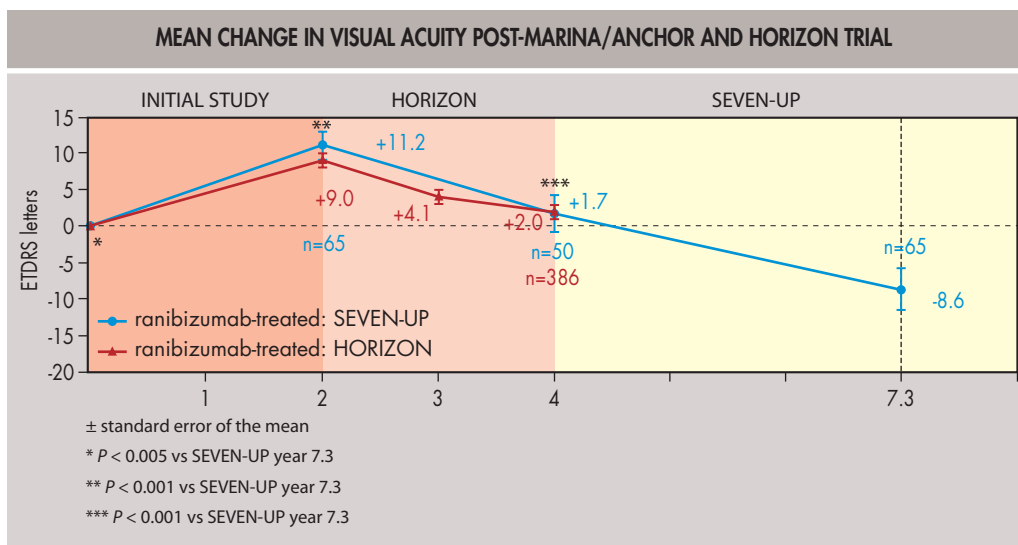


**Fig. 6.29.17** The different treatment strategies using anti-vascular endothelial growth factor (VEGF) therapy for neovascular age-related macular degeneration (AMD).



**Fig. 6.29.18** Mean Change from Baseline in Visual Acuity at 24 Months in the HARBOR Study. (From Ho AC, Busbee BG, Regillo CD, et al. Twenty-four-month efficacy and safety of 0.5 mg or 2.0 mg ranibizumab in patients with subfoveal neovascular age-related macular degeneration. *Ophthalmology* 2014 Nov;121(11):2181–92.)





**Fig. 6.29.19** Mean Change in Visual Acuity in the 7-Year Observational Update of Patients With Age-Related Macular Degeneration (AMD) After the MARINA/ANCHOR and HORIZON Trials. (From Rogagha S, Bhisitkul RB, Boyer DS, et al. Seven-year outcomes in ranibizumab-treated patients in ANCHOR, MARINA, and HORIZON. A multicenter cohort study (SEVEN-UP). *Ophthalmology* 2013;120:2292–99.)

with PDT and ranibizumab achieves better visual outcomes, more complete polyp regression, and fewer injections compared with ranibizumab monotherapy.<sup>186</sup>

### Anti-VEGF Therapy Plus PDGF Inhibitors

Combination pharmacotherapy with other targeted agents is also being explored in the hopes of enhancing antiangiogenic activity. Platelet-derived growth factor (PDGF) binds to PDGF receptors, which are located on fibroblast, pericytes, and vascular smooth muscle.<sup>187</sup> Experimental studies have shown that PDGF inhibitors disturb the pericyte–endothelial interaction, sensitizing VEGF-resistant vessels and facilitating regression of neovessels. Additionally, blocking PDGF also appears to inhibit recruitment of profibrotic cells, such as fibroblasts and macrophages.<sup>188,189</sup> Therefore, dual inhibition of VEGF and PDGF has the potential to be a more potent inhibitor of the neovascularization as well as prevent fibrosis. Two multicenter, randomized, double-masked, controlled phase 3 clinical studies comparing the anti-PDGF agent Fovista (pegpleranib) in combination with ranibizumab to ranibizumab monotherapy showed that there was no visual acuity benefit at month 12 with this combination therapy.<sup>190</sup> The phase II CAPELLA (Study of Intravitreal REGN2176-3 in Patients With Neovascular (“Wet”) Age-Related Macular Degeneration) study evaluating the efficacy of aflibercept co-formulated with rinucumab, an anti-PDGFR-beta antibody, also showed no visual acuity benefit compared with aflibercept monotherapy at 12 weeks.<sup>191</sup> Despite these disappointing results, other targets remain under investigation for potential combined anti-angiogenic therapies.

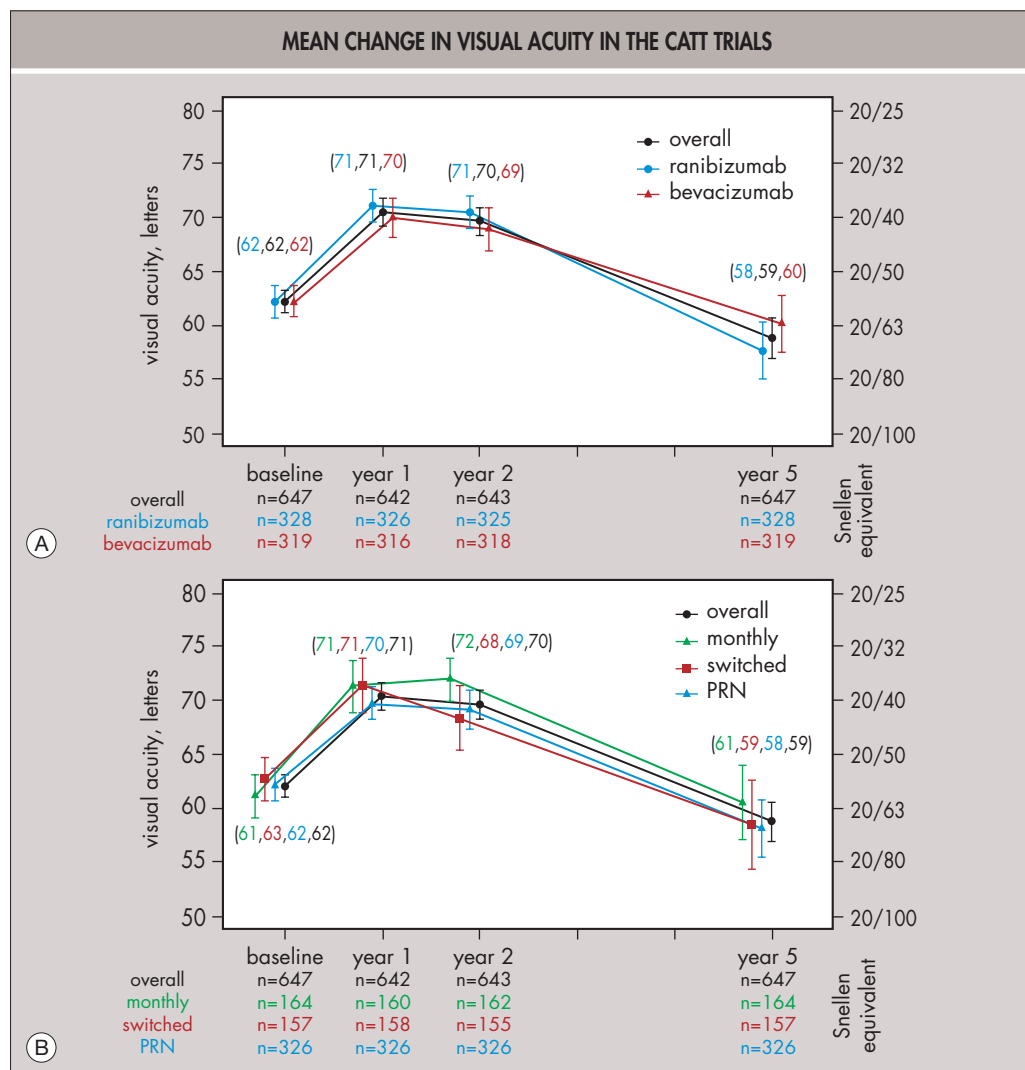
### Long-Term Outcomes With Anti-VEGF Therapy

Compared with the results of anti-VEGF therapy in clinical trials with monthly dosing, long-term visual outcomes in the “real-world” clinical setting appear inferior. The SEVEN-UP study evaluated long-term outcomes in patients enrolled in the ANCHOR, MARINA, and HORIZON trials.<sup>192</sup> Sixty-five patients were followed up for a mean duration of 7.3 years (range, 6.3–8.5 years) after entry into the ANCHOR or MARINA trials. Thirty-seven percent of the eyes had visual acuity better than 20/70, 23% maintained visual acuity better than 20/40, and 37% had visual acuity of

20/200 or worse. Forty-three percent of study eyes had a stable or improved letter score ( $\geq 0$ -letter gain) compared with ANCHOR or MARINA baseline measurements, whereas 34% declined by 15 letters or more, with overall a mean decline of 8.6 letters ( $P < 0.005$ ). After exiting the HORIZON study, study eyes had received a mean of 6.8 anti-VEGF injections during the mean 3.4-year interval; a subgroup of patients who received 11 or more anti-VEGF injections had a significantly better mean gain in letter score compared with time of HORIZON exit ( $P < 0.05$ ) (Fig. 6.29.19). After exit from the CATT trial, 647 patients (71%) were followed up for average of 5.5 years.<sup>193</sup> The mean number of examinations for AMD care after the clinical trial ended was 25.3, and the mean number of treatments was 15.4. Sixty percent of the patients were treated  $\geq 1$  time with a drug other than their assigned drug in CATT. At the 5-year visit, 50% of eyes had visual acuity better than 20/40 and 20% had visual acuity worse than 20/200. Mean change in visual acuity was  $-3$  letters from baseline and  $-11$  letters from the 2-year CATT visit, demonstrating that vision gains were not maintained at 5 years (Fig. 6.29.20).

## CONCLUSIONS

AMD continues to be the leading cause of irreversible visual acuity loss worldwide among older adults. Vitamin supplementation, dietary modifications, and smoking cessation currently remain the only strategies that may slow the progression of dry AMD. For the treatment of wet AMD, ranibizumab, bevacizumab, and aflibercept have revolutionized the prognosis for patients. For the first time, patients can be treated with the expectation that their vision may improve. However, not all patients improve, with 10% losing  $\geq 15$  letters in the course of 2 years, as shown in the phase III ranibizumab trials, and long-term studies<sup>191,192</sup> suggest that the visual acuity gains are not maintained after 5–7 years. The long-term vision loss may be, in some part, related to undertreatment, but it is likely that continued progression of the underlying neurodegenerative process plays a greater role. A multifaceted approach involving prevention, improved drug delivery, and neuroprotective and regenerative strategies will be required to achieve further progress in treatment of AMD.<sup>194</sup>



**Fig. 6.29.20 Mean Visual Acuity Change for 647 Patients in the Comparison of Age-Related Macular Degeneration Treatments (CATT) Trials.** (From Comparison of Age-related Macular Degeneration Treatments Trials (CATT) Research Group. Five-year outcomes with anti-vascular endothelial growth factor treatment of neovascular age-related macular degeneration. *Ophthalmology* 2016;123:1751–1761.)

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# Secondary Causes of Choroidal Neovascularization: Conditions Associated With Breaks in Bruch's Membrane

6.30

Richard F. Spaide

**Definition:** Fibrovascular ingrowth associated with defects in Bruch's membrane, which, in turn, can be caused by a number of disease entities.

## Key Features

- Defects in Bruch's membrane resulting from trauma or disease.
- Neovascular proliferation extending into the subretinal space through the defects in Bruch's membrane.
- Hemorrhage and exudation.
- Late scarring.

## Associated Feature

- Each main cause of angioid streaks has associated findings that are helpful in making the correct diagnosis.

The retina, particularly the inner segments, consumes more oxygen per gram compared with any other tissue in the body, yet these same cells have no direct blood supply. Deep to the retina and retinal pigment epithelium is the choroid, a structure with the highest relative blood flow in the body. Separating retina and choroid are two thin, but important layers: the retinal pigment epithelium (RPE) is a single layer of cuboidal cells whose basement membrane forms the innermost aspect of Bruch's membrane, a 2–4 micron thick multilamellar composite. On the outer side of Bruch's membrane is a dense layer of capillaries, the choriocapillaris, whose basement membrane forms the outer aspect of Bruch's membrane. Between these layers are three additional layers, an inner collagenous zone, a middle elastic zone, and an outer collagenous zone. In youth, Bruch's membrane appears to be a tough pliable structure that appears to lose elasticity with aging and disease. Physical defects in Bruch's membrane may develop in a variety of conditions, as will be discussed in this chapter, and all of them have the development of a sight-threatening problem, choroidal neovascularization (CNV), as a potential complication. The clinical course and treatment of CNV varies somewhat with each underlying cause, and understanding of the disease pathogenesis in each can aid in formulating an ideal treatment strategy.

## TRAUMATIC RUPTURES OF BRUCH'S MEMBRANE

Mechanical defects in Bruch's membrane can arise from significant direct trauma to the eye.<sup>1</sup> For example, a racquet ball fits perfectly into the orbit and, when traveling at >100 km/hr, delivers an impressive amount of kinetic energy. The anteroposterior diameter of the eye is suddenly collapsed, and because of increased hydraulic pressure, there is an equatorial expansion of the eye. The induced stresses in the posterior portion of the eye cause curved ruptures of Bruch's membrane that usually course for various distances away from, but concentric with, the optic disc. The close association with the choriocapillaris sets up the significant morbidity that ruptures in Bruch's membrane may portend. The schism in Bruch's

membrane has the potential to rip the choriocapillaris vessels, leading to hemorrhages that dissect up to the subretinal space. The healing response after choroidal rupture includes fibroblast invasion, RPE hyperplasia, and varying degrees of associated neovascularization.<sup>2</sup> The observed neovascularization is a physiological wound healing response that, for most eyes, follows a stereotypical course. The vessels form as part of the fibroproliferative response and eventual scar formation. In the concluding phases of the wound healing response, the vessels ordinarily regress within the scar, leaving bland fibrous tissue. In some eyes, the CNV seems to take on a life of its own and may secondarily cause further tissue damage through bleeding, fluid exudation, and exaggerated scarring. The reasons for the seemingly excessive neovascular response may include greater inflammatory activity, exaggerated wound healing responses, or any number of variations in cytokine responses.

## Treatment

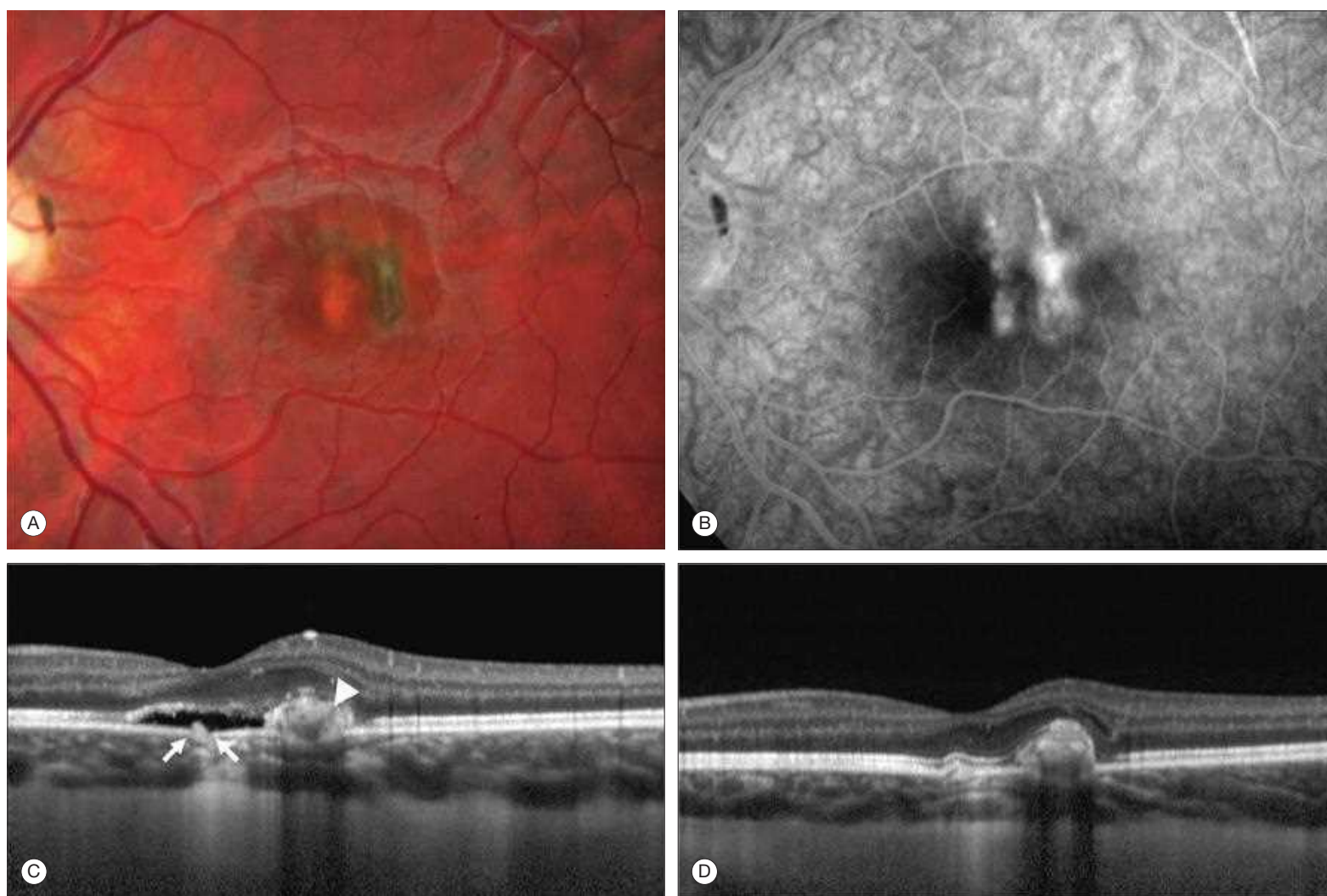
CNV from traumatic choroidal ruptures usually occurs in younger patients, possibly because of the tendency for them to suffer trauma, not because of an inherently increased risk of secondary CNV. The driving forces behind the development of CNV include interplay between vascular endothelial growth factor (VEGF) and potentially many other proinflammatory cytokines. Agents directed against VEGF are a logical part of any treatment strategy, but concurrent anti-inflammatory treatment with a short course of corticosteroids is a reasonable addition for some eyes, particularly if there is clinically evident intraocular inflammation. CNV might not immediately be recognizable as such in eyes with choroidal ruptures after trauma. There are concurrent hemorrhages, and usually early reactive RPE hyperplasia that impede visualization of the underlying choroidal rupture. Fluorescein angiography (FA) shows a focal or more diffuse fluffy border to the choroidal ruptures when early CNV is present. With time, CNV can extend greater distances away from the rupture. Eyes with CNV secondary to choroidal ruptures usually do not require long-term treatment because the neovascularization appears to be part of the wound healing response in general. Aggressive treatment to halt neovascularization and the associated exudation is the first step, to be followed by additional anti-VEGF injections at periodic intervals to prevent possible recurrence of disease. Over the longer term, it is possible to withdraw treatment and achieve a stable outcome (Fig. 6.30.1). There usually is some late flattening and remodeling of the scar.

## ANGIOID STREAKS

Although overt trauma can cause ruptures of Bruch's membrane, fractures can be seen in some conditions without preceding manifest trauma. Because these branching fissures in Bruch's membrane can look like blood vessels, they have been termed *angioid streaks*. These ruptures in Bruch's membrane may be either curvilinear concentric with or radial to the optic disc. There are numerous diseases that cause angioid streaks, but there are a few that account for most of the observed cases. The most common is pseudoxanthoma elasticum (PXE), but other causes are sickle cell anemia and Paget's disease (Fig. 6.30.2).

PXE is a fascinating recessive genetic disorder with considerable phenotypic variability and affects the connective tissue, particularly involving skin, eyes, and the cardiovascular system.<sup>3</sup> Mutations in the *ABCC6*





**Fig. 6.30.1** A 15-year-old male was hit in the eye with a tennis ball and developed loss of visual acuity a few months later. (A) The color fundus photograph taken at presentation shows two curvilinear choroidal ruptures with varying amounts of pigmentation in the central macula. (B) The fluorescein angiogram shows shaggy hyperfluorescence surrounding the streaks. (C) Enhanced depth imaging optical coherence tomography (OCT) shows a nubbin of scar protruding through a defect in the Bruch's membrane/retinal pigment epithelial complex (arrows) and a mound of choroidal neovascularization extending from another defect. Note what appear to be vascular elements in the mound (arrowhead). (D) After intravitreal anti-vascular endothelial growth factor (VEGF) injections, cessation of exudation, and flattening of the macula in the neovascularization were demonstrated.

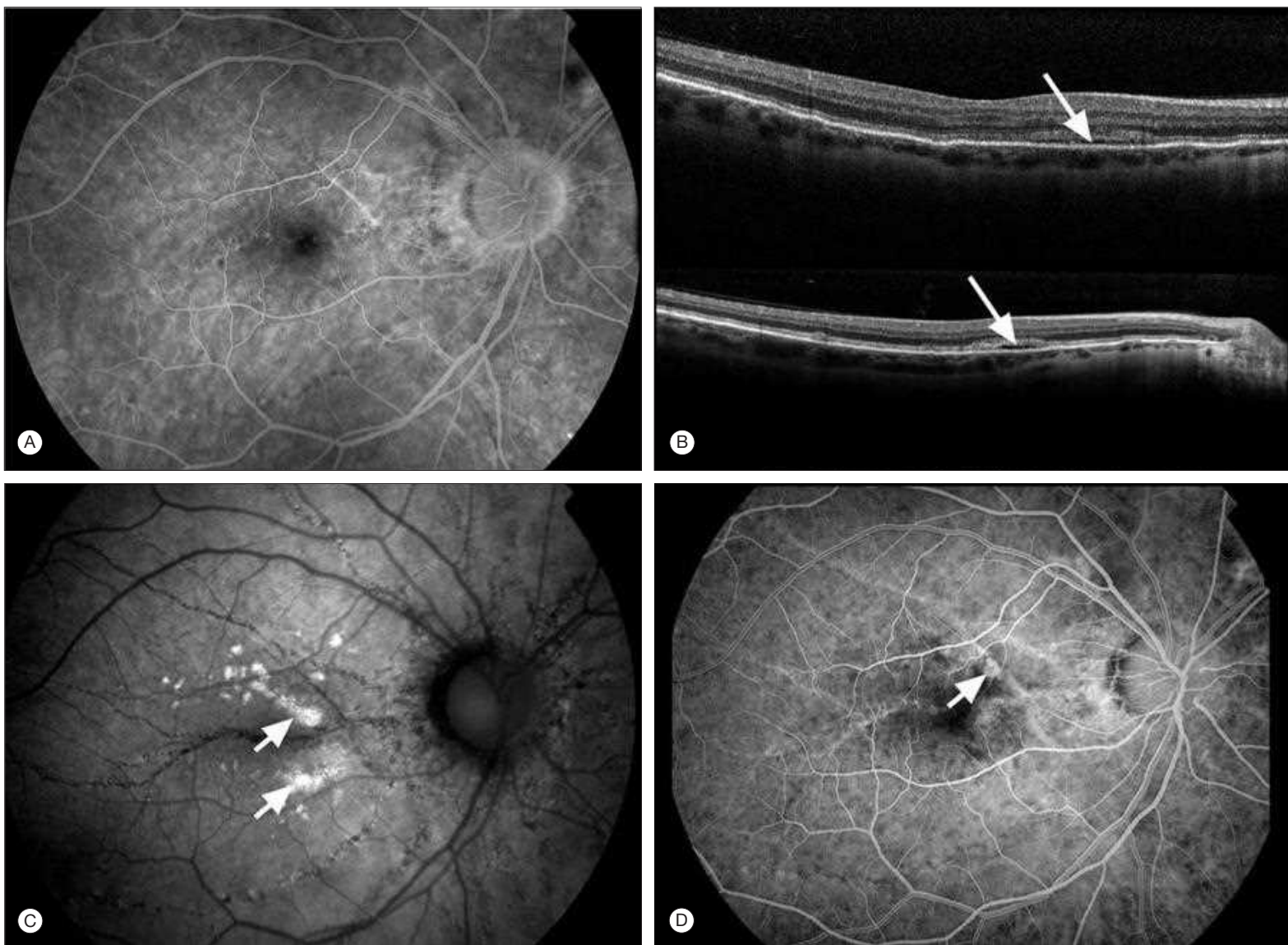
gene have been identified as causing PXE.<sup>4</sup> *ABCC6* has 31 exons and two closely related, but nonfunctional, pseudo-genes, which makes detection of mutations challenging.<sup>5</sup> Estimates concerning the prevalence of PXE vary, ranging from 1 in 25000 to 1 in 100 000.<sup>6</sup> These estimates are probably too low because some of the >300 different loss-of-function mutations within the *ABCC6* gene do not cause skin abnormalities, the chief manifestation that prompts the clinical diagnosis. The gene encodes a 165-kDa protein that is a member of the C-family of adenosine triphosphate (ATP)-binding cassette proteins.<sup>7</sup> PXE causes skin folds and bumps on the neck and in the arm creases. The yellowish papules and creases present have been likened to chicken skin. Although the typical lesions of PXE involve skin, eyes, and the cardiovascular system, the gene is expressed in the liver and kidneys. As such, it has been hypothesized that PXE is, in fact, a metabolic disease with wide-ranging abnormalities.<sup>8</sup>

The ocular findings include, in addition to angioid streaks, drusen of the optic nerve, peau d'orange, comet-like streaks in the periphery, pseudo-drusen, pockets of subretinal fluid, what has unfortunately been called "pattern dystrophy" to include vitelliform accumulations, and areas of RPE atrophy.<sup>9,10</sup> Angioid streaks develop in regions of confluent calcification of Bruch's membrane, whereas peau d'orange is an appearance caused by spotty incomplete calcification of Bruch's membrane.<sup>11</sup> The typical patient with PXE generally will have regions of subretinal fluid for years and then develop pattern dystrophy-like findings.<sup>10</sup> A year or so after the pattern dystrophy, atrophy, CNV or both will develop. The ingrowth of CNV typically occurs at an angioid streak. Histopathological examination shows calcification of Bruch's membrane with fragmentation of elastic fibers.<sup>12</sup> Although the proportion of patients who develop either CNV or widespread RPE atrophy is not known, these conditions appear to eventually affect the majority of patients with PXE.

The angioid streaks occur in a small proportion of patients with sickle cell disease. These patients also have mineralization of Bruch's membrane and can develop skin changes suggestive of PXE.<sup>13</sup> Curiously, Bruch's membrane is mineralized with calcium, not iron, in cases of sickle disease.<sup>14</sup> CNV can occur secondarily in angioid streaks but seems less common than that seen in patients with PXE. Paget's disease, or osteitis deformans, has a less frequent association with angioid streaks, which also appear to be related to abnormal calcification of Bruch's membrane.<sup>12</sup> Many of the minor causes of angioid streaks appear to be related to abnormalities in mineral physiology and include hypercalcinosis, hyperphosphatemia, and hemochromatosis.<sup>12</sup> The physical defect in Bruch's membrane seems to provide an easy access for blood vessels to grow, but the likelihood of this growth may be modulated by other factors, such as the health of the RPE.

## Treatment

CNV is usually readily apparent in the conditions causing angioid streaks and appears as classic CNV above the plane of the RPE. There is associated exudation and frequently bleeding. Consistent with treatment of CNV secondary to age-related macular degeneration (AMD), the treatment strategies for CNV associated with angioid streaks has evolved over time. Laser photocoagulation has yielded poor results, and photodynamic therapy has not been any better. Each of these treatment modalities was associated with a high proportion of patients experiencing recurrence of neovascularization, with the eventual development of large scars with zones of surrounding atrophy of the RPE. Anti-VEGF agents decrease exudation, bleeding, and scarring in many eyes with CNV and stabilize the visual acuity in the process.<sup>14-16</sup> There are difficulties in treating patients with CNV complicating angioid streaks, particularly those with PXE. In



**Fig. 6.30.2** At presentation, both eyes of this 1-year-old male with pseudo-xanthoma elasticum demonstrated small scattered pockets of subretinal fluid. He eventually developed overt signs of choroidal neovascularization (CNV) in the fellow eye about 1½ years after presentation. (A) The angioid streaks were faintly visible in the midphase of the fluorescein angiogram. (B) (Top) A small region of subretinal fluid is shown in the optical coherence tomography section (*arrow*) at presentation and (bottom) in another region 2 years later. Note the accumulation of shed outer segments, which confer increased autofluorescence signal visible in (C) (*arrows*). (D) Nearly 4 years after presentation, the patient was seen to have a small focus of CNV (*arrow*) emanating from an angioid streak. Treatment of the neovascularization with an anti-vascular endothelial growth factor (VEGF) agent resulted in cessation of leakage from the lesion, as seen on fluorescein angiography (FA), but the patient continued to have subretinal fluid as shown in (B). The chronic presence of fluid makes treatment directed by as-needed (prn) strategies impossible.

younger patients, it is possible to quell the CNV and have what appears to be little sign of disease progression, with disease erupting again later with exudation. During quiescent periods, it is difficult to determine the frequency of dosage to the eyes. In some eyes with PXE, chronic fluid may be present prior to the development of CNV. The subretinal fluid does not go away with anti-VEGF therapy, even if FA shows no signs of CNV activity. Therefore, optical coherence tomography (OCT) findings of subretinal fluid may not serve as a useful means of administering anti-VEGF agents. OCT angiography (OCTA) is a convenient method to image neovascularization and also has shown remarkable abnormalities in choriocapillaris flow.<sup>17</sup> Ordinarily, in the care of CNV in AMD, patients seem respond best with frequent periodic dosing. With angioid streaks, there may be theoretical risk to injection. One report described rapid expansion of angioid streaks after anti-VEGF injection.<sup>18</sup> Minor ocular trauma can be associated with rapid expansion of angioid streaks, sometimes with widespread hemorrhage. During resolution of the hemorrhage, careful FA and indocyanine green angiography (ICGA) may be needed to exclude the possibility of concurrent CNV.

## PATHOLOGICAL MYOPIA

Myopia is the most common ocular abnormality found among populations worldwide. Visually significant sequelae increase in frequency and severity with greater degrees of myopia, and the terms *high myopia* and *pathological*

*myopia* are used to refer to those eyes with > −6.00 diopters (D) of refractive error. The proportion of patients with pathological myopia in the general population ranges from 1%–2% in the United States, but 5%–8% in Japan. In East Asia, the proportions are reaching alarming levels, with 21% of 18-year-old students<sup>19</sup> and 38.4% of university students<sup>20</sup> having a refractive error > −6.00 D in Taiwan.

The ocular expansion in pathological myopia leads to thinning and, in some cases, tractional changes in every layer of the eye, including retinal detachment, myopic macular schisis, macular hole, and zonal areas of chorioretinal atrophy. Breaks in Bruch's membrane are frequent, but look different from angioid streaks. In pathological myopia, the breaks in Bruch's membrane are shorter, less wide, usually not red (possibly because of the underlying choroidal thinning and atrophy<sup>21</sup>), and are usually arranged in a crisscrossing network of shorter lines in the posterior staphyloma. As a consequence, these ruptures in Bruch's membrane are referred to as "lacquer cracks." The number and extent of lacquer cracks increases over time<sup>22</sup> but are not associated with the high proportion of bleeding that is seen in traumatic breaks in Bruch's membrane. Lacquer cracks are important risk factors for the development of CNV in pathological myopia.<sup>23</sup>

## Treatment

Intravitreal injection of anti-VEGF agents revolutionized the treatment of myopic CNV. The initially reported studies were patient series using



bevacizumab, which showed visual acuity gains.<sup>24,25</sup> Later, in randomized studies, ranibizumab and aflibercept were used. In the 12-month RADIANCE study,<sup>26</sup> patients with myopic CNV were randomized to one of two groups receiving ranibizumab, and a third group received verteporfin photodynamic therapy. The patients in the ranibizumab arms were treated with one injection and thereafter on the basis of disease activity. The two groups receiving ranibizumab showed 12.1 and 12.5 letter improvement, whereas the photodynamic therapy group had a mean improvement of 1.4 letters. In the 48-week MYRROR study,<sup>27</sup> 122 patients were randomized to intravitreal aflibercept (n = 91) or sham (n = 31). Patients received one injection at baseline and subsequent injections for CNV persistence or recurrence as determined at monthly examinations. By week 48, the aflibercept group gained 13.5 letters, and the sham group gained 3.9 letters.

In as-needed (prn) strategies, the number of required treatments seems much lower than that for patients with CNV secondary to AMD; many patients may require only one injection in the first year, according to findings of the RADIANCE and MYRROR studies. The catch is that prn strategies often rely on detecting changes caused by CNV activity, which can either be subtle or difficult to detect in eyes with high myopia. The vision results of a single dose followed by prn treatment are known, but it is not known if this is the best strategy for long-term acuity improvement. Patients with high myopia often have subjective complaints of vision problems and measurable declines in visual acuity, but no observable change in OCT imaging results. Injection of anti-VEGF agents in these eyes often causes a reduction of symptoms and improvement in visual acuity. Therefore, a wider range of criteria should be used in prn strategies than what is typically done for AMD. Although the treatment may not directly cause atrophy, the development of atrophy is common, as seen with longer-term follow-up of patients treated with anti-VEGF agents for CNV. The atrophy is likely to be related to both the disease process and the underlying widespread choroidal atrophy in these eyes.

## INFLAMMATORY DISORDERS

Inflammation and angiogenesis frequently coexist. In the process of angiogenesis, there is remodeling of surrounding tissue to allow access for the growing vessels. The tissue remodeling is mediated by a number of factors, including matrix metalloproteinases.<sup>28</sup> As such, a physical disruption of barriers, Bruch's membrane being one of them, is not required for ingrowth of neovascularization.<sup>29</sup> The growing tissue is capable of clearing its own path through these barriers. A salient example of this is how CNV frequently can occur in active phases of multifocal choroiditis panuveitis.<sup>30</sup> (Another disorder, termed *punctate inner choroidopathy*, appears to be a subset of multifocal choroiditis and panuveitis and will be included in the more general term.<sup>31</sup>) These patients have multiple foci of inflammation that is centered, not in the choroid but in the sub-RPE space and in the outer retina.<sup>31</sup> Some of these lesions may have associated CNV that presumably breached the Bruch's membrane barrier without the need for any mechanically induced crack or dehiscence. The driving influence for the CNV was inflammation.

In other instances, inflammatory damage may cause collateral damage to barriers, such as Bruch's membrane. After the acute inflammatory stage, a pock mark of scar and tissue loss that creates the "punch out" lesion is seen in presumed ocular histoplasmosis<sup>32</sup> or in multifocal choroiditis and panuveitis. Bruch's membrane within these lesions may be damaged such

that there could potentially be free communication from the choroid to the sub-RPE or subretinal space. In this regard postinflammatory damage has some similarities to the anatomical configuration related to typical cracks in Bruch's membrane seen in angioid streaks. The major differences are the initial state of Bruch's membrane and what caused the defect to occur. In inflammatory conditions, Bruch's membrane has been found to be healthy initially and then suffers damage from inflammation, leading to breakdown of its architectural structure. In angioid streaks, there is a defect in Bruch's membrane that renders it brittle and susceptible to mechanical dehiscence from the ordinary wear and tear of life.<sup>12</sup> In choroidal ruptures, there is application of force through trauma that is beyond the mechanical strength of Bruch's membrane. Although in presumed ocular histoplasmosis, inflammatory cells are not clinically evident, in animal models, nests of lymphocytes have been shown to become activated with antigen challenge well away from the eye.<sup>33</sup> In CNV developing in clinically quiescent periods of posterior uveitis, such as that associated with multifocal choroiditis and panuveitis or serpiginous choroidopathy,<sup>34</sup> neovascularization is typically responsive to corticosteroids in a way that suggests that inflammation is at least playing a part in the neovascular drive seen in these eyes. In addition, long-term immunosuppression reduces the risk of severe visual loss,<sup>35</sup> highlighting the detrimental effect inflammation may have in the development of neovascularization. This suggests that the development of CNV in eyes with inflammatory damage may be a function of both ease of access of blood vessels into the sub-RPE and subretinal spaces through the defect in Bruch's membrane as well as the enhanced tendency toward this because of concurrent inflammation.

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# Central Serous Chorioretinopathy

Ananda Kalevar, Anita Agarwal

6.31

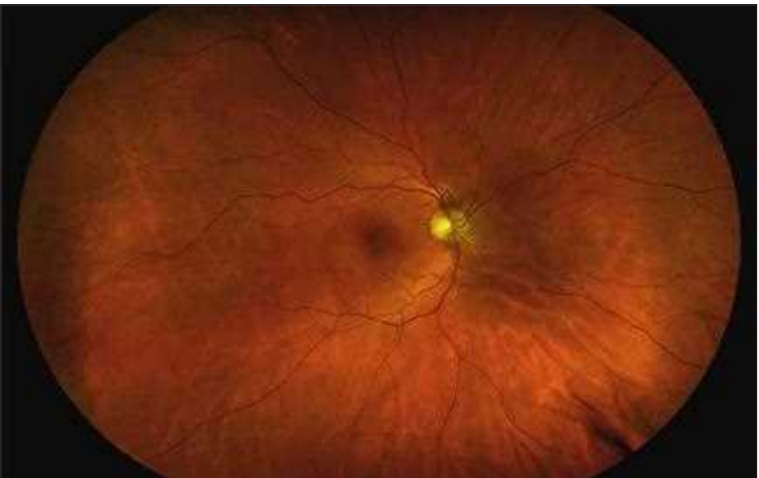
**Definition:** An idiopathic chorioretinal disorder characterized by serous detachment of the neurosensory retina in the macular region.

### Key Features

- One or more focal areas of subretinal fluid in the macula.
- One or more areas of retinal pigment epithelium (RPE) detachment.
- One or more areas of intraretinal fluid.
- One or more focal leaks at the level of the RPE on fluorescein angiography (FA).
- One or more patches of staining at the level of the RPE on FA.
- Hyperpermeability of the choroid on indocyanine green angiography (ICGA).
- Thickening of the choroid on optical coherence tomography (OCT).
- Mottling of the RPE.
- Yellowish white subretinal deposits.
- Unilateral or bilateral involvement.
- Recurrences and chronicity.
- Dependent, bullous retinal detachment.
- Secondary choroidal neovascular membrane.

### INTRODUCTION

Central serous chorioretinopathy (CSCR) is a retinal disorder characterized by serous retinal detachment in the macula (Fig. 6.31.1) affecting mostly young men ages 20–45 years. The male/female ratio varies from 3:1–10:1 in various studies, depending on region and ethnicity.<sup>1</sup> Since its initial description as *relapsing central syphilitic retinitis* by von Graefe in 1866, it has been referred to by many names, including *central serous retinopathy*, *central serous pigment epitheliopathy*, *angiospastic retinopathy*, and *central serous retinitis*. Common symptoms of CSCR include metamorphopsia, blurred vision, and micropsia. If the detachment remains outside the central macula, patients are asymptomatic. Often the serous detachment resolves spontaneously. Visual disturbances typically take several months to resolve. There can be relative preservation of retinal function



**Fig. 6.31.1 Fundus Photograph of Central Serous Chorioretinopathy.** Note the neurosensory retinal detachment the size of two disc diameters in the macular region. (Courtesy West Coast Retina.)

and vision despite prolonged separation of the photoreceptors from the retinal pigment epithelium (RPE). If the macular detachment fails to resolve spontaneously, treatment includes laser photocoagulation<sup>2,4</sup> and photodynamic therapy (PDT),<sup>5-13</sup> which accelerate resorption of subretinal fluid and improves vision.

### EPIDEMIOLOGY AND PATHOGENESIS

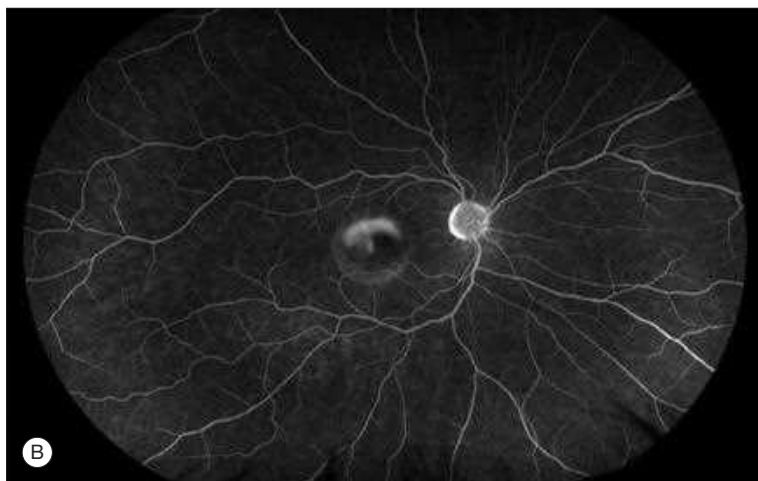
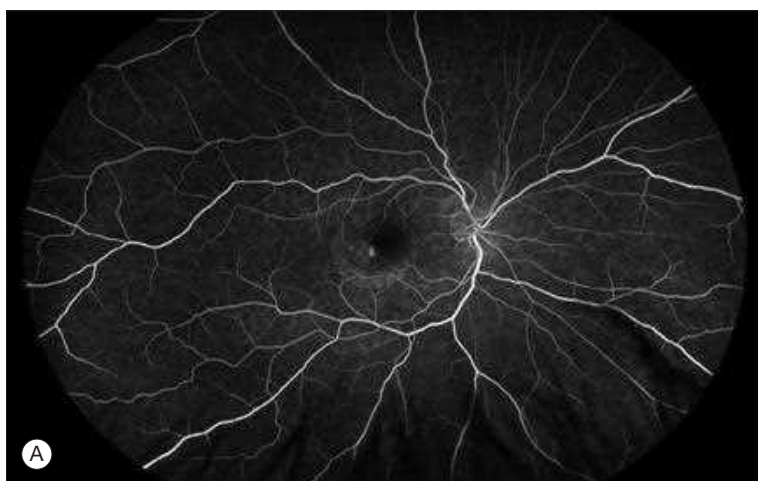
Idiopathic CSCR typically affects young to middle-aged adults. In patients age >50 years, CSCR can be difficult to distinguish from age-related macular degeneration (AMD) or the more recently described pachychoroid maculopathy. Men are much more commonly affected compared with women. The age and sex-adjusted incidence of CSCR in a recent population-based study was found to be 5–6 per 100 000 people.<sup>14</sup> The incidence in males was found to be approximately six times higher than in women.<sup>14</sup> Corticosteroids, either endogenous or exogenous, have been associated with CSCR. Other medications and systemic disorders that have been reported as risk factors are listed in Box 6.31.1. CSCR has been produced experimentally in animals by repeated intravenous epinephrine (adrenaline) injections.<sup>15</sup>

The understanding of the pathogenesis of the disorder is incomplete. Recent multimodal imaging technology has revealed some new information. Few pathological studies are available, and the observations from angiographic, clinical, and experimental models are subject to interpretation. It is known, however, that the subretinal fluid originates from the choroid. Dye leakage through an abnormal focal defect at the level of the RPE and its accumulation in the subretinal space are seen clearly on fluorescein angiography (FA)<sup>2</sup> (Fig. 6.31.2).

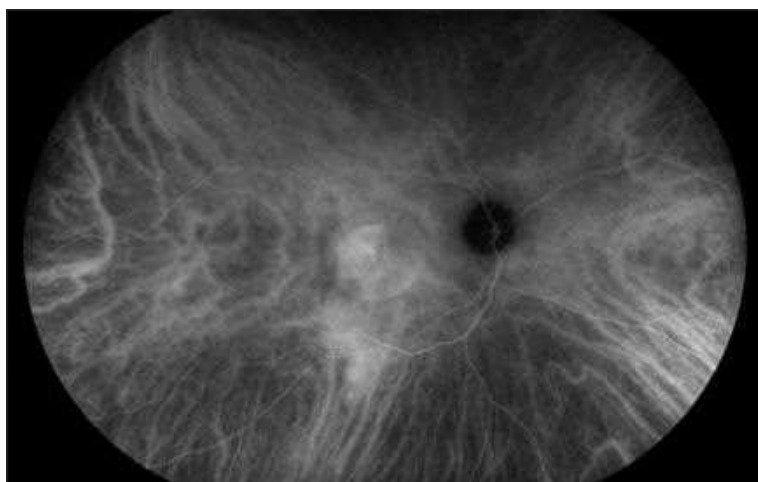
The cause of the focal RPE leak is unclear. Historically, it was believed that a simple breakdown of the blood–retinal barrier at the RPE level was responsible for the leak. However, this theory does not explain the beneficial effect of the permanent RPE barrier breakdown produced as a result of laser photocoagulation. It was later suggested that pathologically hypersecreting RPE cells cause fluid accumulation, but this theory fails to explain the widespread choroidal hyperpermeability seen with indocyanine green angiography (ICGA)<sup>15</sup> (Fig. 6.31.3). Enhanced depth imaging optical coherence tomography (EDI-OCT) has demonstrated increased choroidal thickness and congestion, and this corroborates the theory that choroidal hyperpermeability plays an important role.<sup>16</sup> *Pachychoroid* is a term that has been introduced in the literature to describe a collection of choroidal findings, most notably a thickened choroid seen on EDI-OCT and large choroidal (pachy) vessels.<sup>17</sup> Pachychoroid pigment epitheliopathy is believed to be a “forme fruste” of CSCR, where a constellation of findings, such as a thickened choroid, reduced fundus tessellation, and RPE abnormalities, is

#### BOX 6.31.1 Reported Risk Factors and Associations With Central Serous Chorioretinopathy

Systemic Conditions	Medications
Type A personality	Corticosteroids
Emotional stress	Psychopharmacological medications
Systemic hypertension	3, 4-methylenedioxymethamphetamine
Gastroesophageal reflux disease	Antacids and antireflux medications
Pregnancy	Over-the-counter sympathomimetics
Organ transplantation	Antibiotics
Systemic lupus erythematosus	Antihistamines
Tobacco use	Sildenafil citrate
Alcohol use	
Membranoproliferative glomerulonephritis type II	
<i>Helicobacter pylori</i> infection	
Autoimmune disorders	



**Fig. 6.31.2 Fluorescein Angiogram of Central Serous Chorioretinopathy.** (A) Early phase reveals focal leakage in the center of the macula. (B) Late phase demonstrates a smokestack with delineation of the serous macular detachment. (Courtesy West Coast Retina.)



**Fig. 6.31.3 Indocyanine Green Angiogram of Central Serous Chorioretinopathy.** Contrast enhancement reveals a focal area of hyperfluorescence during the late phase of the study. (Courtesy West Coast Retina.)

seen clinically, and on OCT there is partial or total loss of the choriocapillaris overlying the “pachy” vessels.<sup>17</sup>

Increasing evidence implicates an abnormal choroidal circulation as the cause of CSCR. Using ICGA, Prunte and Flammer<sup>15</sup> showed delayed choroidal capillary lobular filling in areas of hyperpermeability. Choroidal fluid passes through an opening in the RPE and produces a serous retinal detachment.<sup>18</sup> Studies have revealed that corticosteroids can stimulate the production of nitric oxide, prostaglandins, and free radicals within the choroidal circulation.<sup>19</sup>



**Fig. 6.31.4 Fundus Autofluorescence in a Patient With Chronic Central Serous Chorioretinopathy.** Note the extensive hypofluorescence in a descending tract fashion along with hyperautofluorescence along the superior edge. (Courtesy West Coast Retina.)

## OCULAR MANIFESTATIONS

Although unilateral metamorphopsia is the classic symptom of CSCR, patients may also present with unilateral blurred vision, micropsia, impaired dark adaptation, color desaturation, delayed retinal recovery time to bright light, and relative scotoma. Visual acuity ranges from 20/15 to 20/200 with an average of 20/30. A temporary hyperopic shift in refraction may occur. Symptoms typically resolve after several months but may linger even after the fluid resolves as a result of distortion of the receptor endplates; rarely do they persist indefinitely. Permanent sequelae include metamorphopsia, decreased brightness perception, and altered color vision.<sup>2</sup>

CSCR can sometimes present as a bullous, inferior peripheral serous retinal detachment. This is especially true in some patients who receive high doses of corticosteroids either inadvertently for an associated systemic condition or sometimes as a result of misdiagnosis as Vogt-Koyanagi syndrome or sympathetic ophthalmia. The presence of subretinal fluid tracking or “guttering” in recurrent or chronic CSCR, first described by Yannuzzi et al.,<sup>20</sup> from the macular region to the periphery is seen best with wide-field FA and wide-field fundus autofluorescence (FAF) imaging (Fig. 6.31.4).<sup>21</sup>

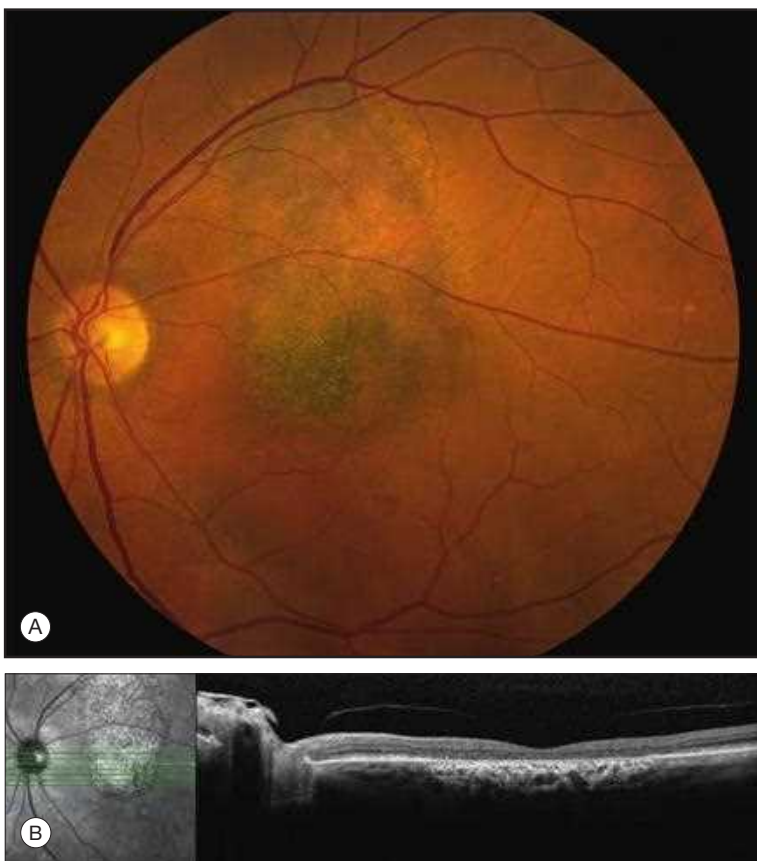
A chronic form of CSCR occurs in about 5% of cases, most commonly in older individuals and in patients receiving long-term low-dose corticosteroids.<sup>19,22</sup> Chronic CSCR is characterized by a diffuse retinal pigment epitheliopathy that progresses in conjunction with persistent or intermittent presence of subretinal fluid. The retinal detachments tend to be shallow and more diffuse than in the classic form. Cystic intraretinal changes can occur late in the presence of chronic subretinal fluid. The visual prognosis is more guarded because of progressive loss of outer retinal elements, and early treatment is strongly recommended.

## DIAGNOSIS

The diagnosis of CSCR is through clinical examination and subsequent confirmation with FA, FAF, and OCT imaging. ICGA also helps establish the diagnosis but is reserved for those eyes with no definite leak observed on FA. The information derived from multimodal testing is critical to detect the extent of the chorioretinal abnormalities, to monitor the disease, and to exclude other diseases.

Biomicroscopically, a transparent or translucent blister in the posterior pole between the neural retina and the RPE is seen. Shallow detachments may be difficult to discern clinically, and OCT is helpful in diagnosing these cases.<sup>2</sup> The subretinal serous fluid within the blister is often transparent. This fluid may have a protein content and fibrin and be turbid or yellowish, especially in patients who are pregnant or have increased pigmentation, have concurrent diabetes, or are on steroids.<sup>2,22</sup> OCT can demonstrated hyperreflective dots consistent with punctate precipitates and white material within the serous retinal detachment just under the retina.<sup>23</sup> Hypotheses for these yellow precipitates range from shed photoreceptor outer segments to accumulations of fibrin or lipid, or macrophages attempting to clear them.





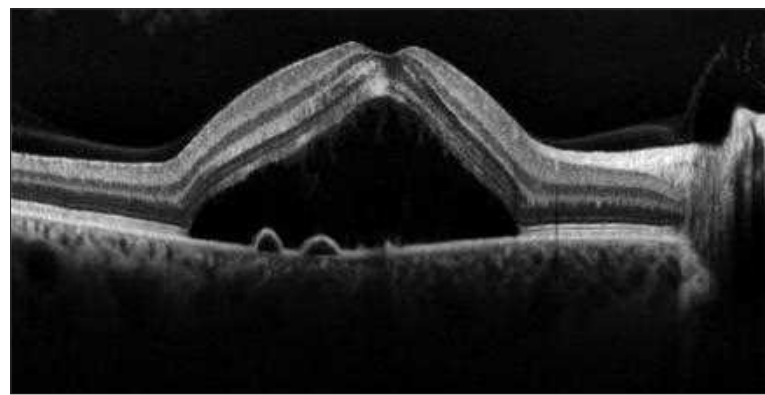
**Fig. 6.31.5** (A) Fundus photograph of an eye with resolved central serous chorioretinopathy. Note diffuse chronic pigmentary changes in the superior macula. (B) Spectral-domain optical coherence tomography (SD-OCT) of the eye with resolved central serous chorioretinopathy. Note the thickened choroid and the outer retinal loss. (Courtesy West Coast Retina.)

Oval, yellow-gray RPE elevations beneath the detachment may also be seen. These are generally less than one fourth of a disc diameter in size and are surrounded by a faint grayish halo. FA and OCT identify them as retinal pigment epithelial detachments (RPEDs) and frequently demonstrate the focal RPE leaks responsible for the serous retinal detachment within their borders. Because subretinal exudative fluid may track inferiorly in response to gravity, a leaking RPED may lie beyond the superior margin of its retinal detachment. Wide-field autofluorescence imaging is invaluable in detecting the hypoautofluorescent tracts left by guttering fluid and the hyperautofluorescence from the protein-rich subretinal fluid.<sup>24,25</sup>

The presence of cystic retinal degeneration, fine RPE mottling, or RPE clumping suggests chronicity of the present episode or a history of a previous CSCR episode (Fig. 6.31.5). Additional ophthalmoscopic findings, such as lipid or hemorrhage, are rare and should call into question the diagnosis of idiopathic CSCR or suggest the presence of choroidal neovascularization (CNV) in the setting of CSCR.<sup>2</sup> The fellow eye may show evidence of either concurrent or previously resolved CSCR, manifesting as focal areas of RPE rarefaction or small asymptomatic RPEDs.

FA is used to exclude the presence of other pathologies that produce serous retinal detachments and to confirm the diagnosis. Classically, dye from the choroid leaks through a focal RPE defect and pools in the subretinal space. In >75% of patients, this pooling occurs within 1 disc diameter of the fovea.<sup>26</sup> Less pooling may be observed in older lesions in which the RPE exudate has become inspissated.<sup>2</sup> FA features of acute central serous chorioretinopathy include the “expanding dot” or “ink blot” sign of a leaking small PED, or a “smoke stack” sign, where the PED has a focal defect in the overlying RPE and the dye streams out of this defect into the surrounding subretinal fluid. In eyes with chronic CSCR, fluorescein shows mottled hyperfluorescence with gradual staining. The inactive lesions show transmission hyperfluorescence at sites of RPE changes. When FA is atypical, ICGA can help exclude the presence of other pathology. ICGA of CSCR classically reveals bilateral multifocal hyperfluorescent areas. These appear during the midphase of the angiographic procedure and are later silhouetted against larger choroidal vessels as the dye diffuses through the choroid.<sup>27</sup>

OCT is a noninvasive technique that can demonstrate the presence of subretinal fluid (Fig. 6.31.6), RPEDs, and thickening of the choroid. In



**Fig. 6.31.6** Spectral-Domain Optical Coherence Tomography (SD-OCT) Image of an Eye With Acute Central Serous Chorioretinopathy. Note the thickened choroid, a couple of pigment epithelial detachments and significant subretinal fluid. (Courtesy West Coast Retina.)

cases of CSCR, OCT is also used to quantify and monitor the amount and extent of subretinal fluid, thickening of the neurosensory retina, and diminution of the choroidal thickening after treatment.<sup>28</sup>

CSCR can be complicated by type 1 sub-RPE CNV, and this can be difficult to distinguish because both entities share many clinical and multimodal imaging features. The treatment algorithms are quite different because CSCR can be treated conservatively and CNV requires anti-vascular endothelial growth factor (VEGF) therapy. Optical coherence tomography angiography (OCTA) is a technique that has the potential to shed light on this dilemma and reveal CNV in CSCR, thereby permitting prompt treatment.<sup>29</sup> OCTA demonstrated the presence of CNV at the level of the choriocapillaris in a 68-year-old man of Japanese descent with myopia (Fig. 6.31.7A and B). This patient responded to monthly bevacizumab injections, with resolution of subretinal fluid after one treatment.

FAF can help delineate the edge of the area of RPE dysfunction. There is hyperautofluorescence secondary to either collection of the shed photoreceptors or abnormal accumulation of lipofuscin and A2E within the RPE (see Fig. 6.31.4).<sup>30</sup>

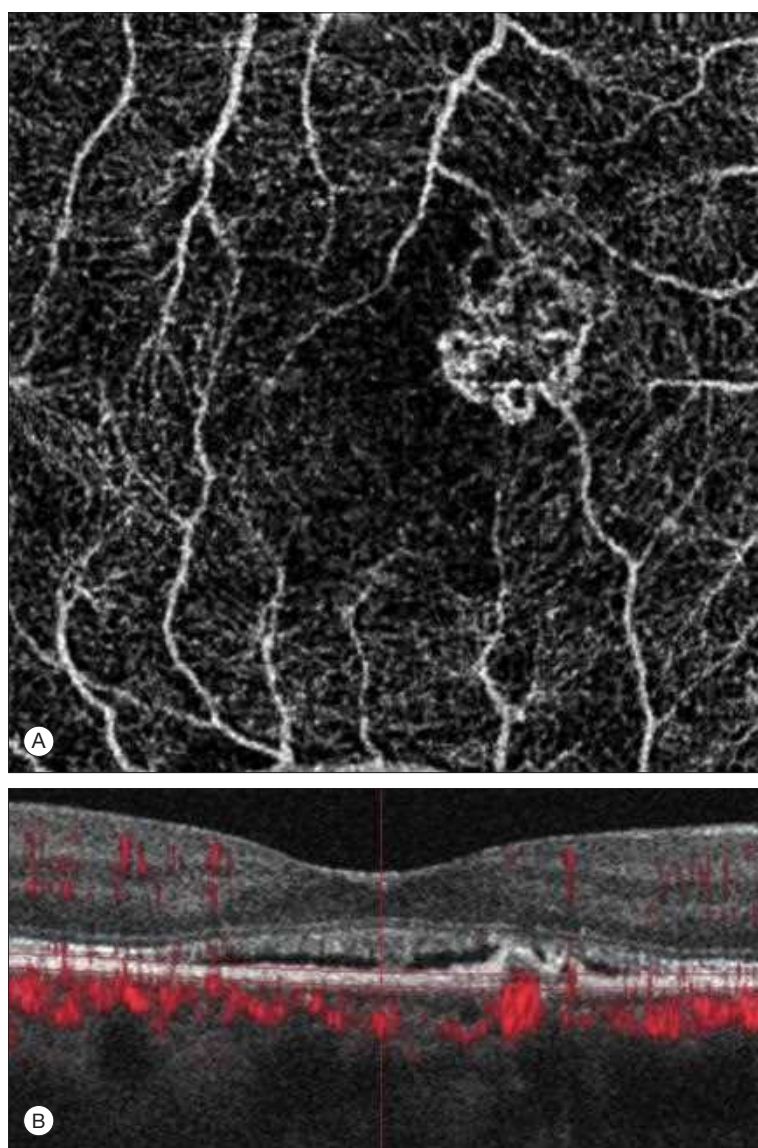
## DIFFERENTIAL DIAGNOSIS

Numerous diseases of the choroid, RPE, and retina can produce serous detachments of the neurosensory retina in the macular region. These include CNV, optic disc pits, polypoidal choroidal vasculopathy, choroidal hemangioma, choroidal melanoma, choroidal metastasis, peripheral retinal breaks, posterior uveitis (e.g., Vogt-Koyanagi-Harada’s disease and sympathetic ophthalmia), optic neuritis, papilledema, vitreous traction, macular holes, and systemic hypertension.

CNV, polypoidal choroidal vasculopathy, or an optic disc pit are important diseases that mimic CSCR by producing similar clinical findings, including serous macular retinal detachment, RPE changes, RPED, and subretinal exudate. Consequently, their presence should be excluded through careful clinical examination and ancillary testing. If the FA result is inconclusive, ICGA and OCT can be performed. ICGA of subretinal CNV usually reveals only one area of hyperfluorescence that progressively enlarges during the later frames of the study. ICGA of polypoidal choroidal vasculopathy demonstrates small-caliber, polypoidal choroidal vascular lesions and no areas of choroidal hyperpermeability.<sup>31</sup> An area of CSCR leakage should remain constant or regress with time, whereas a choroidal neovascular membrane will likely enlarge. OCTA can be particularly helpful where there is suspicion of CNV.<sup>28</sup> OCT and FA of the optic nerve is helpful in evaluating the presence of an optic disc pit. EDI-OCT shows choroidal thickening in CSCR and not in the three other mimicking diseases.<sup>16</sup>

## SYSTEMIC ASSOCIATIONS

Usually, CSCR is an isolated idiopathic ocular disorder. However, numerous risk factors and associations have been reported with CSCR (see Box 6.31.1). The most common association seems to be type A personality traits or a recent episode of stress.<sup>2,32</sup> CSCR has been associated with hypercortisolism and systemic corticosteroid use (oral, intravenous, inhaled, epidural, intra-articular, intramuscular, intranasal, topical dermatological applications).<sup>33-35</sup> The observation of increased CSCR symptoms during periods of increased corticosteroid use, and their subsequent resolution



**Fig. 6.31.7** (A–B) Optical coherence tomography angiogram shows presence of choroid neovascularization (CNV) at the level of the choriocapillaris in a 68-year-old man of Japanese descent with myopia and central serous retinopathy. He responded well to monthly bevacizumab injections, with resolution of subretinal fluid after one treatment. (Courtesy West Coast Retina.)

when dosages are decreased, led to this discovery. Bouzas et al.<sup>33</sup> reported CSCR prevalence of 5% among patients with endogenous Cushing's syndrome. A recent genetic study evaluated glucocorticoid receptor (*NR3C1*) and mineralocorticoid receptor (*NR3C2*) genes and found an association with the variants of *NR3C2* genes with chronic CSCR.<sup>36</sup> It is still too early to interpret the relevance of these findings.

Multiple systemic conditions or diseases have been associated with CSCR. These include systemic hypertension,<sup>19,37,38</sup> pregnancy,<sup>39,40</sup> dialysis,<sup>41</sup> organ transplantation,<sup>42</sup> systemic lupus erythematosus,<sup>43</sup> gastroesophageal reflux disease,<sup>44</sup> membranoproliferative glomerulonephritis type II,<sup>45</sup> *Helicobacter pylori* infection,<sup>46</sup> and autoimmune disorders.<sup>37</sup>

Several classes of medications or drugs other than corticosteroids have also been reported to be significantly associated with CSCR. These medications include the following: psychopharmacological medications,<sup>19</sup> antacids and antireflux agents,<sup>44</sup> over-the-counter sympathomimetics,<sup>47</sup> antibiotics (oral),<sup>37</sup> antihistamines,<sup>37</sup> sildenafil citrate,<sup>48</sup> and 3,4-methylenedioxymethamphetamine.<sup>47</sup> In addition, tobacco and alcohol use have been reported to be risk factors for CSCR.<sup>37</sup>

## PATHOLOGY

There are limited pathological studies due to the benign course of CSCR and the low incidence among older adults. In those few performed, the RPE, choroid, and retinal vessels appear normal. The only histopathological changes observed include serous RPEs, subretinal fibrin, serous

detachments of the collagenous portion of Bruch's membrane, and cystic degeneration in the outer layers of the detached retina.<sup>2</sup>

## TREATMENT

Because the vast majority of cases of acute CSCR resolve spontaneously over time, the initial treatment of choice is observation. If the patient is using corticosteroids, these should be discontinued, if medically possible. Despite isolated reports, no medical therapy has been of proven value. Recently, mineralocorticoid antagonists and rifampin have been proposed as safer alternatives to local treatments.<sup>49–58</sup> At this point, the evidence is inconclusive to support their use, and future studies are needed to elucidate their effectiveness.<sup>59</sup> Local treatment options that have been proven to be effective for CSCR include either laser photocoagulation or PDT. Anti-VEGF agents have been attempted to treat CSCR; however, this remains inconclusive unless CNV is present.<sup>60</sup>

Because most CSCR cases resolve spontaneously, laser treatment is reserved for patients with extrafoveal leaks who fail to improve after 3–6 months, demonstrate permanent changes from CSCR in the fellow eye, demonstrate multiple recurrences, or require improved vision for work. Laser treatment should be avoided if the leak occurs within 200  $\mu$ m of the center of the foveal avascular zone, although PDT with reduced fluence can be considered in these situations in chronic recalcitrant cases after careful discussion with the patient.<sup>4</sup>

Laser photocoagulation is applied to the leakage spot(s) as seen on angiography. Although this has been proven to reduce the duration of the serous detachment, it has no effect on the final visual prognosis, hence is reserved for selected patients.<sup>3,4</sup> It is the only therapy with benefit as proven by large clinical trials. The technique of laser photocoagulation involves using a green-wavelength laser to produce a light gray scar over the focal RPE leak. Typically, 6–12 laser burns of 50–200  $\mu$ m spot size at  $\leq 0.1$ -second duration and power ranging from 75–200 milliwatts (mW) are used. Permanent RPE change is induced at the site of the laser scar.<sup>4</sup> There have been reports of CNV after the use of laser photocoagulation, and EDI-OCT shows the continued presence of a thickened choroid. The only definite benefit from laser therapy is its ability to decrease the duration of the neurosensory detachment.<sup>61</sup> However, there are other reports showing that it neither affects the recurrence rate nor improves the final visual acuity or progression to chronic CSCR.<sup>62</sup>

Complications from laser photocoagulation include CNV and central scotoma. Although rare, they can be visually devastating (Fig. 6.31.8). Complications may be reduced by using larger spot sizes, employing lower power, and avoiding the capillary-free zone.<sup>4</sup> The rapid development of a choroidal neovascular membrane after laser photocoagulation suggests the possibility of an initial misdiagnosis and the likely presence of a pre-existing CNVM.<sup>63,64</sup>

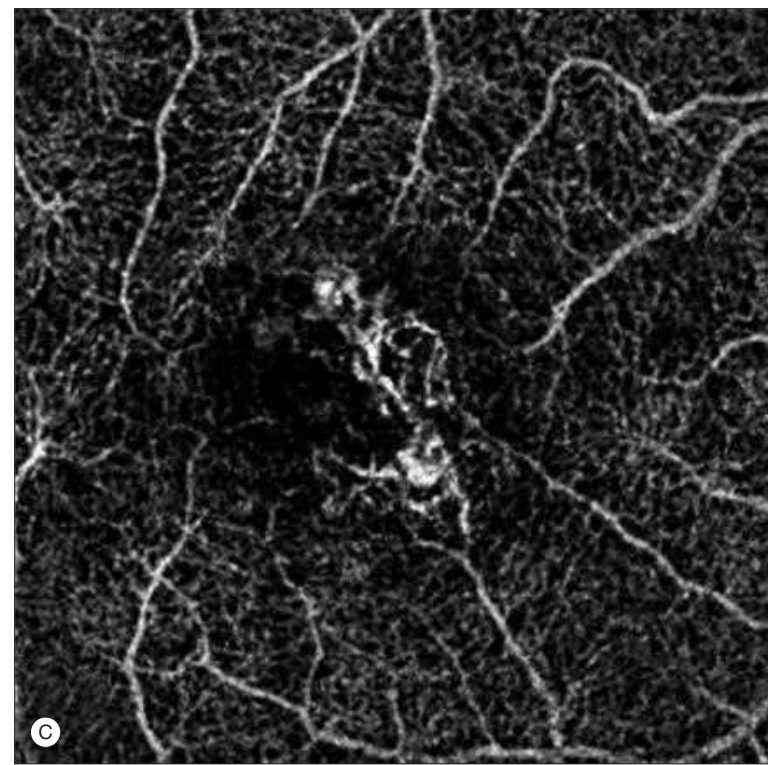
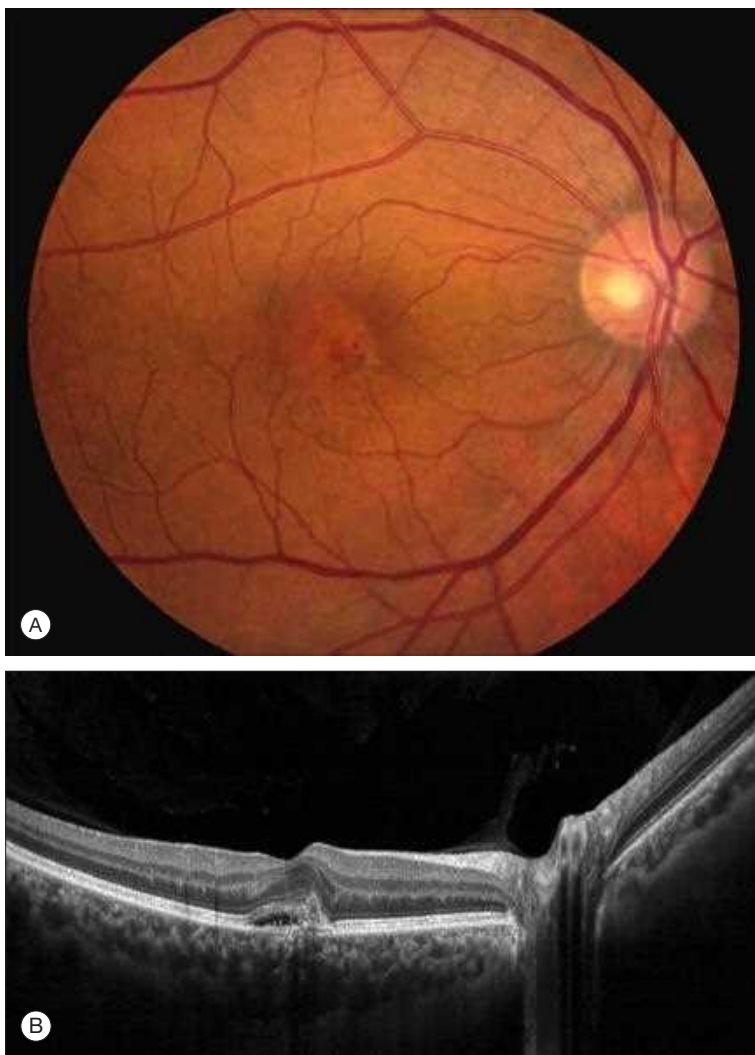
PDT has been increasingly used to treat CSCR over the past decade. It is reportedly effective for both chronic CSCR (defined as  $>6$  months' duration of disease) with diffuse decompensation of the RPE lacking focal FA leaks,<sup>5–11</sup> and acute CSCR with focal RPE leaks.<sup>12,13,65</sup> PDT appears to be a more effective treatment with a lower complication rate for patients with subfoveal or juxtafoveal leaks. Using EDI-OCT, the choroid can be monitored to see if it thins after treatment with PDT.<sup>13</sup>

## COURSE AND OUTCOME

Generally, the visual prognosis for patients with CSCR is good.<sup>66</sup> Most patients suffer no significant permanent visual loss. In a series of 34 eyes with CSCR followed up for an average of 23 months without treatment,<sup>26</sup> visual acuity was no worse than 20/40 in any eye. This was despite large serous retinal detachments, multiple RPE leaks, cystoid macular changes, persistent RPEs, and marked visual loss during acute episodes. The persistent Amsler's grid changes present in 24 of 27 eyes were described as visually insignificant and causing no difficulty.<sup>67</sup> Although visual acuity usually improves, patients may continue to have persistent metamorphopsia probably because of photoreceptor misalignment causing a Stiles-Crawford effect. Rarely, CSCR can produce significant visual damage; usually caused by the chronic form of the disease.<sup>68</sup> RPE atrophy, drusen, and CNV have also been described in eyes with chronic CSCR.<sup>28</sup>

Follow-up FA of eyes with CSCR suggests that in certain patients, CSCR may herald a bilateral progressive RPE disturbance known as *chronic CSCR*.<sup>69</sup> Whether a history of CSCR exacerbates the natural course of AMD remains unresolved. However, recent studies suggest that CSCR in older individuals is more frequently associated with the formation of CNV compared with that in younger patients.<sup>22</sup>





**Fig. 6.31.8 Chronic Central Serous Chorioretinopathy With Choroidal Neovascular Membrane.** (A) Fundus photograph with central retinal pigment epithelium (RPE) changes and subretinal hemorrhage. (B) Spectral-domain optical coherence tomography (SD-OCT) showing subretinal fluid, retinal pigment epithelial detachments (RPED), and thickened choroid. (C) optical coherence tomography angiography (OCTA) at the choriocapillaris level reveals a tangled lesion consistent with a neovascular network. (Courtesy West Coast Retina.)

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# Macular Hole

Andrew A. Moshfeghi, Christos N. Theophanous, Jay S. Duker

# 6.32



**IN THIS CHAPTER**  
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**Definition:** A full-thickness defect in the neural retinal concentric on the fovea.

## Key Features

- Central scotoma with or without metamorphopsia.
- Round, central neural retinal tissue defect.
- Perifoveal cystic retinal edema.
- Yellow spots in the base of the macular hole.
- Surrounding cuff of subretinal fluid.

## Associated Features

- Attached posterior hyaloid initially and can remain even after full-thickness hole develops.
- Epiretinal membrane (commonly).
- Occasionally bilateral (10%–20%), but typically sequentially, not generally with simultaneous onset.
- Simultaneous retinal detachment, rarely, especially in cases of pathological myopia, prior blunt ocular trauma, or chronic cystoid macular edema.

## INTRODUCTION

Until the 1990s, ophthalmologists paid little attention to macular holes because the pathogenesis was obscure and cure impossible. Our understanding of the pathogenesis of macular holes has evolved significantly over the past 2 decades, resulting in the development of a new classification that accounts for premacular hole clinical appearances and gives insight into macular hole formation.<sup>1</sup> In addition, optical coherence tomography (OCT) is now widely available for diagnosis and treatment planning.<sup>2</sup> Surgery helps reverse the visual loss in most cases.<sup>3,4</sup>

## EPIDEMIOLOGY AND PATHOGENESIS

Most full-thickness macular holes are idiopathic but can also form immediately after blunt ocular trauma and numerous rare entities.<sup>5-8</sup>

Macular hole is a rare condition occurring in approximately 1 in 500 patients, most commonly healthy individuals in their sixth or seventh decade of life.<sup>8,9</sup> Women are affected more commonly compared with men by a 2:1 ratio. About 10%–20% of cases eventually are affected bilaterally, but rarely simultaneously.<sup>8,9</sup>

The best available data suggest that abnormal tractional forces of the vitreous on the macula are directly responsible for the pathogenesis of idiopathic macular hole. This can be observed clinically with contact lens examination, ultrasonography, or, most reliably, with OCT.<sup>2</sup> The success of vitreous surgery for macular holes provides strong evidence for a direct role of the vitreous in its pathogenesis.<sup>3</sup>

## OCULAR MANIFESTATIONS

The hallmark complaint of idiopathic macular hole formation is painless development of central visual distortion or blur of an acute or subacute nature. When only one eye is involved, it is not unusual for the visual loss

to go undetected in the affected nondominant eye unless cross-covering is performed. Central visual acuity initially may be diminished only mildly; however, as the hole progresses, the acuity usually deteriorates commensurate with increasing hole diameter, then stabilizes around the 20/200–20/800 (6/60–6/240) level.

The Gass classification system explains the clinically observed appearance of macular holes in four stages and their precursor lesions. The hallmark inciting event of idiopathic macular hole formation is hypothesized to be focal shrinkage of the vitreous cortex in the foveal area.<sup>1</sup> Although Gass' clinical interpretations of the various stages are accepted widely, OCT classification studies imply that the retinal changes that occur in stage 1 holes differ slightly from his clinical classification.<sup>1</sup>

Foveal photoreceptor loss may occur in some cases, although a true retinal operculum rarely is evident. The central scotoma that results from foveal dehiscence is made significantly larger by the surrounding localized retinal detachment. Cystic changes develop in the intact perifoveal retina, and some eyes develop epiretinal membranes. All the factors combine to decrease the central vision. Rarely, rhegmatogenous retinal detachment beyond the macula occurs directly as the result of a macular hole only if abnormal vitreous traction or high myopia with staphyloma is present concurrently. Not uncommonly, idiopathic full-thickness macular holes may be observed during vitrectomy surgery for repair of rhegmatogenous retinal detachment resulting from a peripheral causative retinal break. In addition, macular holes have been observed subsequent to successful repair of rhegmatogenous retinal detachment that was not originally related to a full-thickness macular hole or after previous vitrectomy surgery.<sup>5,6</sup> The pathogenesis in these atypical cases is not entirely understood.

The Gass classification of macular holes is based on slit-lamp biomicroscopy of the retina rather than OCT findings, which had not yet been invented.

## Gass Stage 1 Macular Hole

In a stage 1 macular hole, no true neural retinal defect is present, the photoreceptor layer is intact, and no vitreofoveal separation has occurred. Oblique vitreofoveal traction is responsible and can be observed on OCT. Stage 1 holes are clinically subdivided into stage 1a (small central yellow spot is seen ophthalmoscopically) and stage 1b (a yellow foveal ring is observed).<sup>1</sup> They are typically asymptomatic and spontaneously resolve in half the cases.

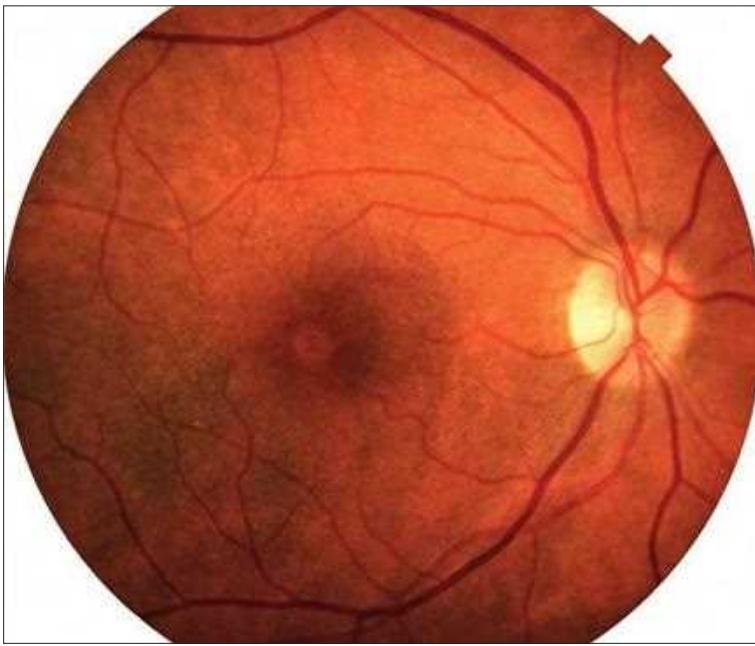
## Gass Stage 2 Macular Hole

Progressive shrinkage of the perifoveal vitreous cortex in stage 1 eyes leads to stage 2 holes, which are small (100–300  $\mu$ m), full-thickness neural retinal defects (Figs. 6.32.1 and 6.32.2). Visual acuity is diminished, usually between 20/50 (6/15) and 20/400 (6/120), and a pseudo-operculum with condensed vitreous may be present. Once a stage 2 hole occurs, it typically progresses irreversibly to stage 3.

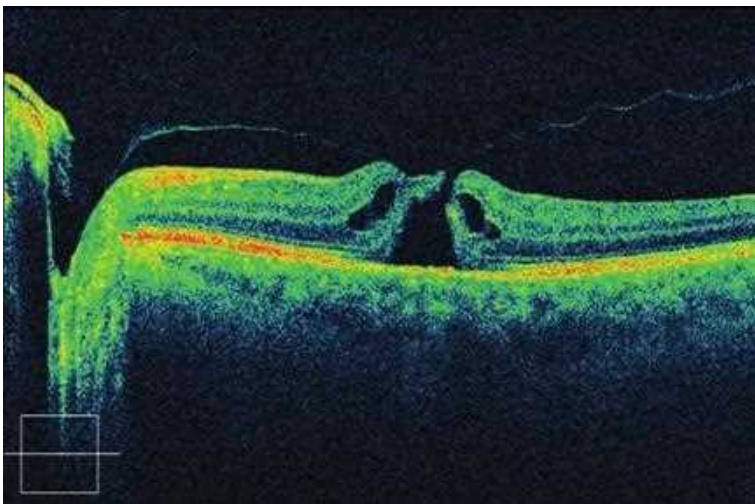
## Gass Stage 3 Macular Hole

Continued vitreofoveal traction results in a stage 3 hole with the classic macular hole appearance. This consists of a round, 350–600  $\mu$ m full-thickness neural retinal defect with smooth edges, and a small, surrounding, doughnut-shaped cuff of subretinal fluid with persistent hyaloid





**Fig. 6.32.1** Gass stage 2 macular hole. Clinical photograph demonstrating a cuff of subretinal fluid.



**Fig. 6.32.2** Gass stage 2 macular hole. Spectral-domain optical coherence tomography demonstrates a full-thickness neural retinal defect and an attached posterior hyaloid at the fovea and optic nerve.

attachment. With time, alterations in the retinal pigment epithelium (RPE; pigmented demarcation line) may develop at the leading edge of the subretinal fluid cuff. Visual acuity typically is between 20/200 (6/60) and 20/800 (6/240).

### Gass Stage 4 Macular Hole

A stage 4 macular hole has all the features of a stage 3 hole, but with complete posterior separation of the vitreous from the fovea. Yellow deposits can be seen in the base of the defect, and perifoveal cystic retinal changes are present (Fig. 6.32.3).

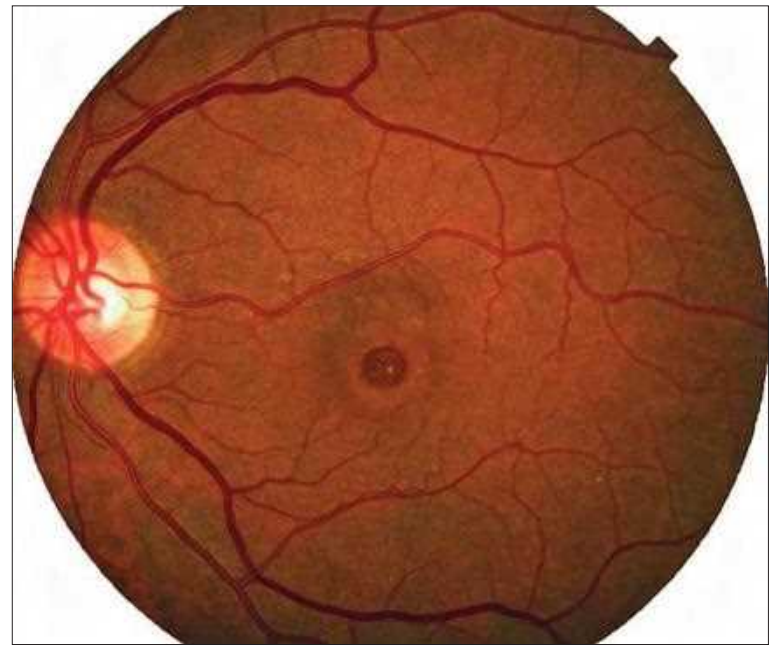
A newer classification of vitreoretinal interface disorders, including macular holes, has been developed based on OCT findings and hole size rather than clinical symptoms or observation, as discussed below.<sup>10</sup>

#### Vitreomacular Adhesion

Vitreomacular adhesion represents a stage of partial, perifoveal separation of the vitreous without other retinal changes. Vitreous attachment is visible within a 3-mm radius of the fovea. Adhesions may be further described as small ( $\leq 1500 \mu\text{m}$ ) or large ( $> 1500 \mu\text{m}$ ). These patients generally do not experience any visual changes.

#### Vitreomacular Traction

With excessive traction, vitreomacular adhesions can lead to retinal changes observed on OCT, such as alteration of the foveal surface, intraretinal



**Fig. 6.32.3** Clinical photograph of a Gass stage 4 macular hole with large basal hole diameter, large cuff of subretinal fluid, and drusen present at the base of the hole.

pseudocyst formation, or separation of the fovea from the RPE. These eyes represent vitreomacular traction (VMT), and patients typically report distorted or diminished vision. These holes may similarly be divided into small ( $\leq 1500 \mu\text{m}$ ) or large ( $> 1500 \mu\text{m}$ ) based on size of vitreous attachment. VMT is equivalent to a Gass Stage 1 macular hole.

### Full-Thickness Macular Hole

Full-thickness macular holes consist of disruption through all neural layers of the retina. The edges typically appear rounded because of the presence of subretinal fluid. These holes are subdivided by size (small:  $\leq 250 \mu\text{m}$ ; medium:  $> 250$ – $\leq 400 \mu\text{m}$ ; and large:  $> 400 \mu\text{m}$ ), presence or absence of vitreomacular traction, and cause (primary: caused by macular traction, secondary: caused by other pathology).

### Lamellar Macular Hole

A lamellar macular hole may represent an aborted macular hole. A round central inner retinal defect is observed, with no thickening, cystic change, or subretinal fluid. No full-thickness neural retinal defect is appreciated on OCT. An overlying retinal operculum is common. Vitreofoveal separation occurs with loss of the inner retinal layers; however, the outer, photoreceptor layer is intact. The vision typically remains good, and there is low risk of progression to macular hole.

### Pseudo-Macular Hole

A lamellar hole is to be distinguished from a pseudo-macular hole, which may appear ophthalmoscopically as a macular hole, but OCT reveals intact neural retina along with an opening in a dense overlying epiretinal membrane.

### “Stage 0” Macular Hole

One study suggests that abnormal vitreofoveal traction observed on OCT in the fellow eye of a patient with a macular hole is associated with an elevated risk (43%) of macular hole formation in the fellow eye. Fellow eyes without this abnormal vitreofoveal traction on OCT had a very low risk of subsequent macular hole formation.<sup>11</sup>

## DIAGNOSIS AND ANCILLARY TESTING

The diagnosis of idiopathic macular hole is clinical, made at the slit lamp with a macular lens, used in either a contact or noncontact fashion. At times, the purely clinical diagnosis can be difficult, especially when a unilateral stage 1 or stage 2 hole is present.<sup>12,13</sup>

Fluorescein angiography (FA) is not generally of benefit, although it can help to rule out other entities that mimic macular hole. In stage 1 macular



**BOX 6.32.1 Differential Diagnosis of Macular Hole**

Epiretinal membrane with macular pseudo-hole  
 Cystoid macular edema  
 Vitreomacular traction without full-thickness macular hole  
 Foveal drusen  
 Choroidal neovascular membrane  
 Central areolar pigment epitheliopathy  
 Pattern dystrophy  
 Solar retinopathy  
 Central serous chorioretinopathy  
 Lamellar (aborted) macular hole  
 Choroiditis

holes, FA commonly is normal or may variably reveal a window defect. The slit-beam test (Watzke–Allen sign) usually is reliable to test subjectively for a full-thickness retinal defect associated with a central absolute scotoma in response to a thin, vertically oriented slit beam focused on the macula. Cross-sectional imaging of the retina with OCT is used to confirm the diagnosis and to assess the attachment of the vitreous to the fovea.<sup>1,12,14</sup> OCT is, by far, the most clinically useful ancillary test. With spectral-domain, high-resolution OCT,<sup>14</sup> in addition to individual raster lines, the physician can also scroll through a digital cube of sampled retina and recreate a three-dimensional view of the vitreoretinal interface. This aids in surgical planning to see precisely where the posterior hyaloid or possible associated epiretinal membrane may be exerting perifoveal tension.

**DIFFERENTIAL DIAGNOSIS**

Macular holes may be confused with epiretinal membrane, cystoid macular edema, or vitreomacular traction (Box 6.32.1).

**PATHOLOGY**

Histopathology shows a round, full-thickness defect through all neural retinal layers. The underlying RPE is intact. Associated intraretinal edema and perifoveal photoreceptor atrophy are common. Epiretinal membrane formation is also common. Fibroglial proliferation across the retinal defect has been observed in pathology specimens from autopsy eyes of patients with closed macular holes.<sup>15</sup>

**TREATMENT**

Prior to 1989, idiopathic macular holes were considered untreatable. Kelly and Wendel<sup>3</sup> were the first to report that vitreous surgery can improve the visual acuity in some eyes with acute, idiopathic macular holes. Since then, vitrectomy for idiopathic macular holes rapidly has become a widely performed procedure throughout the world.

Gass stage 1 holes (VMT) are initially observed for three reasons:

- They have a 50% rate of spontaneous improvement.
- Surgical intervention does not prevent full-thickness macular hole formation universally, and intraoperative macular hole can occur.
- Vitrectomy for a Gass stage 2 hole of recent onset has a very high (>90%) anatomical success rate.

If a Gass stage 1 hole has significantly decreased visual acuity that persists for months, surgery may be considered.<sup>16</sup> Macular hole surgery (Video 6.32.1) typically is performed with the patient under local anesthesia on an outpatient basis. A standard three-port core vitrectomy is completed. Then, the adherent posterior cortical vitreous is engaged, typically by using the aspiration aspect of the vitrectomy instrument, with the cutting function disabled. The attached posterior hyaloid is usually invisible until it is elevated off the retina. Elevation of the cortical vitreous and posterior hyaloid is carried out until complete separation of the vitreous is achieved, and then it is consumed with the vitrector. Care is taken to avoid the crystalline lens in patients with phakia by using an alternate hand vitrectomy. Epiretinal membrane, if present, is peeled by using a bent, sharp needle, a diamond dusted soft-tipped membrane scraper, or fine internal limiting membrane (ILM) forceps. If ILM peeling is felt to be beneficial, it is performed at this stage. The internal limiting membrane can be stained with diluted indocyanine green (ICG) dye, dilute triamcinolone acetate, trypan blue, or brilliant blue to facilitate its surgical removal. An air–fluid exchange follows and air, sulfur hexafluoride (SF<sub>6</sub>) gas (20%–30%), perfluoropropane

(C<sub>3</sub>F<sub>8</sub>) gas (10%–18%), or silicone oil is injected into the vitreous cavity at the conclusion of the case. Patients usually are instructed to maintain strict face-down positioning for 1–7 days postoperatively, although recent reports have described comparable anatomical success rates for macular hole closure with zero face-down positioning.<sup>17</sup>

Greater than 50% of phakic eyes that undergo vitrectomy for a macular hole suffer significant nuclear sclerotic cataracts during the 2-year follow-up, and these can later be removed with standard cataract surgical techniques without undue risk.

Retinal tears, retinal detachment, or both may be seen in up to 10% of eyes that undergo macular hole repair. This incidence is relatively high because of intraoperative traumatic creation of posterior vitreous detachment in the critical step of the procedure.<sup>18</sup>

Less common complications include: intraoperative light; chemical or mechanical toxicity to the macular RPE; and intraoperative enlargement of the macular hole.<sup>18–20</sup> Late reopening occurs in 5% of successfully treated holes and can occur years later.<sup>20</sup> Successfully closed macular holes can reopen after YAG (yttrium–aluminum–garnet) laser capsulotomy or secondary cataract extraction. Therefore, contemporaneous creation of mechanical capsulotomy in patients with pseudophakia or cataract extraction in patients with phakia at the time of macular hole repair has been advocated by some.<sup>21</sup> Peeling of the ILM may decrease the rate of late reopening. Dense, temporal visual field defects have been observed in eyes that have undergone macular hole repair.<sup>22</sup> Intraoperative damage to the nerve fiber layer by either excessive desiccation secondary to air infusion and/or possible toxicity of ICG have been suggested, but adjuvant use of ICG is still common.<sup>23</sup> ICGA can be used under fluidic conditions for 30–45 seconds and then removed with the vitrector, with staining of the ILM posteriorly. In patients with an intact posterior lens capsule, use of ICG under fluidic conditions can also create staining of the posterior lens capsule. Care should be taken to avoid prolonged and direct light pipe illumination of the macular region while ICG is in the eye because this dye does have a photodynamic effect.<sup>23</sup>

Case-series reports have demonstrated that pneumatic vitreolysis (also referred to as “pneumatic maculopexy”) may also be a viable surgical option for the treatment of macular holes. Intravitreal injection of SF<sub>6</sub> or C<sub>3</sub>F<sub>8</sub> induces posterior vitreous detachment and can relieve traction on the retina.<sup>24,25</sup> The precise mechanism through which the procedure induces vitreous detachment is unknown, although it likely relates to liquefaction of the vitreous or expansion of existing vitreous pockets from expansion and contraction of the gas bubble. In a retrospective study of 15 eyes with stage 2 macular holes, two thirds achieved hole closure.<sup>25</sup> Although not studied in large trials, pneumatic vitreolysis may represent an alternative, lower cost surgical treatment for macular holes.

Recently, a less invasive approach for idiopathic full-thickness macular hole management has been described.<sup>26</sup> Following a single intravitreal injection of recombinant microplasmin enzyme (ocriplasmin; Thrombogenics, Inc., Leuven, Belgium), approximately 41% of 153 patients with a Gass stage 2 idiopathic full-thickness macular hole experienced successful hole closure without vitrectomy surgery compared with 17% of patients injected with a saline placebo.<sup>27</sup> In phase III studies, 30% of patients with macular hole achieved full closure following ocriplasmin injection compared with 15% of sham injection controls.<sup>28</sup> This closure rate was reached by 3 months after injection and held steady through 2 years of follow-up. Generally, adverse events were mild and transient, occurring within the first week after injection. Vitreous floaters, photopsia, and abnormal color vision tests are the most common adverse events, each occurring in approximately one third of patients. More serious adverse events, such as retinal breaks or detachments, were comparable between the treatment and control groups, therefore likely attributable to natural disease progression.<sup>28</sup>

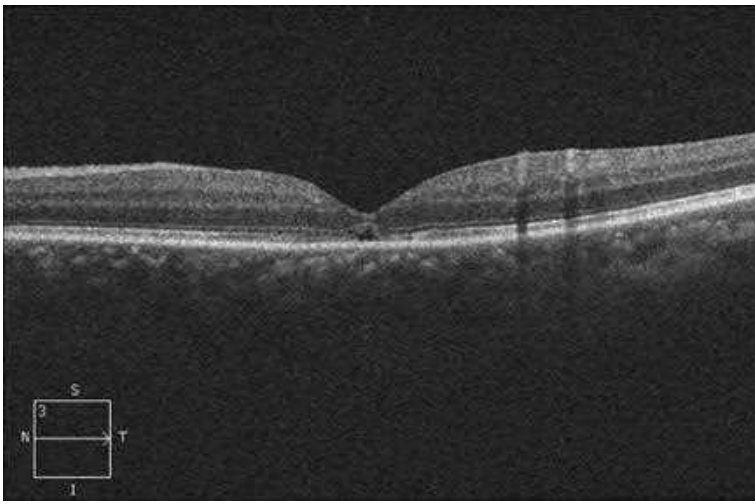
**COURSE AND OUTCOME**

Stage 1 holes have a spontaneous rate of resolution of about 50%. Once a stage 2 hole occurs, visual loss is permanent without surgery. Spontaneous closure of full-thickness macular holes occurs in 2%–4% of eyes.<sup>8</sup>

Without surgery, macular holes tend to stabilize with a visual acuity of 20/200–20/800 (6/60–6/240) and a diameter of about 500  $\mu$ m. Anatomical success can be determined 2–4 weeks after surgery. Anatomical success usually is now defined with OCT as the reapproximation of retinal tissue covering the full-thickness defect. In most instances, when this occurs, the edges of the macular hole are apposed firmly to the RPE, which renders identification of the original location of the hole difficult (Fig. 6.32.4). In their initial series of 52 eyes, Kelly and Wendel<sup>3</sup> found that 42% showed a visual

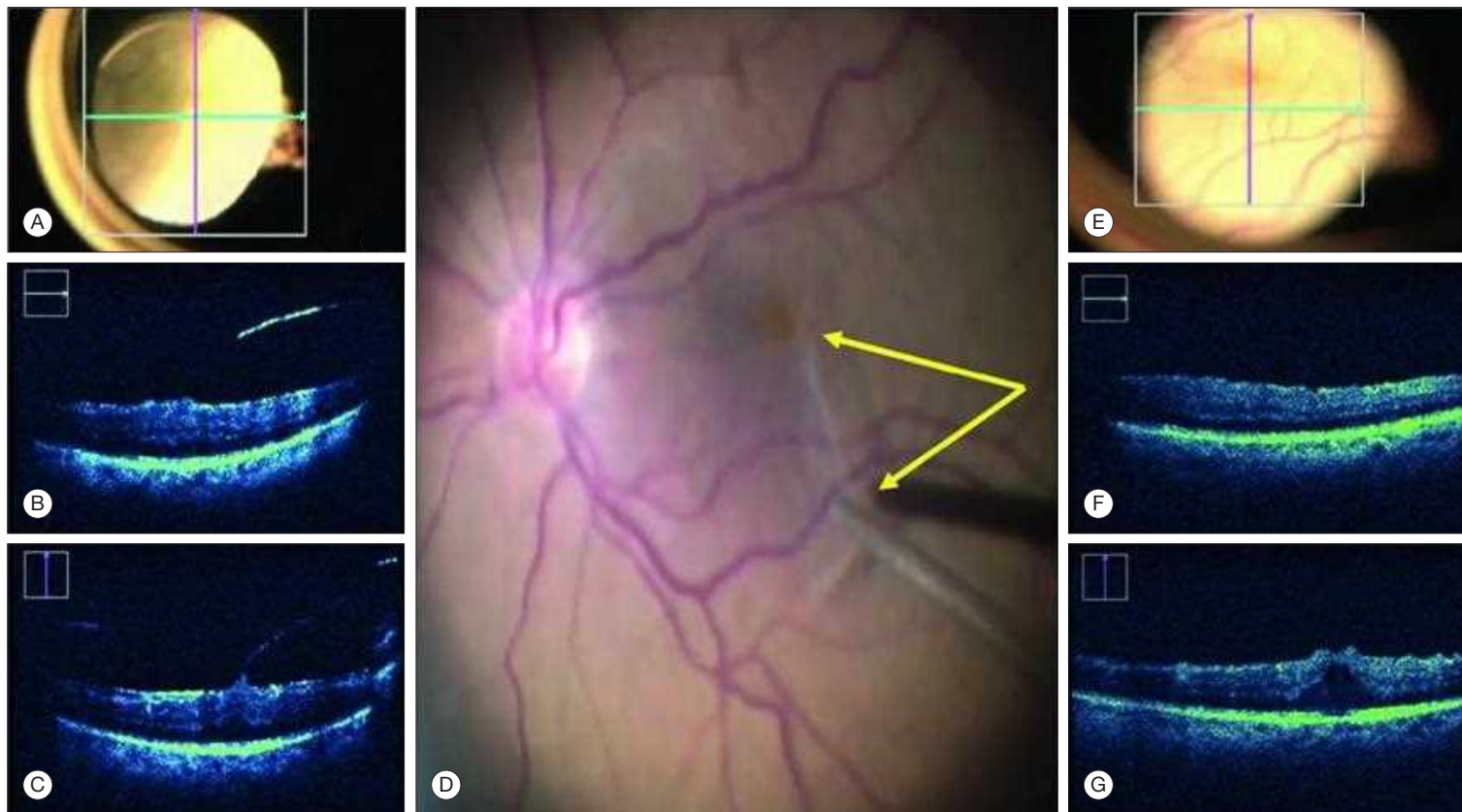


See clip:  
6.32.1



**Fig. 6.32.4** Gass stage 4 macular hole. Postoperative spectral-domain optical coherence tomography appearance of a successfully closed macular hole with slowly resolving subfoveal fluid.

acuity improvement of  $\geq 2$  Snellen lines following surgery. Recent studies confirm that high rates of anatomical success (85%–100%) are achievable in large series of macular holes of all stages treated with vitrectomy, with approximately two thirds of eyes achieving 20/50 or better vision.<sup>29,30</sup> Initially, successful closure of the neural retinal defect may be observed in the presence of persistent subfoveal fluid (Fig. 6.32.5). The patient may have excellent visual acuity despite this persistent fluid or may complain of a persistent area of blurred vision. This may persist for months, but as the fluid is slowly reabsorbed, improved visual function can be observed.<sup>31</sup> Although 20/20 vision can be measured in many patients who had good presenting visual acuity, these patients may still report subtle imperfections in their central vision. Recent findings from spectral-domain OCT research suggest that a disruption in the inner segment/outer segment photoreceptor junction in eyes with closed macular holes may lead to a poorer visual prognosis compared with those with an intact inner junction.<sup>32</sup> Historically, very large Gass stage 4 macular holes (diameter >600 microns), were felt to be best left without surgical intervention, but recent reports have reported some anatomical and visual improvements with the use of the inverted ILM flap technique, in which a pedunculated flap of ILM is purposefully left over the macular hole just prior to the fluid–air exchange to serve as a scaffold to facilitate macular hole closure.<sup>33</sup>



**Fig. 6.32.5** Left column (top to bottom) demonstrates the intraoperative clinical (A) and intraoperative optical coherence tomography (OCT) appearance on horizontal (B) and vertical (C) scans of a Gass stage 1 macular hole demonstrating persistent vitreomacular traction <1500  $\mu\text{m}$ . Middle column demonstrates the intraoperative clinical appearance (D) of the posterior hyaloid as it was being elevated over the macula (arrows point to the posterior hyaloid face being elevated with vacuum and provided by the vitrectomy handpiece along with manual countertraction) with resultant release of traction. Right column (top to bottom) demonstrates the intraoperative clinical (E) and intraoperative OCT appearance on horizontal (F) and vertical (G) scans after traction is released. (Photographs courtesy Dr. Rishi Singh, Cleveland, OH, USA.)

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# Epiretinal Membrane

T. Mark Johnson, Mark W. Johnson

# 6.33



IN THIS CHAPTER  
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**Definition:** An avascular, fibrocellular membrane that proliferates on the inner surface of the retina to produce various degrees of macular dysfunction.

## Key Features

- Transparent, translucent, opaque, or pigmented membrane on the inner retinal surface.
- Tangential traction on the macula.
- Partial or complete posterior vitreous separation.

## Associated Features

- Central vision loss with or without metamorphopsia.
- Glistening light reflex.
- Retinal distortion.
- Macular edema.
- Retinal whitening (axoplasmic stasis).
- Intraretinal or preretinal hemorrhage.
- Macular hole or pseudo-hole.

## INTRODUCTION

The proliferation of fibrocellular membranes on the inner retinal surface in the macular area may occur in otherwise healthy eyes or secondary to retinal breaks and rhegmatogenous retinal detachment, retinal vascular diseases, intraocular inflammation, blunt or penetrating trauma, and other ocular disorders. Common synonyms applied to epiretinal membranes (ERMs) include macular pucker, premacular fibrosis or gliosis, cellophane maculopathy, surface wrinkling retinopathy, and epimacular membrane. Visual symptoms associated with ERMs range in severity, depending on the opacity of the membrane and the amount of macular distortion induced by the contracting fibrocellular tissue. Surgical peeling of ERMs in patients who have significant visual symptoms typically results in improved visual acuity and reduced metamorphopsia.

## EPIDEMIOLOGY AND PATHOGENESIS

The majority of patients who have idiopathic ERMs are age >50 years; however, children and young adults occasionally are affected.<sup>1,2</sup> The prevalence of idiopathic ERMs diagnosed with color fundus photography in population-based studies ranges from 4%–11%.<sup>3–5</sup> The prevalence may be significantly higher in certain racial groups, particularly Hispanics.<sup>6</sup> Autopsy studies demonstrate a similar prevalence, approximately 6%, with increasing prevalence in advancing age groups.<sup>7,8</sup> Many large series suggest a higher prevalence of epiretinal formation in women than in men.<sup>1,9–11</sup> Although idiopathic ERMs are bilateral in 20%–30% of cases,<sup>1,3,7</sup> significant bilateral loss of central vision is uncommon.

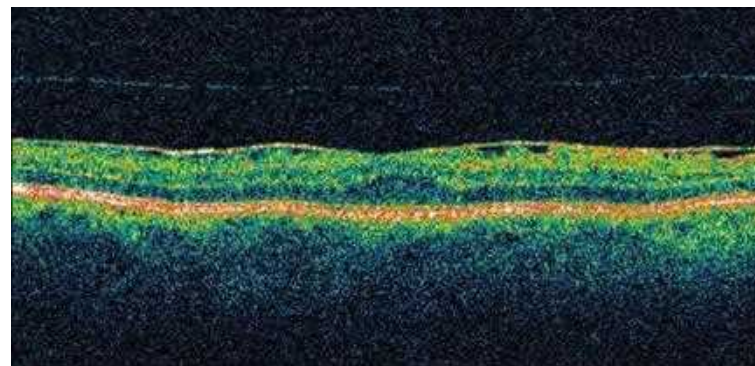
The 5-year incidence of idiopathic ERM formation is approximately 5%.<sup>12</sup> Incident ERMs are more commonly mild cellophane maculopathy (5-year incidence of 3.8%) compared with premacular fibrosis with retinal striae (5-year incidence of 1.5%). The incidence of epiretinal formation is higher in patients with an ERM in the fellow eye at baseline (5-year

incidence of 13.5%).<sup>12</sup> The incidence of symptomatic epimacular membrane formation is 4%–8% after repair of rhegmatogenous retinal detachment,<sup>13–15</sup> and 1%–2% after prophylactic treatment of peripheral retinal breaks.<sup>16</sup> Risk factors for the development of macular ERMs after conventional retinal detachment surgery include older age, preoperative vitreous hemorrhage, macular detachment, preoperative signs of proliferative vitreoretinopathy, large retinal breaks, intraoperative use of cryotherapy, and multiple operations.<sup>13–15,17</sup>

Mild ERM formation occurs commonly in association with blunt or penetrating ocular trauma, vitreous inflammatory conditions, retinal vascular diseases that cause chronic intraretinal edema, and long-standing vitreous hemorrhage.<sup>17,18</sup> Apart from penetrating trauma, these are uncommon clinical contexts in which to find significant macular dysfunction as a result of ERM contracture.

The pathogenesis of ERMs is not completely understood. It appears that the pathogenesis of idiopathic ERMs may differ from that of ERMs occurring after retinal detachment. The development of posterior vitreous detachment appears to be central to the development of idiopathic ERMs.<sup>19</sup> It has been observed that a clinically detectable posterior vitreous detachment is present in approximately 90% of eyes that have idiopathic membranes.<sup>1,10,20–22</sup> Vitreoretinal traction that occurs during the development of a posterior vitreous detachment may create defects in the internal limiting membrane (ILM) that allows migration of retinal glial cells and subsequent proliferation and contraction on the inner retinal surface.<sup>7,23,24</sup> An alternative, and more likely, proposed mechanism for idiopathic ERM formation involves proliferation, fibrous metaplasia, and contraction of hyalocytes left behind on the inner retinal surface after posterior vitreous detachment.<sup>17</sup> Previous studies have reported that 10%–25% of ERMs occur in the absence of a posterior vitreous detachment, suggesting that cellular migration may sometimes occur through pre-existing defects or thinning in the ILM.<sup>25</sup> More recent investigations utilizing ultrasonography and optical coherence tomography (OCT) demonstrate that in eyes with an ERM but without a complete posterior vitreous detachment (PVD), a partial, perifoveal PVD is invariably present<sup>19,26</sup> (Fig. 6.33.1).

ERMs that develop in eyes that have retinal breaks most likely represent a mild form of proliferative vitreoretinopathy caused by retinal pigment epithelium (RPE) cells that are liberated into the vitreous cavity



**Fig. 6.33.1 Epiretinal Membrane Associated with Partial Perifoveal Vitreous Detachment (PVD).** Optical coherence tomography imaging demonstrates a shallow detachment of the posterior hyaloid from the macular region in this eye with epiretinal membrane and no biomicroscopic evidence of PVD.

and proliferate, along with other cellular constituents, to form contractile membranes on the retinal surface.<sup>27</sup> Cellular proliferation stimulated by vitreous inflammation or breakdown of the blood–retinal barrier is a plausible pathogenic mechanism for the remaining types of secondary ERMs.

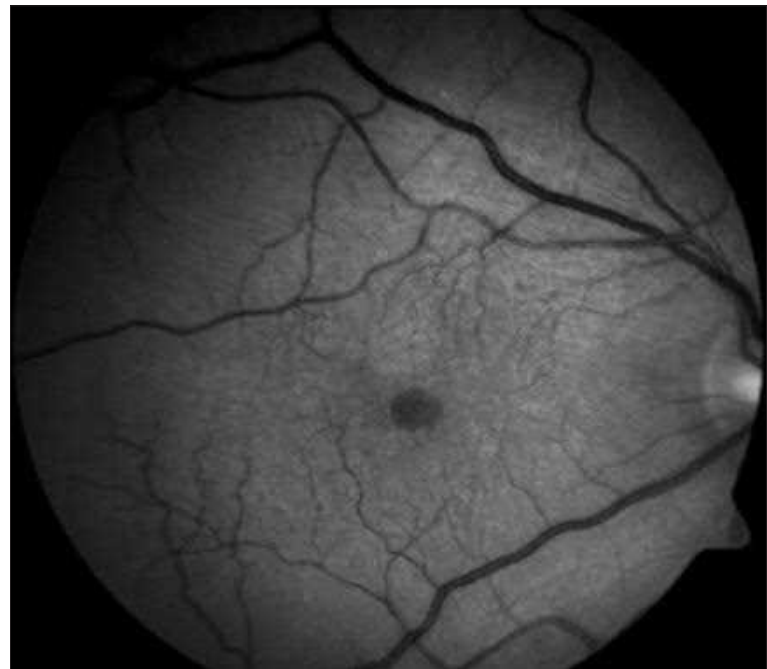
The pathogenesis of visual loss secondary to an ERM remains poorly understood. Theoretical mechanisms of visual loss include a filtering effect of the ERM on the photoreceptors, mechanical distortion of the photoreceptors, obstruction of axoplasmic flow, intraretinal edema, or alterations in macular blood flow. Multifocal ERG studies of patients with idiopathic ERMs demonstrate larger b-wave depression suggesting that the original site of dysfunction is located within the inner retina with photoreceptor dysfunction being a later phenomenon.<sup>28</sup> The biphasic first order response of the multifocal ERG includes an initial negative deflection (N1) followed by a positive peak (P1). The P1 response may include contribution of the Müller and bipolar cells. In one series of idiopathic ERM cases undergoing surgery, the P1 response was shown to be more predictive of final visual outcome than the N1 response reflective of the photoreceptor dysfunction.<sup>29</sup> In this series, only 27% of the patients with poor visual outcomes postoperatively had normal P1 times preoperatively, yet 53% showed no evidence of disruption of the inner segment/outer segment (IS/OS) junction on spectral-domain OCT (SD-OCT) indicative of photoreceptor damage. This again suggests that Müller/bipolar cell dysfunction induced by an ERM may precede photoreceptor dysfunction.

## OCULAR MANIFESTATIONS

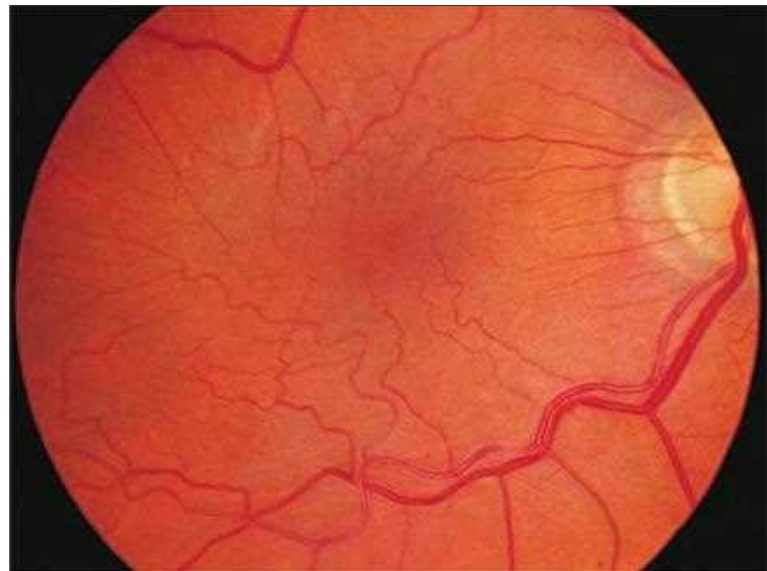
The symptoms of an ERM are largely determined by the thickness of the ERM and the degree of its contracture. In its mildest form, often called “cellophane maculopathy,” the membrane is thin and transparent, produces no distortion of the inner retinal surface, and leaves the patient asymptomatic. With more significant contraction of the membrane, full-thickness distortion, folding, or puckering of the macula typically results in complaints of metamorphopsia, loss of visual acuity, and occasionally central photopsia. In some patients, an eccentrically located ERM may cause lateral displacement of the fovea without detachment from the pigment epithelium (foveal ectopia); this results in relative preservation of visual acuity and symptoms of central binocular diplopia. Other patients who have ERMs that do not result in severe acuity loss complain of macropsia, presumably because of the crowding of photoreceptors caused by tangential retinal traction and thickening in the inner nuclear layer.<sup>30</sup>

The diagnosis of ERMs is primarily clinical, based on biomicroscopic observation. Contact lens biomicroscopy frequently is helpful in the detection of subtle transparent or translucent ERMs, particularly in eyes that have corneal surface irregularities or media opacities. Furthermore, the excellent resolution and stereopsis afforded by the fundus contact lens permit detailed assessment of the extent to which the macula is distorted, thickened, displaced, or detached by the membrane. Detection of subtle membrane edges by contact lens examination may help plan the surgical approach.

The mildest form of ERM may present only an abnormal glistening light reflex from the inner retinal surface (Fig. 6.33.2). Thin membranes that have undergone limited contraction or shrinkage produce a series of fine, irregular striations or wrinkles that are confined to the ILM and inner retinal tissue. The inner retinal striae typically are most apparent where they radiate out from the margins of the membrane but also may develop in a radiating pattern around one or more epicenters of membrane contraction. The fine macular capillaries may be tortuous, even in the absence of large vessel displacement. Thicker, more contracted ERMs produce tangential traction on the full-thickness neural retina, which results in more severe degrees of macular dysfunction. The membrane itself may remain largely invisible despite significant underlying retinal vascular tortuosity or straightening (Fig. 6.33.3). In other cases, the membrane is visible as a gray-white translucent membrane that partially obscures visualization of retinal vessels (Fig. 6.33.4). Some membranes, particularly those that develop subsequent to retinal breaks or rhegmatogenous retinal detachment, are thick and opaque, usually white in color, but occasionally darkly pigmented. Often a significant component of the membrane’s apparent opacity is whitening of the inner retina that underlies the membrane; presumably this results from traction-induced axoplasmic stasis in the nerve fiber layer (Fig. 6.33.5). The tractional effects of the membrane on the retina may cause macular edema, preretinal or intraretinal hemorrhage (Fig. 6.33.6), or traction macular detachment. Traction-induced detachments of the macula may be subtle, shallow, “tabletop” elevations visible only by contact lens biomicroscopy, or obvious ridges of detachment that pass through the macula. The presence of a defect in the prefoveal portion of



**Fig. 6.33.2 Mild Asymptomatic Epiretinal Membrane.** This thin transparent membrane is detectable only from an irregular, glistening (“cellophane”) light reflex from the inner retinal surface. The striae are well demonstrated on the red-free photo.



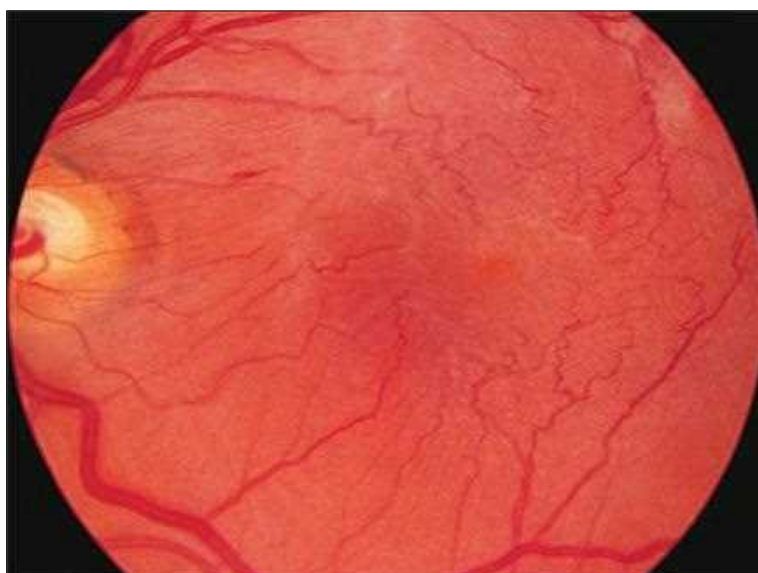
**Fig. 6.33.3** Transparent epiretinal membrane here seen to produce significant retinal vascular distortion.

an ERM may simulate the appearance of a full-thickness macular hole (Fig. 6.33.7). The appearance of a macular “pseudo-hole” is a result of the defect in the epiretinal tissue itself, as well as of the anterior and central displacement of the perifoveolar retina (clivus) during contraction of the ERM.<sup>17</sup> In some cases, a pseudo-hole also involves an inner lamellar macular defect that developed at the time of vitreofoveolar separation. Although it is an uncommon mechanism, tangential foveal traction from contraction of an eccentric ERM occasionally causes full-thickness macular hole formation. Unlike eyes that have true macular holes, those with pseudo-holes usually are minimally symptomatic and have normal or near-normal visual acuities. Biomicroscopic clues that help differentiate a macular pseudo-hole from a true macular hole include the following:

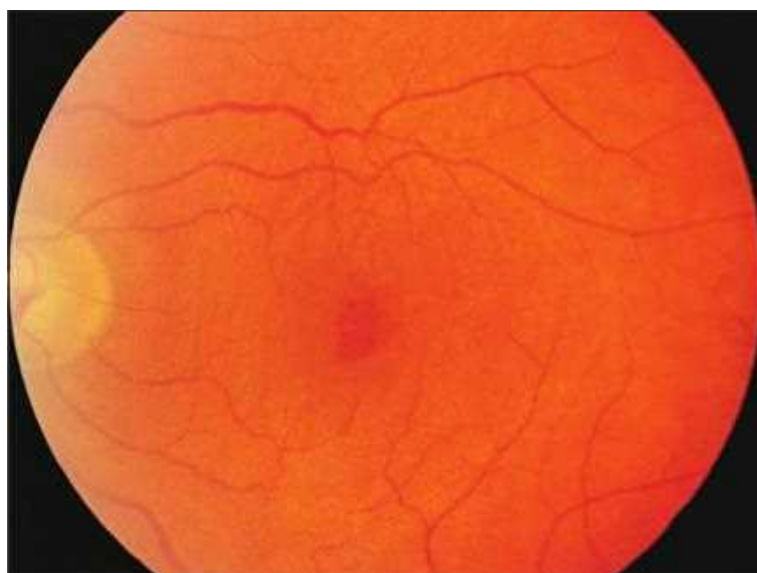
- Wrinkling of the inner retinal surface that surrounds the hole.
- Presence of retinal tissue in the base of the pseudo-hole.
- Absence of characteristic features of full-thickness macular holes, such as yellow RPE deposits in the base of the hole, a halo of neural detachment, and an overlying operculum or pseudo-operculum.

The Watzke–Allen (slit-beam) or laser aiming beam tests may occasionally help to differentiate a macular pseudo-hole from a full-thickness macular hole that complicates an ERM. In equivocal cases, OCT can

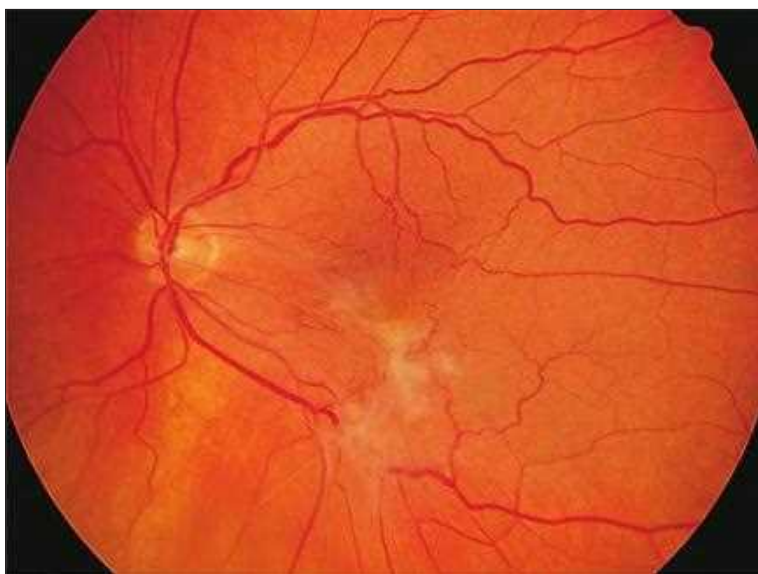




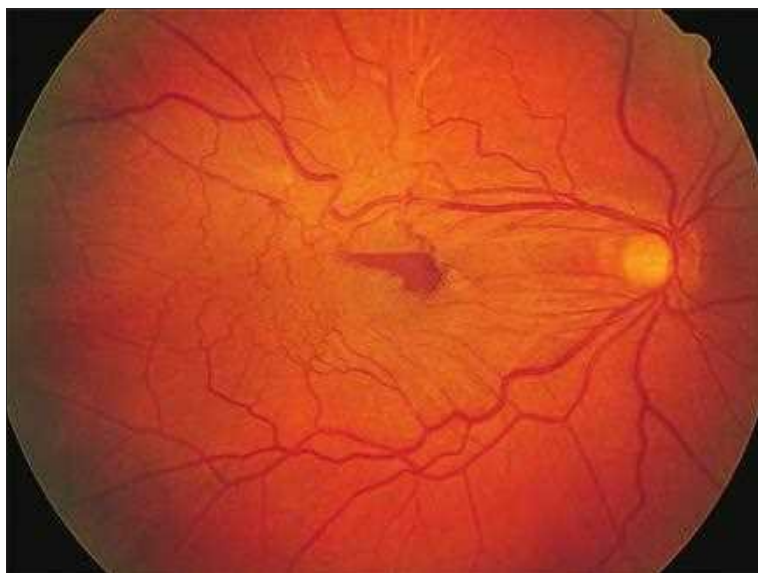
**Fig. 6.33.4 Typical Appearance of Gray-White Translucent Epiretinal Membrane.** Note the partially obscured, distorted retinal vessels and multiple inner retinal striae.



**Fig. 6.33.7 Epiretinal Membrane With Macular Pseudo-Hole.** The visual acuity is 20/25 (6/8) and slit-lamp biomicroscopy shows retinal tissue in the base of the apparent macular hole.



**Fig. 6.33.5 Severe Macular Puckering by an Opaque Epiretinal Membrane After Retinal Detachment Surgery.** Much of the apparent opacity is caused by inner retinal whitening from axoplasmic stasis.



**Fig. 6.33.6 Preretinal hemorrhage induced by traction from an epiretinal membrane.**

distinguish between a full-thickness macular hole and a macular pseudo-hole.

Certain clinical features, although rare, can provide the clinician with clues that the ERM may be secondary to other ocular pathology or indicate a more guarded visual prognosis. Rarely, contracture of an ERM with a central dehiscence causes anterior prolapse of foveal tissue through the hole in the membrane.<sup>31</sup> Long-standing macular traction or retinal vascular leakage induced by ERMs may cause atrophic and/or hypertrophic RPE alterations. Such changes generally are considered poor prognostic signs for visual recovery after surgical removal of the ERM. Occasionally, intraretinal lipid (hard) exudates and/or microvascular changes, such as microaneurysms, are produced by the retinal vascular traction and leakage caused by idiopathic ERMs. Such findings, however, also may signal the presence of associated pathology, such as a choroidal neovascular membrane or long-standing branch retinal vein occlusion, which may require different management approaches and alter the visual prognosis.

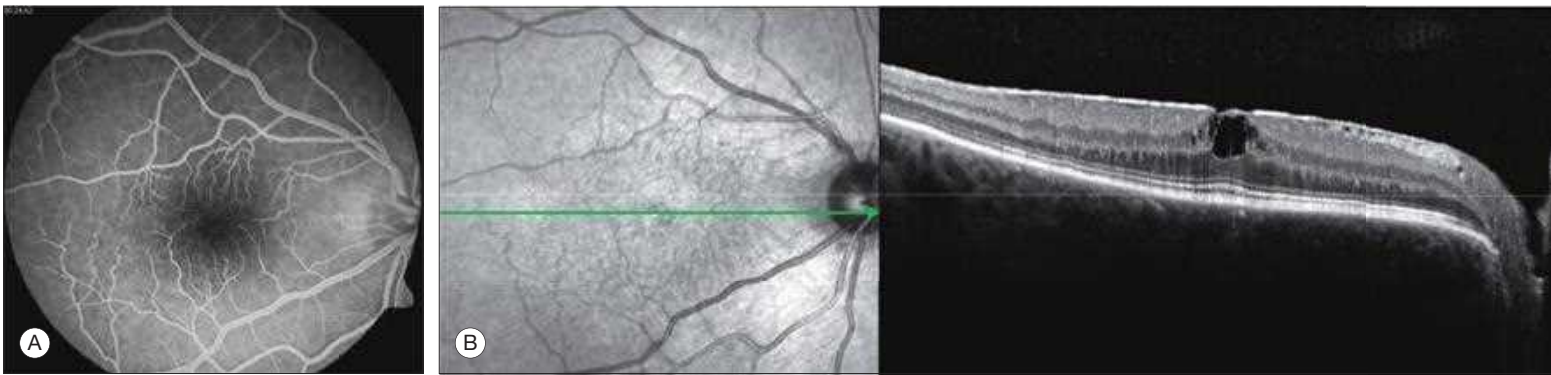
## DIAGNOSIS AND ANCILLARY TESTING

The diagnosis of ERM is primarily clinical. Ancillary testing does play an important role in the evaluation of patients with ERMs. Imaging studies can provide important information when formulating a management plan, including excluding associated macular disease, particularly retinal vascular disease.

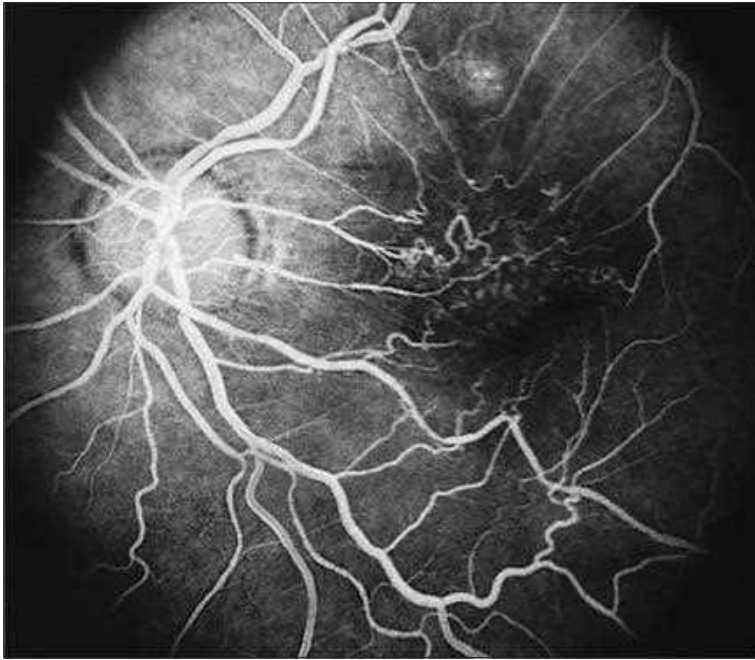
Examination and/or photography of the macula with red-free light may highlight glistening reflexes and thereby assist in assessment of the extent of the membrane. Fluorescein angiography (FA) is useful in the evaluation of patients with ERMs, particularly in eyes that have media opacities that preclude adequate macular examination. A typical fluorescein angiogram in a patient with an ERM will not demonstrate any significant late leakage (Fig. 6.33.8). In some cases, there may be minimal irregular, late intraretinal leakage in the macula. The distribution of leakage is usually determined by the location of the ERM. Although cystoid leakage is common, the fluorescein angiogram in a patient with an ERM can be differentiated from the more symmetrical cystoid pattern seen in pseudo-phakic cystoid macular edema. FA also may be valuable to assess the degree of retinal vascular distortion, confirm the presence of foveal ectopia, detect associated macular edema, differentiate pseudo-holes from full-thickness macular holes, and highlight underlying RPE changes. Finally, FA may be critical in the exclusion of associated macular pathology, such as choroidal neovascularization or venous obstructive disease (Fig. 6.33.9).

OCT has emerged as a useful, noninvasive tool for the evaluation of ERMs. ERMs appear as a hyperreflective band anterior to the retina. The majority of ERMs are globally adherent to the retinal surface, however, some appear to have focal adhesions.<sup>32</sup> These focal adhesions may be more common in eyes with secondary ERMs and may reflect differences in pathogenesis.<sup>32</sup> OCT is also useful in the differentiation of macular pseudo-holes from lamellar and full-thickness macular holes. Pseudo-holes typically have a visible gap in the hyperreflective ERM (Fig. 6.33.10). The

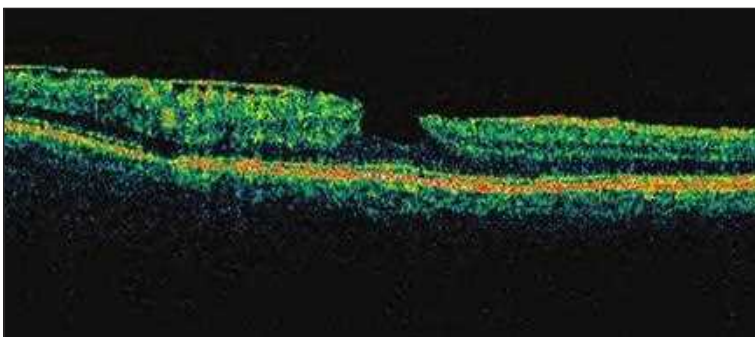




**Fig. 6.33.8 Fluorescein Angiogram of Patient With Idiopathic Epiretinal Membrane.** (A) Fluorescein angiogram without significant fluorescein leakage. (B) Horizontal spectral-domain optical coherence tomography demonstrating intraretinal cystoid changes.



**Fig. 6.33.9 Fluorescein Angiography of an Epiretinal Membrane That Complicates an Old Branch Retinal Vein Occlusion.** Note the collateral vessel formation, in addition to the marked vascular distortion.

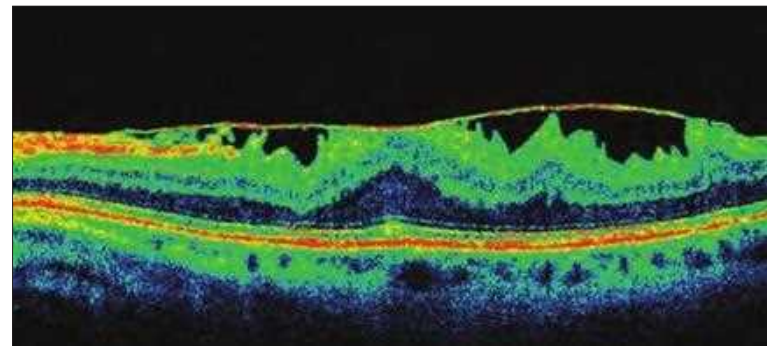


**Fig. 6.33.10 Optical coherence tomography (OCT) of an epiretinal membrane with a central pseudo-hole.**

foveal thickness is near normal, whereas the parafoveal retina is thickened.<sup>32</sup> Lamellar holes are often observed to have medium, homogeneous, hyperreflective epiretinal proliferation that may coexist with typical ERM. This lamellar hole associated epiretinal proliferation is generally not associated with contractile effects in the retina and may be more common in larger, thinner lamellar holes.<sup>33</sup> OCT is also useful for confirmation of the presence of vitreomacular traction (Fig. 6.33.11). OCT may be predictive of visual outcome with ERM surgery.<sup>34</sup> The hyperreflective line above the RPE demonstrates the IS/OS junction of the photoreceptors (Fig. 6.33.12). Several studies have demonstrated that an intact, continuous IS/OS junction is predictive of better visual outcome at 12 months.<sup>29,35</sup> SD-OCT may provide better visualization of the IS/OS junction, particularly in the setting of inner retinal edema secondary to ERM.<sup>35</sup>



**Fig. 6.33.11 Optical coherence tomography (OCT) with an epiretinal membrane and vitreomacular traction.**



**Fig. 6.33.12 Optical Coherence Tomography (OCT) of Patient With Epiretinal Membrane Demonstrates Significant Surface Retinal Distortion and Inner Retinal Edema.** The outer retina is relatively unaffected, and the patient has 20/25 visual acuity.

## DIFFERENTIAL DIAGNOSIS

The differential diagnosis of ERMs is given in Fig. 6.33.12. The most common diagnoses that must be differentiated from ERM and its associated features include the vitreomacular traction syndrome, postoperative cystoid macular edema, and full-thickness macular hole (as opposed to ERM with macular pseudo-hole). Such differentiations are important to make because each of these clinical entities (discussed in detail in the chapters listed) differ from ERM in their management and prognosis.

## PATHOLOGY

Histopathological and ultrastructural studies have shown that ERMs consist of a fibrocellular sheet of varying thickness, in which both native vitreous and newly synthesized collagen have been found.<sup>7,8,17,23-25,27,36,37</sup> Fragments of ILM are seen commonly in surgical specimens,<sup>37</sup> which suggests that the inadvertent or intentional removal of this membrane does not preclude good visual outcomes.

The cellular elements of most ERMs include one or more of the following: RPE cells, fibrous astrocytes, fibrocytes, and macrophages. The cell types found in a particular membrane may depend, in part, on the associated ocular disorders.<sup>7,27,36,37</sup> Furthermore, the precise identification of the cells of origin within ERMs is hampered by the ability of each of the common constituent cells to transform into cells with similar morphology

and function.<sup>17</sup> The observation that RPE cells are the main cell type in many cases of idiopathic ERM is poorly understood<sup>36</sup> but possibly may involve transretinal migration of RPE cells in response to biochemical stimuli.<sup>38</sup> Most of the cell types found in ERMs have the capacity to assume myofibroblastic properties, which allows them to change shape and cause the membrane to contract.<sup>17</sup> ERM formation in association with vitreomacular traction may differ slightly in pathogenesis, with histopathological studies demonstrating a strong predominance of myofibroblasts.<sup>39</sup> In addition, in this series, it was noted that patients with ERM associated with vitreomacular traction syndrome had a thin layer of remnant native vitreous collagen trapped between the cellular myofibroblast layer and the ILM. This suggests that the residual vitreous plays an important role in ERM development.<sup>39</sup> Soluble growth factors may influence cell migration in the development of ERM. Case-control studies of vitreous samples of LR11, a regulatory growth factor for adherent cells, have shown that LR11 is higher in cases of ERM with premacular fibrosis compared with those with cellophane maculopathy.<sup>40</sup>

## TREATMENT

Mild ERMs typically produce minimal symptoms. In many cases, no intervention is required. Population-based photographic studies of patients with ERMs show that patients with cellophane maculopathy rarely demonstrate progressive visual loss.<sup>12</sup> In the same study, patients with more significant premacular fibrosis and retinal striae appeared to be equally stable with little progression of the ERM or visual loss.<sup>12</sup> Because ERMs often show little or no progression after the initial diagnosis, surgery is not performed prophylactically on mild membranes.

Patients who have more severe membranes that produce significant visual loss and/or metamorphopsia usually benefit from vitreous surgery with peeling of the ERM from the surface of the macula. The goal of membrane peeling is to reduce or eliminate the most common mechanisms of visual loss, including macular distortion, traction macular detachment, foveal ectopia, tissue that covers the fovea, retinal vascular leakage with macular edema, and traction-induced obstruction of axoplasmic flow. In general, most patients considered for vitrectomy have significant visual impairment. In some cases, patients with significant visual symptoms but relatively preserved visual acuity may also benefit from surgery.<sup>41</sup> The best candidates for surgery are those who have membranes for a relatively short period because the potential for visual recovery decreases with increasing duration of preoperative symptoms.<sup>9</sup> However, excellent visual recovery is not necessarily precluded in patients who have symptoms that have lasted >1 year. Careful preoperative evaluation of all eyes should exclude additional causes of vision loss, such as choroidal neovascularization, macular ischemia from previous retinal vascular occlusion, or other pre-existing macular disease.

Conventional pars plana vitreous surgical techniques are used to remove the vitreous gel, which, in most cases, has separated previously from the posterior retina. A variety of techniques have been described to elevate and remove the ERM.<sup>42</sup> An edge of the ERM is engaged with a vitreoretinal pick or forceps or created with a sharp bent-tip needle. After developing an edge, the membrane is typically peeled from the retina with forceps, usually as a single piece. Rarely, sites of firm adhesion to the retina are encountered; at these, the membrane may be amputated in preference to the creation of retinal breaks in the macular area.

Several controversies exist in the surgical management of ERMs. In recent years techniques have been developed that allow removal of the ILM along with the ERM. In theory, removal of the ILM may reduce the chances of persistent or recurrent ERM. Several comparative studies confirm that ILM removal reduces the risk of recurrent or persistent ERM; however, no clear benefit to visual recovery has been demonstrated.<sup>43,44</sup> Identification of the ILM and, in some cases, the extent of the ERM can be difficult. Some vitreoretinal surgeons have advocated the use of vital dyes, such as indocyanine green (ICG), trypan blue, or brilliant blue G, to assist in these tasks. Although these adjuncts assist in surgical identification of the ILM and ERM, they have not clearly been demonstrated to improve the visual outcome.<sup>45-47</sup> In addition, there is some controversy regarding the potential toxicity of ICG dye.<sup>45,46</sup> Toxicity issues of ICG are not clearly understood, given that the dye concentrations, osmolalities, and exposure times have varied among studies.<sup>48</sup>

Of the patients undergoing vitrectomy, >75% will have improved visual acuity. Predictors of better visual outcomes include preoperative visual acuity better than 20/100, shorter duration of symptoms and absence of tractional retinal detachment.<sup>22</sup> Preoperative cystoid macular edema may be a poor prognostic sign.<sup>49,50</sup> Newer retinal imaging studies, including

OCT and multifocal-electroretinography (mERG), may also be predictive of visual outcome. Shorter P1 times appear to correlate with better final visual acuity.<sup>29</sup> Younger patients experience benefits similar to those of ERM surgery; however, the recurrence rate appears to be higher, approaching 25%.<sup>51,52</sup>

The most common surgical complication is progressive nuclear sclerotic cataract, which occurs in 60%–70% of eyes within 2 years after surgery, with a much lower incidence in patients age <50 years.<sup>11,53</sup> Other less common complications include peripheral retinal breaks, rhegmatogenous retinal detachment, posterior retinal breaks, photic maculopathy, and endophthalmitis. Late postoperative recurrence of symptomatic epiretinal tissue occurs in approximately 5% of patients.<sup>9,11</sup>

## COURSE AND OUTCOMES

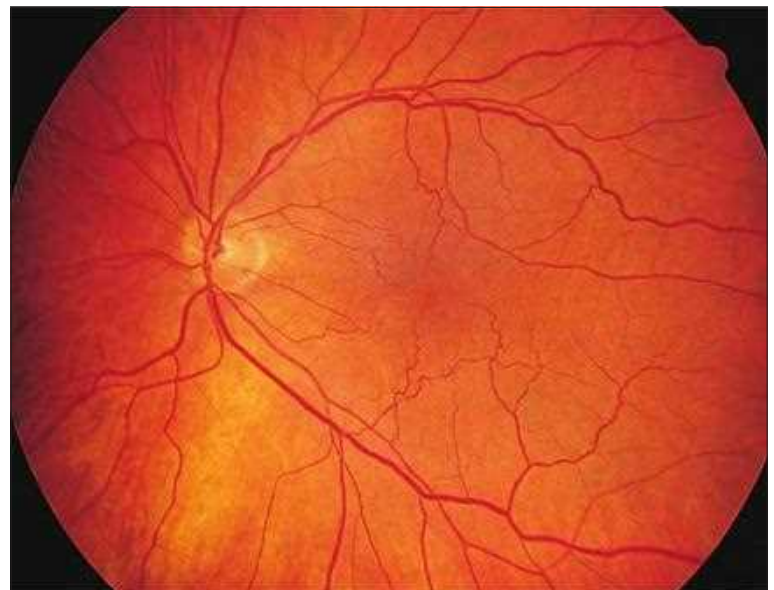
Most patients who have ERMs experience little or no symptom progression after the initial diagnosis, which implies that membrane contraction usually occurs soon after its formation and then stabilizes. Only 10%–25% of eyes show a decline in visual acuity over time—rates of progression vary from over several months to many years.<sup>9,12,17</sup> Rarely, ERMs separate spontaneously from the retina, which results in visual improvement.<sup>17</sup> Approximately 20% of patients who develop macular pucker after scleral buckling experience spontaneous improvement in visual acuity, as a result of resolution of the macular edema and relaxation or partial peeling of the ERM.<sup>13</sup>

Following surgical removal of ERMs, most of the macular distortion and all of the retinal whitening resolves, typically within days or weeks of the operation (Fig. 6.33.13). Associated cystoid macular edema may resolve or persist chronically. Even in eyes that appear quite normal postoperatively, OCT typically shows some degree of persistent foveal thickening indefinitely (Fig. 6.33.14). Visual improvement of  $\geq 2$  Snellen lines occurs in 60%–85% of eyes and may continue for 6–12 months after surgery.<sup>9,11,22</sup> A small number of eyes (2%–15%) have worse visual acuity postoperatively.<sup>9,11,22</sup> (Video 6.33.1).

Although visual acuity improves and metamorphopsia is reduced significantly in most eyes after ERM peeling, the visual function rarely returns to normal. Studies of pre- and postoperative multifocal ERG shows an improvement in the oscillatory potentials, a- and b-waves, however, they rarely reach the levels of the unaffected fellow eye.<sup>28</sup> Patients commonly are advised to expect improvement in visual acuity that is approximately halfway between the preoperative acuity and normal. Preoperative factors prognostic of the final visual acuity include the level of preoperative visual acuity, duration of symptoms before surgery, and nature of previous macular damage, such as by retinal detachment involving the macula.<sup>11,50</sup> Eyes that have lower levels of preoperative visual acuity typically improve by the most number of lines but tend to have lower final acuities than eyes that had better preoperative vision.<sup>47</sup> Although the prognostic value of preoperative macular edema is controversial, FA probably does not help predict the visual outcome in patients who undergo surgery for idiopathic ERM.<sup>11,54</sup> OCT parameters may be better prognostic factors for

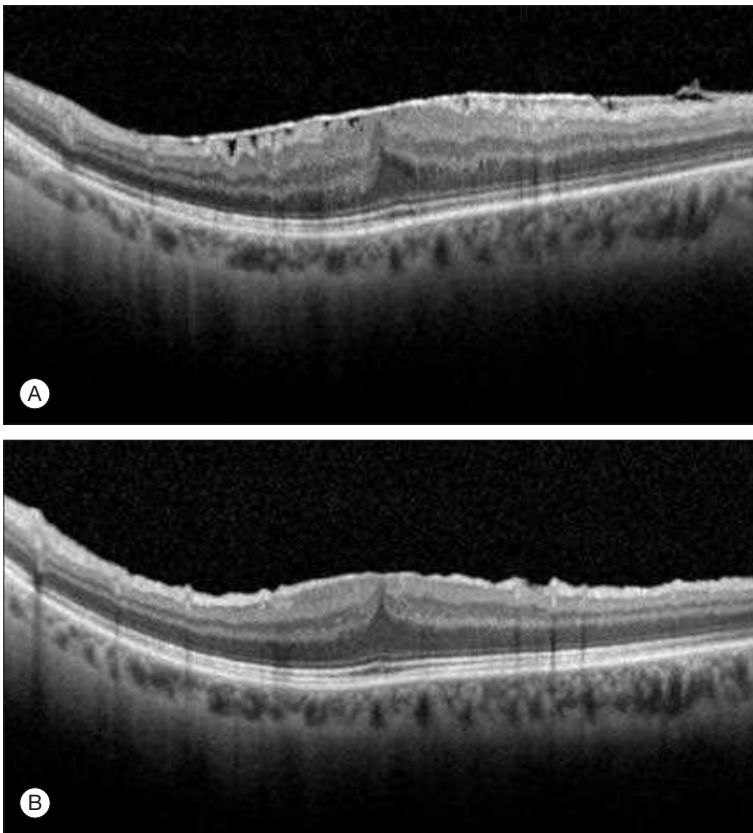


See clip:  
6.33.1



**Fig. 6.33.13 Postoperative Appearance of the Eye Shown in Fig. 6.33.4.** After membrane peeling, the retinal whitening and most of the macular distortion has resolved. The visual acuity improved from 20/100 (6/30) to 20/30 (6/9).





**Fig. 6.33.14 Pre- and Postoperative Optical Coherence Tomography (OCT) Images of Patient Undergoing Successful Epiretinal Membrane Surgery.** (A) Preoperative OCT with retinal edema and visual acuity 20/60. Postoperative visual acuity improved to 20/25. (B) However, there is continued irregularity evident on OCT.

improvement in vision with vitrectomy. Lesser central foveal thickness at baseline, good integrity of inner/outer segment junction, and thinner ganglion cell/inner plexiform layer appear to be predictive of improvement.<sup>55</sup>

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# Vitreomacular Traction

William E. Smiddy

# 6.34



**Definition:** Incomplete anomalous, posterior vitreous detachment with a varied degree of preretinal tissue proliferation and associated traction via a variably sized zone of persistent vitreous attachment is best diagnosed with optical coherence tomography.

## Key Features

- Distortion of the internal limiting membrane with retinal striae and vascular tortuosity.
- Intraretinal edema spaces associated with the vitreomacular attachment site.
- Possible localized traction-related macular detachment.

## Associated Features

- May manifest a “pseudo-macular hole” configuration clinically.
- Should be distinguished from vitreomacular attachment, which is most commonly a normal finding but may be a precursor form.

## INTRODUCTION

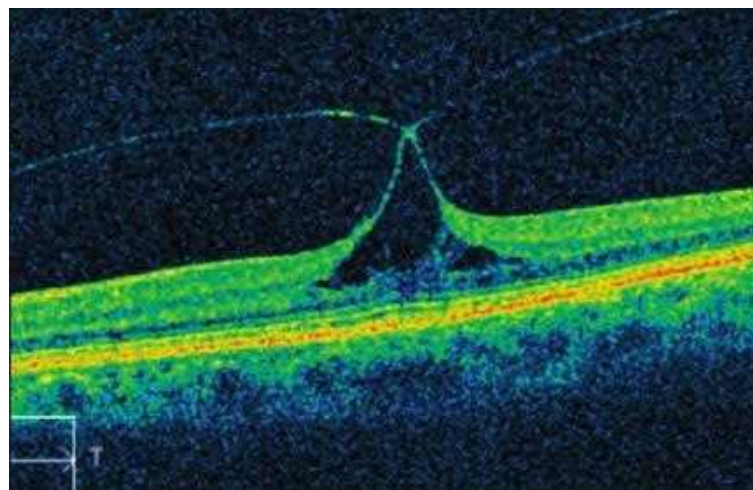
The interaction of the vitreous and macular surfaces may take on a variety of configurations. The extent and location of this interaction define a corresponding range of conditions, including full-thickness macular hole (FTMH), forms of lamellar macular hole, myopic traction maculopathy (MTM), cystoid macular edema (CME), epiretinal membrane (ERM), and vitreomacular traction (VMT).<sup>1-8</sup> These may be unified in the concept that they represent a family of conditions characterized by the spectrum of variations of anomalous posterior vitreous detachment (PVD).<sup>9</sup>

The moniker *vitreomacular traction syndrome* (VMTS) was originally coined on the basis of clinical, ophthalmoscopic findings of visibly persistent, variable extensive vitreous attachment at the macula associated with epiretinal proliferation,<sup>10-13</sup> essentially a macular pucker without complete PVD.

Optical coherence tomography (OCT) became available with increasingly finer resolution, and definitively revealed much more anatomical details than could be observed or even inferred clinically.<sup>14</sup> It has become the defining tool for what is now recognized as a host of macular conditions. Subsequently, a more subtle entity is now generally referred to by the same name—in this chapter, it will be referred to as VMT—as defined in accordance with the OCT features.<sup>15-18</sup> The VMT configuration is not rare, being present in about 2% of eyes.<sup>19</sup>

This chapter will focus on the contemporary entity of VMT, rather than the previously defined VMTS. The clinical embryogenesis of the current entity of VMT is closer to the impending (stage 1) macular hole entity, which was the focus of much attention in the late 1980s,<sup>20-23</sup> before the successes of macular hole surgery became apparent.<sup>24-30</sup> This similarity has been refined through OCT images.

OCT has verified that the posterior hyaloid may even split in such a way as to simulate a PVD, yet still maintaining a gossamer attachment posteriorly in VMT cases (Fig. 6.34.1). Now, as was the case with an impending



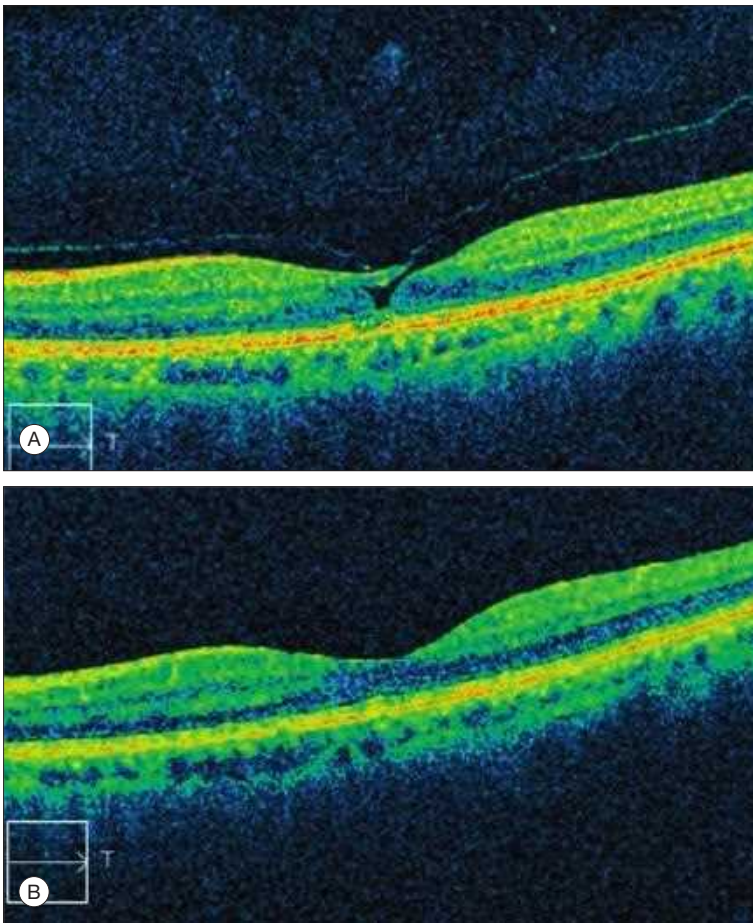
**Fig. 6.34.1** A 78-year-old woman with visual acuity of 20/30 OS (left eye) as a result of vitreomacular traction, but with only minimal metamorphopsia. The other eye is 20/200 with a macular scar. Optical coherence tomography shows gossamer attachment of the vitreous at the fovea, where distortion of inner retinal layers suggests traction. There was spontaneous resolution 2 months later.

macular hole, a treatment objective includes pre-emption to avoid formation of full-thickness macular hole and its incumbent visual loss. As will be discussed in the next section, only a minority of VMT cases progress to FTMH. Hence, the primary treatment objective in VMT cases with decreased visual acuity is to restore some of the lost vision. The ongoing conundrum is how to identify cases that are at highest risk to progress to further loss of vision or to FTMH formation. This uncertainty has hampered optimal application of the several treatment options that have now been developed.

## NATURAL HISTORY OF VITREOMACULAR TRACTION

A logical, even necessary, point of departure to bring some order to therapeutics is a better definition of the natural history so that therapeutic intervention can be optimally applied. Although randomized controlled trials may offer more definitive information, it is difficult to perform them from logistical, ethical, and study design perspectives. Hence, natural history studies, even if restricted to relatively milder cases, offer the best foundation available. It has been long recognized that spontaneous resolution may occur even among the more severe, clinically evident cases of VMT<sup>17,19,31,32</sup> (Fig. 6.34.2), but the earliest studies suggested frequencies of only ≈10%.<sup>33</sup> More recently published surveys, albeit of selected cases (generally milder degrees of vision loss), have demonstrated spontaneous resolution rates of OCT-defined cases as being ≈30%, and the rate of those not progressing has been up to 60%, depending loosely on the anatomical configuration.<sup>34,35</sup> Some attempts to grade the severity of the tractional effects have yielded the conclusion that, paradoxically, those with more severe tractional effects are the most dynamic—they have the highest risk





**Fig. 6.34.2** (A) Optical coherence tomography (OCT) of a 76-year-old man with visual acuity of 20/40 and central visual blurring. There is insertion of vitreous into the fovea with slight disruption of inner layers. (B) There was spontaneous resolution by a follow-up examination 6 weeks later and improvement to 20/25.

of progression but also the highest likelihood of spontaneous resolution. This further complicates optimizing treatment targeting.

## DIAGNOSIS AND ANCILLARY TESTING

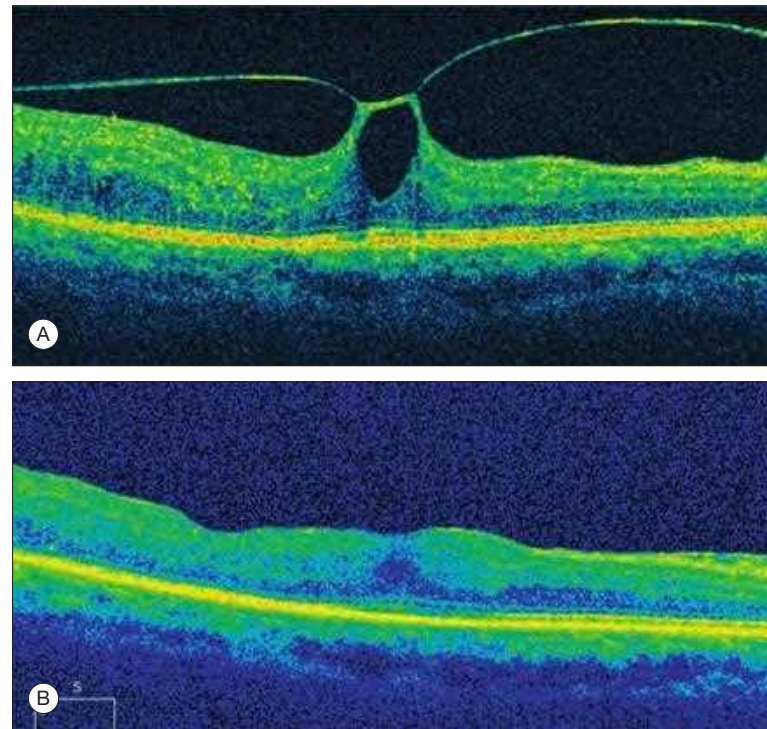
Fastidious macular examination with fundus contact lens (or even suspended precorneal lens) at the slit lamp provides ideal visualization of the vitreomacular interface anatomy but does not offer as much objective detail as OCT. OCT demonstrates the characteristic vitreoretinal attachment and preretinal tissue better than any other imaging.<sup>15</sup> Lack of leakage on fluorescein angiography (FA) is characteristic of VMT; although this might complement the OCT diagnosis, it is rarely contributory, hence usually unnecessary.

## DIFFERENTIAL DIAGNOSIS

There are two aspects to differential diagnosis as they relate to VMT—determining the proper diagnosis as well as staging. Principally, OCT easily allows distinguishing VMT from an FTMH, lamellar macular hole, or an ERM—entities with different treatment objectives and even prognoses. Myopic traction maculopathy is less commonly confused with VMT, especially when taken in context.<sup>36,37</sup> Secondly, OCT characterizes or stages the process. The presence of an ERM and the extent of the vitreomacular attachment are important prognostic factors; the extent of any disruptions of deep retinal layers might be important as well. Moreover, it is important to verify that the symptoms or degree of visual loss is attributable to the anatomical derangement when considering treatment.

## PATHOLOGY

There are no histopathological studies of tissues removed from cases of VMT, but the inference from ongoing macular hole studies is that the tissue at, and adherent to, the foveal surface is composed of posterior hyaloid lamella and typical ERM or VMTS cellular elements.<sup>38,39</sup>



**Fig. 6.34.3** (A) A 71-year-old man with loss of central visual acuity to 20/70 for 6 weeks and prominent vitreomacular traction. Intravitreal ocriplasmin was tried, but there was no change in the appearance or symptoms after another month. (B) Vitrectomy with removal of the posterior hyaloidal attachment and peeling of the internal limiting membrane restored a foveal contour by 1 month postoperatively and visual acuity improvement to 20/40.

## TREATMENT

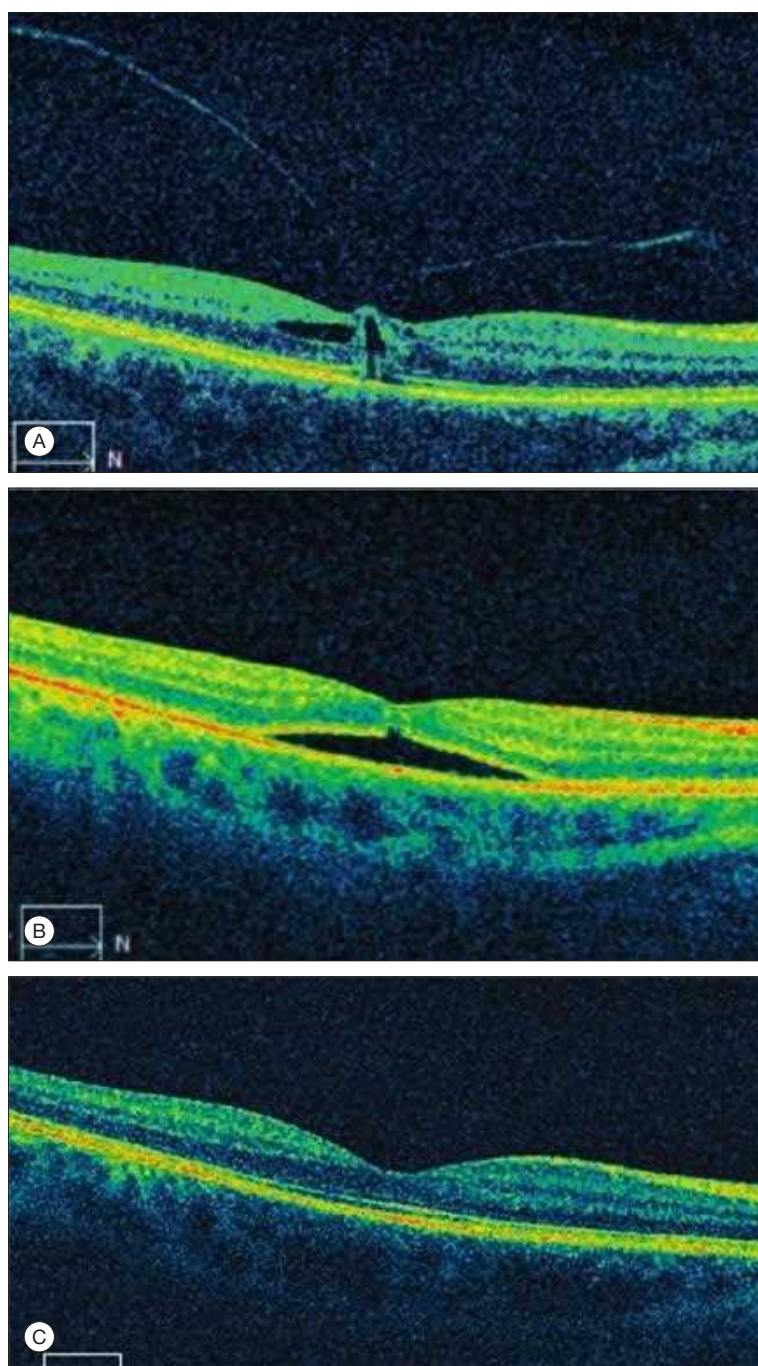
### Vitrectomy

The incomplete understanding of the natural history has not prevented investigation into treatment options. The immediate therapeutic objective is to release the vitreomacular tractional adherence. Currently, there are three interventional options to consider: vitrectomy, intravitreal ocriplasmin, and pneumatic vitreolysis.

Standard vitreous surgical techniques,<sup>40-48</sup> including removal of anterior-to-posterior traction, disinsertion or amputation of the vitreous insertion site at the fovea, and removal of preretinal tissue, are employed (Fig. 6.34.3). Although it is difficult to standardize cases within series, much less between series, the rate of visual improvement has been reported to range from 45%–91%.<sup>41,44-47</sup> (Video 6.34.1). The posterior hyaloidal attachment may be separated by using an adaptation of the en bloc approach, with incision through the posterior hyaloid paracentrally to offer a more controlled, monitorable release while minimizing the risk of unroofing the attenuated inner foveal layer. Alternatively, gentle suction on the posterior hyaloidal layer (as with a flexible tipped extrusion probe) so as to complete the PVD has been employed, but no comparative trial has been undertaken to define the optimal surgical method. The surgical anatomy may include an apparent “double layer” of (split) vitreous with or without preretinal cellular proliferation, probably correlating to a splitting of the posterior hyaloid (vitreoschisis), in contrast to the monolayer of preretinal tissue in standard macular pucker. Searching with a flexible tipped extrusion probe might allow detection of any residual “second” vitreous layer or, conversely, certify the presumption that all was effectively removed. Whether removal of internal limiting membrane (with or without the use of dyes) enhances outcomes is debated but is often pursued to verify that any preretinal mediator of traction has been eliminated, at least in cases where visually this seems to be cleavable at the fovea without inducing a macular hole. Similarly, the routine use of an intraocular gas bubble has not been established. Certainly, in cases where an FTMH is suspected to have occurred intraoperatively or if undue attenuation of the innermost foveal layer is suspected, this should be pursued. There is a substantial risk of postoperative macular hole formation, so this author has adopted a lower threshold for performing this procedure.<sup>48</sup>

See clip:  
6.34.1





**Fig. 6.34.4** (A) A 46-year-old woman with visual acuity of 20/30 but complaining of marked central metamorphopsia OD (right eye). There is a fine vitreomacular attachment and mild disruption of the inner layer, but also slight parting of the outer retinal layers. She had had macular hole surgery 2 years previously OS (left eye) with 20/30. Intravitreal ocriplasmin was injected. (B) There was still a pocket of subretinal fluid under the fovea 5 months later, and the patient was bitterly disappointed with deterioration of vision to 20/60 from postoperative week 1 onward. (C) Finally, 1 year after the injection, her visual acuity had improved to 20/20, and the foveal contour had normalized.

## Pharmacological Vitreolysis

Pharmacological weakening of the vitreomacular attachment has been more broadly sought for many years but has found application in the form of microplasmin for VMT (Fig. 6.34.4). This was reported to be effective in inducing completion of the persistent vitreomacular attachment and may hold promise as an alternative to surgical intervention.<sup>49</sup> The MIVI-TRUST (Microplasmin for Intravitreal Injection–Traction Release without Surgical Treatment) studies, two parallel prospective randomized series, have demonstrated that a release of the vitreomacular attachment is experienced in 26.5% of ocriplasmin-treated eyes compared with 10.1% of placebo-treated eyes (see Fig. 6.34.4). Eyes with focal adhesion of the vitreous (<1500 microns in diameter) and without coincident ERMs are better candidates for effective release.<sup>49,50</sup> Several follow-up, after approval,

and real-world studies have been presented, generally suggesting that the actual success rates can be optimized by targeting the ideal patient population.<sup>51</sup>

Of concern, however, is that, as in vitrectomy, postoperative macular hole formation is not rare. Thus, although this option avoids surgical intervention, albeit with a lower anatomical success rate, it is not clear that it does so with a lower rate of trauma to the inner foveal layer.<sup>49</sup> Moreover, there have been several reports of transient and persistent visual obscurations, either from the mechanical extrication or hypothetically from side effects of the lysis action on other tissues, such as the extracellular matrix.<sup>52,53</sup> Although eyes suffering toxicity with ocriplasmin cannot be predicted, are relatively rare, and are frequently transient, they may be quite distressing to individual patients. Persistent or even appearance of subfoveal fluid has been described after release of VMT, whether surgically or pharmacologically induced; although self-limiting, this may persist for several months.<sup>54</sup>

What is clear from the preclinical studies is that the recommended dosage should *never* be increased, and a second dose should *never* be administered, as there is a high rate of zonular dehiscence (and possibly other consequences parallel to the same biochemical action).<sup>55</sup> Although pharmacological therapy intuitively seems less invasive and less expensive, the complication rate is not trivial and is still being defined. Rudimentary calculations, furthermore, suggest that it is not as cost effective as vitrectomy, yet is cost effective compared with other medical interventions.<sup>56</sup> The better prognosis for eyes without ERMs and with smaller attachment sites may optimize the application and role of ocriplasmin.

## Pneumatic Vitreolysis

The newest therapeutic strategy is pneumatic vitreolysis. This approach was initially introduced >20 years ago for early macular holes before OCT was available to aid in diagnosis,<sup>57</sup> and there has been a resurgence of interest as a result of its potential to be effective without surgery or pharmacological side effects. Preliminary studies have reported results of 80% lysis of VMA, with subsequent improvements in visual acuity.<sup>58,59</sup> Although pneumatic vitreolysis also offers the benefit of avoiding surgical intervention, its complication rate, such as induced macular holes, are incompletely defined; in addition, because new retinal tears occur in many eyes undergoing pneumatic retinopexy for retinal detachment repair, the same might prove true in this application (see Fig. 6.34.4).

## CONCLUSIONS

OCT offers unprecedented imaging of vitreomacular traction, effectively defining what we now call VMT syndrome. Although there have been many studies of various treatment modalities, the optimal treatment options at this point have not been fully defined, and only deduced recommendations exist from these as well as a meta-analysis.<sup>60,61</sup> Hence it is left to the clinician's judgment to individualize treatment decisions.

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# Cystoid Macular Edema

Matthew T. Witmer, Peter Coombs, Szilárd Kiss

# 6.35

**Definition:** Pathological swelling of the layers of the macular neurosensory retina with the formation of cystic spaces.

## Key Features

- Intraretinal fluid accumulation into “cyst-like” pockets within the retina.
- Increase in thickness of the central macula.
- Loss of foveal depression.
- Classic fluorescein angiography appearance consists of leakage of dye in a “petalloid” configuration surrounding the fovea.

## Associated Features

- Optical coherence tomography the most sensitive method of detection.
- Evidence of ocular (anterior chamber or vitreous) inflammation.
- Optic nerve head edema.
- Subretinal fluid.
- Loss of foveal reflex.
- Decreased visual acuity.
- Other evidence of retinal vascular incompetence, such as intraretinal hemorrhages and micro- or macroaneurysms.

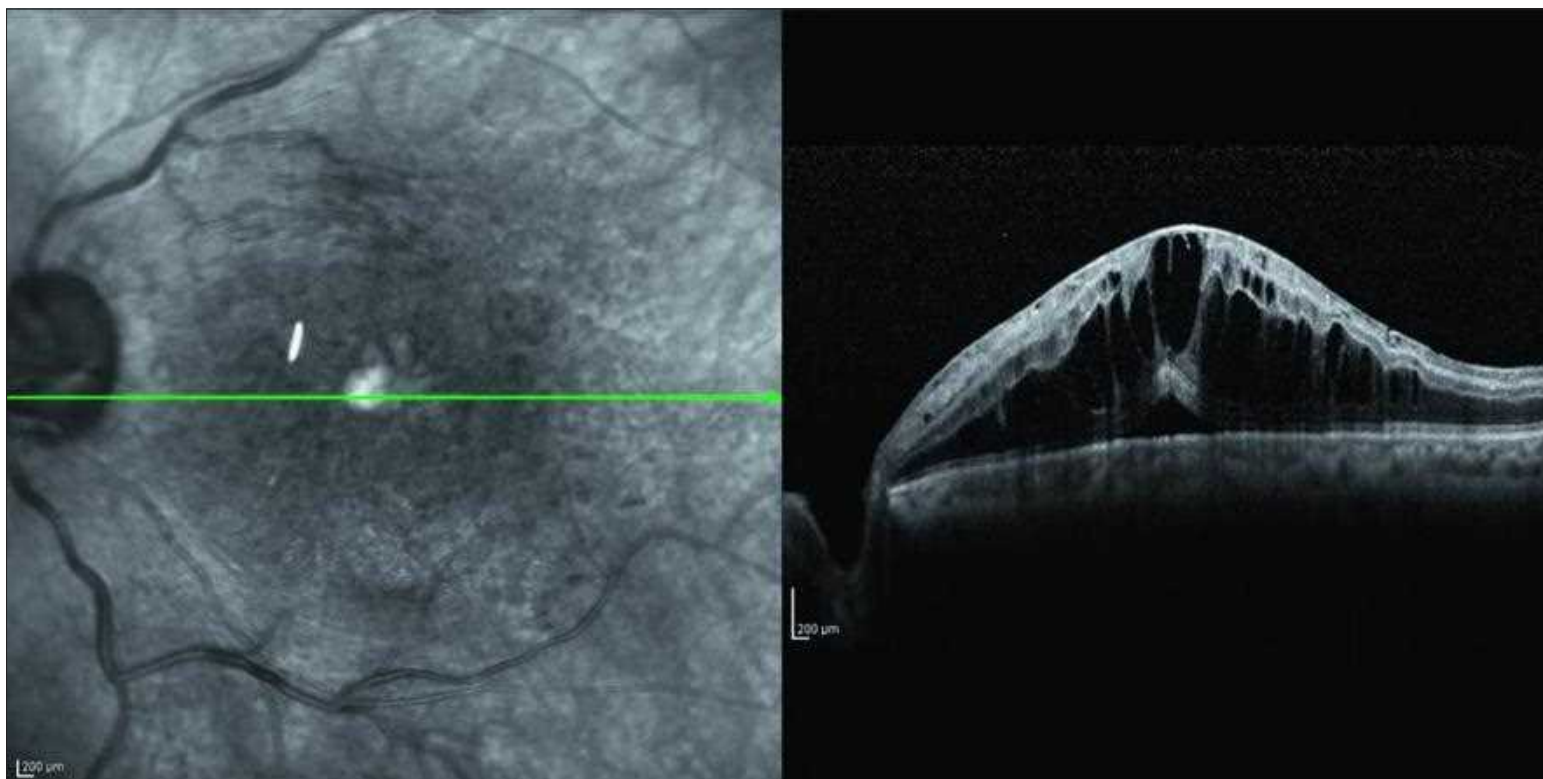
## INTRODUCTION

Cystoid macular edema (CME) is swelling of the layers of the neurosensory retina within the macula. When excess fluid builds in the retina, it typically collects in “pockets,” referred to as “cysts” (Fig. 6.35.1). Classically, CME has been defined as being located extracellularly, within the outer plexiform layer of the retina. However, neither the exact cellular location (intracellular versus extracellular) nor the precise retinal layer of fluid accumulation is definitively known. In fact, improved imaging techniques suggest that the fluid may be located simultaneously within multiple layers of the retina.<sup>1</sup> CME is a subtype of macular edema with specific clinical, angiographic, and optical coherence tomography (OCT) characteristics.

CME may have severe implications for the function of the retina, including decreased visual acuity and contrast sensitivity. Acute or chronic edema causes anatomical disruption that may result in cellular dysfunction and death. Treatment of CME is important because chronic edema may result in degenerative changes in the macula and permanent loss of vision.<sup>2-6</sup> In addition, large cystic changes in the retina may lead to thinning and loss of inner retinal tissue or to formation of lamellar holes.<sup>7,8</sup>

## PATHOGENESIS AND ETIOLOGY

Physiologically, intraretinal fluid may accumulate into CME by one of three possible mechanisms.<sup>3</sup> The first two mechanisms consist of a breakdown of normal anatomical barriers: inner and outer blood–retinal barriers. The inner blood–retinal barrier consists of tight junctions between



**Fig. 6.35.1** Optical coherence tomography (OCT) image of a patient with cystoid macular edema (CME) from a central retinal vein occlusion (CRVO). The image demonstrates large intraretinal cystic spaces and subretinal fluid.

the endothelial cells of the retinal blood vessels as they traverse the inner retina. Several inflammatory mediators, such as prostaglandins, leukotrienes, protein kinase C, nitric oxide, vascular endothelial growth factor (VEGF), and various other cytokines, may cause incompetence of this barrier. The outer blood–retinal barrier is formed between adjacent retinal pigment epithelium (RPE) cells and is maintained by tight junctions, known as the *zonulae occludens*. The failure of the integrity of either of these barriers may allow fluid to accumulate in the retina.

The third mechanism results from the failure of a normal physiological process. In a normal functioning retina, the RPE cells constantly act to eliminate fluid from the retina. If this function is compromised, fluid may accumulate in the retina.

The etiologies of CME are numerous and heterogeneous but can be grouped according to the most likely pathological mechanism of retinal dysfunction (Box 6.35.1).

## Vascular

Macular edema, in particular CME, is the leading cause of vision loss in patients with diabetes mellitus. Long-term hyperglycemia produces retinal vascular damage mediated by several inflammatory factors, including VEGF. Histologically, edema is typically associated with basement membrane thickening, pericyte loss, endothelial cell death, and retinal vessel capillary closure. The severity of CME is typically correlated with the extent of diabetic retinopathy. Intensive glycemic control decreases the risk of the development of retinopathy and slows the progression of existing retinopathy.<sup>9</sup>

Central retinal vein occlusion (CRVO) and branch retinal vein occlusion (BRVO) are also common causes of CME (see Fig. 6.35.1). It is theorized that once venous occlusion occurs, pressure in the capillaries of the retinal vessels increases, with subsequent leakage of fluid into the retina as a result of the elevated capillary pressure.

Retinal macroaneurysms are a dilation of a retinal vessel wall in an area of vessel weakness. This condition may cause a breakdown of the inner blood–retinal barrier and may also allow intravascular fluid to accumulate within the outer neurosensory retina.<sup>10</sup>

Damage to retinal blood vessels may also account for the development of retinopathy from radiation exposure. The fundoscopic evidence of damage is typically delayed in onset from the time of radiation exposure. Clinically and histologically, the retinopathy resembles the vasculopathic changes seen in diabetic retinopathy. Microaneurysms, cotton-wool spots, retinal hemorrhages, and optic nerve edema may also occur.

Juxtafoveal retinal telangiectasis (JRT) leads to intraretinal exudation through retinal capillary vessel incompetence (Fig. 6.35.2). Clinically, this condition may be identified by the appearance of telangiectasias in the temporal macula but, histologically, resembles diabetic retinopathy. Gass and Blodi classified the condition into three groups, based on laterality and clinical appearance.<sup>11</sup> Type I appears to be a retinal vascular disorder akin to focal Coats' disease. Type II, however, may be a neurodegenerative disorder affecting Müller cells. Type II JRT manifests with loss of retinal tissue that can appear cystic on OCT. There will be leakage on fluorescein angiography (FA) but no true CME.

Coats' disease is a retinal vascular disorder that presents with retinal telangiectasia, ectatic arterioles, microaneurysms, and vessel exudation accompanied by retinal detachment. The edema may extend from the periphery into the macula.

CME has also been identified in neonates with retinopathy of prematurity (ROP).<sup>12–14</sup> In the majority of these patients, it is not identifiable with indirect ophthalmoscopy but requires OCT imaging. CME has been reported to be present in 50% of neonates at risk for ROP (median age 26 weeks), with the cystoid spaces most commonly found in the inner nuclear layer, and almost always bilaterally.<sup>13</sup> The presence and severity of the CME has been associated with plus disease, higher ROP stage, and subsequent need for laser treatment.<sup>13</sup>

Choroidal neovascularization (CNV) may lead to severe vision loss through photoreceptor damage, chorioretinal scarring, and CME (Box 6.35.2). CNV is an “ingrowth” of new vessels from the choriocapillaris into the retina, through a break in Bruch's membrane. In the older population, the most common cause of CNV is age-related macular degeneration (AMD; see Chapter 6.29).

Acutely elevated blood pressure may lead to a serous retinal detachment and CME. It has been speculated that the increase in blood pressure may damage blood vessel walls and cause ischemic damage to the RPE.<sup>15</sup> Damage to the RPE can potentially cause a breakdown of the outer blood–retinal barrier.

## BOX 6.35.1 Ocular Diagnoses Associated With Cystoid Macular Edema

### Vascular

- Retinal vascular
  - Diabetic retinopathy
  - Retinal vein occlusion—branch or central
  - Retinal artery macroaneurysm
  - Radiation retinopathy
  - Juxtafoveal retinal telangiectasis
  - Coats' disease
  - Retinopathy of prematurity
  - Ocular ischemic syndrome
- Choroidal vascular
  - Choroidal neovascularization (CNV) (see Box 6.35.2)
  - Hypertensive retinopathy

### Postoperative

- Irvine–Gass syndrome
- Penetrating keratoplasty
- Scleral buckle
- Laser treatment (Argon or yttrium–aluminum–garnet [YAG])
- Cryotherapy
- Panretinal photocoagulation

### Inflammatory

- Uveitis
- Human leukocyte antigen (HLA)-B27
- Birdshot chorioretinopathy
- Behçet's disease
- Eales' disease
- Vogt–Koyanagi–Harada disease
- Sarcoidosis
- Scleritis
- Pars planitis
- Immune recovery uveitis
- Infectious uveitis (cytomegalovirus, toxoplasmosis, herpesvirus)
- Neuroretinitis
- Multiple infectious causes (i.e., *Bartonella*, Lyme, syphilis, viral)
- Idiopathic retinal vasculitis, aneurysms, neuroretinitis (IRVAN)

### Medication Use

(See Box 6.35.3.)

### Retinal Dystrophies

- Retinitis pigmentosa
- Autosomal dominant cystoid macular edema
- Gyrate atrophy
- Goldman–Favre (enhanced S-cone) syndrome
- Juvenile X-linked retinoschisis

### Tractional

- Epiretinal membrane
- Vitreomacular traction syndrome
- Vitreoretinal traction associated with myopia
- Macular hole

### Anatomical

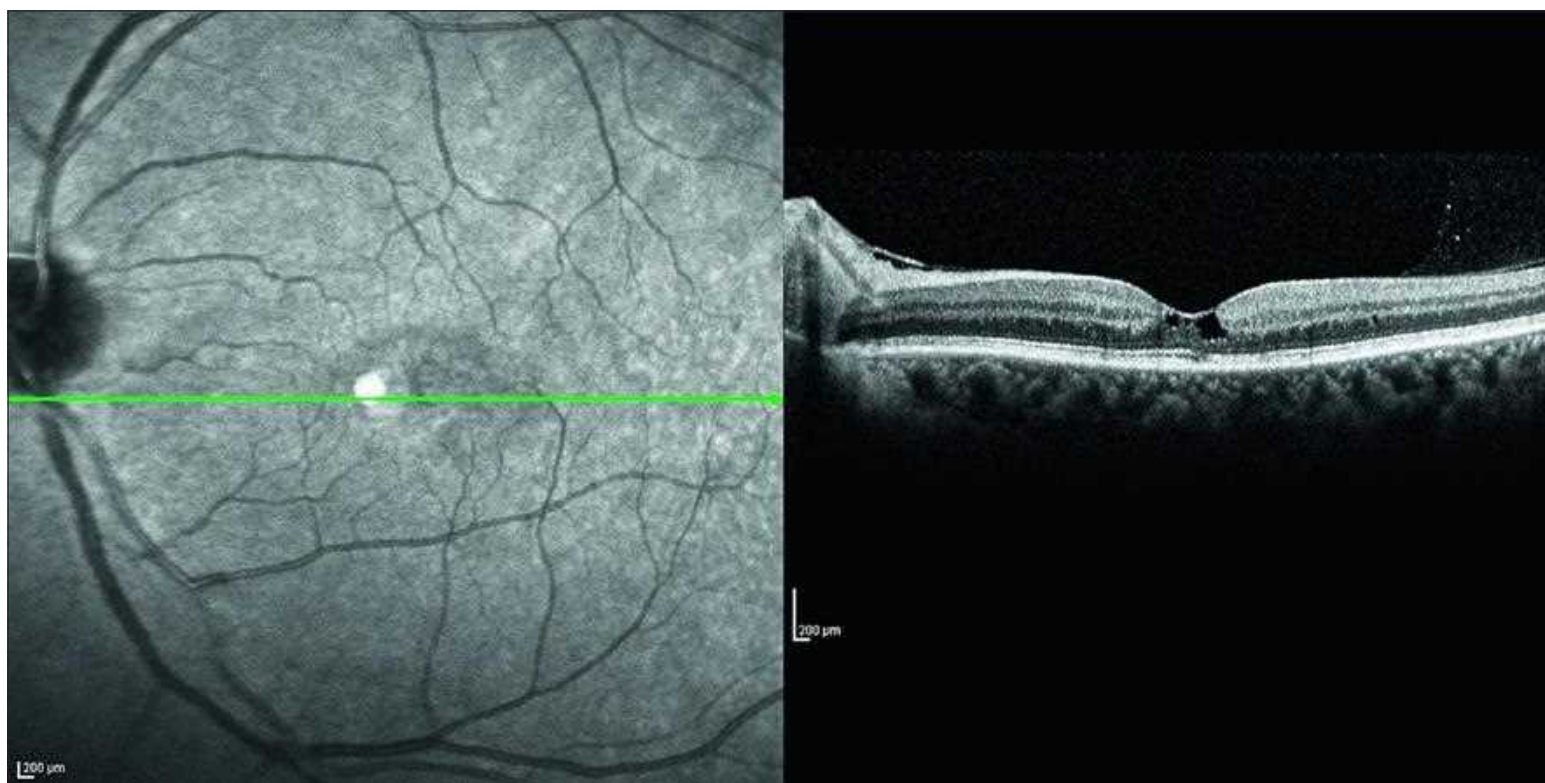
- Optic nerve
  - Optic pit maculopathy
  - Optic disc coloboma
  - Morning glory disc anomaly
- Retina
  - Retinal detachment

### Neoplastic

- Tumors
  - Retinal—hemangiomas
  - Choroidal—melanoma, hemangioma, osteoma

## Postoperative

CME is a frequent complication following cataract surgery and is also known as Irvine–Gass syndrome.<sup>16</sup> Angiographic CME may be detected in as many as 20% of uncomplicated surgeries but is only visually significant in 1%–2%.<sup>17</sup> This makes CME the most common cause of vision loss after



**Fig. 6.35.2** Optical coherence tomography (OCT) image of a patient with apparent cystoid macular edema (CME) from juxtafoveal retinal telangiectasis (JRT) type 2. Note the normal foveal contour. The CME is typically located near the foveola. Although cysts appear on OCT in this condition, loss of retinal tissue may be the underlying cause as opposed to excess fluid.

### BOX 6.35.2 Causes of Choroidal Neovascularization

#### Degenerative Diseases

- Age-related macular degeneration
- Myopic degeneration
- Angioid streaks
- Juxtafoveal retinal telangiectasis
- Vitelliform macular dystrophy
- Pattern dystrophies
- Stargardt macular dystrophy

#### Inflammatory

- Vogt–Koyanagi–Harada syndrome
- Behçet's syndrome
- Sympathetic ophthalmia
- Multifocal choroiditis
- Serpiginous
- Laser photocoagulation
- Punctate inner choroiditis

#### Infectious

- Toxocariasis
- Toxoplasmosis
- Ocular histoplasmosis

#### Trauma

- Choroidal rupture

#### Choroidal Masses

- Choroidal osteoma
- Choroidal melanoma
- Choroidal hemangioma

#### Idiopathic

as prostaglandins, leukotrienes, and histamine, which may make retinal vessels more permeable.

CME may also occur as a complication of intraocular laser therapy. This includes panretinal photocoagulation (PRP) and neodymium:yttrium–aluminum–garnet (Nd:YAG) laser. Possible pathological mechanisms of this phenomenon include the release of inflammatory mediators or the increase of macular blood flow leading to transudation.<sup>3</sup> This provides the rationale for treating pre-existing CME prior to initiating PRP. The incidence of CME after YAG is quite low (<3%), although it may be increased if the laser is performed early in the postoperative period.<sup>23,24</sup>

Cryotherapy, which is typically used in the treatment of retinal tears or detachment, may also cause CME.<sup>25,26</sup>

Several surgical procedures other than cataract surgery are also suspected to cause CME. These include penetrating keratoplasty, vitrectomy, and scleral buckling. The incidence of CME after a scleral buckling procedure is low (<5%).<sup>27</sup>

### Uveitis-Related

CME is the most common cause of decreased vision in patients with ocular inflammatory disease.<sup>28,29</sup> The causes of uveitis are varied and can be classified according to the suspected etiology or location of inflammation. Although CME is most commonly associated with posterior uveitis, it may also be associated with intermediate or anterior uveitis. The pathological mechanism of CME in uveitis likely relates to the compromise of the inner blood–retinal barrier as a result of exposure to intraocular inflammatory mediators, such as prostaglandins, leukotrienes, tumor necrosis factor- $\alpha$ , and VEGF,<sup>30</sup> among others.

Intraocular inflammation that affects the optic nerve and macular retina is called *neuroretinitis*. There are infectious (i.e., *Bartonella henselae*, *Toxoplasmosis*, *Toxocariasis*, *Syphilis*, etc.) and noninfectious etiologies of this condition (i.e., sarcoidosis, etc.), which also displays CME<sup>31</sup> (see Part 7: Uveitis and Other Intraocular Inflammations).

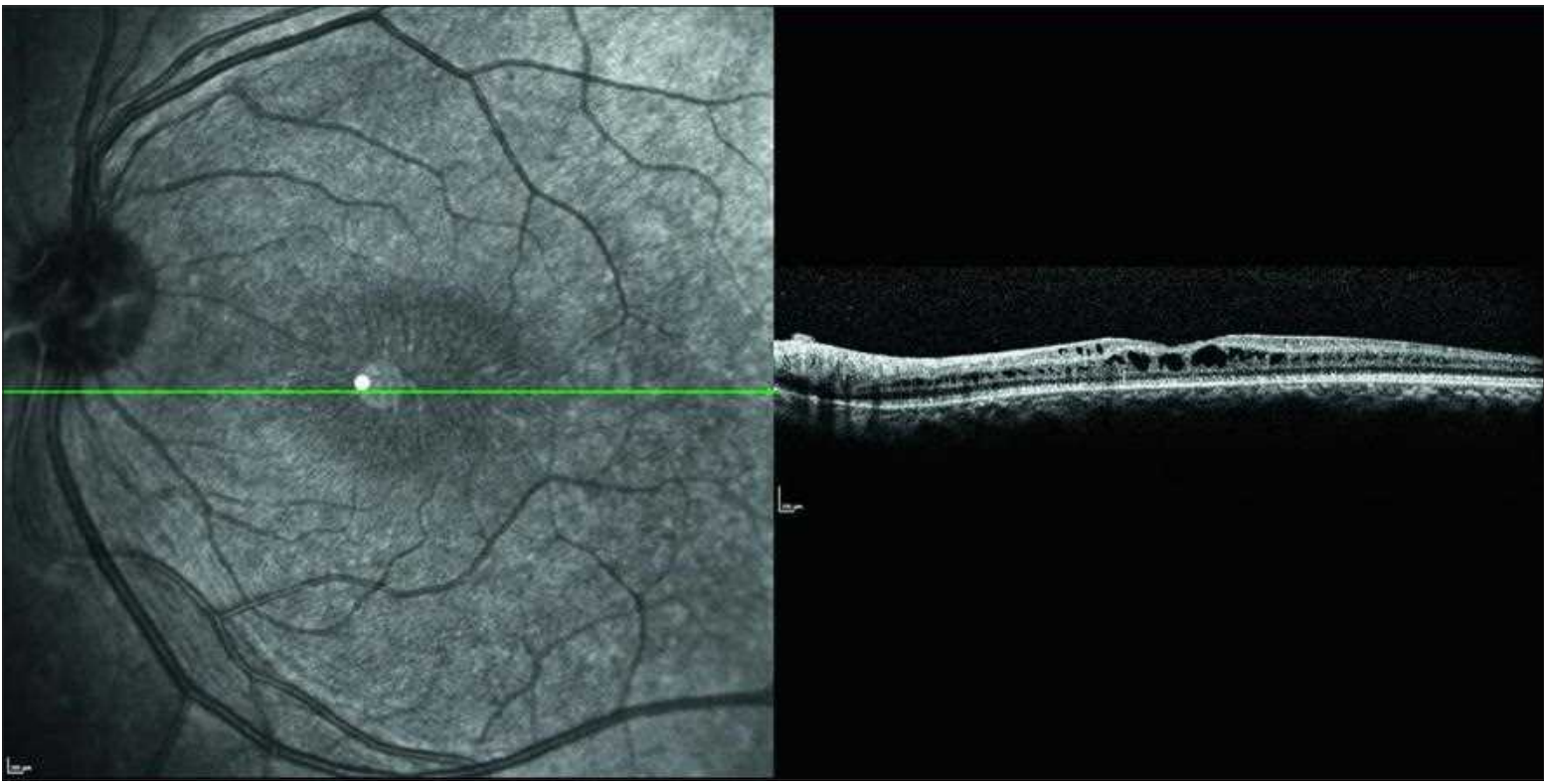
### Medication-Related

Several medications have been linked to the development of CME (Box 6.35.3).<sup>32–46</sup> The most commonly used topical medications that have been linked to CME are the prostaglandin analogues.<sup>43</sup> It is thought that prostaglandins might lead to the vascular incompetence of retinal vessels through their proinflammatory effects within the eye. Fingolimod,

cataract surgery. Certain preoperative and operative characteristics may increase the incidence of postoperative CME, such as diabetes,<sup>18</sup> uveitis,<sup>19</sup> intracapsular versus extracapsular surgery,<sup>20,21</sup> and intraoperative vitreous loss.<sup>22</sup>

The pathological mechanism for Irvine–Gass syndrome is unknown, although it may be related to the production of intraocular inflammation. The surgery causes the release of inflammatory mediators, such





**Fig. 6.35.3** Optical coherence tomography (OCT) image of a patient with juvenile X-linked retinoschisis. There are several schisis cavities noted throughout the macula.

#### BOX 6.35.3 Medications Causing Macular Edema

- Benazalkonium chloride<sup>32</sup>
- Carmustine (BCNU)<sup>33,34</sup>
- Docetaxel<sup>35</sup>
- Epinephrine<sup>36,37</sup>
- Fingolimod<sup>38</sup>
- Glitazones<sup>39</sup>
- Ipilimumab<sup>40</sup>
- MEK inhibitors<sup>41</sup>
- Niacin<sup>42</sup>
- Paclitaxel<sup>43</sup>
- Prostaglandin analogues<sup>44</sup>
- Tamoxifen<sup>45</sup>
- Timolol<sup>32,46</sup>

which is used to treat multiple sclerosis, can cause CME in 0.2%–1% of patients by altering S1P receptor signaling and altering endothelial integrity. It typically presents in the first 3–4 months of therapy.<sup>47,48</sup> Newer chemotherapy agents have been implicated. MEK inhibitors are associated with CME.<sup>41</sup> Cytotoxic T lymphocyte antigen 4 (CTLA4) antagonists, such as ipilimumab, are rarely associated with uveitis and concomitant CME.<sup>40</sup> Paclitaxel, used to treat breast cancer and other cancers, is associated with CME, does not leak on FA, and may be related to Müller cell dysfunction.<sup>49</sup>

### Retinal Dystrophies

Several macular dystrophies are also associated with the development of CME. Among these are retinitis pigmentosa (RP),<sup>50</sup> dominantly inherited macular edema,<sup>51</sup> Goldman–Favre syndrome (Fig. 6.35.3), gyrate atrophy, and juvenile X-linked retinoschisis.

Although the precise mechanism for CME in RP is unknown, it is hypothesized that the accumulation of fluid is the result of the failure of the RPE pump to function properly.<sup>52,53</sup> CME in RP may remain subclinical for many years with retention of good visual acuity. There appears to be an association between the presence of antiretinal antibodies and the presence of CME in RP<sup>54</sup> (see Chapter 6.14).

### Tractional Causes

The tractional causes of CME include epiretinal membrane (ERM), vitreomacular traction (VMT) syndrome, myopic traction maculopathy (myopic macular schisis), and macular holes.

ERMs are proliferations of cells that form an avascular fibrous membrane along the surface of the inner retina. They are often associated with CME that is unresponsive to topical medication (Fig. 6.35.4).

VMT syndrome is a condition in which the vitreous becomes detached anteriorly but remains attached at the macula. The tractional forces of the attached vitreous are associated with CME. In a retrospective study of 53 symptomatic eyes with this syndrome, 81% were found to have cystoid macular changes.<sup>55</sup> A variant of this syndrome, termed *tractional CME*, also has been described.<sup>56</sup>

Similar to the traction in VMT, severe traction with macular edema and a retinoschisis-like appearance can also develop in highly myopic patients with posterior staphylomas (see Chapter 6.34).

### Anatomical

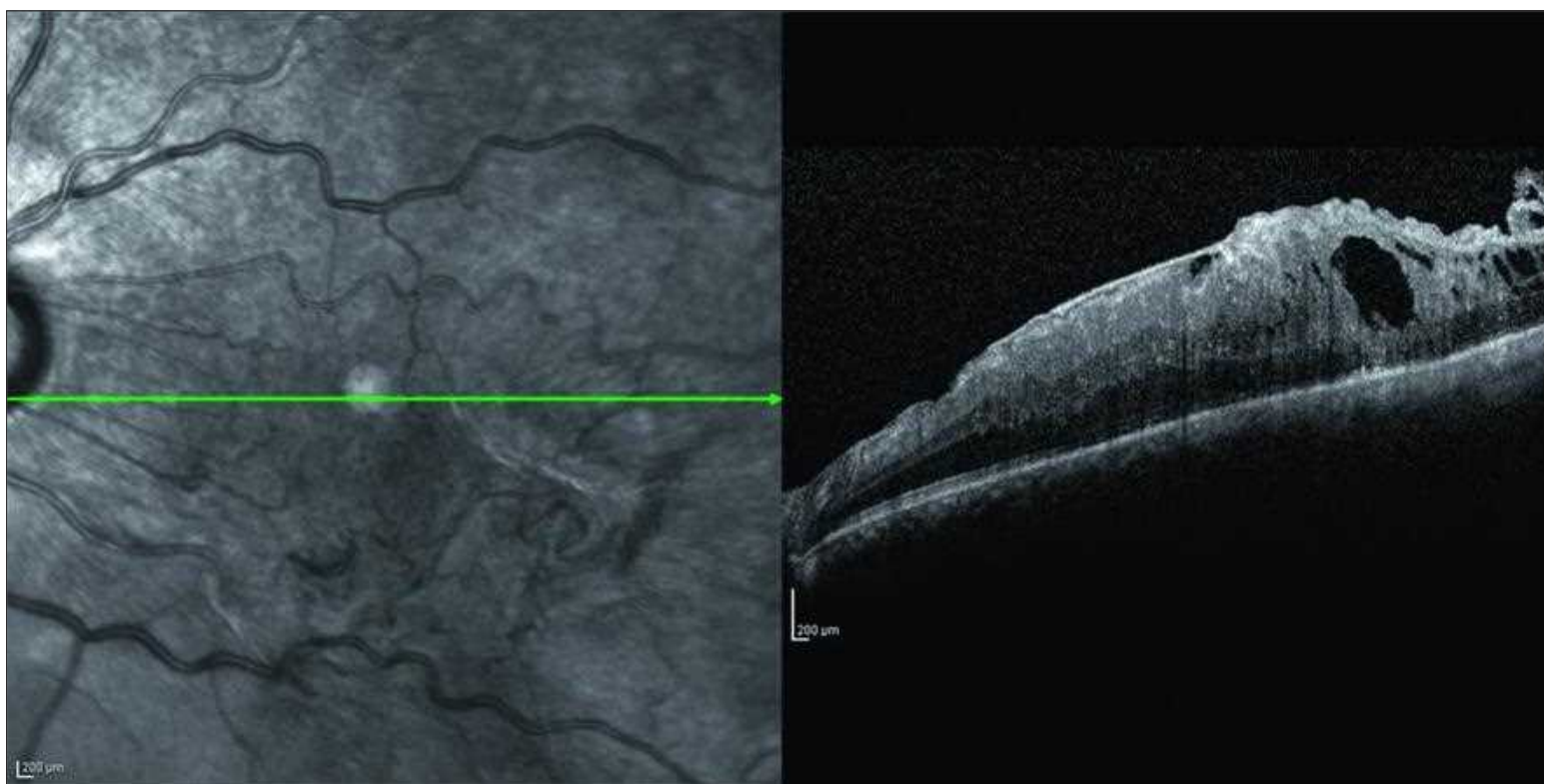
Patients with optic nerve head anomalies may also develop intraretinal fluid that appears cystoid. These lesions include optic nerve colobomas, optic nerve pits, and morning glory disc anomaly.

Optic nerve pits are congenital anomalies that may allow for fluid to infiltrate the retina.<sup>57</sup> The origin of the intraretinal fluid is controversial, but the most likely sources are the vitreous cavity and the subarachnoid space. A recent study using high-resolution OCT revealed that fluid was found in the outer nuclear layer of the retina in 94% of eyes with optic pit maculopathy and in the inner nuclear layer of the retina in 81%<sup>1</sup> (see Chapter 6.36).

Retinal detachments of various etiologies may also demonstrate CME. The exact origin of the fluid is not known; however, damage to both the inner and outer blood–retinal barriers and the RPE pump mechanism have been implicated.

### Intraocular Neoplasms

Several intraocular tumors, including choroidal melanomas, choroidal hemangiomas, and vasoproliferative tumors, may also present with CME.<sup>58,59</sup> The presence of CME associated with choroidal melanomas can often be directly related to a mass located underneath the fovea and is often associated with subfoveal exudate.<sup>59</sup> The molecular basis for CME



**Fig. 6.35.4** Optical coherence tomography (OCT) image of a patient with large cystic cavities as the result of traction from an epiretinal membrane.

associated with an intraocular tumor is unclear; however, it may be related to disruption of the RPE pump and/or barrier function resulting from compression from the choroidal mass.

## DIAGNOSIS AND ANCILLARY TESTING

### Fundoscopy

Clinical examination reveals intraretinal cystic structures extending radially from the foveola. The cysts often form a tear-drop configuration as they taper to a point toward the center of the fovea.<sup>60</sup> Additional fundoscopic signs include evidence of intraocular inflammation, optic nerve edema, subretinal fluid, retinal thickening, and loss of the foveal reflex.

### Optical Coherence Tomography

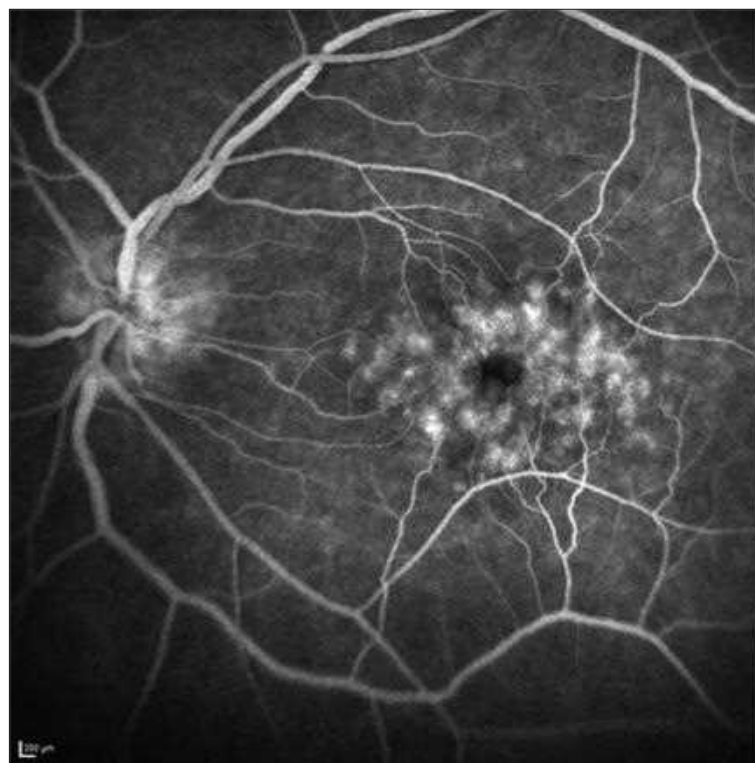
OCT is a very sensitive modality for visualization of CME.<sup>61</sup> The resolution of this diagnostic instrument now approaches the level of histological examination, at less than 10  $\mu\text{m}$ . Several studies have investigated the ability of spectral-domain OCT (SD-OCT) to image CME from a variety of causes and compare it with conventional retinal imaging modalities, such as FA<sup>62,63</sup> (see Chapter 6.7).

### Autofluorescence

Autofluorescence can also be used to detect CME. Imaging will reveal subtle areas of hyperfluorescence in the areas containing cysts. This is thought to result from the thinning of macular pigments in the fovea from the CME, which would typically block the background choroidal hyperfluorescence.<sup>60</sup>

### Fluorescein Angiography

FA of eyes with CME typically demonstrates a gradual increase in hyperfluorescence throughout the diagnostic study. The initial hyperfluorescence occurs as a result of thinning of the macular pigment in the fovea and loss of blocking of the choroidal hyperfluorescence, whereas gradual increase in hyperfluorescence occurs as the cysts fill with fluid that leaks from the perifoveal capillaries. Because of the anatomical arrangement of the outer plexiform layer, the hyperfluorescence often demonstrates a “petaloid” appearance (Fig. 6.35.5).



**Fig. 6.35.5** Fluorescein angiogram from a patient with classic “petaloid” appearance of fluorescein leakage in the late phase of the angiogram.

Several causes of macular edema, however, do not hyperfluoresce or “leak” during FA (Box 6.35.4). This difference in FA behavior among entities may provide important diagnostic information for the clinician (see Chapter 6.6).

## TREATMENT

The treatment of CME is dependent on etiology.

**BOX 6.35.4 Etiologies of Cystoid Macular Edema Without Leakage on Fluorescein Angiography**

- Epinephrine
- Epiretinal membrane retinoschisis
- Goldman–Favre syndrome (enhanced S-cone) syndrome
- Juvenile X-linked retinoschisis
- Myopic retinoschisis
- Niacin
- Retinitis pigmentosa
- Taxanes—docetaxel or paclitaxel
- Vitreomacular traction syndrome

**Vascular****Diabetic Macular Edema (See Chapter 6.22, Diabetic Retinopathy)**

In 1985, the “gold standard” for the treatment of diabetic macular edema was established as focal laser photocoagulation.<sup>64</sup> The treatment of “clinically significant macular edema” reduces the risk of vision loss and increases the chance of visual improvement.

More recently, prospective studies suggest that either monotherapy with an anti-VEGF antibody (ranibizumab) or combined ranibizumab plus deferred focal laser photocoagulation resulted in the best visual outcome with the least complications in a period of 2 years compared with laser alone or intravitreal corticosteroids alone.<sup>65</sup>

**Retinal Venous Occlusive Disease (See Chapter 6.20, Venous Occlusive Disease of the Retina)**

Treatment options for CME associated with retinal venous occlusive disease have historically evaluated BRVO and CRVO independently.

**Branch Retinal Vein Occlusion**

For over 2 decades, vision loss caused by CME resulting from BRVO had been treated with laser photocoagulation.<sup>66</sup> Intravitreal triamcinolone has also been shown to be as effective as laser to treat CME resulting from BRVO, but with more adverse effects.<sup>6</sup> Recently, monotherapy with anti-VEGF agents have emerged as the first-line therapy for CME secondary to BRVO.<sup>67</sup>

**Central Retinal Vein Occlusion**

Until the past decade, the treatment of CME from CRVO consisted of observation.<sup>68</sup> Subsequently, prospective trials demonstrated that both intravitreal anti-VEGF agents<sup>69</sup> and corticosteroids<sup>5</sup> were effective in treating CME secondary to CRVO. Because of their superior efficacy and safety, anti-VEGF agents are now the treatment of choice.<sup>5</sup>

**Macroaneurysms (See Chapter 6.28, Retinal Arterial Macroaneurysms)**

The macular edema associated with macroaneurysms has been treated with laser photocoagulation applied to the surface of the leaking vessel with large spot sizes and light burns with little evidence that it is effective.<sup>70</sup> More recently, anti-VEGF therapy has been used to treat macular edema from this condition and has demonstrated efficacy in small case reports.<sup>71</sup>

**Juxtafoveal Retinal Telangiectasias (See Chapter 6.25, Coats’ Disease and Retinal Telangiectasia)**

CME from group 1 JRT may be treated with laser photocoagulation to the leaking vascular anomalies. In eyes with group 2 JRT, however, treatment with laser photocoagulation not only has shown limited success in terms of increasing visual acuity but also can stimulate secondary CNV formation.<sup>72</sup> The use of intravitreal anti-VEGF medication is able to decrease retinal thickness, but not improve visual acuity.<sup>73</sup> In fact, recommendations from a prospective trial have recommended against the use of monthly ranibizumab to treat macular edema from group 2.<sup>74</sup> The use of anti-VEGF medication to treat edema related to choroidal neovascularization in JRT<sup>75,76</sup> or edema associated with a foveal detachment,<sup>77</sup> however, has demonstrated benefit in small case series.

**Coats’ Disease (See Chapter 6.25, Coats’ Disease and Retinal Telangiectasia)**

The treatment of Coats’ disease centers on the application of laser photocoagulation or cryotherapy to leaking retinal capillaries.

**Radiation Retinopathy (See Chapter 6.26, Radiation Retinopathy and Papillopathy)**

CME associated with radiation retinopathy may be treated with laser photocoagulation to close incompetent vessels; however, intravitreal triamcinolone has also demonstrated the ability to stabilize or improve visual acuity in these eyes.<sup>78</sup> In a small case series, ranibizumab was also found to improve visual acuity in patients with radiation maculopathy.<sup>79</sup>

**Age-Related Macular Degeneration (See Chapter 6.29, Age-Related Macular Degeneration)**

Because CME related to exudative AMD is caused by underlying CNV, the treatment of the CME consists of treatment of the CNV. The treatment of CME related to AMD has evolved rapidly in recent years. Anti-VEGF agents are now the treatment of choice and have a beneficial effect on intraretinal fluid from CNV.<sup>80-84</sup>

**Postoperative**

Treatment of pseudo-phakic CME consists of several options. In many instances, however, no treatment is necessary because the natural history of the disease often results in resolution of the edema.<sup>85,86</sup> Despite the vast amount of treatment options, no prospective, placebo-controlled, double-masked, randomized controlled trial has been performed to evaluate the treatment options for acute pseudo-phakic CME.<sup>87</sup>

Medical treatment options include nonsteroidal anti-inflammatory drugs (NSAIDs). These can be delivered topically, locally, or systemically. Topical NSAIDs are effective for both prophylaxis and treatment of pseudo-phakic CME.<sup>88</sup> Topical ketorolac 0.5%, specifically, has been shown to increase the visual acuity in patients with chronic CME after cataract surgery.<sup>89</sup> The use of NSAIDs prophylactically in high-risk patients has also increased in recent years. Despite the fact that several new NSAIDs have been developed, none of these medications have been shown in humans to have a distinct advantage in outcomes over the use of ketorolac.<sup>90</sup>

The use of corticosteroids has been shown to have significant benefits in the treatment of pseudo-phakic CME. These may be delivered topically, periocularly, intravitreally, or systemically. The use of a topical corticosteroid (prednisolone acetate 1%), combined with the use of topical ketorolac 0.5%, has been shown to be more likely to lead to an increase in visual acuity compared with treatment with either agent alone.<sup>91</sup> Topical difluprednate, a more potent topical corticosteroid, may also be used to treat pseudo-phakic CME.<sup>92</sup>

Additional medications that may be beneficial in pseudo-phakic CME include carbonic anhydrase inhibitors and anti-VEGF agents. A retrospective study suggested that intravitreal bevacizumab may be beneficial for the treatment of refractory pseudo-phakic CME.<sup>93</sup> This, however, requires further study in a prospective, randomized manner.

Surgical treatment for pseudo-phakic CME may be indicated if vitreous traction on the retina or iris is stimulating intraocular inflammation. Pars plana vitrectomy in eyes with chronic pseudo-phakic CME and vitreous adhesions in the anterior segment after cataract surgery may improve visual acuity.<sup>94,95</sup> Alternatively, laser (typically, Nd:YAG) may be used to release the traction that may be causing inflammation and CME.

**Inflammatory (See Part 7: Uveitis and Other Intraocular Inflammations)**

The treatment of uveitis-related CME consists primarily of controlling the source of inflammation. When an infectious etiology has been ruled out, treatment often begins with the use of NSAIDs and corticosteroids. These may be delivered in a topical format, locally, intravitreally, or systemically. In a recent clinical trial of the treatment of chronic noninfectious posterior uveitis, a sustained delivery implant of fluocinolone acetonide demonstrated efficacy.<sup>96</sup>

In patients unable to tolerate corticosteroids for the treatment of uveitis or in those who need chronic immunosuppression to control intraocular



inflammation, systemic immunomodulatory medication may be necessary to control inflammation and decrease CME.<sup>97</sup>

## Medication Induced (See Chapter 6.45, Retinal Toxicity of Systemically Administered Drugs)

In patients with CME related to medication use, cessation of the medication, if possible, is advised. CME caused by fingolimod or CTLA4 antagonists may be responsive to ocular corticosteroids.<sup>40,41</sup> CME resulting from use of paclitaxel has been treated with topical dorzolamide 2%.<sup>49</sup>

## Retinal Dystrophy (See Chapter 6.14, Progressive and 'Stationary' Inherited Retinal Degenerations)

The treatment options for CME associated with RP are limited. Oral acetazolamide was found to be effective in improving visual acuity in a small set of patients with CME caused by RP.<sup>98</sup> Topical dorzolamide has also been shown to be effective in decreasing the amount of edema in many patients with RP and CME.<sup>99,100</sup> The use of oral acetazolamide, however, may be more effective than the topical use of dorzolamide in terms of improving the resolution of edema and improving visual acuity, however, the side effects of systemic medications are potentially more numerous and require close monitoring.<sup>88</sup> Injection with intravitreal corticosteroids, such as triamcinolone, has also been attempted for CME from RP, although the results were variable and not sustained.<sup>53</sup> Similarly, the use of bevacizumab has not demonstrated efficacy in RP-related CME.<sup>101</sup>

## Tractional (See Chapter 6.32, Macular Hole, Chapter 6.33, Epiretinal Membrane, Chapter 6.34, Vitreomacular Traction Syndrome)

The treatment of CME associated with a tractional etiology has focused on relief of the traction. For eyes with an ERM, surgical peeling typically allows for the edema to resolve.<sup>102</sup> Similarly, in eyes with macular holes, closure of the hole often resolves the edema.

Vitrectomy to remove the vitreous adhesion to the macula in VMT syndrome<sup>103,104</sup> and in myopic eyes with a retinoschisis-like appearance<sup>105</sup> is often effective. Recently, the use of intravitreal microplasmin to create a posterior vitreous detachment pharmacologically has been performed.<sup>106-108</sup> This treatment, however, requires further study.

## Anatomical Abnormalities (See Chapter 6.36, Coexistent Optic Nerve and Macular Abnormalities)

Previous treatments of optic disc maculopathy include pars plana vitrectomy, laser photocoagulation to the temporal margin of the optic disc, internal tamponade with gas, internal drainage of submacular fluid, or

insertion of a sponge explant.<sup>109</sup> Currently, however, there is no "gold standard" in terms of optimal treatment.

Retinal detachment repair often allows resolution of CME related to this condition.

## Neoplastic (See Part 8: Intraocular Tumors)

Treatment of intraocular tumors with radiation, cryotherapy, or laser photocoagulation often results in resolution of subretinal fluid and intraretinal edema.

## CONCLUSIONS

CME is a significant cause of vision loss. The treatments of this condition are as varied as its etiologies. The crucial step in the evaluation and management of this condition is determining the correct etiology. When a diagnosis is reached, an appropriate therapeutic option, with the least potential risk and greatest potential benefit can be administered.

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# Coexistent Optic Nerve and Macular Abnormalities

## 6.36

Odette M. Houghton

**Definition:** A heterogeneous group of optic nerve disorders that have secondary pathological effects on the macular retina.

### Key Features

- Structural changes of the optic nerve.
- Secondary retinal detachment, schisis-like retinal degeneration, neovascularization, macular edema.

### Associated Features

- Optic nerve pit.
- Morning glory optic disc anomaly.
- Optic nerve coloboma.
- Choroidal neovascularization.
- Optic nerve abnormalities may be associated with macular abnormalities, the most common being retinal detachment.
- Choroidal neovascularization, macular edema, schisis-like degeneration, and lipid exudation may also be found.

## INTRODUCTION

The optic nerve head (optic disc) is the primary site of many congenital and acquired ocular disorders. The optic disc is the location where unmyelinated retinal derived axons become myelinated, and the central retinal artery and vein enter and exit the globe. This portion of the optic nerve borders the retina, retinal pigment epithelium (RPE), Bruch's membrane and choroid. Anomalies of this crucial juncture often lead to marked physiological consequences and macular abnormalities.

## CONGENITAL ANOMALIES OF THE OPTIC DISC

### Congenital Optic Disc Pit

Congenital optic disc pits are isolated excavations in the optic nerve head.<sup>1</sup> They are believed to be secondary to a disturbance in the development of the primitive epithelial papilla, but the exact cause is uncertain.<sup>2</sup> Occasionally, optic disc pits can be associated with other congenital disc anomalies, such as colobomas.

Optic disc pits are thought to occur in approximately 1 per 10000 patients,<sup>2</sup> without gender or racial predilection.<sup>1</sup> Pits present unilaterally in enlarged optic discs with a frequency of about 85%.<sup>2</sup> Rarely, more than one pit can be seen on a single optic disc.<sup>1</sup>

Optic disc pits appear as gray (60%), white/yellow (30%), or black (10%) and round or oval depressions in the optic nerve head.<sup>1</sup> The average size of an optic pit is  $\frac{1}{2}$  disc diameter.<sup>1</sup> Although over 50% of pits are located on the temporal aspect of the optic disc, they can be located in any sector. There is usually disturbance of the peripapillary retinal pigment epithelium (RPE) or choroidal atrophy associated with eccentrically located pits.

Histopathological studies and optical coherence tomography (OCT) of optic disc pits demonstrate herniation of dysplastic retina into a connective tissue-lined pocket that often extends into the subarachnoid space through a defect in the lamina cribrosa.<sup>3-5</sup> Condensed vitreous strands terminate at the margin of the pit (Fig. 6.36.1).<sup>2,6,7</sup>

Optic disc pit-associated maculopathy develops in 25%–75% of eyes and is more common with temporally located pits.<sup>1,2</sup> This maculopathy can

occur at any age but is most frequently observed in early adulthood.<sup>1,2</sup> The characteristic features of optic disc pit-associated maculopathy include retinoschisis-like degeneration of the nasal macula and shallow retinal detachments of the central macula (Fig. 6.36.2).<sup>7,8</sup> Spectral-domain OCT has advanced our understanding of the ultrastructural characteristics of optic disc pit-associated maculopathy. OCT analysis supports the theory that fluid originating from the pit can directly enter and extend into all layers of the retina, including the sub-internal limiting membrane (ILM) space, ganglion cell layer, inner nuclear layer, outer nuclear layer, and subretinal space (Fig. 6.36.3).<sup>9</sup> The fluid forms schisis-like cavities with intact vertical bridging elements in the retinal stroma. The retinal separation appears to be most prominent in the outer nuclear layers and may be combined with a striking elevation of the ILM.<sup>9,10</sup> The fluid may exit through a visible lamellar foveal hole or invisible breaks in the outer retina into the subretinal space.<sup>8,9</sup>

The precise pathogenesis of optic disc pit maculopathy is unclear. Various hypotheses regarding the conduit and source of fluid have been proposed. The most plausible origin of subretinal fluid associated with optic disc pits is the vitreous cavity<sup>1,2,7,10-12</sup> or the subarachnoid space.<sup>6,13</sup> The lack of extension of hyperfluorescence from the optic pit into the subretinal space on fluorescein angiography (FA) indicates that an increase in vascular permeability is not the source of fluid.<sup>2</sup>

Communication among the schisis cavities, subretinal space, and optic disc pit has been suggested to occur through either a visible or an invisible sieve-like fenestration in the membrane overlying the optic disc.<sup>11,12,14</sup> Evidence supporting communication between the vitreous cavity and subretinal space includes transport of India ink from the vitreous cavity into the pit and subretinal space in Collie dogs with cavitory disc anomalies (Fig. 6.36.4); subretinal migration of vitreous substitutes<sup>2,12</sup>; and intraoperative drainage of intraretinal and subretinal fluid through the disc anomaly.<sup>10,12</sup>

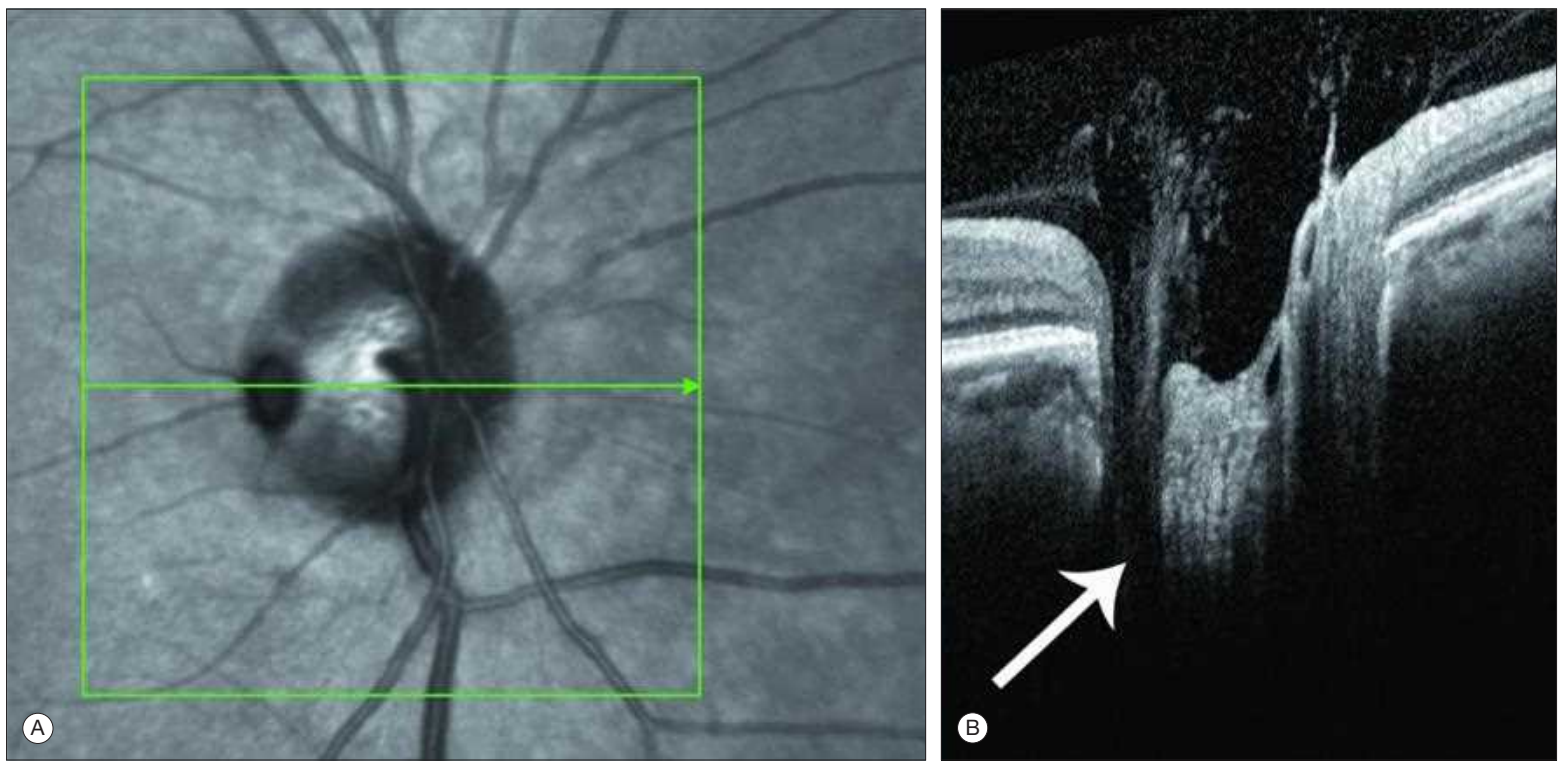
The herniated dysplastic retina, which extends into the subarachnoid space via the optic nerve pit, may be incompletely differentiated and porous.<sup>6</sup> The vitreous, subarachnoid space, and subretinal space may therefore be variably connected. Communication of fluid with the subarachnoid space is supported by OCT studies<sup>15</sup> and reports of intracranial migration of the silicone oil following vitrectomy.<sup>6,12,14</sup>

OCT has also demonstrated the presence of vitreomacular traction and vitreous strands over the optic disc, which may play an important role in the development of optic disc pit maculopathy.<sup>8,10,14,15</sup> The high postoperative recurrence rate and subretinal migration of vitreous substitutes argue against vitreous traction being the sole cause of fluid accumulation.<sup>12</sup> Johnson and Johnson proposed a mechanism whereby normal intermittent pressure fluctuations of the central spinal fluid are transmitted to the optic pit via the subarachnoid space.<sup>12</sup> In eyes with an impermeable optic pit capsule, the pit acts like a bulb syringe sucking in liquefied vitreous fluid during a drop in intracranial pressure. A later rise in intracranial pressure could force the vitreous fluid into the pit and into the retinal tissue or subretinal space. Traction may facilitate access to the intraretinal and subretinal space.<sup>10</sup>

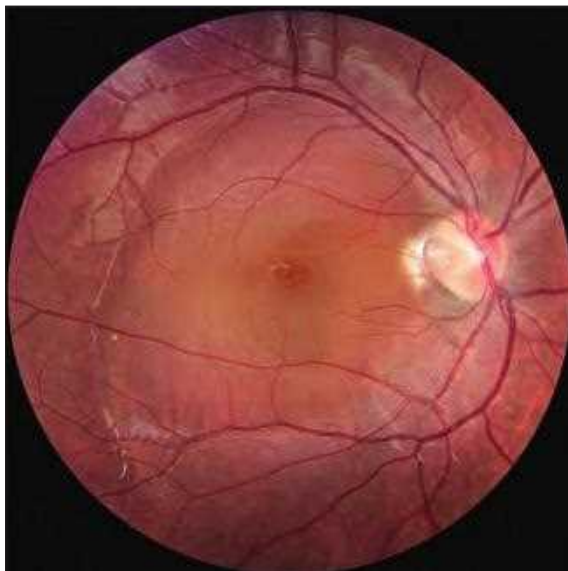
Retinal detachments associated with optic disc pits may fluctuate and occasionally resolve without therapy. Because the visual prognosis in untreated cases is so poor, current recommendations include some form of aggressive treatment.

### Morning Glory Optic Disc Anomaly

The morning glory disc anomaly is a congenital malformation of the optic nerve. The precise pathogenesis of this disc anomaly is unknown. Theories



**Fig. 6.36.1** (A) Spectral-domain optical coherence tomography (SD-OCT) slice (*green arrow*) at the level of a temporally located congenital optic disc pit (B, *white arrow*), without associated maculopathy. Dense vitreous strands emerge from the optic disc pit and enter into vitreous cavity. (Courtesy Dr. Maurice B. Landers, III, Spectralis OCT, Heidelberg Engineering, Heidelberg, Germany.)



**Fig. 6.36.2** Temporally located congenital optic pit associated with a localized retinal detachment in the macula. Peripapillary retinal pigment epithelial changes are seen adjacent to the pit. Small yellow subretinal precipitates seen within the temporal aspect of the detachment. Precipitates appear as hyperreflective accretions adherent to the outer retina on optical coherence tomography (*not illustrated*) and punctate areas of intense autofluorescence on fundus autofluorescence imaging (*not illustrated in this figure*).

include faulty closure of the fetal fissure (i.e., a variant of optic nerve coloboma); a primary mesenchymal abnormality; a primary neuroectodermal dysgenesis; and dilation of the optic nerve head due to dysgenesis of the terminal optic stalk.<sup>16</sup> No definite genetic defect has been associated with this anomaly.

Morning glory disc anomaly is usually unilateral. It is characterized by a conical excavation of the posterior fundus that includes the optic nerve, a central tuft of glial tissue, peripapillary subretinal fibrosis, and straightened vessels emerging from the peripheral nerve in a radial pattern.<sup>17</sup> Macular involvement can occur in up to 50% of patients (Fig. 6.36.5).<sup>17</sup>

Contractility of the morning glory disc anomaly, with transient monocular vision loss corresponding to the contractions, has been reported.<sup>16</sup> Studies have correlated this phenomenon to the presence of intrascleral smooth muscle within the distal optic nerve.<sup>18</sup>

It is critical to distinguish this anomaly from optic nerve coloboma because these two entities have different systemic associations. Morning glory disc anomaly tends not to occur as part of a multisystem disorder. It can, however, be associated with basal encephalocele, hypopituitarism, and other central nervous system and cerebrovascular abnormalities.<sup>17</sup>

Patients with morning glory disc anomaly often present as infants with strabismus or leukocoria. Vision is typically poor and ranges from 20/200 to finger counting. However, cases with 20/20 vision and no light perception have been reported.<sup>16</sup> Decreased retinal function appears to be proportional to the extent of peripapillary retinal involvement.

Approximately one third of reported cases of this anomaly have been associated with nonrhegmatogenous retinal detachment. Retinal detachment typically occurs during the first or second decade of life. The retinal detachments may be large but are usually confined to the peripapillary retina or posterior pole.

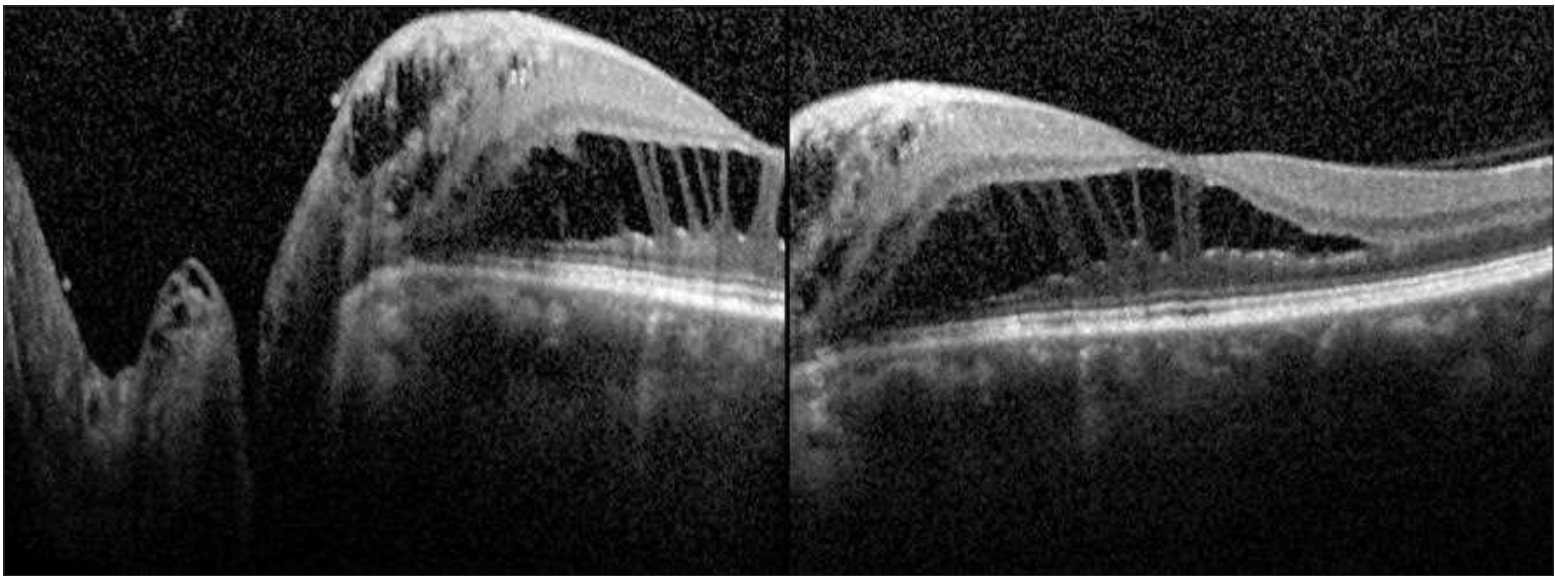
As with optic disc pits, the pathogenesis and origin of subretinal fluid in morning glory disc anomaly remains undetermined. Evidence supporting communication between the subarachnoid space and subretinal space in morning glory disc anomaly includes the migration of metrizamide from cerebrospinal fluid into the subretinal space; and migration of gas from the vitreous cavity into the perineural subarachnoid space at the time of optic nerve sheath fenestration.<sup>18,19</sup> Peripapillary retinal breaks, identified intraoperatively, with OCT or biomicroscopy, together with reports of vitreous substitutes migrating into the subretinal space, suggest a vitreal origin.<sup>19,20</sup> It has been postulated that the glial tuft in morning glory disc anomaly can contract creating breaks or inducing abnormal communication between the subretinal and subarachnoid spaces.<sup>19,20</sup>

## Optic Nerve Coloboma

Colobomas can arise anywhere along the line of fusion of the embryonic fissure, which extends from the optic disc posteriorly to the inferior pupillary frill of the iris anteriorly. Inadequate closure of the superior end produces an optic nerve coloboma, whereas more widespread failure to close causes a retinochoroidal coloboma.

Optic nerve colobomas may be unilateral or bilateral. They appear as a white excavation, which typically involves the inferior part of the nerve and can extend inferiorly into the choroid and retina. The superior rim of the optic nerve is usually spared (Fig. 6.36.6).<sup>16</sup> There are often areas of pigment clumping at the junction of normal fundus and the colobomatous defect (Fig. 6.36.7). As with morning glory disc anomaly, there is contractility of some colobomatous optic discs, which is thought to be due to the presence of heterotopic intrascleral smooth muscle.<sup>16</sup>





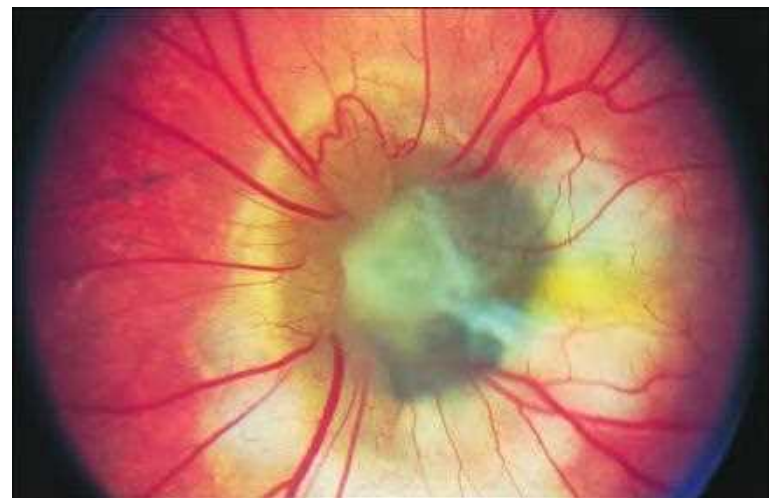
**Fig. 6.36.3** Optical coherence tomography (OCT\*) slice at the level of the optic nerve pit (left). Multilayered schisis-like separation of the nasal inner retina and intact vertical bridging elements in the central outer nuclear layer, without retinal detachment (left and right). (Courtesy Dr. Maurice B. Landers III \* Spectralis OCT, Heidelberg Engineering, Heidelberg, Germany.)



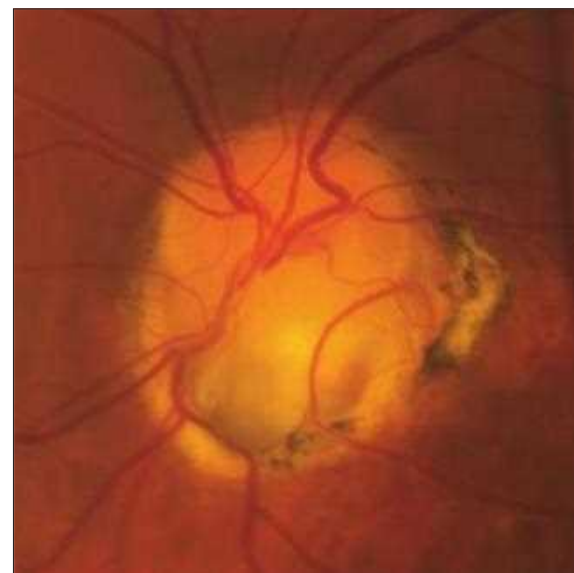
**Fig. 6.36.4** Histopathology of a Collie dog's eye with a congenital optic pit and associated serous retinal detachment. Vitreous gel has entered the pit from the vitreous cavity, and a connection exists between the pit and the subretinal space (periodic acid–Schiff.)

Both retinochoroidal and optic nerve colobomas may be associated with systemic abnormalities arising from midline defects. One syndrome found in conjunction with retinochoroidal colobomas is CHARGE (coloboma, heart disease, atresia choanae, retarded growth, genital hypoplasia, ear anomalies, with or without deafness) syndrome.

Papillorenal syndrome is an autosomal dominant condition in which renal and urinary tract malformations are associated with optic nerve coloboma, retinochoroidal coloboma, congenital optic pit, and morning glory disc anomaly. A mutation of the *PAX2* gene has been noted in 50% of such patients.<sup>21</sup> Papillorenal syndrome has also been associated with serous retinal detachment,<sup>22</sup> foveal hypoplasia, and pigmented macular atrophy (see Fig. 6.36.7).<sup>21</sup>

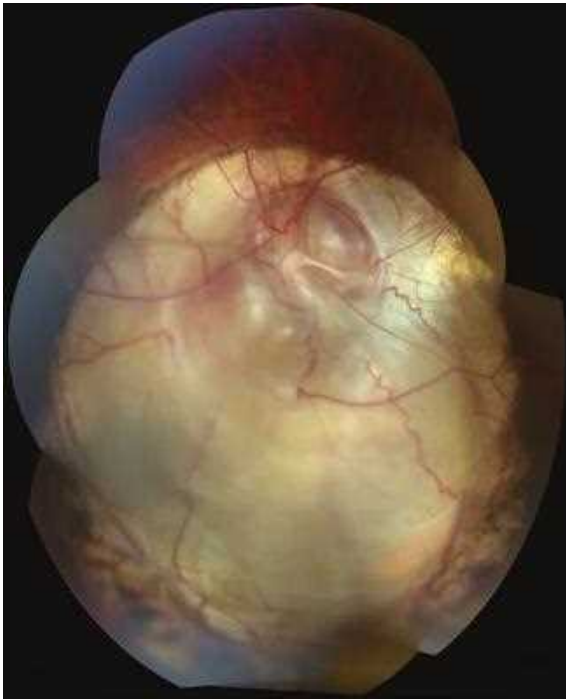


**Fig. 6.36.5** Morning glory optic disc in this left eye is associated with a shallow retinal detachment. The yellow pigment that overlies the area of subretinal fibrosis at the 3 o'clock position is caused by the xanthophyll pigment in the fovea, which is abnormally close to the disc.



**Fig. 6.36.6** Congenital optic nerve coloboma involving the inferior part of the nerve and sparing the superior rim of the optic nerve. (Courtesy Sarah Armstrong CRA, C-OCT.)





**Fig. 6.36.7** Montage fundus photograph showing a retinochoroidal coloboma involving the optic nerve in a patient with CHARGE (coloboma, heart disease, atresia choanae, retarded growth, genital hypoplasia, ear anomalies, with or without deafness) syndrome. A deep ectatic area is noted inferior nasal to the identifiable optic disc. Blood vessels emerge at the inferior border of this area. Superficial blood vessels are visualized coursing over the colobomatous defect. Deep choroidal blood vessels are seen in the base of the inferior defect. There is pigment disturbance at the junction of the normal fundus and colobomatous defect. The surrounding normal retina is attached. (Courtesy Dr. Travis A. Meredith.)

Among the ocular abnormalities associated with both optic nerve and retinochoroidal coloboma are rhegmatogenous, serous, or traction retinal detachments.

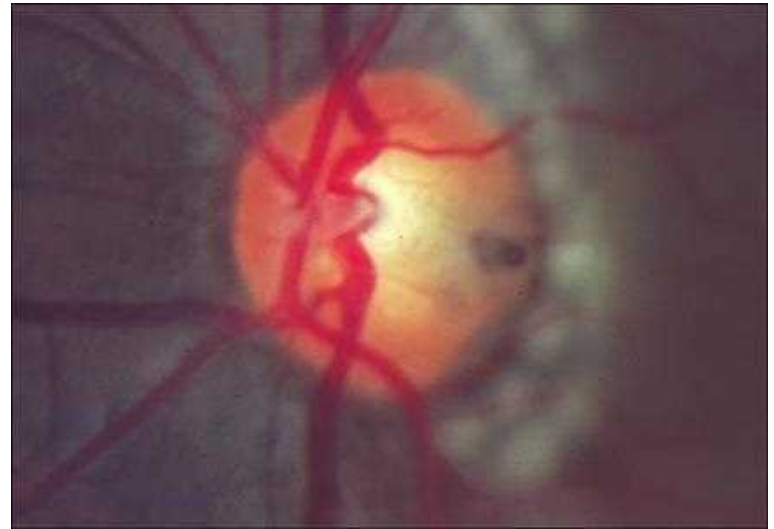
## Treatment of Retinal Detachments Secondary to Congenital Anomalies of the Optic Disc

Retinal detachments associated with congenital anomalies of the optic disc have many similarities.

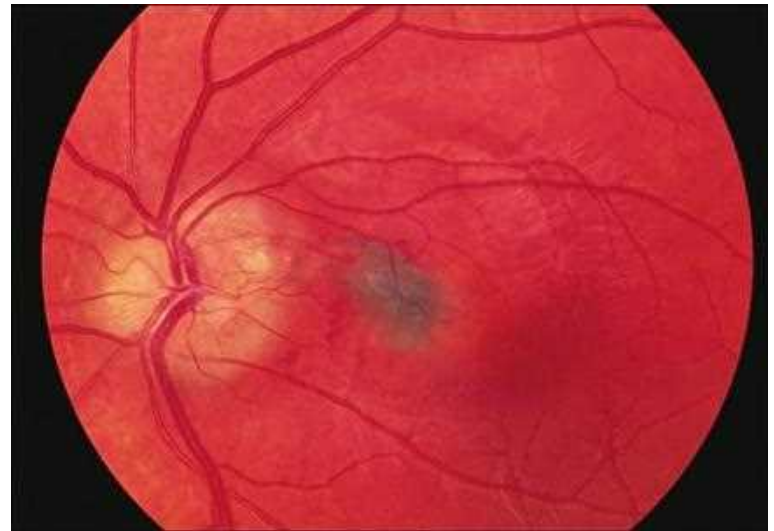
If subretinal fluid seen in conjunction with an optic disc anomaly is minimal and borders only a portion of the optic disc, peripapillary photocoagulation alone can be considered. The most widely used technique is the placement of 2–5 rows of 200 micron spot-size burns along the disc margin, extending into flat retina on either side of the subretinal fluid (Fig. 6.36.8).<sup>23,24</sup> If the photocoagulation is ineffective, it can be repeated 2 months later. The greater the separation of the peripapillary retina from the underlying RPE, the less likely it is that the treatment will be successful.

More extensive retinal detachments will require vitrectomy, with separation of the posterior hyaloid and careful dissection of all peripapillary fibroglial tissue. If a retinal break is present, it is important to relieve the surrounding traction. A fluid–gas exchange should be performed, draining the subretinal fluid over the optic disc or, in the case of retinochoroidal colobomas, a break in the dysplastic retina overlying the colobomatous defect. Endophotocoagulation should be applied to the margin of the defect.<sup>19</sup> In the case of retinochoroidal colobomas, if the retinal break is located peripherally, scleral buckling surgery may be effective.

Successful displacement of the subretinal fluid with an intravitreal gas injection alone has been reported in detachments associated with optic disc pits. However, the beneficial effects of this technique may only be temporary secondary to recurrence of fluid movement into the subretinal space from persistent inner layer cavities.<sup>14</sup> Vitrectomy, either with or without ILM peel in eyes with optic disc pit maculopathy, has yielded promising results.<sup>23,25</sup> A combination of carefully titrated preoperative juxtapapillary laser photocoagulation with immediate vitrectomy and gas tamponade has been reported to be effective in a series of 11 patients.<sup>26</sup> Conversely, Hirakata et al. reported a high success rate in the treatment of detachments secondary to optic disc pits with induction of posterior vitreous detachment during vitrectomy, without gas tamponade or



**Fig. 6.36.8** Two rows of 200  $\mu$ m spot-size laser burns applied to the peripapillary fundus in an eye with a congenital optic pit and macular retinal detachment. The treatment is carried into flat retina superiorly and to the area of detachment inferiorly, so the retinal pigment epithelium can adhere to the retina and, hopefully, to continue that adherence centrally.



**Fig. 6.36.9** Pigmented peripapillary choroidal neovascular membrane developing in an eye with optic nerve head drusen.

photocoagulation.<sup>10</sup> Promising results have been demonstrated with placement of tissue adhesive, autologous sclera, fibrin, or platelet concentrate over the optic pit.<sup>23,27-31</sup>

Novel treatments proposed for optic disc pit maculopathy include macular scleral buckling and vitrectomy with inner retina fenestration.<sup>2</sup> Both methods have been reported to produce favorable anatomical and functional results. However, there has not been widespread adoption of these techniques. Optic nerve sheath decompression has also been reported to treat retinal detachments associated with morning glory disc anomaly, although its exact role is uncertain.<sup>16</sup>

Silicone oil should be avoided in eyes with excavated defects of the optic nerve. Migration of intraocular silicone oil into the subretinal space and even the subarachnoid space has been reported to occur in eyes with an optic disc pits. In the case of subarachnoid migration, central nervous system related symptoms occurred.<sup>32,33</sup>

## OTHER OPTIC NERVE ABNORMALITIES ASSOCIATED WITH MACULAR PATHOLOGY

### Optic Nerve Abnormalities Associated With Choroidal Neovascularization

A number of optic nerve abnormalities have been associated with peripapillary choroidal neovascularization (CNV), including optic disc pits (Fig. 6.36.9), morning glory disc anomaly, retinochoroidal coloboma involving

the optic nerve, tilted disc syndrome, optic disc drusen; papilledema; and papillitis secondary to idiopathic multifocal chorioretinitis. It is believed that in these cases, new vessel growth is influenced by disruption of the choroid, RPE, and Bruch's membrane.<sup>34</sup>

Peripapillary CNV related to optic nerve abnormalities is uncommon. Our knowledge regarding the prognosis and management of peripapillary CNV has been derived, mainly, from studying peripapillary CNV secondary to macular conditions independent of optic nerve abnormalities.<sup>35</sup>

Thermal laser therapy was the first intervention described for peripapillary CNV. The guidelines were derived from the Macular Photocoagulation Study (MPS). Many advocate treatment of peripapillary CNV prior to it extending within 2500 microns from the center of the foveola.<sup>35</sup> The morbidity associated with such treatment is lower than that associated with extension of the neovascularization and associated sequelae into the fovea. A wide margin of photocoagulation to normal tissue around the edge of any angiographic abnormality is recommended. According to the MPS guidelines, patients are considered ineligible for laser treatment if the lesion is >4.5 clock hours; a large adjacent submacular hemorrhage is present; and 1.5 clock hours of temporal peripapillary retina is not spared.<sup>35</sup> Cases of peripapillary CNV secondary to bilateral optic nerve drusen and retinochoroidal colobomas have been successfully treated with laser photocoagulation.<sup>36</sup>

Photodynamic therapy (PDT) with verteporfin results in less local tissue damage than use of a thermal laser. The successful treatment of peripapillary CNV associated with optic nerve head drusen using PDT has been reported.<sup>36</sup> It is controversial whether the PDT treatment field can include the optic nerve. There are concerns about optic nerve damage if the PDT laser spot extends closer than 200 microns from the edge of the optic nerve. However, in treating peripapillary CNV, several investigators have included part of the optic disc within the PDT field without complication.<sup>35</sup>

Surgery has also been described for the treatment of patients with peripapillary CNV. One patient with peripapillary CNV secondary to optic nerve head drusen showed recovery without recurrence following subretinal membrane removal.<sup>37</sup>

Anti-vascular endothelial growth factor (anti-VEGF) agents are most commonly used in the treatment of neovascularization from a variety of causes. Anti-VEGF treatment is advantageous because it can preserve the papillomacular bundle and can be useful in cases where proximity of the lesion to the fovea precludes other treatment modalities.

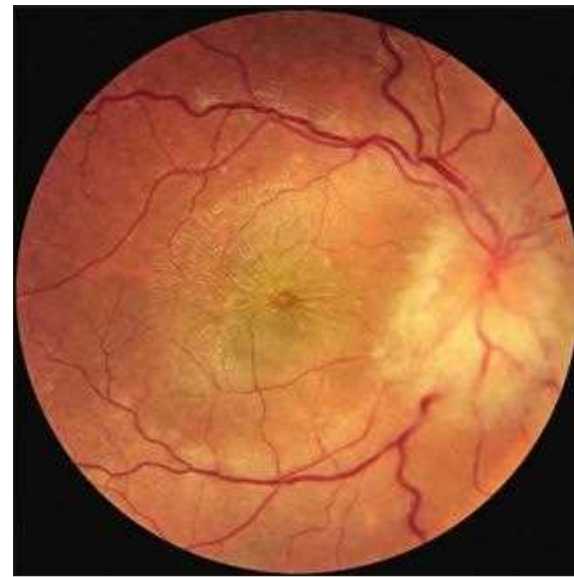
Anti-VEGF agents alone or combined with photocoagulation have been described for the treatment of peripapillary CNV secondary to optic nerve head drusen. In all cases, treatment resulted in anatomical and functional improvement.<sup>36,38</sup>

## Abnormalities Associated With Exudation

Abnormalities that cause papillitis can lead to severe chronic leakage of plasma and lipid products that extend into the central macula. The lipid is located within the outer plexiform layer (Henle's fiber layer) and often has the configuration of a hemi- or full macular star (Fig. 6.36.10). When this hard exudate is present, retinal thickening (macular edema) is often seen concomitantly. FA shows leakage of the optic nerve vessels without leakage of the macular vessels. The exudates appear as hyperreflective foci in the outer plexiform layer on OCT and have decreased autofluorescence on imaging.<sup>39</sup>

The specific entities that can cause papillitis and subsequent hard exudation into the macula include idiopathic optic neuritis (Leber's stellate optic neuropathy), sarcoidosis, infectious neuroretinitis, idiopathic intracranial hypertension, malignant hypertension, radiation optic neuropathy, and anterior ischemic optic neuropathy. In infectious neuroretinitis, the macular star becomes prominent over first 3 weeks, and the neuroretinitis resolves over 6–8 weeks. When the underlying cause is systemic arterial hypertension, resolution of the hard exudate usually occurs within weeks to months after the blood pressure returns to normal.<sup>40</sup>

The most common causes of infectious neuroretinitis include *Bartonella henselae* infection, Lyme disease, and syphilis. Infectious causes are



**Fig. 6.36.10** Unilateral optic disc edema and associated macular star pattern of hard exudates in a 9-year-old girl with neuroretinitis secondary to infection by *Bartonella henselae*.

usually unilateral and may be associated with mild vitritis. *B. henselae* is the causative organism of cat scratch disease, and diagnosis can be supported by serum antibody titers. It may take 4–6 weeks for seroconversion to occur. In seronegative cases, repeat serology is recommended in 2 months.<sup>39</sup> Other macular abnormalities associated with cat scratch disease include macular edema, focal chorioretinitis and choroidal infiltrates, vasculitis, vascular occlusions, and subretinal angiomatous lesions.<sup>39</sup>

No specific treatment is indicated for these exudative maculopathies other than alleviation of the underlying problem, when possible. In cases of *B. henselae* infection, the prognosis is usually good even without treatment. Treatment options include 4–6 weeks of doxycycline with rifampin, systemic gentamicin, trimethoprim–sulfamethoxazole, or ciprofloxacin. The role of corticosteroids is not known.<sup>40</sup>

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## Peripheral Retinal Lesions

William Tasman<sup>†</sup>

6.37

**Definition:** A heterogeneous group of anatomical variations, degenerative changes, and pathological processes that can be observed ophthalmoscopically in the anterior neural retina and ora serrata region.

**Key Features**

- Anatomical variations in the anterior neural retina and ora serrata region.
- Degenerative changes in the anterior neural retina and ora serrata region.
- Pathological processes in the anterior neural retina and ora serrata region.

**Associated Features**

- Best observed with indirect ophthalmoscopy and scleral depression.
- Contact lens examination may assist.
- Possible association with premature vitreous collapse and retinal detachment.
- Usually stable over time.

**INTRODUCTION AND ANATOMY**

Many variations occur in the ophthalmoscopic appearance of the peripheral neural retina. In most cases, these variations are not of clinical significance; however, certain anatomical changes can render eyes at higher risk for retinal breaks and rhegmatogenous retinal detachment.

The fundus may be roughly separated into central (posterior) and peripheral (anterior) portions by a circle that passes through the posterior edge of the scleral entrance of each vortex vein ampulla. The anatomical equator is located approximately two disc diameters (3 mm) anterior to the entrance of the scleral canals. Thus, the vortex veins become important landmarks when separating the peripheral fundus from the posterior pole.

The fundus also may be divided by natural features into superior and inferior halves by the long ciliary nerves and arteries that form a horizontal boundary nasally and temporally.<sup>1</sup>

In the peripheral fundus, it often is difficult or impossible to distinguish between arterioles and venules on the basis of size, color, or pattern.<sup>2</sup> The most practical method of identification is to trace the vessels back to the posterior fundus. The retinal arterioles and venules generally do not course together but are evenly distributed throughout the periphery. Most of them become very small and disappear before reaching a distance of 0.5 disc diameter from the ora serrata. The arterioles disappear first, whereas the venules tend to extend closer toward the ora serrata.

**Ora Serrata**

In the ora serrata region, the retina becomes opalescent and often is marked by small rows of cystoid cavities.<sup>3</sup> This is normal. Extensive cystoid changes do not represent pathology. The underlying pigment epithelium appears darker and more granular than that seen posteriorly. The neural retina stops abruptly at the ora serrata and is continued by the nonpigmented ciliary epithelium, which appears considerably thinner than the retina. The pars plana corporis ciliaris is more deeply pigmented than the peripheral retina, and thus the choroidal pattern is obscured by that of the pigment epithelium. The development of the ora serrata is incomplete at birth and continues during early life.<sup>4,5</sup>

Because ora bays and teeth (or dentate processes) frequently are difficult to identify temporally, the exact number of ora teeth is not easy to calculate. Salzmann,<sup>5</sup> in 1912, identified 48, whereas Straatsma et al.<sup>6</sup> noted 16 dentate processes along the average ora serrata. In the chapter author's experience, the number varies, but usually between 20 and 30 dentate processes can be counted reliably, corresponding in position to the intervals between the ciliary processes.

**Vitreous Base**

One of the most significant structures in the peripheral fundus is the vitreous base. It is of clinical importance because retinal breaks frequently occur along its posterior border and, in the case of traumatic detachment, occasionally along the anterior border, as well.<sup>7</sup> The vitreous base involves the full circumference of the peripheral fundus and measures approximately 3.2 mm in width. Generally, it is wider nasally than temporally and may have an irregular posterior border (Fig. 6.37.1). It represents an area in the fundus in which the vitreous, neural retina, and pigment epithelium all are firmly adherent, one to the other. It is for this reason that in some cases of traumatic detachment, the vitreous base is avulsed with its underlying neural retina and pigment epithelium, to create a retinal dialysis and a "garland" that hangs down into the vitreous cavity (Fig. 6.37.2). The vitreous base may be prominent in some individuals, especially those with a darkly pigmented choroid.

The pars plana is delineated at its posterior margin by the ora serrata. The sensory retina continues into the pars plana as the nonpigmented ciliary epithelium. The vitreous base, which straddles the ora serrata, has its anterior border in the pars plana, where it parallels the configuration of the ora serrata.

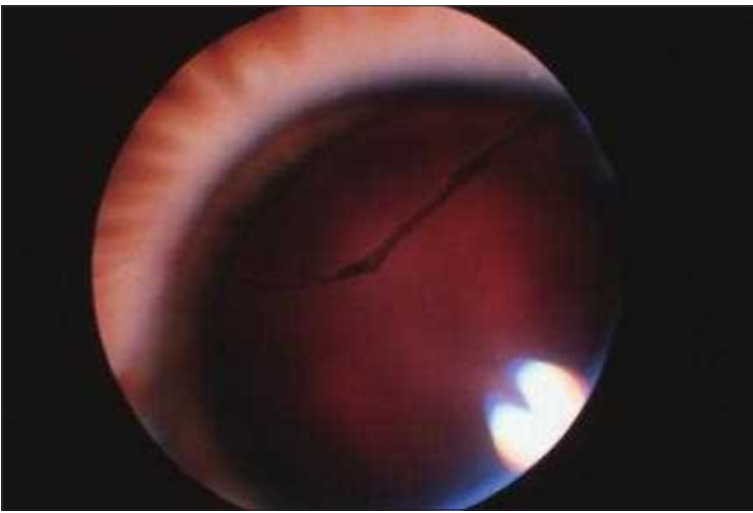
**OCULAR MANIFESTATIONS AND DIAGNOSIS OF PERIPHERAL RETINAL LESIONS****Meridional Folds or Radial Folds**

Meridional folds, or radial folds, which usually involve all neural retinal layers, are a common, normal variant seen in the peripheral fundus. As a

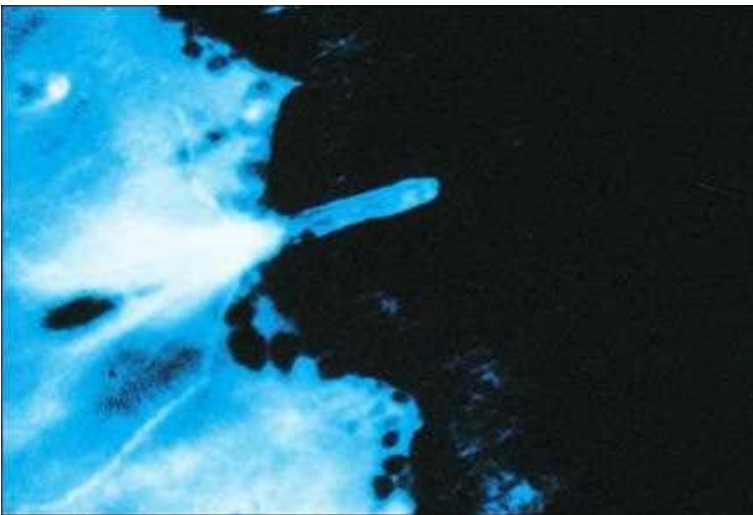


**Fig. 6.37.1** The anterior border and posterior border of the vitreous base. The posterior border is irregular. Areas of paving stone degeneration that extend across the ora serrata into the pars plana can also be seen.

<sup>†</sup>Deceased



**Fig. 6.37.2** Avulsed vitreous base.



**Fig. 6.37.3** Meridional fold with a small break at the base of the fold.

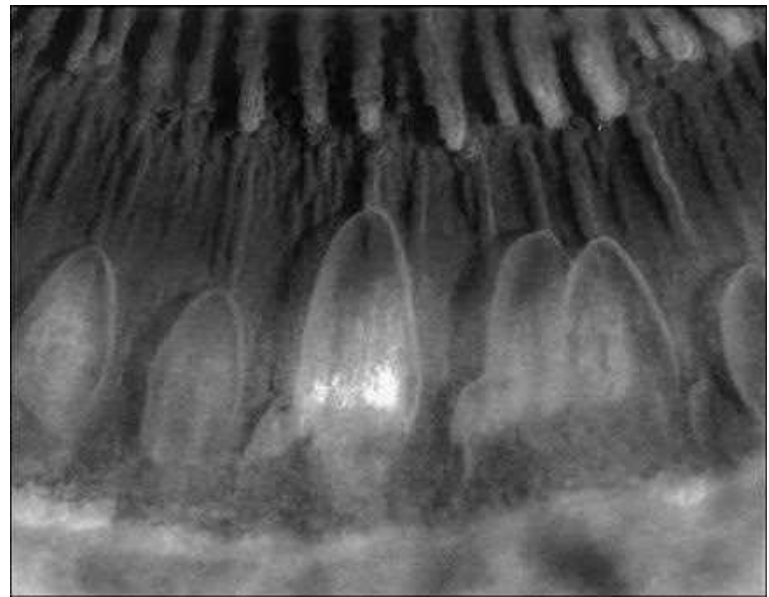
rule, a meridional fold begins in the ora serrata and runs posteriorly and perpendicularly to it in a meridional fashion. It is a radially aligned elevation of the peripheral retina and may be associated with retinal breaks (Fig. 6.37.3). Meridional folds are found significantly more often nasally than temporally and especially in the upper nasal quadrant.<sup>3,8</sup> They are found in 20% of eyes examined during autopsy.<sup>9</sup> In cases of rhegmatogenous retinal detachment, the posterior edges of meridional folds must be examined carefully for retinal breaks.

### Pars Plana Cysts

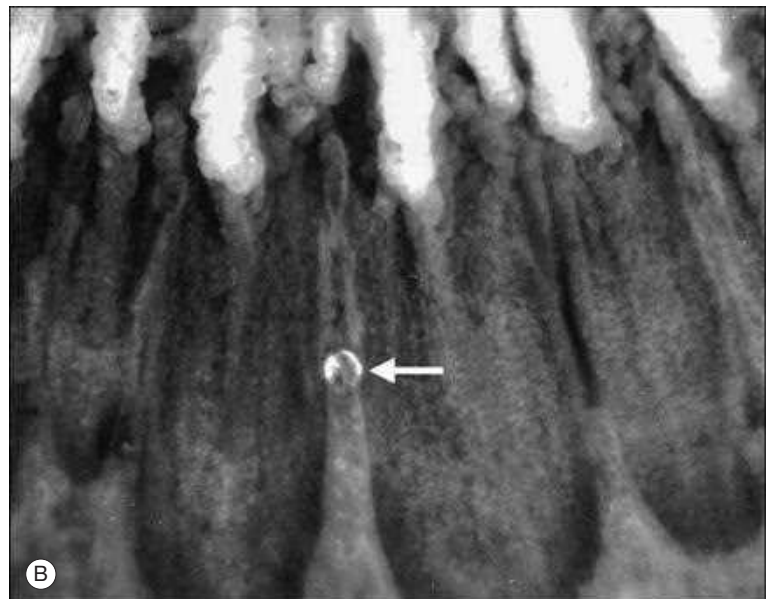
Cysts of the pars plana corporis ciliaris are another variant seen in the fundus periphery.<sup>10</sup> These consist of a clear cystoid space between the pigmented and nonpigmented epithelia located anterior to the ora serrata (Fig. 6.37.4). The cysts, which have the appearance of half-inflated balloons, lie between the pars plana radiations. Generally, the overlying vitreous and its surrounding ciliary pigment epithelium remain unchanged. Occasionally, patients who are highly myopic demonstrate a marked degree of cyst formation along the entire pars plana.

### Ora Serrata Pearls

Still another change that may be noted in the fundus periphery is the ora serrata pearl. This glistening opacity (Fig. 6.37.5A, B), which usually forms over an oral tooth, varies from pinpoint to pinhead in size.<sup>11</sup> It appears in all age groups but increases significantly in incidence with advancing age.<sup>12</sup> Pearls are not related to other fundus pathology and are probably of developmental origin. They occur throughout the ora serrata region and are drusen-like structures that show the staining qualities of an acid carbohydrate on pathological examination.



**Fig. 6.37.4** Pars plana cysts. The radial striations can also be seen directed between the ciliary processes. (Courtesy Dr. Ralph Eagle, Jr.)

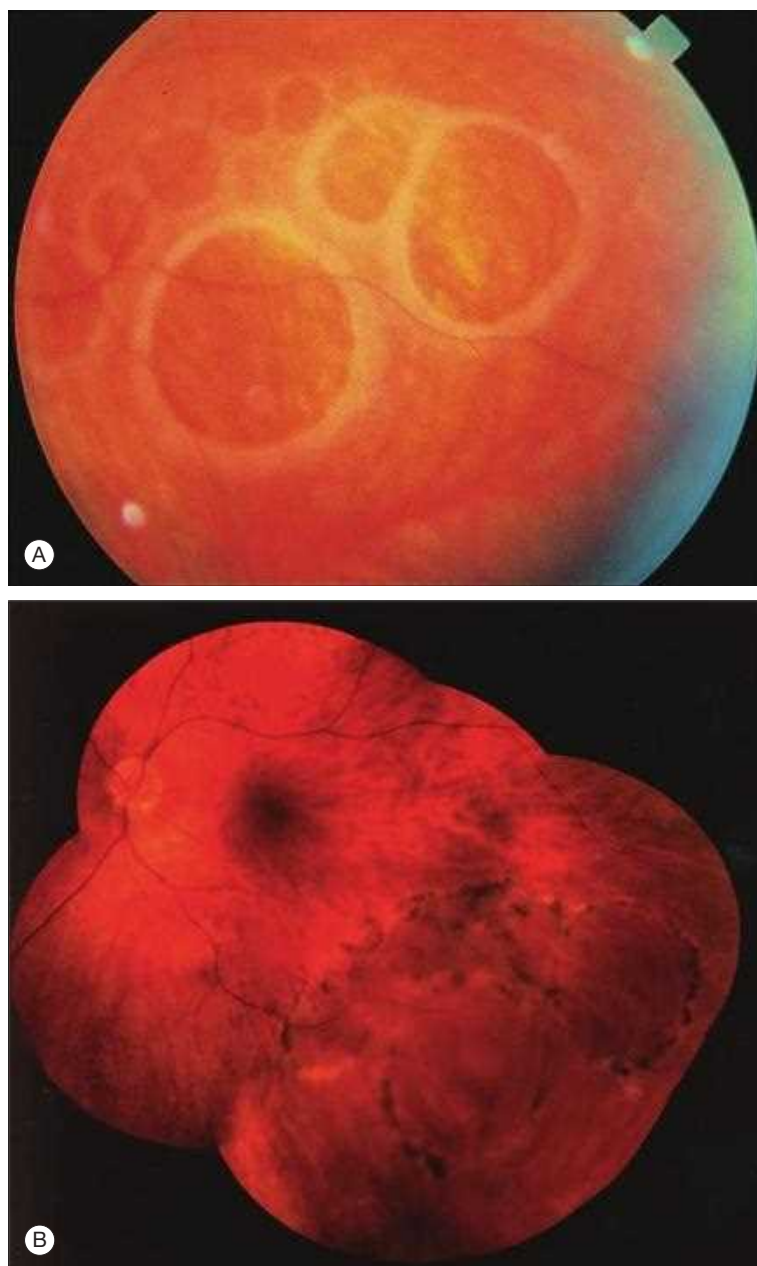


**Fig. 6.37.5** (A) Ora serrata pearl. (B) The pearl lies on an oral tooth. Again, radial striations are directed between the ciliary processes.

### Degenerative Adult Retinoschisis

Degenerative retinoschisis usually is bilateral, often symmetrical, and commonly bullous. It frequently first appears in the inferotemporal quadrant and may be slowly progressive.





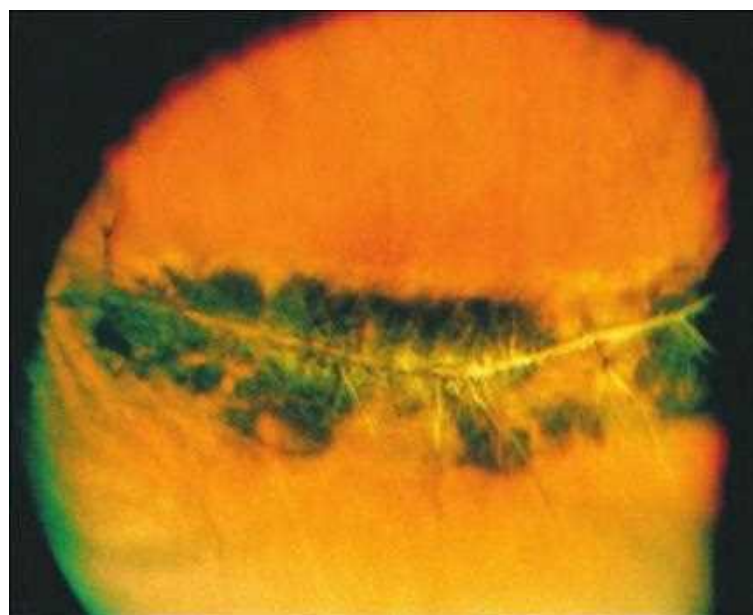
**Fig. 6.37.6** (A) Outer layer breaks. (B) Over a 3-year period, pigmentation developed around the breaks.

Bullous types of retinoschisis appear clinically as thin, elevated layers of tissue, best observed in the inferotemporal periphery. The retinal vessels often are sheathed terminally, and fine white spots may occur on the inner surface. These represent the Müller fibers that traverse the schisis cavity.

Large outer layer holes may develop over time, often with a rolled edge (Fig. 6.37.6A). Pigmented demarcation lines are not a clinical feature of bullous retinoschisis. If present, they usually suggest long-standing non-progressive retinal detachment. However, over time, pigmentation around the break(s) may occur, indicating localized retinal detachment which can be monitored (see Fig. 6.37.6B).

The major complication of retinoschisis is retinal detachment. In 987 patients with retinal detachment followed up by Pecold et al.,<sup>13</sup> retinoschisis was present in 25, an incidence of about 2.5%. Retinal detachment occasionally may occur when holes exist in the outer layer of the schisis. In many cases, inner layer holes also occur, but these need not be present for retinal detachment to develop. The detachment may gradually extend beyond the area of retinoschisis, in which case it may resemble a typical rhegmatogenous detachment.<sup>14</sup> When progression of the schisis toward the posterior pole extends posterior to the equator, perimetry reveals an absolute field defect, whereas the defect associated with retinal detachment is relative.

Byer<sup>15</sup> conducted a long-term natural history study of 123 consecutive, unselected patients (218 eyes) who had suffered acquired retinoschisis for 1–21 years (average 9.1 years), to ascertain the natural behavior and prognosis of this disease and formulate reasonable recommendations for



**Fig. 6.37.7** Clinical picture of lattice degeneration showing the typical white lines. These lines represent hyalinized vessels.

its management. The quadrant of maximal involvement was the inferior temporal, and 74% of the lesions had postequatorial posterior borders. Most importantly, degenerative retinoschisis was found to be primarily asymptomatic and nonprogressive. No case of symptomatic progressive retinal detachment occurred, but 14 cases of localized, nonprogressive, and asymptomatic schisis–retinal detachment were noted.

Byer<sup>16</sup> concluded that the only indication for treatment of a schisis is the symptomatic or progressive schisis–retinal detachment that threatens the macula. Laser demarcation of a schisis or treatment of the borders of outer layer retinal breaks should be avoided.<sup>15–17</sup>

## Congenital X-Linked Retinoschisis

Congenital X-linked schisis is characterized by a stellate macular appearance and, often, large nerve fiber layer dehiscentes. Optical coherence tomography (OCT), however, has shown that the split may, in some instances, involve more than just the nerve fiber layer.

## Paving Stone Degeneration

Paving stone degeneration is a chronic, slowly progressive disorder that usually does not produce any symptoms or complications. It is seen more commonly in older patients and is bilateral in one third of the cases.<sup>18</sup>

Paving stone degeneration is characterized by well-delineated, flat yellow foci in the size range of 0.5–2.0 disc diameters (see Fig. 6.37.1). Irregular black pigmentation frequently is present on the margins of the lesions and red lines, which correspond to choroidal blood vessels, may traverse them. With time, the individual lesions may become confluent and form a continuous band of irregular pigment clumping. Although paving stone degeneration may be located in any quadrant, it is most common inferiorly between the equator and the ora serrata but may extend into the pars plana.

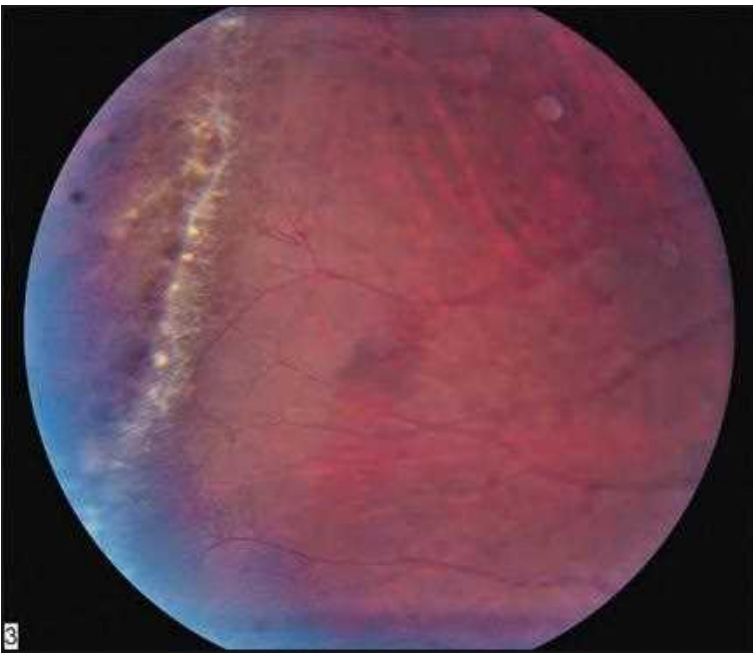
## Lattice Degeneration and Retinal Breaks

In contrast to the conditions previously described, lattice degeneration has greater clinical significance.<sup>19</sup> It is especially important because of its relationship to rhegmatogenous retinal detachment.

Ophthalmoscopically, lattice degeneration appears as one or more linear bands of retinal thinning located in the equatorial region (Fig. 6.37.7). Fine white lines, which account for the term *lattice degeneration*, are present in only about 9% of lesions.<sup>20</sup> Pigmentary disturbances within the band of retinal thinning, however, are present in most cases. Occasionally, lesions separating vascularized from avascular retina may simulate lattice, especially in familial exudative vitreoretinopathy, as can be seen in Fig. 6.37.8.

Using “A” scan axial length measurement, the prevalence of lattice was greater in eyes without staphyloma, in which the whole eye was elongated, versus eyes with staphyloma, in which only the posterior pole was elongated.<sup>20</sup>





**Fig. 6.37.8** Ridge between the vascularized and avascular retina in familial exudative vitreoretinopathy may be confused with lattice.

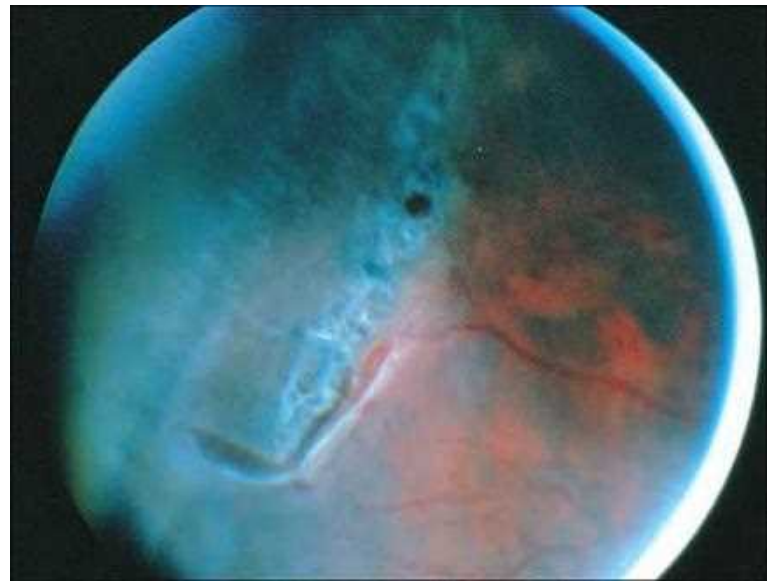
With lattice degeneration, the vitreous gel is attached firmly to the margin of the lesion. Usually, a clear pocket of liquid vitreous is present over the central thin portion of each lesion.

Retinal holes often can be observed in lattice degeneration. Two types of breaks have been recognized. Round or atrophic holes usually are found centrally within the thin portion of the lesion and usually are not associated with vitreous traction. These may lead to retinal detachment in young patients with myopia. Horseshoe-shaped breaks occur most commonly on the posterior edge of the lesion and are associated with severe vitreous traction (Fig. 6.37.9).

Lattice degeneration of the retina is present in about 7%–8% of adult eyes.<sup>21–24</sup> Burton<sup>21</sup> showed that patients with lattice degeneration, ages 40–60 years, and with low to moderate degrees of myopia tend to develop detachments caused by premature posterior vitreous detachment (PVD) and traction tears. However, he pointed out that prophylaxis for this group is not warranted because only 5%–10% will experience PVD during their lives.

Furthermore, up to one fourth of symptomatic acute PVDs show incomplete separation, which may lead to delayed retinal breaks and/or epiretinal membranes.<sup>23–27</sup>

In an evidence-based analysis of prophylactic treatment of asymptomatic retinal breaks and lattice degeneration, a panel of vitreoretinal experts reviewed the English language literature.<sup>27</sup> They concluded that there was insufficient information to strongly support prophylactic treatment of lesions other than symptomatic flap tears.



**Fig. 6.37.9** Horseshoe tear on the posterior and inferior edge of lattice degeneration.

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# Retinal Breaks

Margaret A. Greven, Craig M. Greven

# 6.38

**Definition:** A full-thickness defect in the neurosensory retina.

## Key Features

- A round, oval, or horseshoe-shaped defect.
- Typical location near the vitreous base, but can occur anywhere.
- Subcategories are holes, tears, or dialyses.

## Associated Features

- Pigmented cells in the vitreous (tobacco dust).
- Vitreous traction.
- Vitreous hemorrhage.
- Pigmentary changes in the adjacent retina.
- Localized abnormal vitreous–retinal interface (lattice degeneration).

## INTRODUCTION

Retinal breaks are full-thickness defects in the neurosensory retina. They typically occur in the equatorial and ora serrata regions of the retina but can develop more posteriorly as well. Peripheral retinal breaks do not cause loss of vision, but the associated conditions of vitreous hemorrhage and rhegmatogenous retinal detachment can cause severe visual loss. The first goal in the management of retinal breaks is to differentiate those not likely to cause severe visual sequelae from those more likely to lead to visual loss and retinal detachment. In this chapter, the identification of “high-risk” retinal breaks is discussed, and appropriate management strategies are suggested.

## EPIDEMIOLOGY AND PATHOGENESIS

The incidence of retinal breaks at autopsy in individuals age >20 years is in the range 6%–11%.<sup>1,2</sup> The prevalence of retinal breaks in clinical series of routine patients aged ≥10 years without antecedent ocular disease ranges from 6%–14%.<sup>3,4</sup> The annual incidence of retinal detachment is approximately 12 per 100 000 population per year.<sup>5,6</sup> From these data, it is intuitive that most retinal breaks do not lead to detachment. Therefore, it has been the goal of clinicians to determine which breaks may benefit from prophylaxis.

The occurrence of retinal breaks is age dependent, with increasing incidence accompanying increasing age. However, no statistical difference exists between men and women in the incidence of retinal breaks.<sup>1,3</sup> The prevalence of retinal breaks in myopic eyes is similar to that in eyes of the general population, about 11%.<sup>7</sup> However, cases of myopia account for 42% of all cases of phakic retinal detachments, and, therefore, myopia is considered a risk factor for retinal breaks that lead to retinal detachment.<sup>8</sup>

Lattice degeneration of the retina is another risk factor for the development of retinal breaks. Lattice degeneration is a condition in which peripheral retinal thinning is associated with liquefaction and separation of the overlying vitreous, and a pronounced vitreoretinal adhesion at the margin. Lattice is found on autopsy in 11% of cases, occurs equally in men and women, and increases in incidence with increasing age.<sup>9</sup> It is a bilateral condition in nearly 50% of cases, and approximately 25% of affected eyes have associated retinal breaks.

Ocular contusion and penetrating trauma also increase the risk for development of a retinal break. The most common type of retinal break after ocular contusion injuries is a retinal dialysis.<sup>10,11</sup> Penetrating trauma

may cause retinal breaks immediately at the time of impact, because of direct retinal trauma, or as a result of later vitreous traction.

## OCULAR MANIFESTATIONS

### Retinal Tears

Retinal tears are full-thickness breaks that occur secondary to vitreous traction. The most common inciting vitreous traction is spontaneous posterior vitreous detachment (PVD). These horseshoe or flap tears occur at sites of strong vitreoretinal adhesion, most commonly at the vitreous base. The posterior edge of the tear is its apex, and the anterior extensions are its base (Figs. 6.38.1 and 6.38.2). Symptoms associated with acute horseshoe tears include floaters secondary to vitreous debris (hemorrhage, retinal pigment epithelium [RPE] cells) and flashes that result from persistent vitreous traction.

Firm vitreoretinal adhesions are present at the margins of lattice degeneration. When a PVD occurs, traction at the margin of the lattice degeneration can lead to retinal tears. These tears typically occur at the posterior or lateral margin of a patch of lattice.

### Round Holes With Opercula

Horseshoe or flap tears with persistent traction often avulse the base of the tear to leave a small, round defect in the neural retina with an overlying operculum of retinal tissue. This generally indicates complete relief of vitreoretinal traction in this area (Fig. 6.38.3).

### Round Holes Without Opercula (Atrophic Holes)

Atrophic holes in the retina occur secondary to retinal thinning. Vitreous traction is not the pathogenic mechanism of atrophic retinal holes. Although these can occur in isolation, they often present within areas of lattice degeneration.

### Traumatic Retinal Breaks

Blunt trauma to the globe can induce a variety of retinal breaks, which include horseshoe tears, retinal dialysis, and macular holes. The major mechanism of peripheral break formation is hypothesized to be compression of the globe with subsequent distortion and expansion at the area of the ora serrata and equator. This expansion produces an acute increase in vitreoretinal traction, which often results in a retinal dialysis.<sup>11</sup> Traumatic retinal dialyses most commonly occur inferotemporally and superonasally.<sup>12</sup> Direct contusion injury to the globe can lead to disruption of the retina and necrotic breaks. The retinal defects are typically irregular and located in the region of the vitreous base.

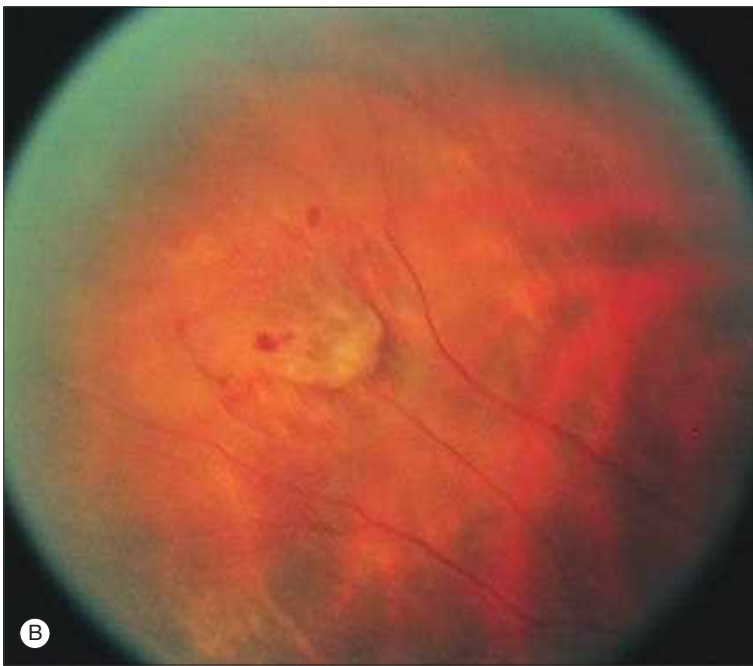
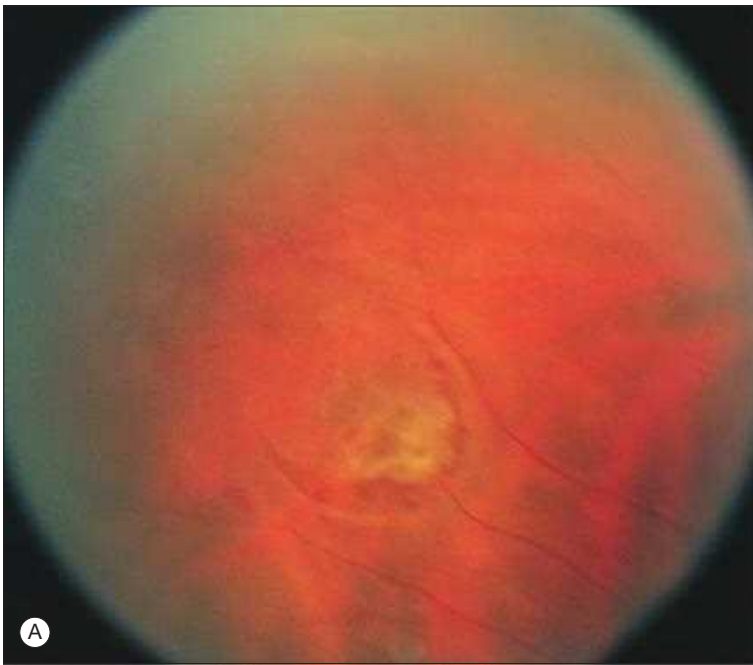
## DIAGNOSIS AND ANCILLARY TESTING

When the media is clear, retinal breaks can be diagnosed with indirect ophthalmoscopy or contact lens examination. In the setting of cloudy media, ultrasonography may detect the presence of retinal breaks, and ultrasound-guided cryotherapy can be utilized.<sup>13</sup>

## DIFFERENTIAL DIAGNOSIS

Many conditions in the peripheral fundus can mimic full-thickness retinal breaks. Obstacles to an accurate diagnosis include inadequate pupillary dilatation, cataract, anterior and posterior capsular opacities in pseudophakic eyes, vitreous opacities, and patient compliance. Binocular indirect





**Fig. 6.38.1 Symptomatic Acute, Superotemporal Horseshoe Tear Anterior to the Equator in the Right Eye.** (A) At presentation. Note the hemorrhage at its margins. (B) The same eye 1 week after cryopexy. Note the affection of retinal pigment epithelium adjacent to the tear.

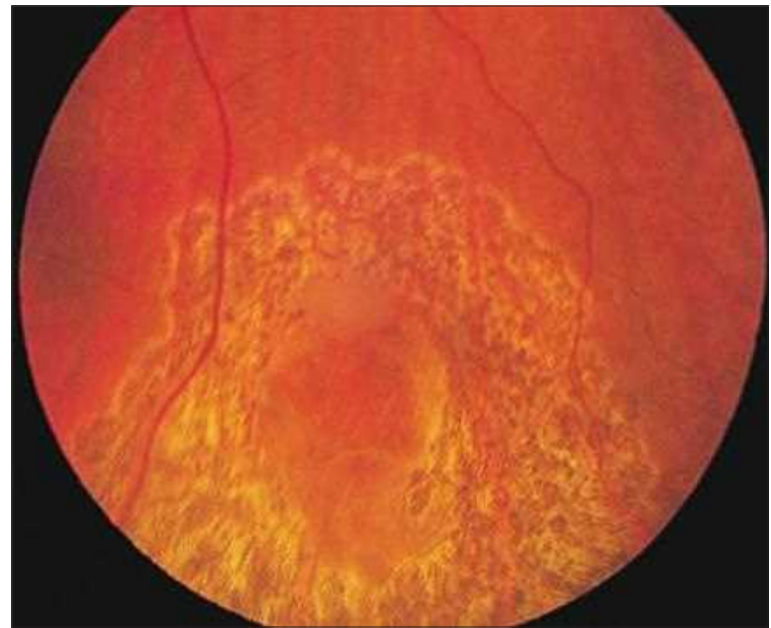
ophthalmoscopy with scleral depression to see the retina in relief, supplemented by Goldmann three-mirror examination, remains the standard method to differentiate these lesions. The differential diagnosis of retinal breaks is given in [Box 6.38.1](#). (See Chapter 6.37 for a more detailed discussion.)

## SYSTEMIC ASSOCIATIONS

The majority of retinal breaks occur in patients who have no predisposing systemic association. However, certain systemic conditions, such as Marfan's syndrome, Ehlers–Danlos syndrome, and homocystinuria, as well as hereditary hyaloideoretinopathies, such as Wagner's syndrome and Stickler's syndrome, can predispose to retinal break formation (see Chapter 6.15).

## TREATMENT OF RETINAL BREAKS

Upon discovery of a retinal break, the initial decision is whether the benefits of treatment (to prevent retinal detachment) outweigh the risks and cost of treatment. In each case, many factors should be considered



**Fig. 6.38.2** Symptomatic inferior horseshoe tear 6 weeks after cryopexy.

and the risks and benefits of treatment discussed with the patient. The factors under consideration in each case include the presence or absence of symptoms; age and systemic health of the patient; refractive error of the eye; location, age, type, and size of the break; status of the fellow eye; and whether the patient has aphakia or pseudo-phakia or is scheduled to undergo cataract surgery.

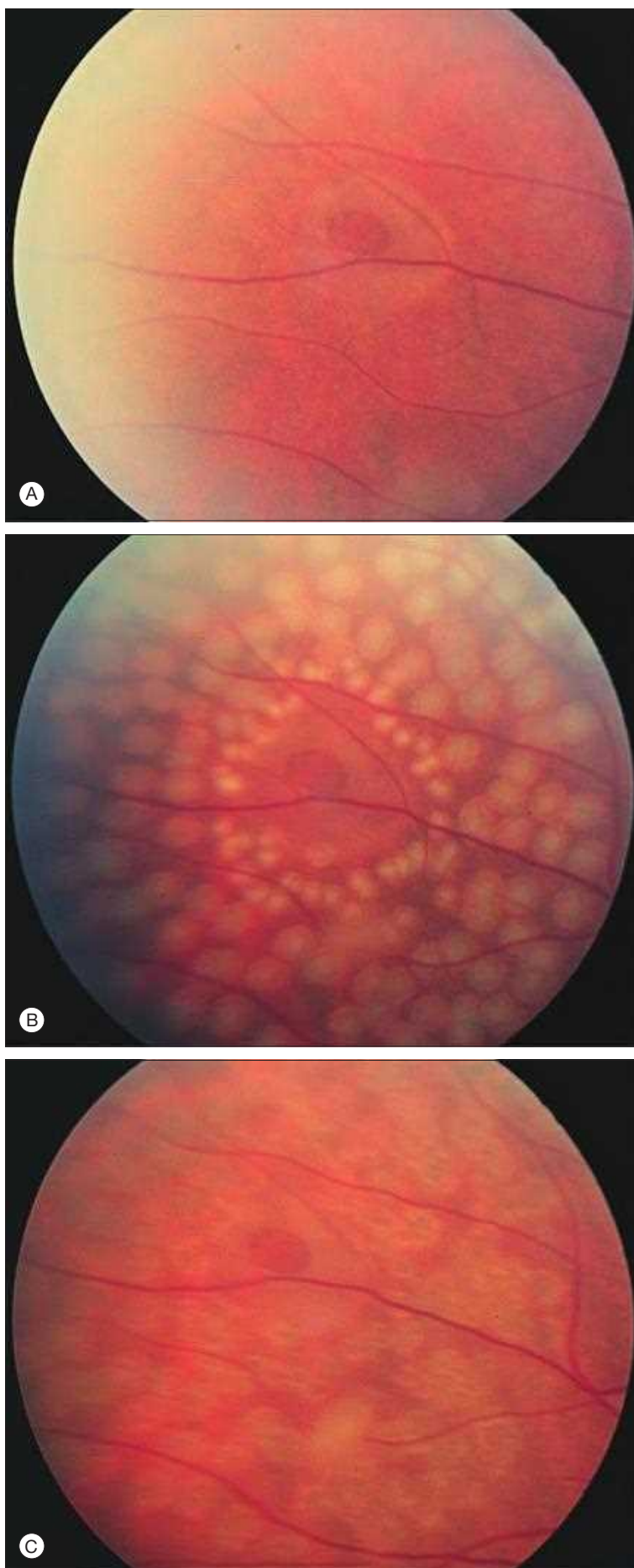
The typical symptoms associated with an acute retinal break are new floaters and flashes. These symptoms occur secondary to an acute PVD. Studies have shown that the presence or absence of symptoms in association with the onset of the break is the most important prognostic criterion for progression to retinal detachment.<sup>14-16</sup> In a prospective study of 359 asymptomatic retinal breaks in 231 phakic eyes of 196 patients, no clinical retinal detachment had occurred after a minimum 1-year follow-up.<sup>14</sup> Included in this study were 276 round atrophic holes, 50 tears with attached flaps, and 33 tears with free opercula. In phakic patients with no previous history of retinal disease or high myopia and who develop asymptomatic horseshoe tears, atrophic holes, or holes with opercula, prophylactic treatment is rarely indicated. In each case, the patient should be made aware of the symptoms of vitreous traction and retinal detachment and should be instructed on how to assess the peripheral visual field. To date, no randomized clinical trial has been performed to support conclusions regarding the value of treating asymptomatic retinal breaks.<sup>17</sup> In contrast, the rate of retinal detachment in phakic patients who have symptomatic breaks is 35%.<sup>15</sup> Therefore, it is recommended that all acute, symptomatic retinal breaks be treated to prevent retinal detachment.

Age and systemic health status of the patient are other variables to be considered in the management of a retinal break. As an example, a superotemporal horseshoe tear in a 27-year-old patient is more likely to cause a subsequent retinal detachment than is one in an 80-year-old patient who has metastatic lung cancer. Refractive error is considered in the management of retinal breaks. The increased incidence of retinal detachment in patients who have  $>-6.00$  diopters (D) of myopia may increase the likelihood for treatment of an asymptomatic retinal tear.

The age of the patient and the location and size of a retinal break are also considered when its management is determined. Long-standing tears often have RPE changes adjacent to them. These changes reflect chorio-retinal adhesion and indicate to the clinician the decreased likelihood of retinal detachment. Although no increased incidence of retinal detachment occurs with a retinal break in any particular quadrant, a greater likelihood of a macula-off retinal detachment is present as a result of superotemporal breaks than of either inferior breaks or nasal breaks. Although small retinal breaks can lead to retinal detachment, most ophthalmologists agree that, in general, larger breaks are more likely to cause retinal detachment.

The type of break should be a consideration in whether prophylactic treatment is offered. A horseshoe tear with persistent traction or a retinal dialysis is much more likely to result in a detachment compared with an atrophic hole.

Some controversy exists about the management of asymptomatic horseshoe tears in patients who need cataract surgery, in patients with aphakia or pseudophakia, and in patients who have retinal detachments in their



**Fig. 6.38.3 Symptomatic Operculated Hole.** (A) At presentation. (B) Immediately after laser treatment. (C) 1 month postoperatively. Operculum is best seen in part C.

### BOX 6.38.1 Differential Diagnosis of Retinal Breaks

- Pars plana cysts
- Enclosed oral bays
- Meridional folds/complexes
- Ora serrata pearls
- Granular tags
- Paving stone degeneration
- Chorioretinal scars
- Peripheral cystoid degeneration
- White with/without pressure
- Retinal erosions
- Vitreous condensation

fellow eye.<sup>17-19</sup> In general, because of the increased incidence of detachment in these scenarios, strong consideration should be given to prophylaxis in these cases.

Retinal dialyses, whether traumatic or idiopathic, have a high association with the development of retinal detachment. In these cases, prophylaxis is usually indicated.

Asymptomatic holes in lattice degeneration rarely lead to detachment and usually receive no prophylaxis.<sup>20</sup> However, retinal tears at the margin of lattice degeneration, particularly in symptomatic eyes, are more likely to result in the development of a retinal detachment and require prophylactic therapy. Prophylactic treatment should be considered in patients with lattice degeneration who have had a retinal detachment in the fellow eye.

### Cryopexy

Cryotherapy is delivered transconjunctivally. It destroys the choriocapillaris, RPE, and outer retina to provide a chorioretinal adhesion between the tear and the adjacent retina, thus preventing liquid vitreous access through the hole and into the subretinal space. The adhesion with cryotherapy is not immediate; a period of 1 week is required to achieve partial adhesion and up to 3 weeks for the full adhesive effects to occur.

Under indirect ophthalmoscopic visualization, the cryoprobe is placed on the conjunctiva that overlies the break, and cryotherapy is delivered until the retina adjacent to the tear becomes gray-white. Approximately 2 mm of retinal whitening should be obtained around the entire break. Applications are placed until the break is surrounded completely with confluent treatment (see Figs. 6.38.1 and 6.38.2). In horseshoe tears, the anterior retina between the tear and the ora serrata should be treated, as anterior extension of the tear secondary to continuous vitreous traction can lead to retinal detachment. Cryopexy can be delivered adequately despite the presence of extensive cataract, anterior or posterior capsular opacity, or relatively dense vitreous hemorrhage.

### Photocoagulation

Laser photocoagulation treatment of retinal breaks typically utilizes the argon green or diode laser. Two main delivery systems are used: the slit lamp and the indirect ophthalmoscope. In contrast to cryotherapy, chorioretinal adhesion occurs the instant that the laser photocoagulation is applied, but maximal adhesion occurs 7–10 days later.

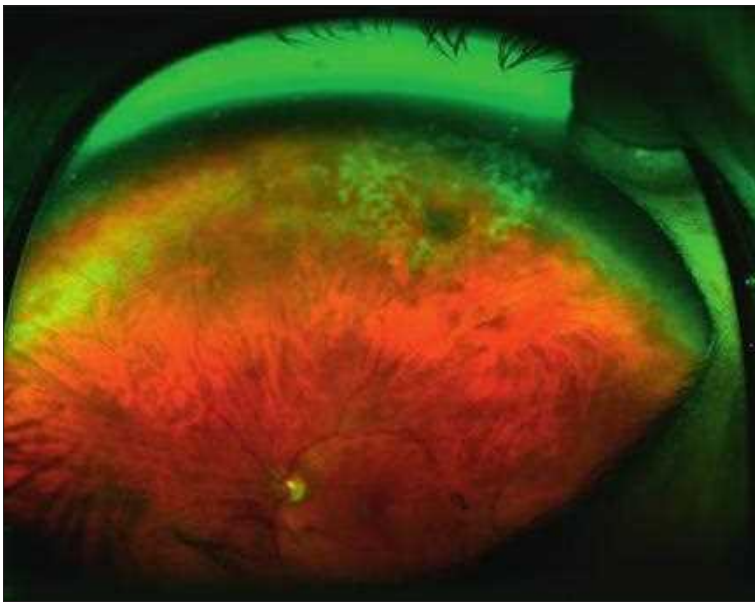
The Goldmann three-mirror lens or panfunduscope lens is used when treatment is with slit-lamp delivery. The tear should be surrounded completely by 3–4 rows of laser burns. Although the spots need not be confluent, there should be no more than half a spot size of untreated retina between burns. Typically, the settings are 200–500 mm spot size and 0.1–0.2 second application at the power necessary to generate a gray-white burn. Treatment with the diode laser with long duration and larger spot size can be successfully utilized.<sup>21,22</sup> The indirect laser delivery system can also be used to treat retinal breaks (Fig. 6.38.4). An advantage of this technique is that simultaneous scleral depression allows treatment of anterior tears and even dialysis.

As with cryopexy, care should be taken to thoroughly treat the anterior margin of horseshoe tears to prevent anterior traction that reopens the break.

### Anesthesia

Eyes that undergo laser photocoagulation can often be treated with topical anesthesia alone. If multiple large breaks are present and the patient is





**Fig. 6.38.4** Wide angle fundus imaging showing retinal tear immediately after laser retinopexy.

unable to tolerate the treatment, retrobulbar anesthesia may facilitate completion of the procedure. In patients treated with transconjunctival cryotherapy or indirect laser photocoagulation with scleral depression, topical anesthesia may be supplemented with placing cotton-tipped applicators soaked in 4% lidocaine on the conjunctiva that overlies the retinal breaks. In some cases, 2% lidocaine injection subconjunctivally via a 30-gauge needle may be necessary.

## COURSE AND OUTCOME

The eye is typically examined a few weeks following treatment. Although vigorous patient activity is often discouraged initially, no clinical study has documented that diminished activity improves treatment results. A firm chorioretinal adhesion is present by 3 weeks after either technique.

Failure rates for prophylactically treated retinal breaks depend on many factors, which include the type of retinal break, indications for treatment,

length of follow-up, and definition of failure. Reported failure rates range from 0%–22%.<sup>23,24</sup> In one large series of prophylactically treated retinal breaks, 22% of eyes required an additional procedure to prevent or repair a retinal detachment.<sup>24</sup> Risk factors for failure in this series included aphakic or pseudophakic status, acute symptoms, retinal detachment in the fellow eye, and male gender.

Epiretinal membrane and macular pucker are other visually significant complications associated with prophylactic treatment of a retinal break; they occur in 1%–5% of treated eyes.<sup>24,25</sup> As epiretinal membranes occur in eyes that have retinal breaks and receive no treatment, it is not entirely clear whether the macular pucker is exacerbated by the treatment modality or is solely a result of the disease process itself.

More rare complications that can occur include Adie's pupil, subretinal and vitreous hemorrhage, and breaks in Bruch's membrane. An exceedingly rare but potentially devastating complication of cryotherapy in patients who have staphylomatous sclera is scleral rupture.

In eyes that fail prophylactic therapy, retinal detachment repair by pneumatic retinopexy, scleral buckling, or vitrectomy is usually successful in the anatomic reattachment of the retina.

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# Rhegmatogenous Retinal Detachment

Vishal S. Parikh, Rajesh C. Rao, Gaurav K. Shah

# 6.39



IN THIS CHAPTER  
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**Definition:** Separation of the neural retina from the underlying retinal pigment epithelium (RPE) as a result of vitreous passing through a retinal defect into the subretinal space.

## Key Features

- Elevation and separation of the neural retina from the underlying RPE.
- One or more retinal breaks (holes, tears, or dialyses).

## Associated Features

- Vitreous liquefaction.
- Posterior vitreous detachment ("complete" or partial).
- Vitreoretinal traction.
- Vitreous cells (pigment and/or hemorrhage).
- Flashes (photopsia) and floaters.
- Scotoma corresponding to the area of retinal elevation.

## INTRODUCTION

Rhegmatogenous retinal detachment (RRD) is an important cause of visual disability. Untreated, symptomatic RRDs generally progress to total blindness. Prompt recognition of the associated symptoms helps ensure timely treatment and sustain useful vision. Environmental and hereditary factors play significant roles in RRD development. Knowledge of these diverse features helps identify high-risk patients.

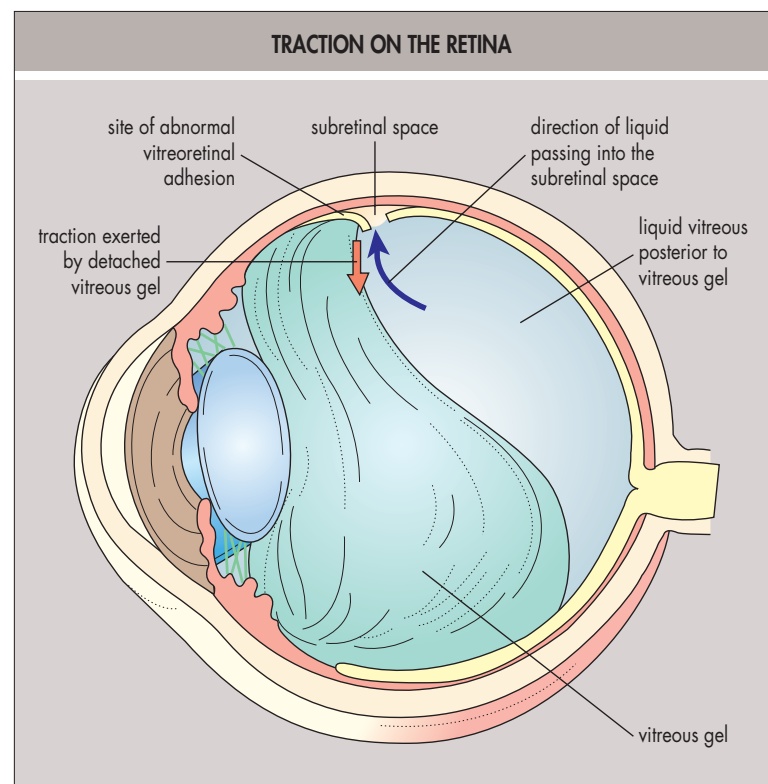
## EPIDEMIOLOGY AND PATHOGENESIS

The incidence of RRD ranges from 5.3–12.6 cases per 100 000.<sup>1</sup> RRD is defined as egress of vitreous into the potential subretinal space between the neural retina and the RPE via a retinal break (rhegma = rent or rupture). Pathogenesis of this entity arises from vitreous collapse (syneresis) and liquefaction (synchysis) as a result of degenerative changes in the collagen fibril-hyaluronan matrix, which leads to posterior vitreous detachment (PVD) and focal retinal traction.<sup>2</sup> Vitreous traction can produce retinal breaks, most commonly in the peripheral retina, where the vitreous base remains most adherent to retina (Fig. 6.39.1). Liquefied vitreous migrates from the intravitreal cavity to dissect into the subretinal space, causing scotomata. Fluid currents related to eye movements can extend the detachment into the macula, leading to central vision loss, the main morbidity associated with RRD.

## Factors Causing Retinal Detachment

Vitreous syneresis, synchysis, and PVD are the chief factors in RRD; indeed, conditions in which these events occur prematurely are associated with a higher risk of RRD. However, the majority of eyes with retinal breaks do not develop retinal detachment because normal physiological forces keep the retina in place. Retinal attachment is maintained by the following<sup>3</sup>:

- An interphotoreceptor matrix in the subretinal space.
- Oncotic pressure differences between the choroid and subretinal space.
- Hydrostatic or hydraulic forces related to intraocular pressure.
- Metabolic transfer of ions and fluid by the RPE.



**Fig. 6.39.1 Classic Pathogenesis of Rhegmatogenous Retinal Detachment (RRD).** The detached vitreous gel has caused a retinal tear by exerting traction on the retina at the site of a vitreoretinal adhesion. Liquid in the vitreous cavity passes through the break into the subretinal space. (Courtesy Charles P. Wilkinson.)

Retinal detachment occurs when the combination of factors that promote retinal detachment overwhelms the normal attachment forces.

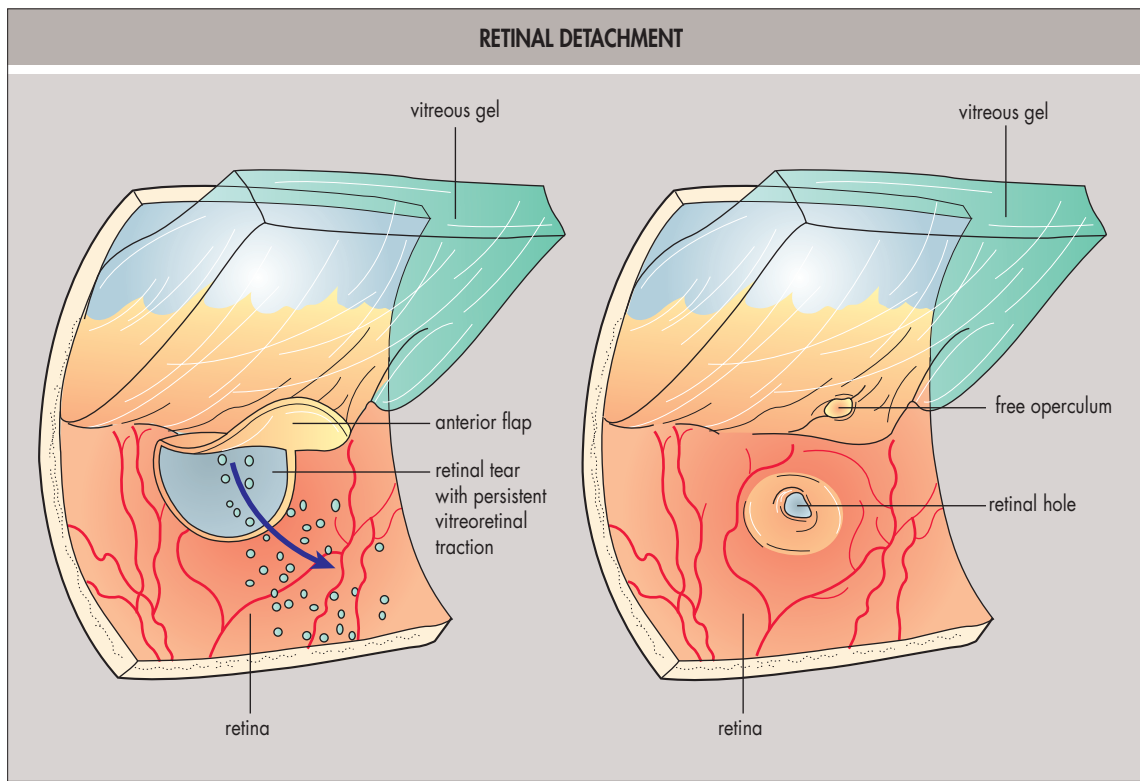
## Retinal Breaks

The nature of the vitreoretinal adhesion associated with the retinal break remains the principal consideration in determining progression to RRD and choice of treatment. A retinal hole is a round, full-thickness defect. In this case, vitreoretinal traction is generally relieved, sometimes in the presence of an overlying operculum. A retinal hole is less likely to progress to a RRD and is generally observed (Fig. 6.39.2). A full-thickness retinal break with persistent vitreoretinal traction, such as a retinal flap tear, is more likely to progress to RRD and is generally treated with laser or cryoretinopexy (see Fig. 6.39.2).

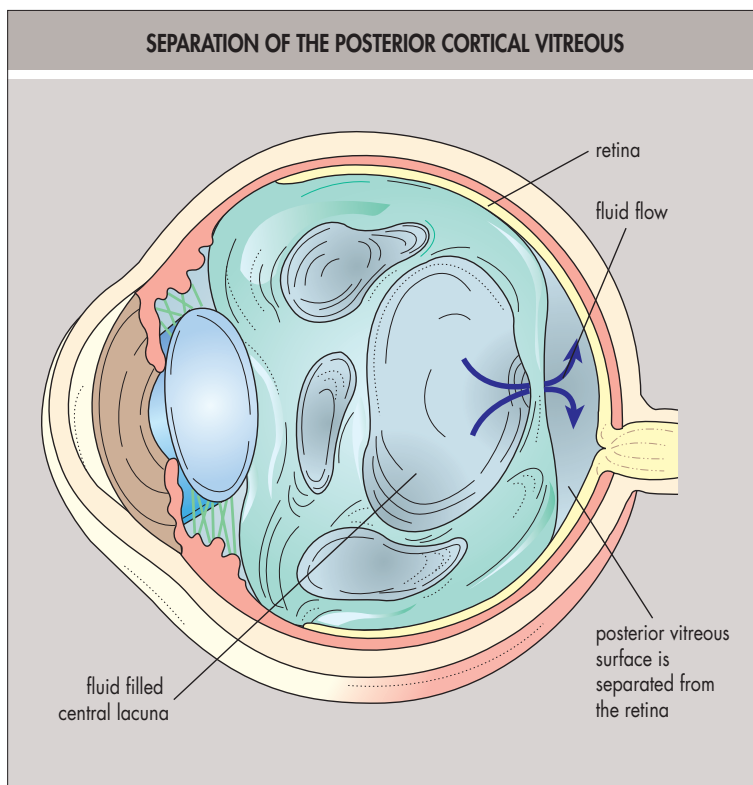
Dialyses are linear or circumferential retinal breaks that occur along the ora serrata. Although most are associated with blunt ocular trauma, dialyses can occur spontaneously.

## Vitreous Liquefaction and Detachment

The degeneration of the collagen-hyaluronan matrix of the vitreous results in liquefaction at multiple sites, forming lacunae. Progressive liquefaction, shrinkage, and coalescence of lacunae eventually lead to vitreous collapse



**Fig. 6.39.2 Retinal Detachment.** Retinal tears are caused by vitreoretinal traction. Persistent traction frequently causes extensive retinal detachment (on left). If the traction results in a break that is not associated with persistent vitreoretinal traction (on right), the tear acts as a retinal hole and detachment is quite unlikely. (Courtesy Charles P. Wilkinson.)



**Fig. 6.39.3 Separation of the Posterior Cortical Vitreous.** An acute event, posterior vitreous detachment usually begins with an apparent break in the cortical vitreous that overlies the macula. Fluid from a central lacuna flows through this hole and separates the cortical vitreous from the retina. (Courtesy Charles P. Wilkinson.)

and, in turn, to PVD. Intravitreal fluid then egresses from lacunae to fill the potential space between the posterior vitreous and retinal surface (Fig. 6.39.3). Interestingly, some authorities consider PVD to actually be vitreous schisis because cortical vitreous often remains adherent to the retina.<sup>4</sup> The mechanism of progression of a partial PVD to a “complete PVD” (vitreous attached only at the vitreous base) is not fully understood, but it can be rapid (within several weeks). Regardless of the type of separation, the vitreous exerts asymmetrical tractional forces at regions where vitreous is most adherent, such as the vitreous base, a common site for formation

of retinal breaks. Conditions associated with early vitreous liquefaction and detachment, such as pathological myopia, surgical and nonsurgical trauma, intraocular inflammation, and a variety of other congenital, inherited, or acquired ocular disorders, are associated with a higher risk of RRD.

### Traction on the Retina

The mechanisms of vitreoretinal traction vary. Progressive syneresis can cause shrinkage and collapse of the gel with accompanying traction at points of contact with the retinal surface, causing full-thickness retinal breaks and entry points for subretinal egress of intravitreal fluid. Rotational and saccadic eye movements may also play a role.<sup>5</sup> When the eye rotates, the inertia of the detached vitreous gel causes it to lag behind the rotation of the eye wall and the attached retina. The vitreous gel, because of its inertia, exerts an equal and opposite force on the retina, which can cause a retinal break or separate the neural retina farther from the pigment epithelium if subretinal fluid is already present (Fig. 6.39.4). At areas where vitreous remains attached to the retina, such as a horseshoe tear flap at the vitreous base, eye movements allow asymmetrical traction at the flap, holding it “open” while liquefied vitreous migrates into the subretinal space, allowing enlargement of retinal detachment (Fig. 6.39.5). When the rotational eye movement stops, the vitreous gel continues its internal movement and exerts vitreoretinal traction in the opposite direction.

In combined, tractional–RRDs, contractile fibrovascular membranes that occur in uveitic disorders, trauma, retinopathy of prematurity, proliferative diabetic retinopathy, retinovascular disorders, and other ischemic retinopathies, can create a retinal break.

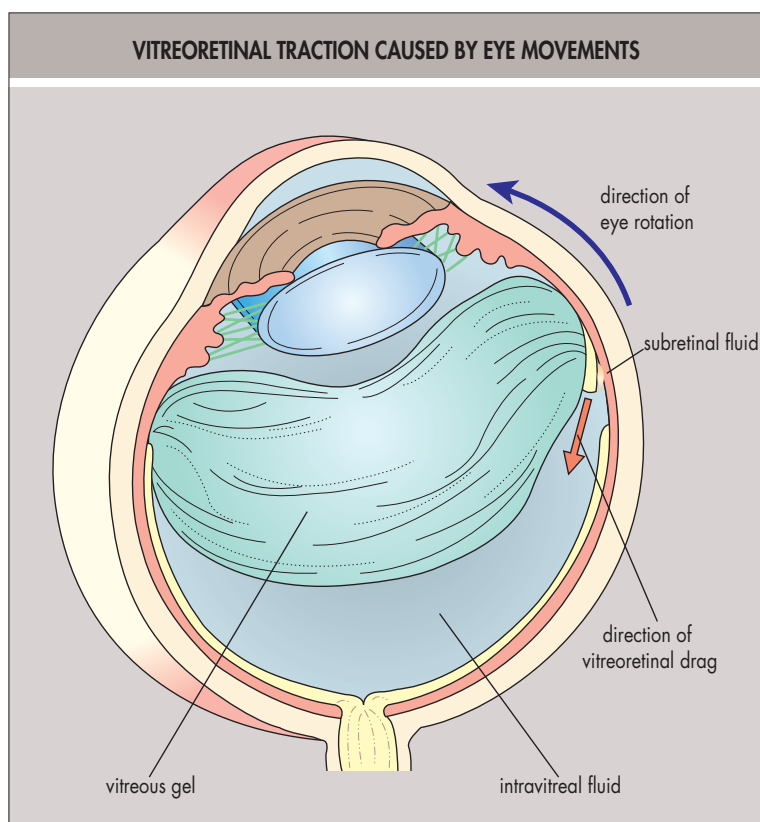
### Liquid Currents

The development of an RRD requires that fluid flow into the subretinal space overwhelm the capacity of the RPE to pump fluid from this potential space. Rotary eye movements coupled with the viscosity and inertial quality of the subretinal fluid can cause further extension of the retinal detachment (Fig. 6.39.6).

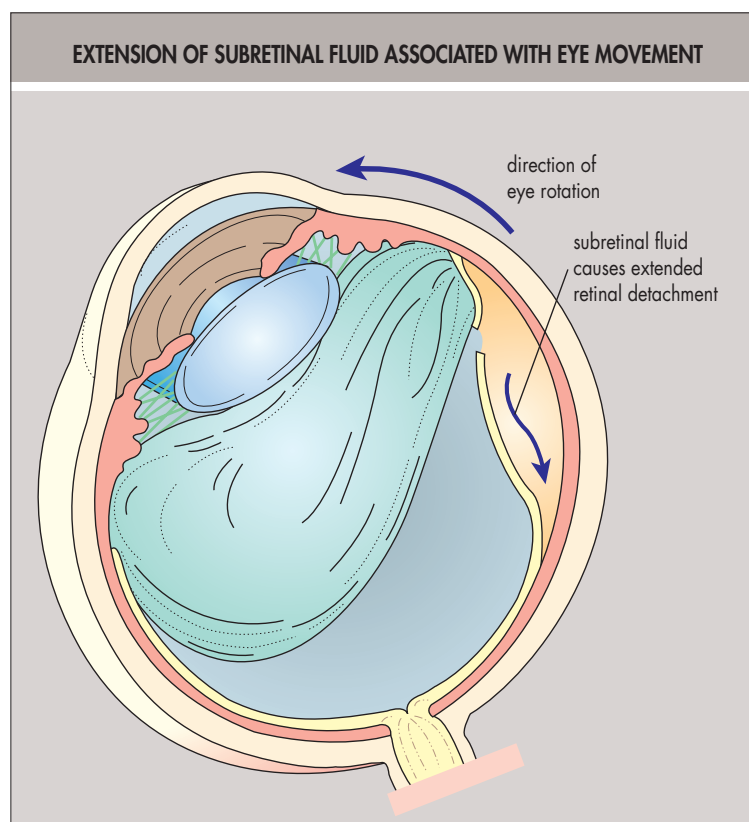
## Conditions Predisposing an Eye to Retinal Detachment

Although uncommon in the general population, RRDs occur with higher frequency in a variety of conditions associated with early PVDs: pseudo-phakia, aphakia, high myopia ( $>-6.00$  diopters [D]), and hereditary collagen–vascular disorders, such as Stickler’s and Marfan’s syndromes. Other causes of RRDs, not necessarily related to premature PVD development, include proliferative retinopathy (breaks caused secondarily by

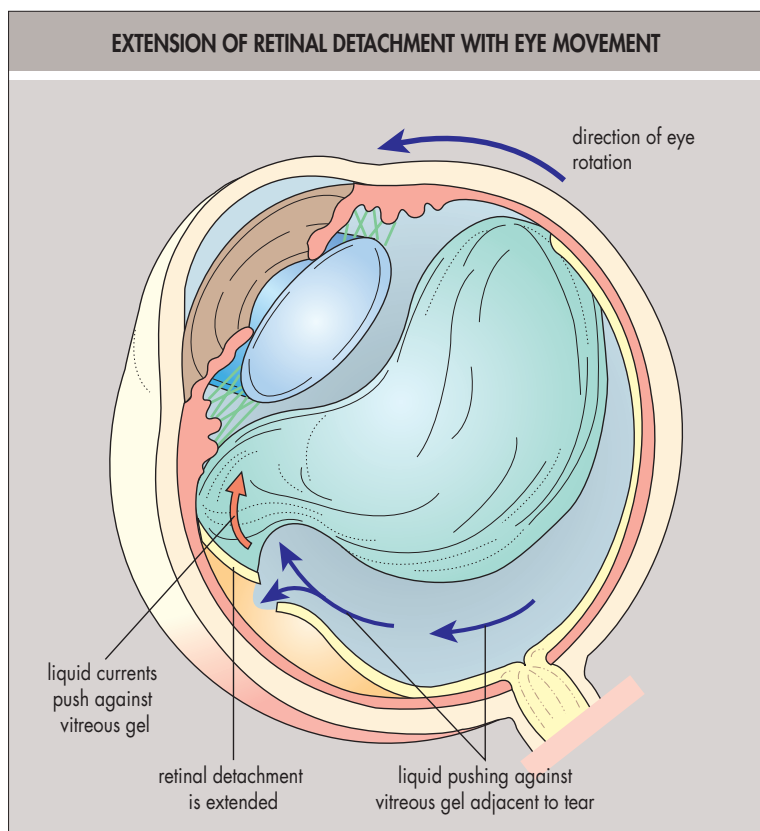




**Fig. 6.39.4 Vitreoretinal Traction Caused by Eye Movements.** When the eye rotates, the inertia of the vitreous gel causes it to lag behind the eye movement, which effectively causes vitreoretinal traction (“drag”) in the opposite direction and the production of a retinal tear, with a small amount of associated subretinal fluid. (Courtesy Charles P. Wilkinson.)



**Fig. 6.39.6 Extension of Subretinal Fluid Associated With Eye Movements.** In addition to exacerbating vitreoretinal traction, rotary eye movements have an inertia effect on subretinal fluid that causes it to dissect further between the retina and pigment epithelium. (Courtesy Charles P. Wilkinson.)



**Fig. 6.39.5 Extension of Retinal Detachment Associated With Eye Movements.** Rotary eye movement causes movement of the vitreous gel, which increases traction on the retinal break. In addition, liquid currents dissect beneath the edge of the retinal tear and push against the vitreous gel adjacent to the tear. All three factors promote extension of the retinal detachment. (Courtesy Charles P. Wilkinson.)

contractile tractional membranes), trauma, and viral retinitis associated with immunodeficiency.

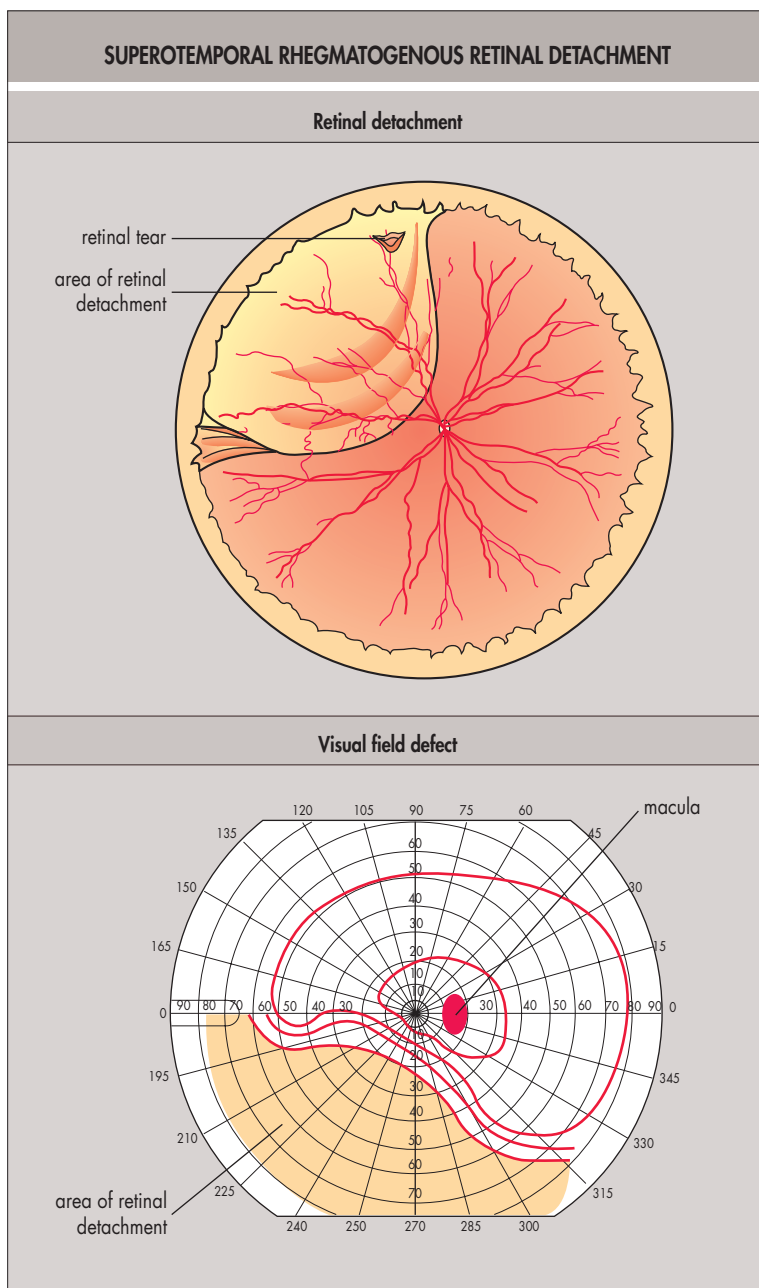
Up to 40% of eyes with retinal detachment have had prior cataract surgery, even though risk of RRD after cataract extraction is approximately 0.7%.<sup>6</sup> Among this population with pseudo-phakia, patients who are male, of younger age, and experience intraoperative posterior capsular rupture carry a higher risk of RRD.<sup>7</sup> Crystalline lens extraction is believed to increase the risk of retinal detachment as a result of early induction of PVD. Although the status of the posterior capsule has been considered a factor in RRD development, especially with regard to neodymium:yttrium–aluminum–garnet (Nd:YAG) laser capsulotomy, various studies have reported mixed conclusions.<sup>8,9</sup>

Risk factors for retinal detachment are not mutually exclusive and may be additive. For example, prior cataract extraction and nonsurgical trauma are more likely to be complicated by retinal detachment in myopic eyes. Pathological vitreoretinal changes often occur bilaterally—patients who have a retinal detachment in one eye have a significantly increased risk of retinal detachment in the fellow eye, provided that additional acquired risk factors are comparable. There is conflicting evidence regarding an association between the use of oral fluoroquinolones, an antibiotic linked to tendon rupture secondary to collagen degeneration, and RRD development.<sup>10-12</sup>

## OCULAR MANIFESTATIONS

The early symptoms of RRD remain indistinguishable from acute PVD: sudden appearance of floaters, frequently associated with fleeting photopias (flashes). These symptoms are more noticeable in the dark and following rotary eye movements. Subclinical RRDs can be asymptomatic and are associated with limited dissection of subretinal fluid (<2 disc diameters from the break). Rarely, but especially in young patients with myopia, slowly progressive asymptomatic retinal detachments develop without PVD. This most commonly occurs temporally and inferiorly and secondary to atrophic holes in lattice degeneration.<sup>9</sup>

Because of the persistent attachment of vitreous at the vitreous base after PVD, most retinal breaks occur anteriorly. The accumulation of subretinal fluid produces relative scotomata, which, when the detachment progresses posterior to the equator, can be symptomatic with loss of



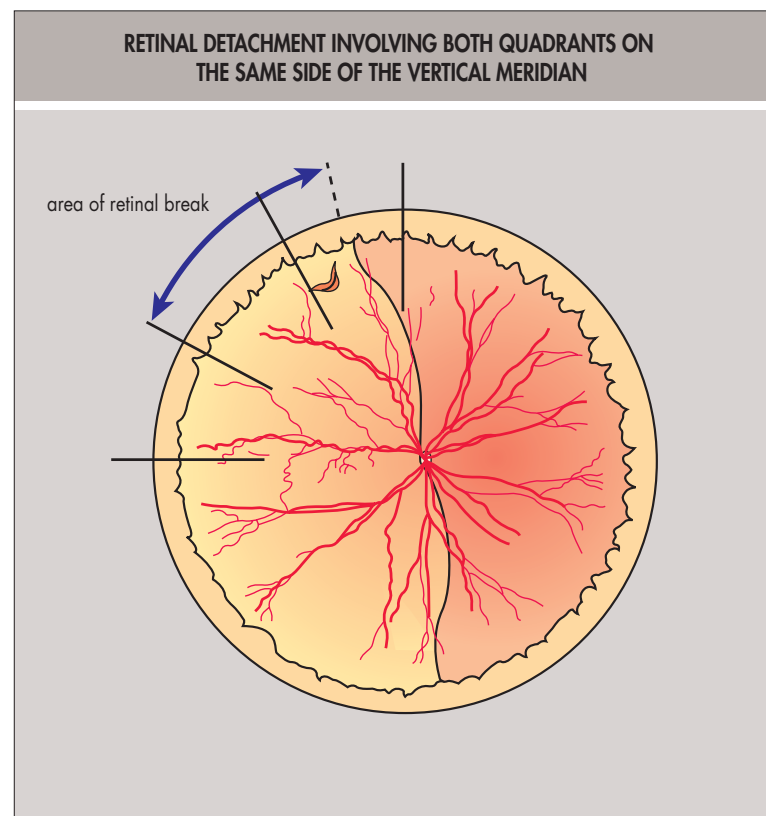
**Fig. 6.39.7 Superotemporal Rhegmatogenous Retinal Detachment (RRD).** The neural retina is elevated in the area of detachment and the macula remains uninvolved. Visual field defect associated with retinal detachment shows that peripheral vision is lost inferonasally, corresponding to the area of detachment. The visual defect is an inverted image of the retinal detachment. (Courtesy Charles P. Wilkinson.)

peripheral vision, producing the sensation of a “curtain falling” over the visual field (Fig. 6.39.7). Central visual acuity is lost when subretinal fluid passes beneath the macula. Frequently, patients do not notice any symptoms until the macula becomes involved.

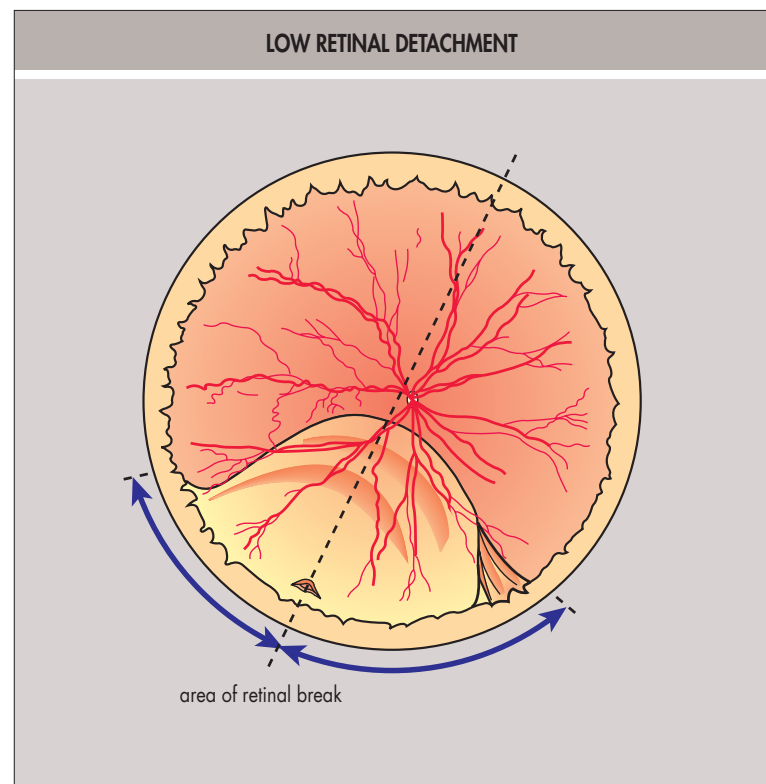
The location of the RRD generally predicts the most likely locations of the retinal break(s).<sup>13</sup> Retinal breaks are usually present superiorly within the area of detachment (Fig. 6.39.8). Retinal detachments that involve the inferior quadrants tend to follow the same rules, but the progression of the detachment is often much slower, and symmetrical spread of subretinal fluid may occur on both sides of the break. Therefore, detachments that involve one or both inferior quadrants may have a break near a superior margin of the detachment or in the meridian that bisects the area of detachment (Fig. 6.39.9).

## DIAGNOSIS

The majority of causative retinal breaks associated with RRD are found by binocular stereoscopic examination of the entire retina, with scleral indentation of the peripheral retina. Areas of retinal detachment are recognized by elevation of the neural retina from the RPE and loss of pigment epithelial and choroidal detail beneath the elevated retina (Fig. 6.39.10). In

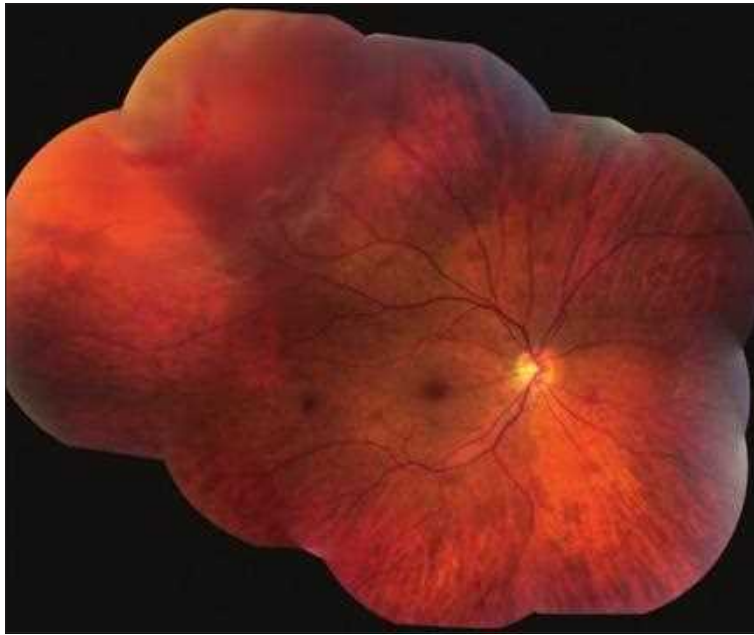


**Fig. 6.39.8 Location of the Retinal Break.** Retinal detachments that involve both quadrants on the same side of the vertical meridian are usually caused by a retinal break within 1–1.5 clock hours of the superior margin of the detachment. (Courtesy Charles P. Wilkinson.)



**Fig. 6.39.9 Location of the Retinal Break.** Retinal detachments that involve both lower quadrants but extend farther superiorly on one side are usually caused by a retinal break within 1–1.5 clock hours of the superior margin of the retinal detachment or by a break in a meridian that bisects the margins of the retinal detachment. (Courtesy Charles P. Wilkinson.)

pseudo-phakic RRD, all breaks may not be visible because of very small tears; and adjunctive treatment maneuvers may be employed at the time of RRD repair (e.g., 360° circumferential laser retinopexy). In eyes with opaque media, the presence of a retinal detachment is usually determined ultrasonographically; the location and identification of the causative retinal



**Fig. 6.39.10 Rhegmatogenous Retinal Detachment (RRD).** There is full-thickness retinal break in the superior temporal retina associated with RRD. The subretinal fluid makes visualization of the pigment epithelium and choroid relatively difficult.

#### BOX 6.39.1 Differential Diagnosis of Rhegmatogenous Retinal Detachment

##### Traction Retinal Detachment

- Proliferative diabetic and other retinopathies
- After penetrating trauma

##### Exudative Retinal Detachment

- Inflammatory disorders
- Choroidal neoplasms
- Retinal vascular tumors and other disorders

##### Retinoschisis

- Age-related
- Congenital gender-linked

##### Elevated Choroidal Lesions

- Choroidal detachments
- Choroidal tumors

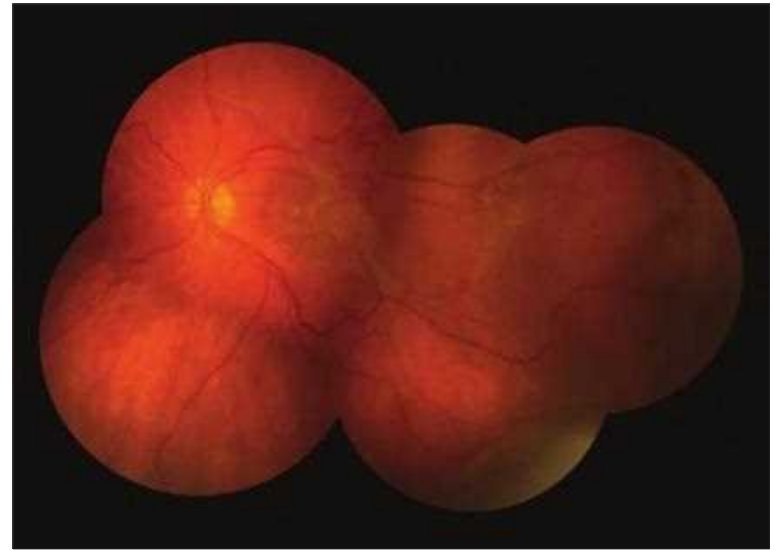
##### Vitreous Hemorrhage

breaks are based on the configuration of the detachment as well as on the patient's history and associated findings.

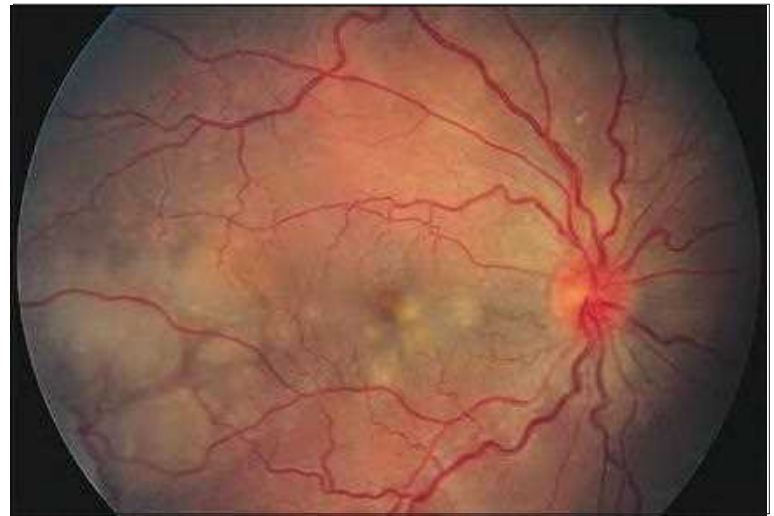
## DIFFERENTIAL DIAGNOSIS

RRDs must be distinguished from serous or tractional retinal detachments and retinoschisis (Box 6.39.1). Choroidal lesions that elevate the overlying retina and intravitreal pathology that simulates an elevated retina may also be confused with retinal detachment.

The distinction between different types of retinal detachment can be difficult in eyes with small or undetectable retinal breaks, opaque media, and features associated with intraocular proliferation or exudation. In some cases, a combined mechanism that involves both rhegmatogenous and traction components, or an exudative component may be a clue to the pathogenesis of the detachment. This is particularly common in eyes with proliferative diabetic retinopathy and retinal detachment. Traction detachments usually have a concave surface, and the shape, location, and extent of the detachment can be accounted for by the evident vitreous traction (Fig. 6.39.11). Exudative detachments from a variety of causes are characterized by shifting subretinal fluid, which assumes a dependent position beneath the retina. In most cases, the fluid is located inferiorly and its cause within or beneath the retina may be apparent (Fig. 6.39.12) or quite subtle. Retinoschisis tends to have a smooth, noncorrugated, bullous appearance that may be associated with inner and outer retinal holes.



**Fig. 6.39.11 Traction Retinal Detachment.** The central and temporal areas of retinal elevation are caused by areas of visible vitreoretinal traction associated with proliferative vitreoretinopathy. The traction of the epiretinal membranes has caused a full thickness break (rhegmatogenous component) at the temporal periphery.



**Fig. 6.39.12 Exudative Retinal Detachment.** The small amounts of subretinal fluid (note the retinal striae) are due to leakage from an inflammatory process that involves the choroid and retinal pigment epithelium. (Courtesy Charles P. Wilkinson.)

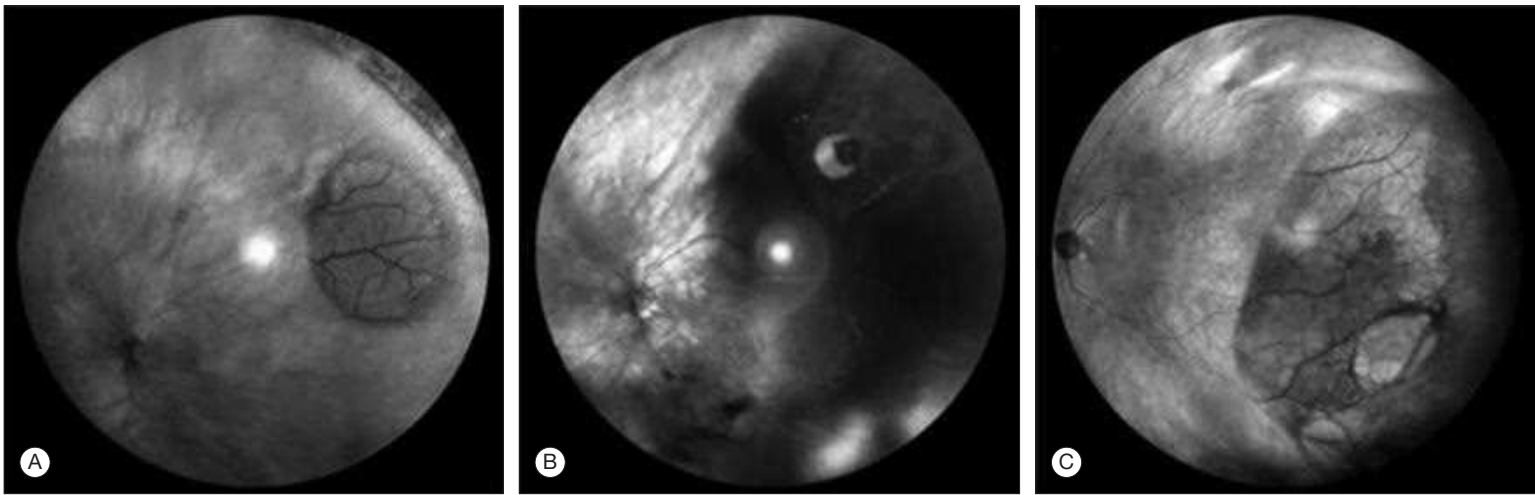
Although typically observed, retinoschisis with an outer retinal hole may lead to a true retinal detachment that requires treatment. In chronic cases, a demarcation pigment line suggests the presence of fluid egress via an outer wall hole into the subretinal space, creating a detachment. Wide-field infrared imaging can aid in differentiating retinoschisis, RRDs, and combined retinoschisis/RRDs (Fig. 6.39.13).<sup>14</sup>

## PATHOLOGY

Retinal breaks, liquefaction and collapse of the vitreous gel, and visible vitreoretinal adhesions have been well documented histopathologically. Nutrition of the outer retina is lost during retinal detachment, so the first visible pathological retinal changes occur in the outer segments of the photoreceptors.<sup>15</sup> Optical coherence tomography (OCT) images of the macula in patients with macula-off RRDs confirm the aforementioned retinal changes in vivo with loss of the photoreceptor inner and outer segment (IS/OS) junction.<sup>16</sup> Long-standing retinal detachments are associated with further atrophy of the photoreceptor layer, intraretinal cystic degeneration, pre- and subretinal cysts, and membrane formation. Photoreceptor outer segments from RRD have been identified in the aqueous fluid and irido-corneal angle and can lead to glaucoma.<sup>17</sup>

Successfully repaired retinal detachments show a variety of histopathological abnormalities. There is a high incidence of epiretinal membrane (ERM) formation.<sup>18,19</sup> Cystoid macular edema is common as well, along with significant photoreceptor atrophy in many eyes.





**Fig. 6.39.13 Wide-Field Infrared Imaging of Retinoschisis Versus Rhegmatogenous Retinal Detachment (RRD).** (A) Retinoschisis appears light and translucent with prominent vasculature. (B) RRDs appear dark and opaque. (C) Combined retinoschisis/RRDs exhibit mixed reflectivity patterns.

### BOX 6.39.2 Options for the Management of Primary Retinal Detachment

- Observation (very rarely employed)
- Laser demarcation
- Permanent scleral buckling
  - Encircling with/without drainage
  - Segmental with/without drainage
- Temporary scleral buckling
  - Lincoff balloon
  - Absorbable buckling materials
- Pneumatic retinopexy
  - Routine
  - With drainage of subretinal fluid or intravitreal liquid
- Primary vitrectomy
- Combinations of the above techniques

## TREATMENT

The aim of retinal detachment therapy is to counter the factors and forces that cause retinal detachment and to re-establish the physiological conditions that normally maintain contact between the neural retina and pigment epithelium. The main goal of surgery (i.e., to close each retinal break) is usually sufficient to reattach the retina. Long-term closure of retinal breaks may also require permanent reduction or elimination of vitreoretinal traction, accompanied by maneuvers designed to offset the harmful effects of fluid currents in the vitreous cavity.

At present, many retinal surgeons continue to use scleral buckling techniques and the creation of a chorioretinal adhesion around each break to eliminate and counteract vitreoretinal traction, especially in younger patients without PVD (see Chapter 6.11). Vitrectomy techniques have emerged as the predominant approach in repair of pseudo-phakic RRD (see Chapter 6.12). A prospective clinical trial has demonstrated some benefit to visual acuity provided by scleral buckling versus vitrectomy in phakic RRDs, but vitrectomy has been shown to result in better anatomical success in pseudo-phakic RRDs.<sup>20</sup> As a result of advances in instrumentation, vitrectomy, with or without concurrent scleral buckling, continues to gain popularity. The use of primary scleral buckling (i.e., without concurrent vitrectomy) continues to decline because of lack of training in many vitreoretinal training fellowships. This approach, however, remains a useful and important procedure primarily in patients with phakia and a formed vitreous. Although earlier studies have shown a significant rate of strabismus and extrusion (e.g., as high as 24.4%), newer analyses have shown clear improvements in scleral buckling–associated morbidity.<sup>21, 22</sup> Pneumatic retinopexy is a third technique that is frequently employed in selected cases. Contemporary options in the management of RRD are listed in Box 6.39.2.

## COURSE AND OUTCOME

RRD was essentially untreatable until approximately 80 years ago. Surgical success rates have improved profoundly and are equally high and comparable for vitrectomy, scleral buckling, and a combined scleral buckling/vitrectomy.<sup>23</sup> A recent meta-analysis reported that combining scleral buckling and vitrectomy increases the rate of primary reattachment, but the final success rate for both procedures individually was equally high.<sup>24</sup> Pneumatic retinopexy can have a high surgical success rate, up to 82% with appropriate case selection and proper adherence to postoperative care by patients.<sup>25</sup> Approximately 95% of all retinal detachments can be successfully repaired (i.e., the retina is returned to its normal anatomical position with no residual subretinal fluid).

The three most common reasons for failure of retinal detachment surgery are as follows:

- Failure to identify and/or close all retinal breaks.
- New retinal breaks.
- Proliferative vitreoretinopathy.

The choice of the initial procedure determined the subsequent rate for secondary intervention, including silicone oil insertion and lensectomy. Recurrent retinal detachment that occurred after a primary scleral buckling procedure required, on average, one subsequent procedure, whereas eyes initially repaired with primary vitrectomy or scleral buckling combined with vitrectomy were associated with 1.5 subsequent procedures. The primary vitrectomy and combined scleral buckling–vitrectomy groups were also associated with lensectomy and silicone oil insertion.

Unfortunately, postoperative best-corrected visual acuity (BCVA) does not always correlate with the high rate of anatomical success of surgery. Postoperative BCVA is most dependent on the extent of damage to the macula caused by retinal detachment. If the macula is detached by subretinal fluid, some degree of permanent damage to vision usually occurs in spite of surgical reattachment. In eyes with a macula-on detachment, 73% can be expected to have postoperative  $\geq 20/40$  vision  $\geq 2$  months after surgery.<sup>26</sup> In eyes with a macula-off detachment, postoperative mean visual acuities depend on the duration of macular detachment (DMD), with acuity of  $\geq 20/40$  in 71% of eyes with DMD of  $\leq 10$  days, 27% of eyes with a DMD of 11 days to 6 weeks, and 14% of eyes with a DMD of  $> 6$  weeks.<sup>27</sup> OCT images of the macula in patients with macula-off RRDs confirm loss of the photoreceptor IS/OS junction compared with those in patients with macula-on detachments. In macula-off detachments, decrease in postoperative visual acuity correlates to loss of signal from the IS/OS and external limiting membrane.<sup>16</sup> Additional studies have suggested other metrics from OCT images, such as the integrity of the intermediate line and outer nuclear layer and presence of a foveal bulge, an increase in combine RPE–IS/OS junction thickness, may be important predictors of postoperative visual acuity after successful reattachment of the retina.<sup>28–30</sup>

Disappointing postoperative vision may also result from nonexclusive complications caused by the following:

- Subsequent reattachment surgery.
- Progressive ischemic or infectious retinal damage.
- Persistent subretinal fluid despite closure of all retinal breaks.<sup>31, 32</sup>



See clip:  
6.39.1

The most common of such entities, other than macular damage from the detachment, are cystoid macular edema (5%–10%) and postoperative ERM. Scleral buckling has been associated with a 3%–8.5% rate of postoperative ERM formation.<sup>33,34</sup> Postoperative ERM formation following vitrectomy has been estimated at 12.8%–34.3%; secondary surgery for subsequent ERM removal in these series ranged from 4.3%–9.4%.<sup>19,35</sup> The higher rate associated with vitrectomy may have resulted from enhanced intraocular liberation of membrane-forming elements, such as RPE, during retinotomy creation. Peeling the internal limiting membrane (ILM) during primary RRD detachment repair reduces the formation of postoperative ERM.<sup>19,36,37</sup> Previously, in retinal detachment secondary to proliferative vitreoretinopathy, a 27.3% rate of postoperative ERM was reduced to 0% after ILM peeling during primary RRD repair.<sup>19,38</sup> The technique of ILM peeling during primary RRD repair may appear challenging, but with the use of adjuncts, such as triamcinolone acetonide, fluid–fluid exchange through an existing break or a retinotomy site, and proper instrumentation, ILM can be stripped consistently in most cases (Video 6.39.1). Perfluorocarbon liquid can also be used to stabilize the macula to achieve safer ILM peeling.

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# Serous Detachments of the Neural Retina

6.40

Benjamin J. Thomas, Thomas A. Albini

**Definition:** An elevation of the neural retina caused by the accumulation of subretinal fluid in the absence of a retinal break or significant preretinal traction.

## Key Features

- Subretinal fluid that shifts with postural changes.
- Lack of rhegmatogenous or tractional component.
- Occurs secondary to local ocular or systemic etiology.

## Associated Features

- Involves a breakdown in the blood–retina barrier.
- Absence of retinal corrugations or fixed folds in the detached retina.
- Clear or lipid-rich exudate within the subretinal fluid.
- Presence of local ocular pathology or systemic disease associated with serous detachments.

## INTRODUCTION

Serous detachment of the neural retina, like its rhegmatogenous and tractional counterparts, represents a breakdown of the normal anatomical arrangement of the retina and its supporting tissues, causing accumulation of fluid between the neural retina and the retinal pigment epithelium (RPE). However, rather than resulting from a retinal break or traction on the retina, serous detachments stem from more subtle disruptions of the forces underlying the normal apposition of the retina, RPE, Bruch's membrane, and choroid.

Because any disruption can lead to accumulation of fluid in the subretinal space, the differential diagnosis for serous detachments is broad and heterogeneous, encompassing etiologies from choroidal neoplasms to congenital structural defects. Nonetheless, there are certain features that define all serous retinal detachments. These include accumulation of serous fluid (with or without associated exudates) in the subretinal space without an associated retinal tear or tractional membrane, a characteristic shifting of this fluid to a dependent position with postural changes, a smooth dome-shaped appearance of the detached retina that lacks corrugations or fixed folds, and the presence of associated systemic or local pathology.

## PATHOPHYSIOLOGY

Fully appreciating the means whereby serous detachments occur requires an understanding of the forces necessary to maintain retinal attachment. Consequent to the embryological development of the retina and the RPE, the adhesion of these two layers depends on the interdigitating processes of their apical surfaces and the surrounding extracellular matrix.<sup>1</sup> These adhesive forces are easily overcome if proper movement of fluid from the vitreous to the external layers of the posterior eye is disrupted. This movement begins from the vitreous to the RPE, where the resistance provided by an intact retina helps “push” the retina down onto the choroid and limits the amount of fluid being presented in the subretinal space (see Chapter 6.1). Next, the RPE, through a system of adenosine triphosphate-driven pumps, moves solute and fluid from the subretinal space into

the underlying choroid.<sup>2</sup> Reflux of fluid is minimized by tight junctions between RPE cells. The choroid, which is both highly vascular and highly permeable, employs both hydrostatic and osmotic forces to “pull” fluid through the RPE and out through the venous drainage, effectively creating a vacuum to pull the retina into apposition with the RPE. Finally, any fluid that cannot be removed by way of the choroid escapes through the sclera, completing internal to external fluidic movement.<sup>1</sup>

Serous detachments occur when this fluid movement through the choroid is misdirected or inhibited, as when choroidal neoplasms disrupt choroidal fluidics, or changes in the scleral thickness, as can occur in nanophthalmos, decrease fluid outflow. Further, any disruption of the RPE, or its active transport, will lead to fluid accumulation in the subretinal space. Taken together, these three mechanisms—alterations in choroidal flow, poor scleral outflow, and breakdown of the RPE—serve as convenient headings for the grouping of the various etiologies that lead to serous retinal detachments and will be treated in this order.

## ALTERATIONS IN CHOROIDAL FLOW

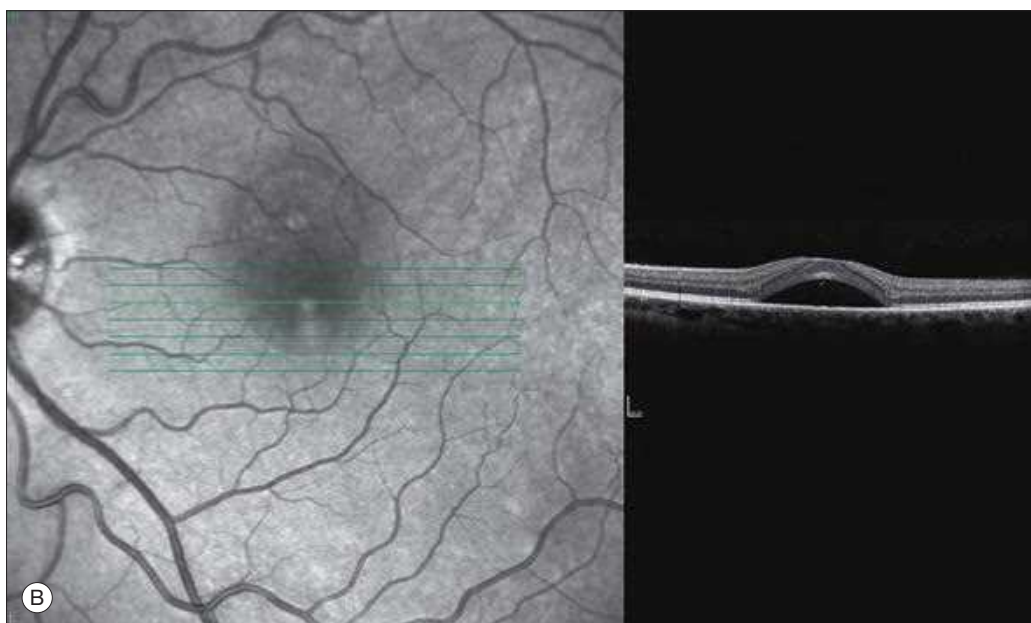
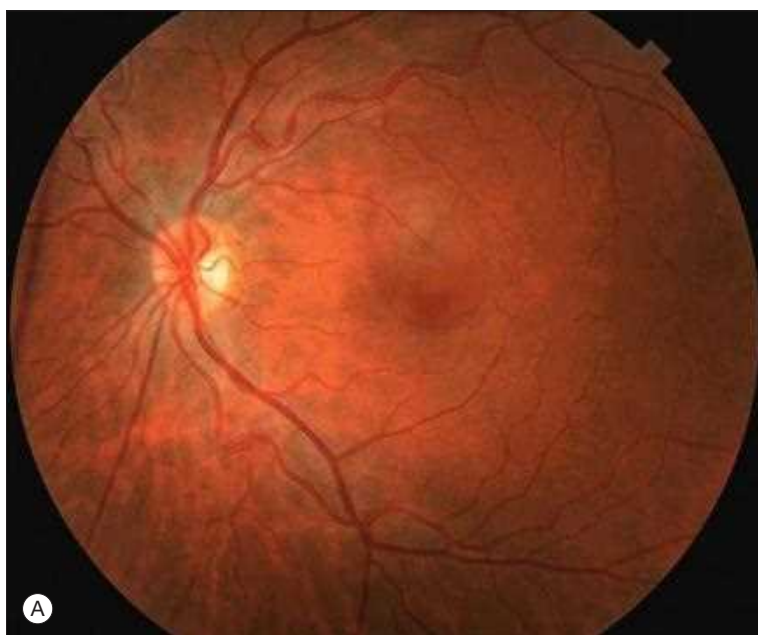
### Idiopathic Central Serous Chorioretinopathy

One of the more commonly seen etiologies of serous retinal detachment is idiopathic central serous chorioretinopathy (ICSC), which often affects young, otherwise healthy individuals in the third to fourth decade of life. A significant male predominance exists, and there is likely an association with both type A personalities and patients using exogenous corticosteroids. Pregnancy also carries an increased risk of ICSC (Fig. 6.40.1).<sup>3</sup> These patients experience decreased vision, metamorphopsia, and decreased color vision, and although spontaneous return of vision is common, long-term dysphotopsias are a frequent complaint.

In ICSC, fluorescein angiography (FA) reveals defects in the integrity of the RPE, most commonly as an “expansile dot” of leakage or, classically, a “smokestack” pattern of focal leakage. Late pooling within the areas of retinal detachment is also seen. Additionally, two other forms of ICSC have been reported: a chronic form, also known as *diffuse retinal pigment epitheliopathy*, and a more bullous form, which often manifests in the inferior retina.<sup>1</sup>

Debate continues as to whether ICSC is primarily a defect of the RPE or the choroid. The primary finding on FA is a focal loss of integrity of the RPE; however, more recent studies using indocyanine green angiography (ICGA) have shown that underlying these focal RPE defects are areas of choroidal hyperpermeability, seen in the middle phases of angiography. Observation of hyperpermeable choroid, interspersed with areas of delayed filling, has led some researchers to propose a pathological mechanism of primary choroidal vasculopathy or thrombosis, perhaps leading to focal RPE defects and subsequent overlying retinal detachment. This theory implicates a thrombotic mechanism leading to focal disruption or necrosis of the RPE and may represent a pathological mechanism similar to that which produces serous retinal detachments in some diseases, such as immunoglobulin A nephropathy, type II glomerulonephritis, and cryoglobulinemia.<sup>2</sup>

Treatment has traditionally been observation, as most cases resolve spontaneously. However, in atypical or recurrent cases, or in rare cases with associated choroidal neovascularization, one can consider focal laser photocoagulation or anti-vascular endothelial growth factor (VEGF). In addition, reduced fluence photodynamic therapy (PDT) with verteporfin has been employed, most commonly for the chronic form of ICSC.<sup>3</sup> Finally, oral agents that block aldosterone, primarily spironolactone



**Fig. 6.40.1** A 21-Year-Old Woman in the Third Trimester of Pregnancy With Acute Idiopathic Central Serous Chorioretinopathy in the Left Eye. (A) Fundus photo shows area of neurosensory detachment superior to and involving fovea. (B) Optical coherence tomography (OCT) confirms subfoveal fluid.

and eplerenone, have demonstrated reductions in subretinal fluid and improved visual acuity.

## Tumors of the Choroid and Retina

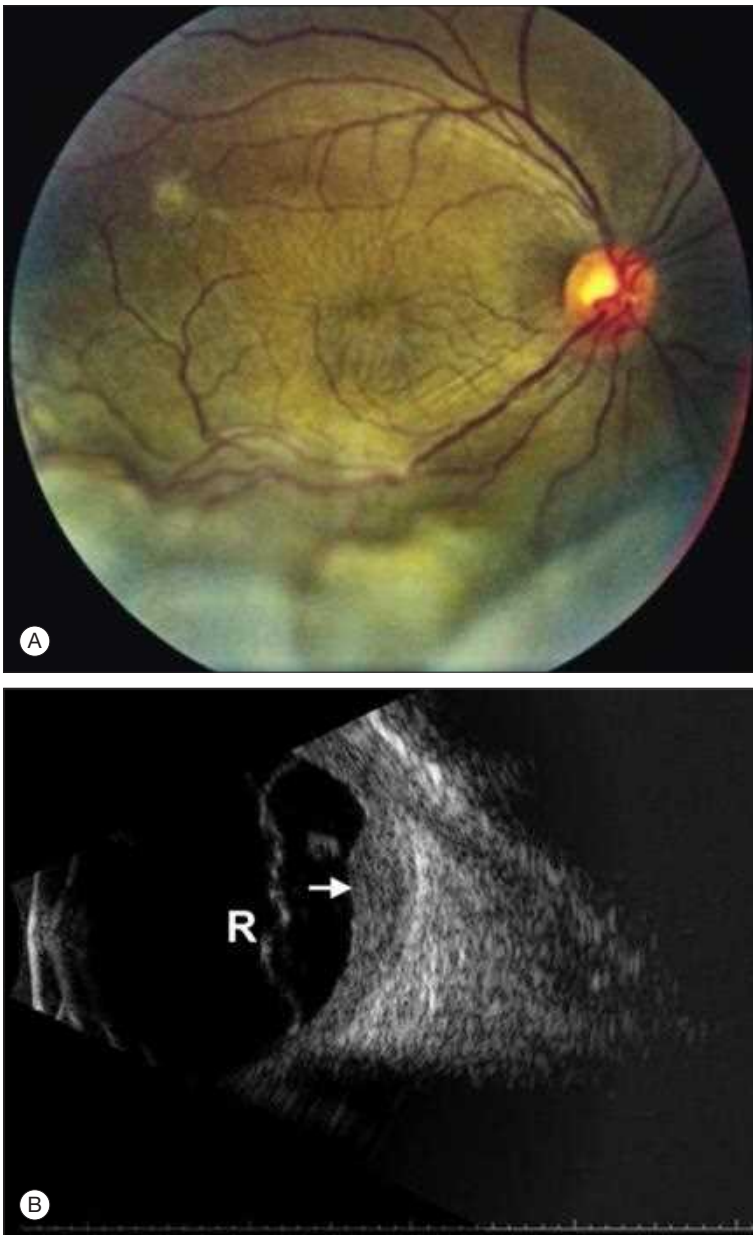
Choroidal melanomas and nevi, hemangiomas, metastatic choroidal lesions, and even retinoblastoma, can cause serous retinal detachments. Aberrant vascular patterns with increased permeability (mediated, perhaps, by VEGF), or physical disruption of the net flow from vitreous to choroid, leads to breakdown in the normal internal to external fluid movement and subsequent serous detachment.<sup>1</sup> Additionally, rapid growth of a lesion with outstripping of its blood supply and ischemia can lead to overlying RPE damage and retinal detachment and may serve as a marker of malignant transformation, especially in the setting of choroidal nevi and melanoma. However, benign lesions, such as nevi and hemangiomas, can also cause serous retinal detachments, seen both clinically and by optical coherence tomography (OCT).<sup>4</sup>

Choroidal hemangiomas occur in two forms: the diffuse hemangioma associated with Sturge-Weber disease, described as having a “tomato catsup” appearance, and a clinically isolated form usually having a single subretinal lesion that is well-circumscribed and often located near the optic nerve or macula. These tumors are well vascularized, with contributions from both ciliary and choroidal vessels, and tend to induce changes in the overlying RPE ranging from atrophy to hypertrophy. Serous retinal detachments are a common feature.<sup>5</sup>

Choroidal melanomas are often dome-shaped subretinal lesions that can be variably pigmented, although “mushroom-shaped” (if the tumor violates Bruch’s membrane, which forms a “collar” between the sub-RPE “stalk” and the subretinal “cap”) and diffuse presentations are also possible. On FA, these tumors appear hyperfluorescent because of their dilated, highly permeable vascular networks, often with a speckled pattern at the margins. In addition, they may also show a distinct “double circulation” pattern, with midphase hyperfluorescence highlighting the permeable vasculature and late hyperfluorescence the fluid extravasated within the tumor substance.<sup>6</sup> These disrupted vascular patterns seen within melanomas lead to the fluid disruptions causing serous detachments.<sup>1</sup>

This is likely the same mechanism whereby serous retinal detachments are caused in metastatic lesions of the choroid. Choroidal metastases most commonly arise from breast adenocarcinoma in women (Fig. 6.40.2) and from lung adenocarcinoma in men, although primary lesions are not determined in a number of choroidal lesions.<sup>7</sup> Metastases often show late hyperfluorescence on FA, often with pooling of dye into overlying serous detachments.<sup>1</sup> Treatment is aimed at the underlying primary malignancy and should be coordinated with an oncologist.

Rapidly growing retinoblastomas, often exophytic in growth, are also highly vascularized tumors and can be seen to produce large serous detachments of overlying and surrounding retina. As the most common primary intraocular malignancy in children, retinoblastomas often manifest as a chalky white tumor with extensive calcification. Treatment traditionally consisted of enucleation, but significant advances in globe- and



**Fig. 6.40.2** A 56-Year-Old Woman With a History of Breast Cancer Presents With Serous Retinal Detachment and Choroidal Metastasis. (A) Fundus photo of right eye shows serous retinal detachment. (B) Longitudinal B-scan shows extensive retinal detachment (R) overlying an irregularly shaped choroidal metastasis (arrow). (Courtesy M. Bernadete Ayres, Echography Department, Bascom Palmer Eye Institute.)

vision-sparing therapy have been made through the use of localized chemotherapy.<sup>8</sup>

### Systemic Disease With Disrupted Choroidal Blood Flow

Other, more systemic processes which disrupt normal choroidal flow and lead to overlying serous retinal detachments include malignant hypertension, disseminated intravascular coagulation, thrombotic thrombocytopenic purpura, renal failure, and pre-eclampsia. Although diverse in pathophysiology and presentation, each of these entities produces a thrombotic, occlusive state that causes focal areas of choroidal and retinal ischemia.<sup>2</sup> Signs of retinal ischemia, such as cotton-wool spots, are common in each disease, and can be seen in association with optic nerve swelling and peripapillary leakage, as well as placoid RPE and choroidal lesions. These areas of atrophy can resolve to form the Elschnig's spots and Siegrist's streaks associated with malignant hypertension and pre-eclampsia. FA reveals areas of patchy hypofluorescence, demonstrating focal areas of occlusion and disrupted choroidal blood flow, and these choroidal lesions are often associated with overlying serous retinal detachments. Treatment is directed at the underlying pathology.<sup>1</sup>

### Vasculitis and Autoimmune Disease

In addition to the systemic conditions above, there are several vasculitic syndromes that cause intraocular inflammation and serous retinal detachments, including systemic lupus erythematosus (SLE), Wegener's granulomatosis, polyarteritis nodosa, relapsing polychondritis, dermatomyositis, and Goodpasture's disease. Each produces vascular leakage and/or acute occlusion of the choriocapillaris, or precapillary choroidal arterioles, resulting in necrosis of the overlying RPE and retinal detachment by the mechanism described above.<sup>2</sup>

SLE—a chronic, systemic, immunologically mediated disease of unknown etiology—in addition to its protean effects throughout the body, is able to affect almost every ocular structure. One more common ocular manifestation is a retinopathy consisting of cotton-wool spots, retinal arteriitis and vascular occlusion, and secondary retinal neovascularization and vitreous hemorrhage. Although rare, associated choroidopathy with serous retinal detachment can complicate this retinopathy and is usually associated with severe SLE, secondary hypertension, and renal involvement. Diagnosis of SLE, and other inflammatory diseases, is best done in conjunction with a rheumatologist, and treatment is directed at systemic control.<sup>9</sup>

### POOR SCLERAL OUTFLOW

#### Nanophthalmos and Uveal Effusion Syndrome

Given the role of normal scleral outflow in removing excess fluid from the choroidal interstitium, any impedance of this outflow can result in disruption of the normal flow of fluid from out of the subretinal space and subsequent serous detachment of the neural retina. Nanophthalmos, although rare, illustrates this point. Nanophthalmos is an uncommon disorder of ocular development characterized by short axial length, high hyperopia, high lens-eye volume ratio, and a predisposition to angle closure, which shows variable genetic inheritance patterns. Patients universally have abnormally thickened sclera and can exhibit serous retinal detachments in the absence of other inciting factors.<sup>10</sup>

This association helped classify nanophthalmos as a distinct class of uveal effusion syndrome (Fig. 6.40.3), along with eyes of normal axial length with abnormal scleral collagen and eyes of normal axial length and normal scleral collagen. In addition to serous detachments, these patients exhibit dilated conjunctival vessels, shallow anterior chambers, ciliochoroidal effusions, and increased risk of glaucoma. On FA, these patients often demonstrate a diffuse “leopard spot” pattern that notably lacks focal points of leakage, and ICGA shows diffuse hyperfluorescence. Although the exact mechanism of impedance is uncertain, decreased fluid movement through the sclera is the cause of fluid accumulation in the subretinal space, and treatments improving scleral outflow—such as the creation of scleral “windows”—successfully treat the detachments.<sup>10</sup>

### Posterior Scleritis

Other mechanisms of decreasing scleral outflow similarly lead to serous retinal detachment. Posterior scleral inflammation and edema, as seen in posterior scleritis and orbital cellulitis, have been reported with serous detachments.

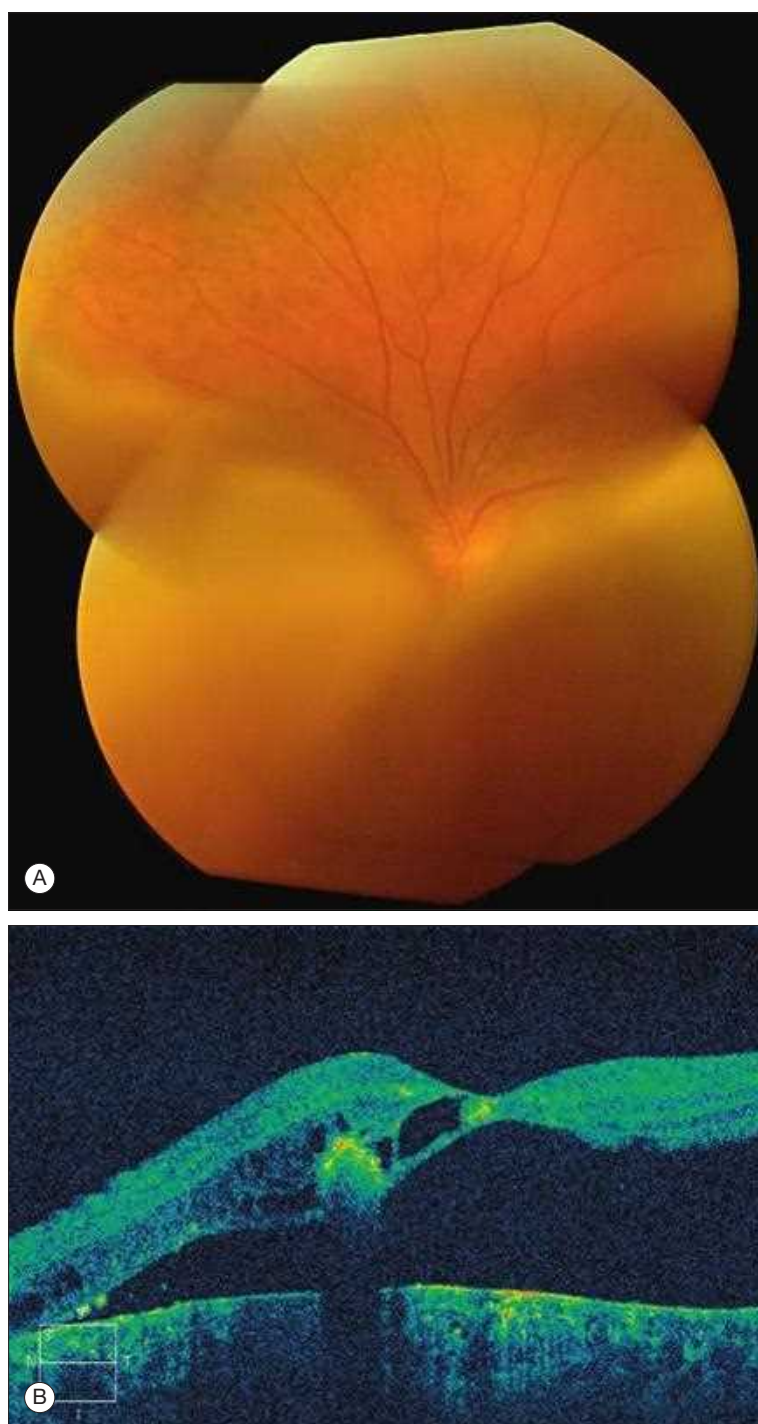
Posterior scleritis presents with severe retrobulbar pain, decreased vision, and posterior segment inflammation. Ultrasonography is useful for diagnosis and reveals diffusely thickened posterior sclera.<sup>1</sup> Treatment, similar to other forms of scleritis, consists of high-dose corticosteroids. Orbital cellulitis, although able to cause posterior scleral inflammation and decreased fluid outflow, is less commonly associated with posterior retinal changes and only rarely exhibits serous retinal detachment.<sup>11</sup> Other infectious etiologies affecting the posterior globe, such as Lyme disease and cat scratch disease, can exhibit small peripapillary serous detachments. Treatment consists of antibiotic therapy tailored to the particular infectious agent.

### BREAKDOWN OF THE RPE AND RETINA

#### Vogt–Koyanagi–Harada Disease, Sympathetic Ophthalmia, and Sarcoidosis

A more diverse group of pathological entities—inflammatory, infectious, degenerative, and vascular—can cause focal disruption of the RPE and





**Fig. 6.40.3** A 60-Year-Old Man With Chronic Uveal Effusion Syndrome and Hyperopia. (A) Fundus photo shows extensive inferior serous retinal detachment of left eye. (B) Optical coherence tomography (OCT) of subretinal fluid throughout macula with chronic degenerative cysts and hyperreflective lesions in subretinal space and outer retina.

retina, overwhelming the natural outflow of fluid into the choroid and causing accumulation of fluid in the subretinal space.

Vogt-Koyanagi-Harada disease (VKH) is an inflammatory disease found more commonly in Asian and Native American populations, defined principally by intraocular inflammation (panuveitis) associated with exudative retinal detachments (Fig. 6.40.4). Vision loss is nearly universal, with associated headache, meningismus, poliosis, vitiligo, and hearing loss. The pathological mechanism is an autoimmune response to melanin-containing tissues, which explains the predilection for the RPE and the highly pigmented choroid.<sup>12</sup>

In patients with VKH disease, FA reveals patchy filling of the choroid, followed by multiple pinpoints of hyperfluorescence and eventual pooling of dye in areas of exudative detachment. ICGA reveals diffuse hyperpermeability of the choroidal vasculature, in contrast to the lobular pattern seen in ICSC, indicating diffuse inflammatory damage present within VKH

disease.<sup>1</sup> RPE breakdown, formation of sub-RPE Dalen-Fuchs nodules, and choroidal inflammation involving the choriocapillaris are key features of this damage, which leads to subretinal fluid accumulation and exudative retinal detachment. Sympathetic ophthalmia (SO), characterized by an immune reaction to ocular tissue in the wake of a penetrating ocular injury, is rarer, but can present a similar pathological picture.<sup>13</sup>

Another inflammatory condition, sarcoidosis, can also present with associated serous retinal detachment. Sarcoidosis is a systemic granulomatous disease of unknown etiology that affects the eye in approximately 25% of patients. Association with RPE detachments has been described in patients with sarcoidosis, presumably from inflammation leading to RPE breakdown and subretinal fluid accumulation.<sup>14</sup>

## Infectious Diseases

Various infections can damage the retina, RPE, and choroid, leading to RPE breakdown and serous retinal detachment. Toxoplasmosis, a protozoal infection and the most common cause of posterior uveitis, causes a necrotizing chorioretinopathy that leads to characteristic scarring. Almost a quarter of patients with *Toxoplasma* retinochoroiditis in one series demonstrated serous detachment. These detachments were, in the majority of cases, associated with areas of retinal and vascular damage, as well as likely RPE breakdown, although some patients showed associated areas of choroidal ischemia, suggesting a mixed mechanism for serous retinal detachment.<sup>15</sup> Treatment is aimed at the underlying infectious process and leads to resolution of the associated retinal detachment. Syphilis and cytomegalovirus have also been reported in association with serous retinal detachments.<sup>2</sup> Additionally, Lyme disease (caused by *Borrelia burgdorferi*), tuberculosis, histoplasmosis, coccidiomycosis, and cryptococcosis have all been associated with serous retinal detachment, and cat scratch disease (caused by *Bartonella henselae*) and other neuroretinitides can cause peripapillary serous detachments.<sup>16</sup>

## Retinal Vascular Diseases

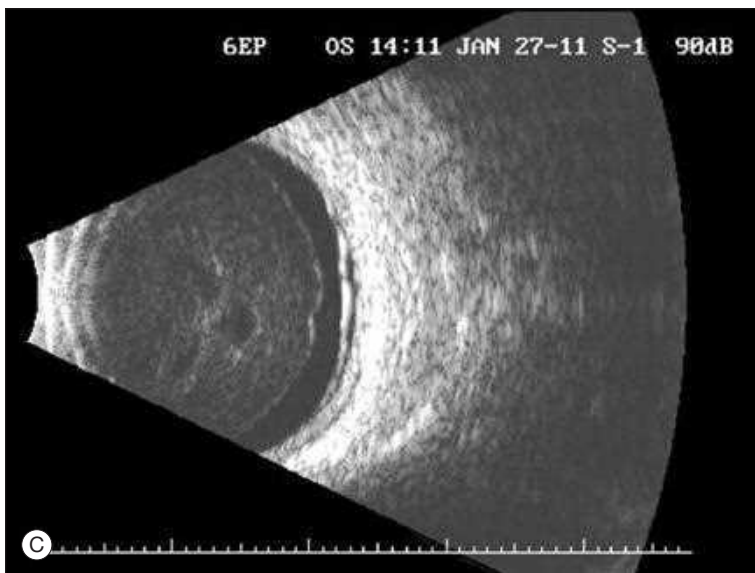
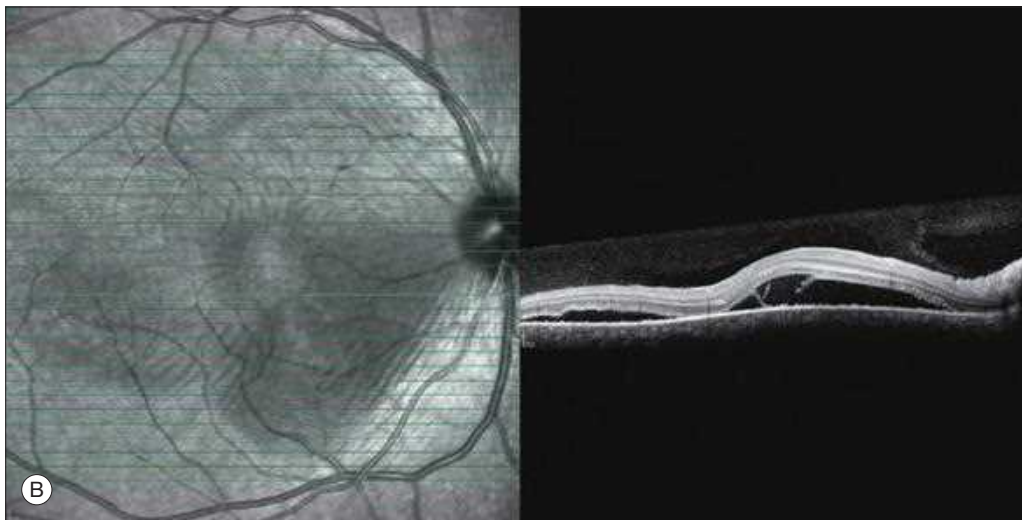
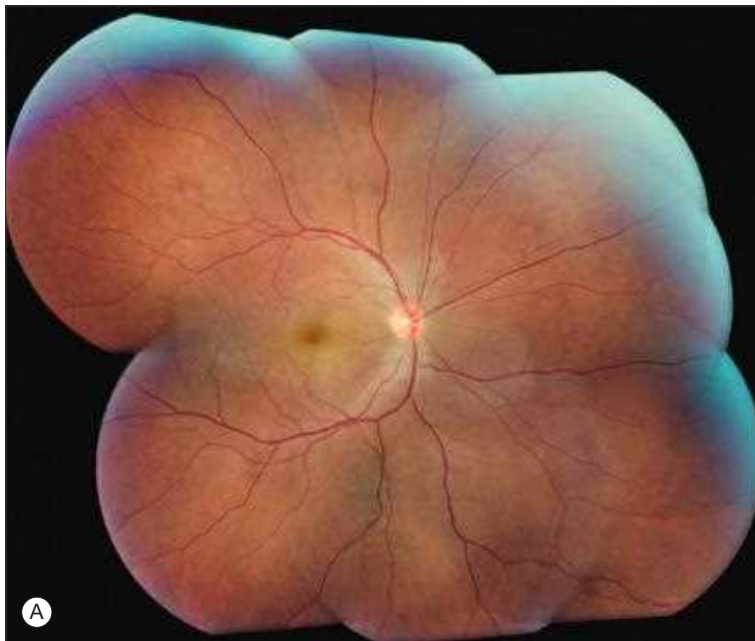
Other vascular pathologies, each involving leakage of abnormal retinal vessels or breakdown of normal ones, can cause serous detachments. Congenital vascular abnormalities with associated retinal detachment include those seen in Coats' disease, familial exudative vitreoretinopathy (FEVR), and retinal angiomas. Coats' disease, a rare disease of unknown inheritance with a 3:1 male predominance, presents at an early age and is classically thought to be a unilateral disease. The characteristic presentation is capillary nonperfusion and telangiectasias, with massive exudation of fluid and cholesterol.<sup>17</sup> FA demonstrates "light bulb" aneurysms of the congenitally weakened vessels, and arterioles, capillaries, and venules are all affected. The leakage and exudation leads to serous retinal detachment, compounding the vascular damage and eliciting a progressive cycle of worsening detachment. Treatment usually involves laser photocoagulation, although recent studies have evaluated the use of anti-VEGF therapy.<sup>1</sup>

Congenital retinal vascular abnormalities causing pathologically increased flow and focal leakage are also present in FEVR and retinal angiomas. Capillary hemangiomas of the retina can be seen in isolation (von Hippel's disease), or in association with systemic tumors, such as central nervous system hemangioblastomas and renal cell carcinoma (von Hippel-Lindau disease).<sup>1</sup> Again, treatment of retinal lesions is commonly laser photocoagulation, although PDT has been used with some success. Suspected von Hippel-Lindau disease requires further imaging to rule out associated neoplasms.

Acquired vascular damage can also lead to serous retinal detachment, as has been reported in association with retinal vein occlusions, diabetic macular edema, retinal macroaneurysms, and exudative age-related macular degeneration (AMD).

## MISCELLANEOUS

- Multiple myeloma/immune gammopathies/paraproteinemias.
- Postoperative (e.g., retinal detachment repair, phacoemulsification).
- Medication-related: interferon, ribavirin, mitogen-activated protein kinase kinase inhibitors, phosphodiesterase inhibitors, ipilimumab, dabrafenib, trametinib, deferoxamine.
- Congenital optic nerve anomalies (optic pit, coloboma, morning glory).
- Myopia-related: dome-shaped maculopathy, posterior staphyloma, tilted disc syndrome.
- Bilateral diffuse uveal melanocytic proliferation (BDUMP).



**Fig. 6.40.4 A 45-Year-Old With Man With Acute Vogt-Koyanagi-Harada (VKH) Disease.** (A) Fundus photograph of right eye with minimal vitritis and shallow serous retinal detachment in macula. (B) Optical coherence tomography (OCT) shows hyperreflective fibrinous structures lining retinal pigment epithelium (RPE) and photoreceptor layer in areas of neurosensory detachment, including formation of a fibrinous membrane extending through subretinal space. (C) B-scan of another patient with VKH disease shows diffuse thickening of retinochoroidal layer, shallow serous retinal detachment, and posterior vitreous detachment with inflammatory debris in vitreous.

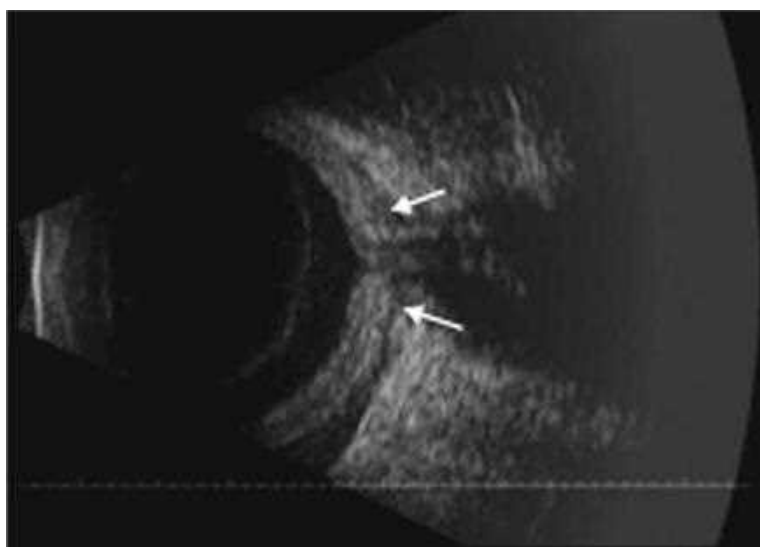
## DIAGNOSTIC AND ANCILLARY TESTING

The presence of a serous retinal detachment is most readily established by clinical examination using indirect ophthalmoscopy, unless precluded by hazy ocular media. Initial examination should include careful evaluation for retinal breaks or tractional membranes. Observation of fluid shifting with changes in head position, as well as the absence of retinal corrugations or tractional membranes, is an important diagnostic clue. Complete

ocular examination for structural abnormalities, inflammatory manifestations, tumors, or vascular disease helps narrow the diagnosis, and a thorough review of systems is critical.

Ancillary imaging serves two purposes: first, evaluation in the setting of hazy ocular media or retrobulbar pathology, as with B-scan ultrasonography and computed tomography/magnetic resonance imaging (CT/MRI); second, demonstration of various pathological patterns, assisting in diagnosis. Additionally, blood testing (as with infectious and autoimmune





**Fig. 6.40.5** A 43-Year-Old Woman With Posterior Scleritis. Transverse B-scan in the peripapillary region shows diffuse thickening of the retinochoroidal layer and sclera. The edematous distention of the sub-Tenon's space produces the "T" sign (arrows). (Courtesy M. Bernadete Ayres, Echography Department, Bascom Palmer Eye Institute.)

etiologies) and cerebrospinal fluid sampling (as with VKH disease) can be useful.

### Diagnostic Ultrasonography

B-scan ultrasonography, which assists in the examination of patients with hazy ocular media, can also provide important diagnostic information. Serous retinal detachments usually appear as smooth, dome-shaped collections of subretinal fluid. Fluid shifting can also be appreciated by ultrasonography. Associated macrostructural pathology, such as choroidal tumors or thickening of the posterior sclera (e.g., the "T" sign in posterior scleritis; Fig. 6.40.5), can be seen. Diffuse choroidal thickening can be seen in both VKH disease and SO.

### Optical Coherence Tomography

OCT provides in vivo, cross-sectional images of the retina with resolution sufficient to distinguish cell layers, by evaluating beams of light as they are directed at the retina and variably reflected back. Thus, OCT can differentiate between detachment of the retina and that of the RPE, distinguish retinal detachments from schisis cavities, establish the presence of subretinal exudation or neovascular membranes, identify discontinuities in the RPE, and monitor the resolution of subretinal fluid during treatment. Recently, modification of this imaging technique through enhanced depth imaging–OCT (EDI-OCT) has been used to evaluate choroidal changes in various diseases, such as ICSC and VKH disease.

### Fluorescein Angiography and Indocyanine Green Angiography

Imaging of the retinal and choroidal vasculature using fluorescein and ICG is critical in elucidating the different patterns of posterior segment disease, as well as in providing in vivo evidence of the likely pathological mechanisms, as seen in recent ICGA studies of ICSC showing choroidal hyperpermeability underlying areas of serous detachment. These imaging techniques help distinguish various diseases, identify specific areas of leakage, and can direct focal laser treatment and PDT, if necessary.

### Optical Coherence Tomography Angiography

By utilizing flow differences between sequential B-scans, optical coherence tomography angiography (OCTA) can generate a rapid, noninvasive angiographic picture of the retinal vessels and the underlying choroidal

vasculature, as well as abnormal vascular patterns, such as neovascular membranes. Although demonstrations of consistent diagnostic utility are pending, early studies utilizing OCTA showed promise in the management of pathologies that involve disruptions of macular blood flow (Fig. 6.40.6).

## Computed Tomography and Magnetic Resonance Imaging

The broader imaging modalities of CT and MRI can also be used to evaluate posterior ocular and retrobulbar pathology associated with serous retinal detachment, such as with orbital cellulitis. Appropriate use of contrast in these studies can improve evaluation of inflammatory and neoplastic disease.

## DIFFERENTIAL DIAGNOSIS

- Retinoschisis.
- Tractional retinal detachment.
- Rhegmatogenous retinal detachment.
- Choroidal detachment.
- Retinal or subretinal cyst.
- Choroidal or retinal tumor.

## TREATMENT

As mentioned earlier, treatment of serous retinal detachments must address the underlying local or systemic disease, which includes antibiotic therapy (retinal and choroidal infections, orbital cellulitis), systemic immunosuppression (posterior scleritis, vasculitides, autoimmune disease, idiopathic frosted branch angiitis), blood sugar or blood pressure management, or chemotherapy (choroidal neoplasms, multiple myeloma, and BDUMP). In some diseases (e.g., ICSC), simple observation is sufficient. Timely consultation with other medical specialists, when indicated to initiate treatment, is critical.

Additionally, certain ocular treatments can address more focal pathologies, most notably laser photocoagulation in the treatment of vascular anomalies (Coats' disease) and tumors (capillary hemangiomas). In ICSC that does not resolve spontaneously, focal laser can be applied to sites of RPE leakage that are sufficiently distant from the fovea. Laser can also be applied to well-circumscribed choroidal hemangiomas, although external beam radiotherapy is indicated for more diffuse lesions.

PDT has been recently employed for the treatment of other types of choroidal disease, although the complication of vision loss associated with choroidal infarct remains a serious concern. Improvement of serous detachments in ICSC, most especially the chronic form, with half- and minimal-fluence treatments has been demonstrated.

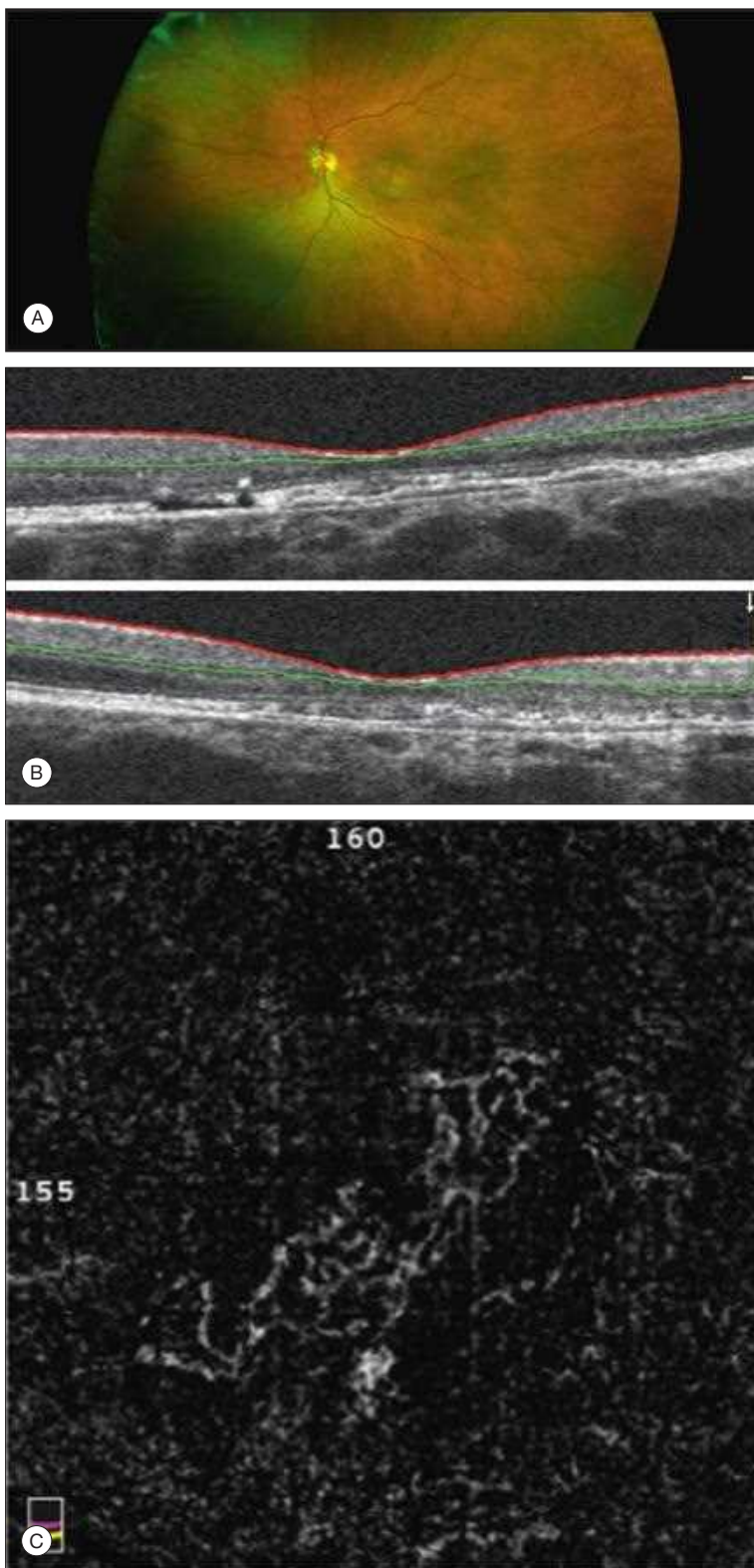
Given the presence of VEGF in a number of retinal diseases, including exudative AMD, Coats' disease, and choroidal melanomas and hemangiomas, the use of intravitreal anti-VEGF therapy can be valuable in the treatment of these etiologies of serous retinal detachment. Intravitreal and peribulbar corticosteroids are also used for treating inflammatory diseases.

Finally, in certain cases of serous retinal detachment, surgical intervention is warranted. The creation of scleral windows in uveal effusion syndrome serves as one example of a primary surgical intervention. However, in occasional cases of inflammatory disease or ICSC, especially with long-standing bullous detachments, surgical intervention has been used with some benefit when all other options have been exhausted.

## COURSE AND OUTCOME

Variable etiologies make for variable outcomes, and the disease courses associated with serous retinal detachment range from the most acute to the most chronic. As a rule, resolution of subretinal fluid occurs with observation or appropriate treatment of the underlying local or systemic pathology. However, the longer a serous detachment is present, the less likely it is that full resolution and, more importantly, restoration of visual function can be achieved. Involvement of the macula also portends a poorer outcome. Visual outcomes with serous detachment tend to be better than with chronic rhegmatogenous and tractional detachments, and this can help to reassure patients as appropriate treatment is initiated.





**Fig. 6.40.6** A 67-Year-Old Man With Chronic Idiopathic Central Serous Chorioretinopathy and Choroidal Neovascularization. (A) Scanning laser ophthalmoscopy demonstrating multifocal areas of retinal pigment epithelium (RPE) changes and central macular hemorrhage. (B) Horizontal (*top*) and vertical (*bottom*) spectral domain optical coherence tomography (OCT) showing subretinal and sub-RPE fluid. (C) OCT angiography of outer retina demonstrating abnormal vessels in the outer retina consistent with choroidal neovascularization. (Courtesy Caroline R, Bauman, Department of Ophthalmology, Tufts University School of Medicine.)

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# Choroidal Hemorrhage

Michael A. Kapusta, Radwan S. Ajlan, Pedro F. Lopez

# 6.41



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**Definition:** A hemorrhage in the suprachoroidal space that can occur spontaneously, intraoperatively, or traumatically, or is associated with intraocular vascular anomalies.

## Key Features

- One or more dome-shaped choroidal protrusions.
- Forward movement of the iris, lens, and vitreous body.
- Elevated intraocular pressure.

## Associated Features

- Intraoperative darkening of the red reflex.
- Intraoperative excessive bleeding of conjunctiva and episcleral tissues.
- Severe pain, even under local anesthetic.
- Breakthrough vitreous hemorrhage.
- Rhegmatogenous, exudative, or tractional retinal detachment.

## INTRODUCTION

Choroidal hemorrhage is a serious ocular condition that may be associated with permanent loss of visual function. Both limited and massive choroidal hemorrhages may occur as complications of most forms of ocular surgery and from trauma. Despite modern vitreoretinal techniques, choroidal hemorrhage is associated with visual loss in most cases.

## EPIDEMIOLOGY AND PATHOGENESIS

Choroidal hemorrhage may occur in a limited form or as a massive event. Massive choroidal hemorrhage is of sufficient volume to cause extrusion of intraocular contents outside the eye or to move retinal surfaces into or near apposition (“kissing”). Massive choroidal hemorrhage may be expulsive or nonexpulsive, immediate (intraoperative), or delayed hours to weeks postoperatively; it may occur spontaneously, with choroidal mass lesions (e.g., choroidal hemangioma), or with surgical or noniatrogenic trauma.<sup>1-3</sup>

Limited choroidal hemorrhage occurs in over 3% of intracapsular cataract extractions and in 2.2% of nucleus-expression extracapsular cases.<sup>1</sup> It appears to be less common with small incision phacoemulsification techniques. Massive choroidal hemorrhage has complicated 0.2% of cataract extractions and 0.73% of glaucoma filtering procedures.<sup>2</sup> It may occur even more frequently with keratoplasty.<sup>3</sup> Scleral buckling procedures and pars plana vitrectomy may be complicated by either limited or massive choroidal hemorrhage.

Choroidal hemorrhage may occur when a fragile vessel is exposed to sudden compression and decompression events. An intact posterior lens capsule may serve as a tamponade against such intense intraocular decompression during surgery.<sup>3</sup> Retrobulbar anesthetic injection, retrobulbar hemorrhage, or excessive pressure on the globe during surgery may impede vortex venous outflow and lead to choroidal effusion and hemorrhage.<sup>4</sup> Decompression hypotony, created when the eye is entered, and repeated fluctuations in intraocular fluid dynamics may add further insult

to these fragile vessels. The resultant suprachoroidal effusion progresses to stretch the suprachoroidal space and cause further tension on the ciliary vessels. Alternatively, chronic hypotony may facilitate the extension of a pre-existing suprachoroidal effusion toward the anterior ciliary arteries. Either pathway may result in vessel-wall rupture and suprachoroidal hemorrhage. Modifiable risk factors identified for delayed choroidal hemorrhage post pars plana vitrectomy include emesis and extensive use of photocoagulation.<sup>5</sup>

Systemic conditions that may serve as risk factors for massive choroidal hemorrhage include advanced age, arteriosclerosis, hypertension, diabetes mellitus, blood dyscrasias, and obesity. Ocular risk factors include previous surgery, aphakia, glaucoma, uveitis, high myopia, trauma, vitreous removal, laser photocoagulation, and choroidal sclerosis. A scleral buckle placed during vitrectomy is a risk factor for postoperative choroidal hemorrhage. Glaucoma procedures, previous pars plana vitrectomy, and old age serve as risk factors for appositional choroidal hemorrhage.<sup>6</sup> A history of choroidal hemorrhage serves as a risk factor for surgery on either eye. Intraoperative risk factors include increased intraocular pressure, increased axial length, open-sky procedures, and Valsalva maneuvers. Intraoperative tachycardia has been identified as a significant risk factor or an early symptom of expulsive hemorrhage.<sup>7</sup>

The risks of choroidal hemorrhage may be minimized by control of known risk factors. Preoperative massage and a Honan balloon may be used in cases where peri- or retrobulbar anesthetic is used. Intraoperative temporary security sutures may be placed before planned or conversion to an expression delivery of the lens. The watertight wound created for phacoemulsification helps to maintain intraocular turgor; it may reduce the incidence and limit the severity of suprachoroidal hemorrhage.

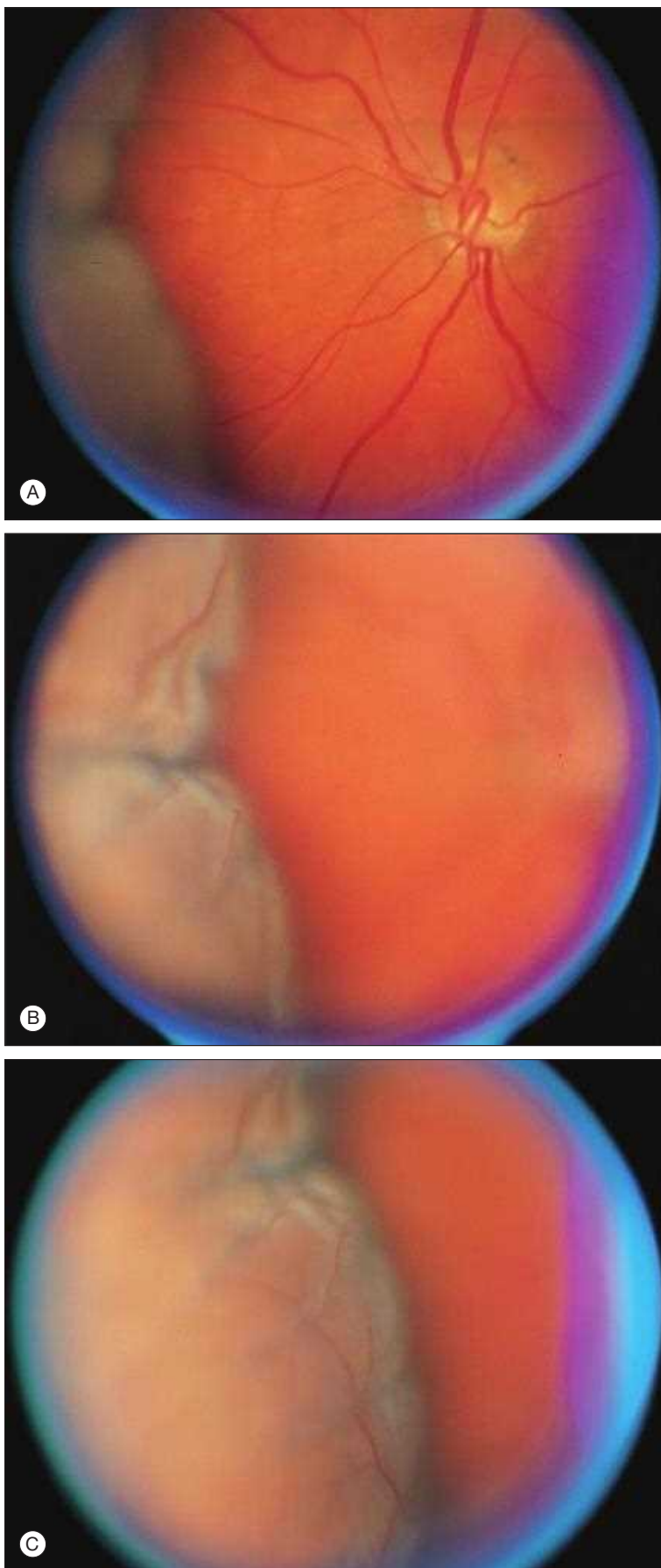
## OCULAR MANIFESTATIONS

Both serous and hemorrhagic choroidal detachments usually decrease vision. Serous choroidal detachment may be asymptomatic, but hemorrhagic choroidal detachment often is painful—sometimes extremely so. Slit-lamp examination reveals a shallow anterior chamber with mild cellular reaction and flare. Ophthalmoscopy demonstrates a smooth, bullous, orange-brown elevation of the retina and choroid. Choroidal detachment that occurs anterior to the equator often extends in an annular fashion around the globe; whereas postequatorial choroidal detachment often is unilobulated or multilobulated, secondary to the periequatorial attachment of the choroid at the vortex vein ampullae. Visualization of the ora serrata without scleral depression may be a sign of pre-equatorial choroidal detachment (Fig. 6.41.1).

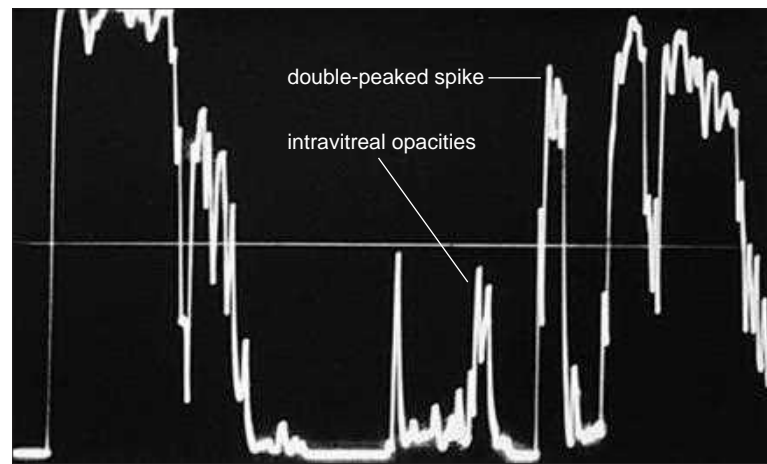
Eyes with limited and massive (delayed) hemorrhagic choroidal detachments generally have elevated intraocular pressure, and the detachments do not transilluminate, may extend to the posterior pole, and are more voluminous posterior to the equator.

The initial intraoperative symptoms of massive choroidal hemorrhage may be paroxysmal onset of severe intraoperative pain despite adequate analgesia. Classically, the pain radiates from the brow to the vertex of the head along the V1 dermatome and is often refractory to further retrobulbar analgesia. The intraoperative signs of massive choroidal hemorrhage may include tachycardia and excessive iris movement or prolapse. This usually is accompanied by forward movement of the lens and vitreous body as the globe tenses. There is an increasing tendency for suprachoroidal





**Fig. 6.41.1 Hemorrhagic Choroidal Detachment Viewed Ophthalmoscopically.** (A) The extent of choroidal protrusion, as evidenced by a fundus photograph focused on the optic nerve. (B) The dome-shaped lobules and orange-brown color of a choroidal detachment. (C) A closer view demonstrates no subretinal fluid, helping to establish that this is a choroidal detachment, not a retinal detachment.



**Fig. 6.41.2 A-Scan Echogram.** This demonstrates intravitreal opacities and the highly reflective, double-peaked, wide spike characteristic of choroidal detachment.

hemorrhage to manifest as the cataract procedure progresses. The peak may occur during irrigation/aspiration maneuvers.<sup>8</sup> Darkening of the red reflex may precede or accompany a choroidal elevation that protrudes into the operative field. Expulsion of intraocular contents may ensue.

## DIAGNOSIS AND ANCILLARY TESTING

The intraoperative diagnosis of massive choroidal hemorrhage is based on recognition of early signs and changing ocular dynamics. Such recognition requires a high index of suspicion. Similarly, the diagnoses of delayed massive choroidal hemorrhage and limited choroidal hemorrhage are made after recent ocular surgery by consideration of the risk factors, symptoms, and signs. Measurement of intraocular pressure, gonioscopy, slit-lamp biomicroscopy, and dilated fundus examination, comparing both eyes, lead the examiner toward the diagnosis.

When the media is opaque or clear, echography may help to establish an accurate diagnosis and may be employed to differentiate serous from hemorrhagic choroidal detachment.<sup>9</sup> An A-scan echogram demonstrates a lesion with medium-high internal reflectivity and a steeply rising, 100% high spike. At low gain, this is observed to be a double-peaked wide spike characteristic of choroidal detachment (Fig. 6.41.2). The first peak may represent the surface of the overlying detached retina or the anterior surface of the choroid. Alternatively, the double peak may represent both the anterior and posterior surfaces of the choroid. On B-scan echograms, a choroidal detachment typically appears as a smooth, thick, dome-shaped membrane in the periphery that exhibits little if any aftermovement on kinetic evaluation. Serous detachment is characterized by low-reflective fluid in these dome-shaped spaces. Ultrasound may be a helpful prognostic tool for determining final visual outcomes when measured in correlation with choroidal hemorrhage severity.<sup>10</sup>

Hemorrhagic detachment with fresh blood clots is seen echographically as a high-reflective, solid-appearing mass, with irregular internal structure and irregular shape. Serial ultrasonography may demonstrate liquefaction of hemorrhage; the suprachoroidal space is filled with low-reflective mobile opacities that have replaced the hemorrhagic clot.<sup>9</sup> Serous elevation of the retina may accompany choroidal detachment and often resolves spontaneously. Clinically, and on ultrasound, the resolution of the retinal detachment may occur days to weeks after resolution of the choroidal elevation. It is imperative to monitor this and ensure that no retinal breaks are associated or develop.

## DIFFERENTIAL DIAGNOSIS

Differential diagnosis consists of choroidal effusion, rhegmatogenous retinal detachment, and melanoma or metastatic tumor of choroid or ciliary body.

## TREATMENT

### Primary Management

The management of serous choroidal detachment usually is conservative. Postoperative serous choroidal detachments often resolve on their own within days. Cycloplegia and topical corticosteroids are general

management measures. Surgical management of serous choroidal detachment may be indicated for refractory progressive shallowing or flattening of the anterior chamber. The threat of corneal decompensation after lens–cornea touch or the apposition of retinal surfaces in kissing choroidal detachment are other potential indications for surgical intervention.

Delayed nonexpulsive limited choroidal hemorrhage generally carries a good prognosis. Limited choroidal hemorrhage usually resolves spontaneously within 1–2 months without ophthalmoscopic evidence of damage. Management remains conservative in this situation and includes the use of cycloplegics and topical corticosteroids. The management of delayed, nonexpulsive, massive choroidal hemorrhage, by contrast, remains controversial. Some reports suggest that irreversible loss of vision may result when intervention does not take place within 1 week. Systemic corticosteroids are employed by some investigators.<sup>11</sup> Surgical drainage should be considered in the following circumstances:

- Massive choroidal hemorrhage associated with severe pain.
- Elevated intraocular pressure.
- Persistently flat anterior chamber.
- Suprachoroidal hemorrhage under the macula.
- Extension of hemorrhage into the subretinal space or vitreous cavity.

Significant vitreous incarceration in the surgical wound and kissing choroidal detachments, which may lead to secondary subacute traction or rhegmatogenous detachment after resolution of the suprachoroidal hemorrhage and its classic “buckle-like” effect, also are potential indications for surgical drainage.<sup>12</sup>

In 1915, Voerhoeff introduced posterior sclerotomy to release suprachoroidal blood for the management of massive choroidal hemorrhage. Intraoperative massive choroidal hemorrhage is managed by tamponade of the eye with direct digital pressure and rapid wound closure. The use of high-viscosity viscoelastics to control anterior chamber depth and progressing intraocular hemorrhage has been advocated.<sup>13</sup> The goal of rapid wound closure is to prevent expulsion or loss of the intraocular contents and incarceration of vitreous or retina in the surgical wound.

## Secondary Management

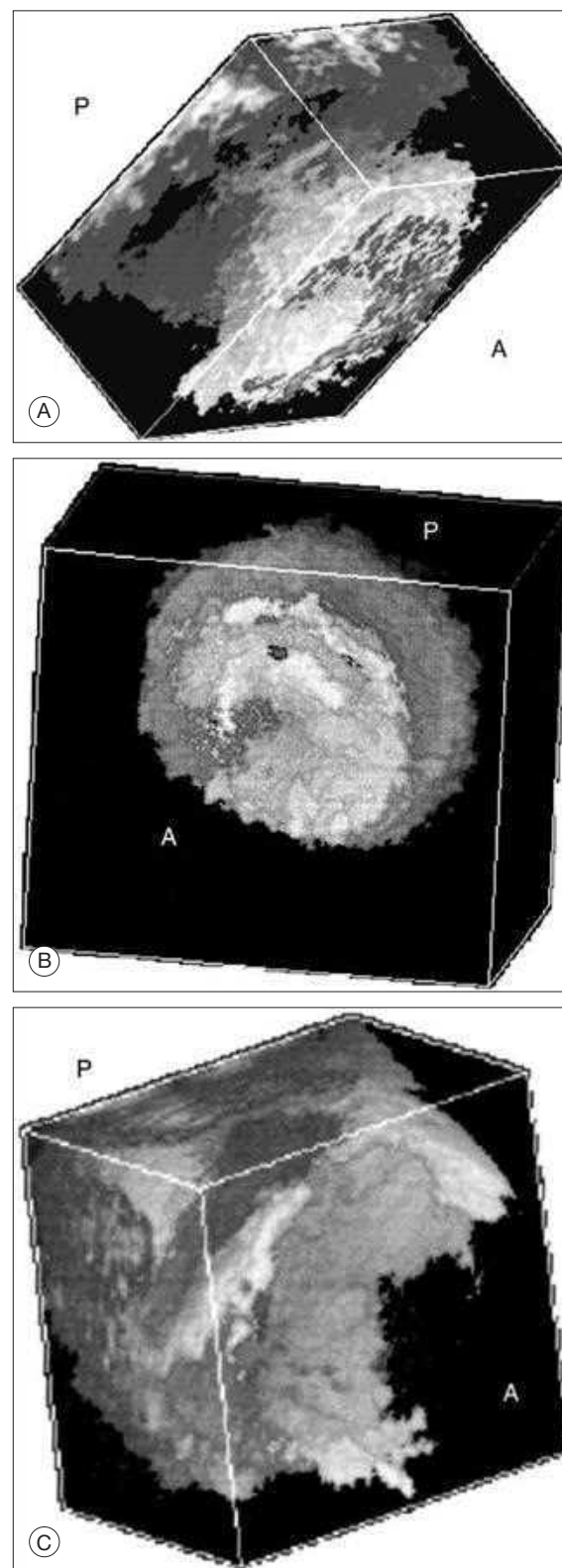
Choroidal hemorrhage that occurs postoperatively, recurs, or meets indications for further surgical intervention should be managed by a vitreoretinal surgeon. The successful management of affected eyes requires that vitreous or retinal incarceration be relieved completely. Patients who have vitreous incarceration are at high risk of developing retinal detachment. Eyes with concurrent vitreous and retinal detachment, at the time of diagnosis, may not be amenable to surgical repair or may be at high risk for proliferative vitreoretinopathy. Surgical intervention to drain choroidal hemorrhage ideally is conducted after liquefaction of the suprachoroidal hemorrhage, which may be assessed by serial echography.<sup>9</sup> Recent reports highlight the successful use of tissue plasminogen activator to achieve earlier clot lysis.<sup>14</sup> Three-dimensional reconstruction of the B-scan is possible with modern ultrasonography. This may assist in localization of the best sites for surgical drainage (Fig. 6.41.3).

The timing of such intervention may be altered by the presence of rhegmatogenous retinal detachment. The primary surgical goal is to separate any kissing choroidal detachments to prevent secondary traction or rhegmatogenous retinal detachment. Surgical goals should also include the separation of kissing choroidal detachments by one-half of their original height.

The initial stages of surgical drainage of massive choroidal hemorrhage include conjunctival peritomy and isolation of the relevant rectus muscles with bridle sutures. Often, all four rectus muscles are isolated to enable exposure if posterior drainage sclerotomies are needed in multiple quadrants to evacuate adequately the suprachoroidal hemorrhage.

Infusion of fluid or air to pressurize the eye and allow more complete evacuation of the suprachoroidal hemorrhage generally is a useful adjunctive procedure. The anterior chamber is entered with a 25-gauge or smaller needle, bent posteriorly, so that the bevel directs the infusion away from the corneal endothelium. Alternatively, a micro-vitreo-retinal blade may be used if a self-retaining or sutured infusion cannula is to be inserted (Fig. 6.41.4). Again, flow should be directed posteriorly. Viscoelastic agents may be employed to deepen the anterior chamber sufficiently to insert the infusion cannula or replace the need for infusion cannula by injecting them into the vitreous cavity.<sup>15</sup>

Posterior sclerotomy sites generally are created in the area of greatest choroidal elevation, with the patient in the supine (surgical) position to optimize drainage of the hemorrhage. Incisions (4–6 mm long) are created

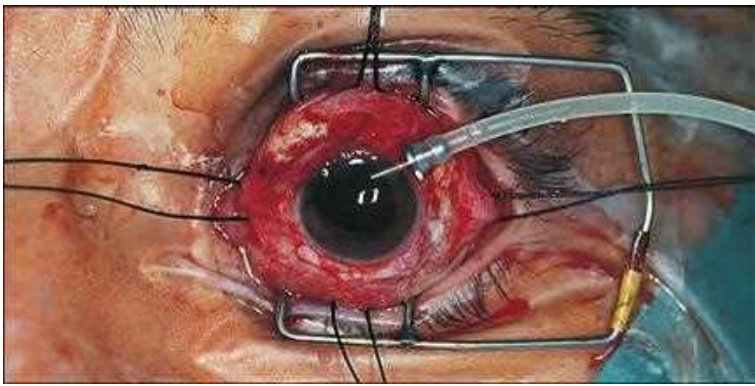


**Fig. 6.41.3** A Three-Dimensional Ultrasonogram of Choroidal Hemorrhage. A, Anterior; P, posterior.

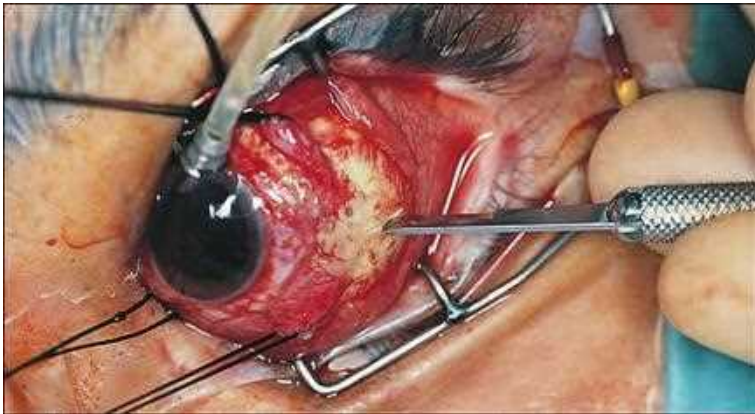
with a round or sharp blade posterior to the rectus muscle insertions, centered at the equator of the globe. Exposure is best in the inferotemporal quadrant, but other quadrants may be incised to achieve optimal drainage, as judged by inspection and ophthalmoscopy (Fig. 6.41.5). The sclerotomy sites may be sutured closed to restore anatomical integrity and stability or left open if further spontaneous drainage is felt likely or necessary. Another approach is to place the sclerotomies in the pars plana region, allowing easier access and suturing of scleral wounds.

A novel technique using the 25-gauge or 20-gauge transconjunctival trocar/cannula systems to drain serous and hemorrhagic choroidal detachments is gaining popularity, especially in eyes with conjunctival thinning and scarring. It comprises the use of a 25-gauge, 23-gauge infusion line or a 20-gauge Lewicky anterior chamber maintainer to keep the anterior

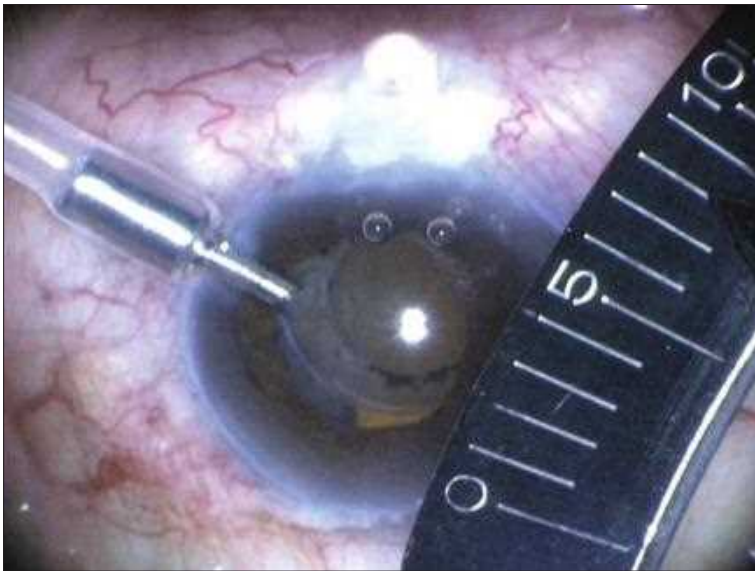




**Fig. 6.41.4** A Self-Retaining Infusion Cannula in the Anterior Chamber.



**Fig. 6.41.5** Creation of a Posterior Sclerotomy Incision to Drain a Choroidal Hemorrhage.



**Fig. 6.41.6** A 20-Gauge Lewicky Anterior Chamber Maintainer. Notice how the pars plana is easily visible behind the intraocular lens because of the mechanical disposition of the choroidal detachment. The caliber is set to the distance between the limbus and the maximum height of the choroidal detachment (8 mm in this photo).

chamber pressurized (Fig. 6.41.6). Then a 20-gauge or 25-gauge trocar/cannula system is used 7.0 mm from the limbus to create a transconjunctival beveled incision at 1 or 2 quadrants where the suprachoroidal detachment height measures at least 7 mm (Fig. 6.41.7) (Video 6.41.1). After drainage, the cannula is removed and the conjunctiva over the incision is cauterized.<sup>16</sup>

If vitreous is incarcerated in the original surgical wound, a vitrectomy probe may be introduced through a second limbal incision and an anterior vitrectomy performed to minimize vitreoretinal traction during the choroidal drainage procedure. Once adequate initial drainage has been achieved, a posterior vitrectomy with scleral depression may be performed to remove residual lens fragments, cortex, and vitreous adhesion to the iris. In the



**Fig. 6.41.7** Transconjunctival Trocar/Cannula Drainage Technique. Diagram illustrating the 25-gauge anterior chamber infusion line and the trocar/cannula inserted 7 mm from limbus away from uveal tissue. Cannula is directed toward the equator, which allows complete drainage without entering the vitreous cavity.

absence of retinal detachment, this may be deferred to later surgical intervention. For rhegmatogenous retinal detachment, a more extensive posterior vitrectomy in conjunction with drainage of the choroidal hemorrhage usually is necessary. Relaxing peripheral retinotomy or retinectomy may be necessary to relieve incarceration of the retina or severe anterior vitreous traction. The use of perfluorocarbon liquids may facilitate the drainage of suprachoroidal hemorrhage and facilitate reattachment of the retina.<sup>17</sup> Scleral buckling or long-term intraocular tamponade with silicone oil may minimize the chances of recurrent retinal detachment in these eyes.<sup>11</sup> The tamponading effect of 100% perfluoropropane (C3F8) was found to be helpful in early drainage of massive suprachoroidal hemorrhage.<sup>18</sup> Preoperative systemic corticosteroids may offer a better primary repair rate.<sup>11</sup>

Central retinal apposition in retinal detachment that follows drainage of choroidal fluid poses a unique surgical challenge. Perfluorocarbon liquids may be used to stabilize the posterior retina. A taper-tip endocautery can preserve hemostasis as the retinal surfaces are teased or cut apart to separate them. The perfluorocarbon level can be raised further to flatten the now-separated surfaces. Endolaser treatment and gas or oil tamponade may then be used. The reduction of risk factors for choroidal hemorrhage should achieve foremost attention at the time of secondary lens implant.<sup>19</sup>

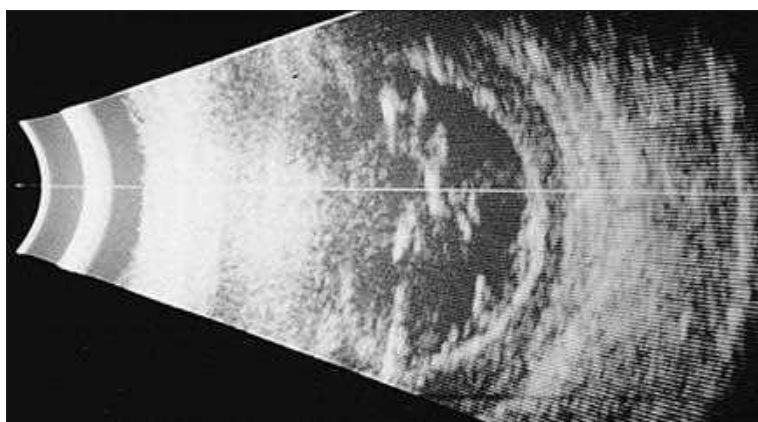
## Choroidal Hemorrhage in Trauma

Choroidal hemorrhage that occurs with noniatrogenic trauma or rupture of the globe may be associated with intraocular structural damage. In addition to contusive injury, fibrocellular proliferation with membrane formation may limit the visual rehabilitation of the eye.<sup>20</sup> The management of these cases must take into consideration the high likelihood of retinal detachment and associated proliferative vitreoretinopathy. Surgery may require evacuation of hyphema. Corneal blood staining may necessitate the use of a temporary keratoprosthesis. The choroidal hemorrhage is drained as described above. Scleral buckling and long-term tamponade with silicone oil may be required to effect repair of an associated rhegmatogenous retinal detachment. The echographic characteristics of choroidal hemorrhages that result from trauma differ from those that arise from other causes. In general, traumatic choroidal hemorrhages tend to be more diffuse and less elevated (Fig. 6.41.8).<sup>9</sup>

## Choroidal Hemorrhage in Other Conditions

Choroidal hemorrhage may occur in association with hemoglobinopathies, with the use of systemic anticoagulants or tissue plasminogen activator,





**Fig. 6.41.8** Transverse B-Scan of an Eye After Repair of a Ruptured Globe. The annular, flat, and diffuse hemorrhagic choroidal detachment is typical of trauma.



**Fig. 6.41.9** A Hemorrhagic Choroidal Detachment Seen in a Patient Using Warfarin. (Courtesy Jeffrey L. Marx, MD.)

with coughing,<sup>21</sup> or spontaneously (Fig. 6.41.9). In one series, patients developed acute angle-closure glaucoma from forward displacement of the lens-iris diaphragm, which resulted from massive hemorrhagic detachment of the choroid and retina. Affected patients often have associated systemic hypertension or a primary or anticoagulant-induced clotting disorder.<sup>22</sup> The source of “spontaneous” hemorrhage in these patients is often choroidal neovascularization in a disciform lesion.

Sturge-Weber syndrome is characterized by a flat, facial hemangioma that follows the distribution of the fifth cranial nerve. Choroidal and episcleral hemangiomas are seen commonly. Trabeculectomy in these cases is complicated by rapid expansion of the hemangioma, with effusion of fluid into the suprachoroidal and subretinal space in 17% of cases. Some surgeons recommend placement of two or three posterior sclerotomies to prevent such expansion. Definitive management includes posterior drainage sclerotomy followed by reformation of the anterior chamber.<sup>23</sup>

Limited choroidal hemorrhage can be mistaken for a choroidal melanoma. Fluorescein angiography and ultrasonography may help to differentiate these entities.<sup>21,24</sup>

## COURSE AND OUTCOME

Delayed, nonexpulsive, limited choroidal hemorrhage generally carries a good prognosis. Choroidal hemorrhages in cataract surgery tend to fare better than those in other forms of ocular surgery or in trauma. Retinal detachment in an eye with choroidal detachment or with choroidal hemorrhage in all four quadrants correlates with a poor visual outcome.<sup>2,25</sup> The extension of suprachoroidal hemorrhage into the posterior pole has been associated with worse visual and anatomical outcomes.<sup>26</sup> Vitreous and, especially, retinal incarceration are associated with a poorer prognosis.<sup>27</sup> Eyes with appositional choroidal detachment, duration of apposition greater than 30 days, a history of uveitis, macular degeneration, or extracapsular cataract extraction are associated with poor visual acuity outcomes.<sup>6</sup> In the absence of retinal adherence, however, kissing choroidal detachments may not portend a worse outcome—the natural history of this condition has not been delineated precisely.

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# Proliferative Vitreoretinopathy

Sidath E. Liyanage, David G. Charteris, G. William Aylward

# 6.42

**Definition:** The proliferation of avascular fibrocellular retinal membranes associated with rhegmatogenous retinal detachment.

## Key Features

- Epiretinal and subretinal fibrous proliferation.
- Contraction of membranes.
- Recurrent or persistent retinal detachment.
- Retinal shortening.
- Reopening of pre-existing retinal breaks.
- Formation of new retinal breaks.

## Associated Features

- Hypotony.
- Vitreous opacity.
- Aqueous flare.
- Iris neovascularization.
- Macular pucker.

## INTRODUCTION

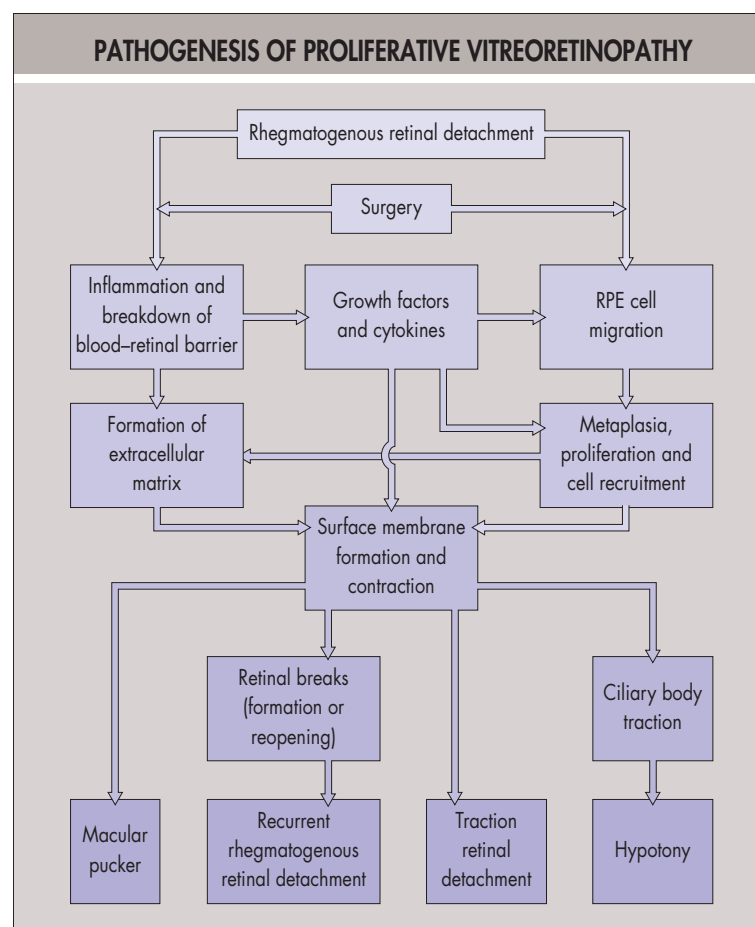
Proliferative vitreoretinopathy (PVR) is the most common cause of ultimate failure after surgical treatment for rhegmatogenous retinal detachment.<sup>1,2</sup> A wound-healing response, PVR is characterized by the formation of surface membranes in the posterior segment. Membranes most commonly form on the inner surface of the neural retina but can also be found in the subretinal space, in the vitreous base, and on the ciliary body. Contraction of these membranes may cause macular pucker, new retinal breaks, recurrent retinal detachment, and ocular hypotony.

## EPIDEMIOLOGY AND PATHOGENESIS

PVR occurs following surgical repair of retinal detachment but can develop in untreated cases, particularly those that are long-standing or with large breaks. It may also occur following large choroidal detachments or in eyes with large, treated retinal tears but no previous retinal detachment. It occurs in 5%–10% of treated rhegmatogenous retinal detachment cases and represents the major cause of ultimate surgical failure,<sup>1</sup> a situation that is unchanged despite advances in vitreoretinal surgical technology, including small-gauge technology.<sup>3,4</sup>

Certain types of retinal detachments are more likely to develop PVR than others. For example, those associated with giant retinal tears (greater than 3 clock hours) have a high incidence of postoperative PVR. Other risk factors have been identified in several studies that used multivariate regression analysis. These include the number and size of retinal breaks, the number of previous operations, the presence of choroidal effusions, the use of cryotherapy, intraocular hemorrhage, aphakia, high vitreous protein levels, and the severity of preoperative PVR.<sup>2,3,5,6</sup> Young patients who have penetrating trauma, especially double perforating injuries, also have a very high risk of PVR.

The pathogenesis of PVR is multifactorial and is summarized in Fig. 6.42.1. The primary event is the formation of a retinal break. Upregulation of the retinal response to injury with retinal glial activation then ensues and plays a central role in PVR development.<sup>3,7</sup> Retinal pigment epithelium (RPE) cells then migrate through the break into the preretinal space, where they settle on the retinal surface. Most of the fibrocellular tissue develops inferiorly, which suggests that gravity influences the distribution



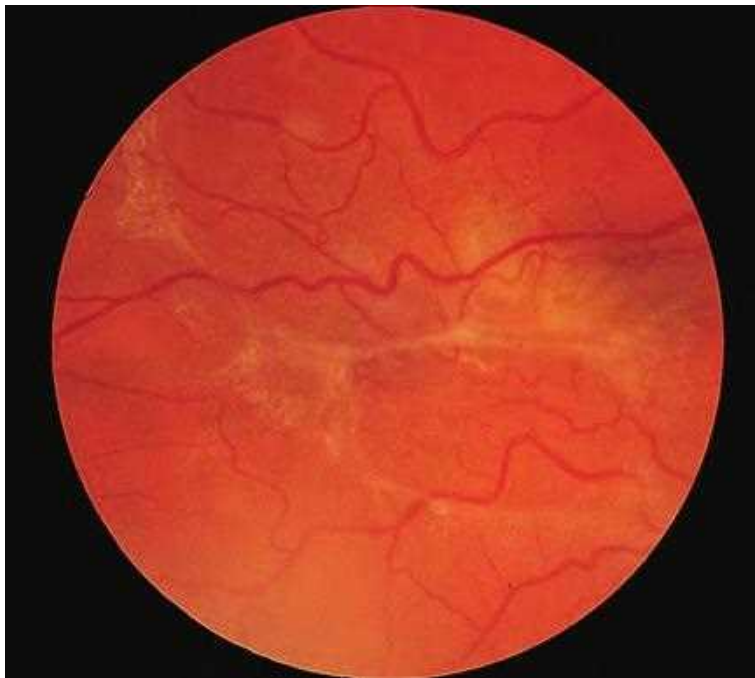
**Fig. 6.42.1 Pathogenesis of Proliferative Vitreoretinopathy.** The flow chart illustrates the interaction of various factors in the pathogenesis of proliferative vitreoretinopathy, from the initial retinal detachment to the serious complications of recurrent detachment and hypotony.

of the RPE cells. Glial cell proliferation and extension of glial processes to the epi- and subretinal spaces follows, and an extracellular matrix is laid down.<sup>7</sup> These cells take on the characteristics of myofibroblasts in that they have contractile elements and deposit collagen.<sup>2</sup> Although the cellular origins of PVR are critical, the extracellular environment plays a decisive role as well. Inflammation and breakdown of the blood–retina barrier are associated with further cellular recruitment modulated by inflammatory mediators and the formation of extensive fibrous membranes.<sup>8</sup> Collagen is produced and the membranes then contract. It is the contraction of surface membranes that produces the clinical features described below. The cycle of cell dispersion, inflammation, membrane formation, and contraction with eventual redetachment of the retina has a typical timescale of 4–6 weeks after the initial detachment.

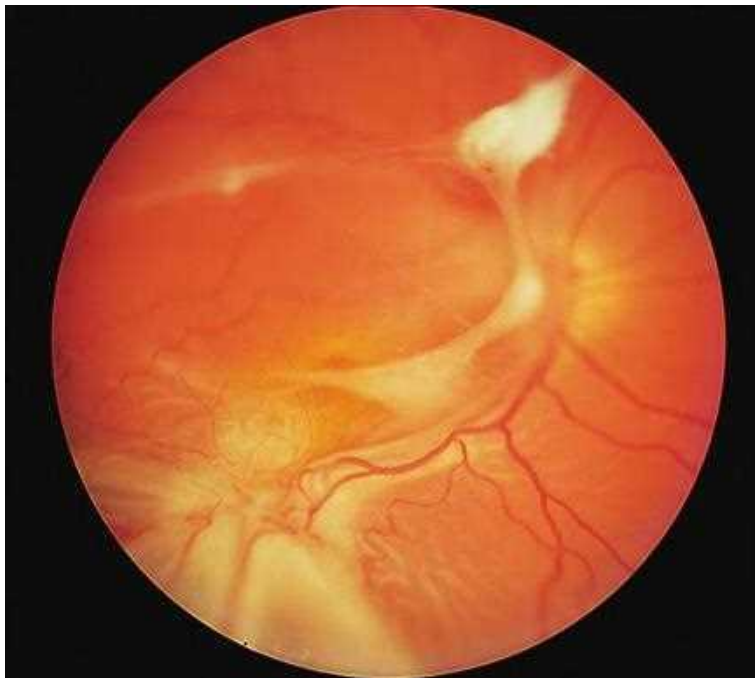
## OCULAR MANIFESTATIONS

The clinical spectrum of PVR varies according to the extent and location of membranes and the presence and position of retinal breaks. Epiretinal membrane formation after successful retinal detachment surgery can be considered a mild form of PVR (Fig. 6.42.2). In its most severe form, membrane contraction produces a total, funnel-shaped detachment with





**Fig. 6.42.2 Macular Pucker Following Retinal Detachment Surgery.** Contraction of a surface membrane at the macula produces symptoms of distortion and reduced visual acuity. Such epiretinal membranes are identical histologically to those removed from elsewhere on the retina in proliferative vitreoretinopathy.



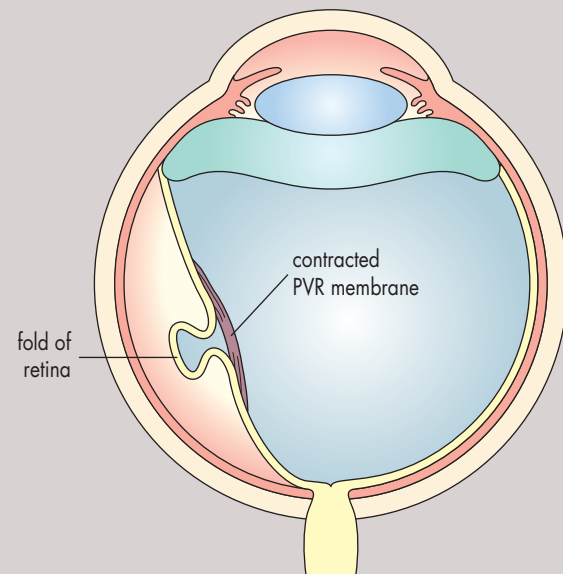
**Fig. 6.42.3 Star Fold From Proliferative Vitreoretinopathy.** Contraction of a focal retinal surface membrane has resulted in the formation of a star fold. In this case, membranes can also be seen on the posterior surface of the partially detached hyaloid face.

retina adherent anteriorly to the ciliary body and even to the iris, which results in hypotony and phthisis bulbi.

The earliest signs of PVR include marked vitreous flare and clumps of pigment in the vitreous. Increased stiffness of the detached retina often occurs, which can be detected with indirect ophthalmoscopy while the patient's eye is making saccades. A fresh retinal detachment without PVR appears to undulate under these conditions, an undulation that is reduced if significant surface membranes are present. The edges of retinal breaks may be rolled over, as a result of contraction on one surface only, and retinal breaks may appear stretched open. Star folds represent localized areas of puckering in detached retina after focal, localized contraction (Fig. 6.42.3).

Subretinal fibrosis may accompany surface membranes to give a “Swiss cheese” appearance to the subretinal space. Some of the subretinal sheets of membrane coil together, which results in broad, subretinal strands.

## RETINAL SHORTENING



**Fig. 6.42.4 Retinal Shortening.** Surface membrane contraction can result in retinal shortening, which prevents break closure and retinal reattachment.

**TABLE 6.42.1 Proliferative Vitreoretinopathy: Retina Society Revised Classification**

Grade A	Vitreous haze, pigment clumps, decreased mobility of posterior hyaloid face
Grade B	Inner retinal wrinkling, stiffness, rolled edges of retinal breaks
Grade C	Full-thickness retinal folds, anterior/posterior extent in clock hours
Type 1	Focal posterior contraction (star fold)
Type 2	Diffuse posterior contraction
Type 3	Subretinal bands/sheets
Type 4	Circumferential contraction (posterior edge of vitreous base)
Type 5	Anterior displacement of vitreous base

From Machemer R, Aaberg TM, MacKenzie Freeman H, et al. An updated classification of retinal detachment with proliferative vitreoretinopathy. *Am J Ophthalmol* 1991;112:159–65.

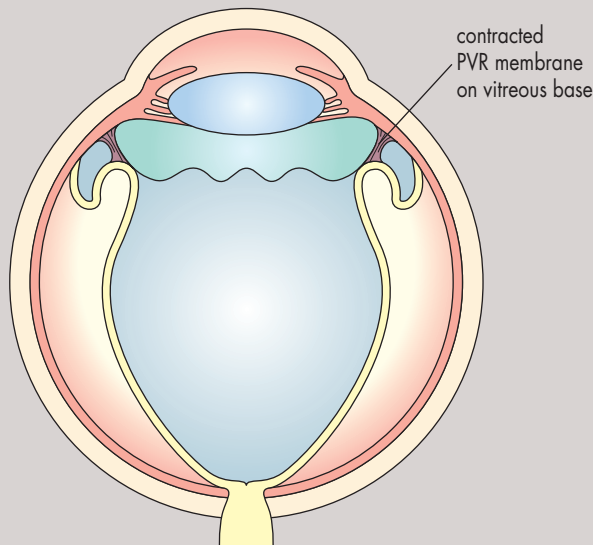
A subretinal “napkin ring” of membrane can surround the peripapillary retina to produce a tight posterior funnel configuration and obscure the optic nerve. Significant amounts of surface traction produce retinal shortening, which makes break closure and retinal reattachment impossible (Fig. 6.42.4). More severe contraction may pull the anterior retina inward, which leads to an anterior funnel appearance. In severe cases, closure of the anterior end of the funnel may make it impossible to visualize the optic disc even if the posterior retina is relatively unaffected. Contraction of the vitreous base leads to circumferential shortening and anterior loop contraction. Surface membranes on the ciliary body may compromise aqueous production, which results in hypotony.

Surface membranes can be difficult to diagnose when the retina is attached. Histopathological examination of the majority of successfully repaired retinal detachments show surface membrane formation. Occasionally, surface membranes can result in localized traction retinal detachments, often seen just posterior to a scleral buckle. These localized traction detachments tend to be stable and should be differentiated from recurrent rhegmatogenous detachments associated with open retinal breaks. Traction retinal detachments have a concave surface generated by the RPE pump pulling against traction, in contradistinction to the convex profile of rhegmatogenous detachments. Should a new retinal break develop acutely or a pre-existing break reopen, already present but unsuspected membranes may result in dramatic contraction of the newly redetached retina to give the clinical impression of sudden development of severe PVR.

Associated anterior segment signs include anterior chamber cells and flare and low intraocular pressure. In some eyes, dilated iris vessels or even iris neovascularization develops.

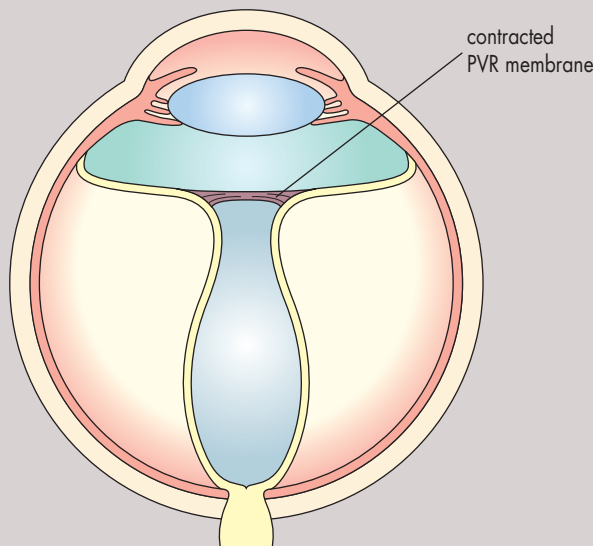
The Retina Society devised a classification scheme for PVR that has been used in clinical trials of treatment.<sup>9</sup> The initial scheme did not distinguish between anterior and posterior PVR, and improvements in the understanding of anterior PVR have led to a modification of the classification (Table 6.42.1).<sup>10</sup> Anterior PVR is characterized by contraction of

## ANTERIOR PROLIFERATIVE VITREORETINOPATHY (1)



**Fig. 6.42.5 Anterior Proliferative Vitreoretinopathy (1).** Fibrous contraction in an anteroposterior direction in the region of the vitreous base pulls up a loop of retina to produce retinal shortening. Coexistent traction on the ciliary body produces hypotony.

## ANTERIOR PROLIFERATIVE VITREORETINOPATHY (2)



**Fig. 6.42.6 Anterior Proliferative Vitreoretinopathy (2).** Contraction of the anterior vitreous produces a funnel configuration.

membranes associated with the vitreous base; it is seen most commonly after failed vitrectomy and gas tamponade for retinal detachment or after penetrating trauma.<sup>11</sup> Anteroposterior traction can pull a fold of retina forward to produce a “trough” with posterior shortening (Fig. 6.42.5), which can be difficult to diagnose preoperatively. Circumferential contraction of the vitreous base produces radial folds in the retina, and perpendicular contraction of the anterior vitreous leads to an anterior funnel-shaped configuration (Fig. 6.42.6).

## DIAGNOSIS

In eyes with clear media, the diagnosis of PVR is straightforward. A history of retinal detachment surgery and the clinical features just described do not generally present a diagnostic problem. In eyes with opaque media, B-scan ultrasonography is necessary to reveal the stiffened, detached retina and associated membranes.

### BOX 6.42.1 Differential Diagnosis of Proliferative Vitreoretinopathy

- Proliferative diabetic retinopathy with traction retinal detachment
- Chronic retinal detachment with retinal edema and/or cyst formation
- Severe choroidal detachments
- Severe vitreomacular traction syndrome with traction retinal detachment
- Severe ocular hypotony

## DIFFERENTIAL DIAGNOSIS

The differential diagnosis of PVR is given in Box 6.42.1.

## SYSTEMIC ASSOCIATIONS

Although no specific systemic associations exist, patients who have Stickler’s syndrome have an increased risk of retinal detachment due to large and/or multiple retinal breaks that make subsequent PVR likely.

## PATHOLOGY

A large body of pathological information exists that confirms the role of glial activation, RPE cells, inflammation, breakdown of the blood–ocular barrier, macrophages, growth factors, cytokines, clotting cascade proteins, adhesion molecules, and extracellular matrices in the development of PVR. In histological specimens, RPE cells are uniformly present, and evidence shows that they can undergo metaplastic change to macrophages or fibroblasts.<sup>12</sup> Glial cells are a major component of PVR membranes and may arise from retinal astrocytes<sup>13</sup> or from Müller cells extending processes to epi- and subretinal membranes.<sup>3,7</sup> Lymphocytes have been identified in excised PVR membranes,<sup>14</sup> and inflammatory cells may play a role in mediating the proliferative response.

The behavior of the RPE cell may be stimulated by several different growth factors that are known to contribute to the wound-healing process in general. For example, platelet-derived growth factor stimulates chemotaxis,<sup>15</sup> and fibroblast growth factor and insulin-like growth factor-1 stimulate RPE cell proliferation.<sup>16</sup> Elevated levels of bFGF, interleukin-1, and interleukin-6 have been detected in the vitreous of patients with PVR.<sup>17,18</sup> In contrast, transforming growth factor- $\beta$  (TGF- $\beta$ ) has an inhibitory effect on cell proliferation in tissue culture.<sup>19</sup> Replicated genetic association studies have suggested a contribution of the SMAD7 (a TGF- $\beta$ -pathway mediator) and TNF (an inflammatory cytokine) genes to the PVR process.<sup>20</sup>

The extracellular matrix associated with PVR consists of various types of collagen, particularly types I and III. Other components include fibronectin and the basal lamina proteins, heparan sulfate, laminin, and collagen type IV.<sup>21</sup> Modeling of the extracellular matrix by matrix metalloproteinases may play a role in the pathogenesis of PVR.<sup>22</sup>

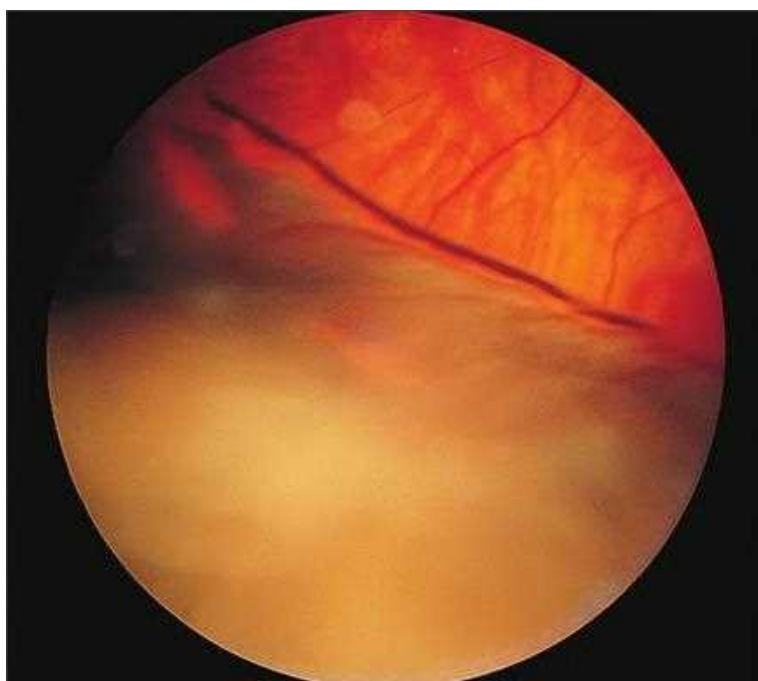
The mechanism of membrane contraction remains poorly understood. Some of the cell types found in membranes are capable of contraction, including fibroblasts and RPE cells.<sup>23</sup> Cytoplasmic myofilaments have been seen in some fibroblastic cells, but simple motility of cells through a collagen matrix may be sufficient to produce shortening.

The retina, at least in the early stages of PVR, remains relatively well preserved, suggesting the potential for functional recovery.<sup>7,24</sup> Photoreceptor apoptosis has, however, been demonstrated<sup>24</sup> together with remodeling changes in the neural retina,<sup>7</sup> which may have a negative effect on visual recovery. The epiretinal membranes in anterior PVR have focal glial attachments to the underlying retina, which may make surgical separation of these tissues difficult or impossible.<sup>7,24</sup>

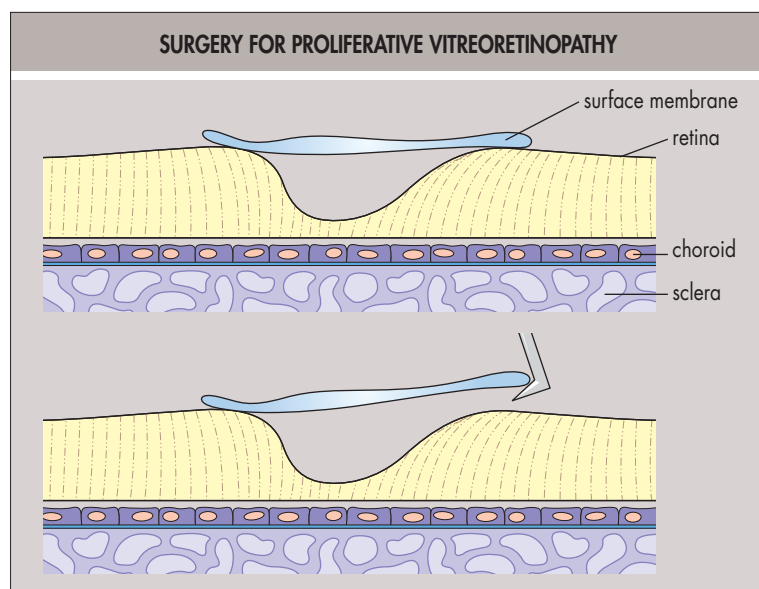
## TREATMENT

In the absence of open retinal breaks, PVR does not require treatment unless the macula is involved. Localized traction detachments posterior to a scleral buckle are stable and asymptomatic. Macular pucker after otherwise successful retinal detachment surgery may be responsible for reduced visual acuity and distortion. Such cases often benefit from membrane peeling.

In rhegmatogenous retinal detachment, the choice of treatment is based on the severity and location of the PVR and the location of the retinal break or breaks. Scleral buckling alone may be successful if the surface membranes do not prevent break closure. For example, the presence of



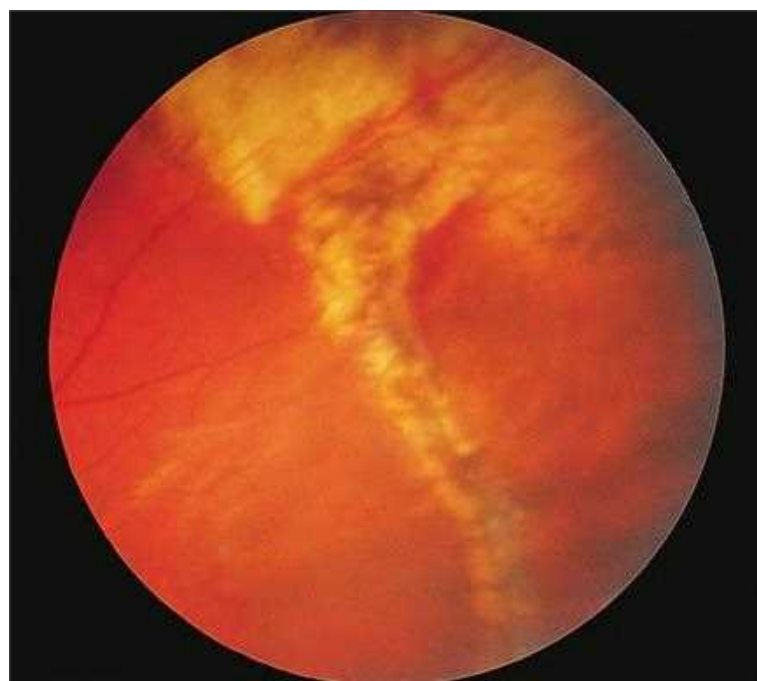
**Fig. 6.42.7 Scleral Buckling in Proliferative Vitreoretinopathy.** The large inferior buckle seen here was used to support inferior breaks associated with proliferative vitreoretinopathy. Recurrent gray proliferative vitreoretinopathy membranes can be seen on the surface of the buckle, but the retina remains attached posteriorly. Note the dark line on the edge of the buckle, which is an optical effect of the silicone oil fill.



**Fig. 6.42.8 Surgery for Proliferative Vitreoretinopathy.** A pick is used to elevate surface membranes prior to removal with forceps.

inferior star folds does not prevent successful closure of a single superior retinal break by means of a scleral buckle. However, it can be difficult to judge the extent of retinal shortening and, therefore, the influence of a star fold on a remote break. If surface membranes occur in close association with retinal breaks, closed intraocular microsurgery with membrane peeling is required to enable break closure, although occasionally a substantial inferior buckle can be used successfully to close breaks associated with a moderate degree of surface contraction<sup>25</sup> (Fig. 6.42.7).

With an internal approach, a complete pars plana vitrectomy is followed by peeling of surface membranes using a combination of a retinal pick and microforceps<sup>26</sup> or curved membrane scrapers (Fig. 6.42.8). The ease with which membranes can be removed varies, and this may be related to membrane-retina glial bridges,<sup>24</sup> but it is important to relieve traction associated with breaks if surgery is to succeed. Perfluorocarbon liquids may assist the process as they highlight the membranes and act as a “third hand” to assist in membrane removal.<sup>27</sup> If long-term intravitreal tamponade with silicone oil is to be used, the membranes may be more visible after oil injection and so are peeled at that stage. If not already present,



**Fig. 6.42.9 A Severe Case of Anterior Proliferative Vitreoretinopathy Treated With a 270° Relaxing Retinectomy.** The line of laser retinopexy at the edge of the retinectomy can be seen to join with an area of chorioretinal adhesion from cryotherapy.

a circumferential scleral buckle is usually applied to support the vitreous base, which typically is shortened circumferentially. Occasionally, peeling of posterior membranes is insufficient to relieve retinal shortening. In such cases, further dissection of the vitreous base may be successful. Alternatively, a relaxing retinectomy can be performed (Fig. 6.42.9).<sup>28,29</sup>

Rarely, subretinal membranes may be present, usually in a band-like configuration. These can tent up the retina, although in most cases simple closure of the break results in complete reattachment. If necessary, the bands can be divided through a small retinotomy or pulled out hand over hand, as they tend to be only loosely adherent to the overlying retina.

After membrane removal, the retina is reattached by means of internal drainage of subretinal fluid, usually accompanied by a fluid–air exchange. Retinopexy with cryotherapy or laser photocoagulation is applied to all breaks. Laser retinopexy is often preferred because of the theoretically increased risk of further PVR associated with the use of cryotherapy.

A long-acting gas or silicone oil is injected for tamponade; the choice of agent depends on a number of factors. The Silicone Study examined the effect of the choice of long-term retinal tamponade on final surgical outcome in PVR cases. The study indicated that both perfluoropropane ( $C_3F_8$ ) gas and silicone oil were of similar benefit in PVR, and both are superior to  $SF_6$ .<sup>30,31</sup> In anterior PVR, the use of silicone oil yields a better visual outcome than  $C_3F_8$ .<sup>32</sup> Silicone oil has certain intraoperative and postoperative advantages over gas, which include improved visualization for retinopexy, less need for positioning, and better vision in the immediate postoperative period.

Recent advances include the utilization of heavier-than-water silicone oils to manage inferior PVR. A randomized controlled trial comparing heavy silicone oil with light silicone oil in eyes with PVR showed no significant differences in either anatomical success or final visual acuity.<sup>33</sup> A systematic review of the above tamponade agents did not highlight any differences in outcomes, suggesting a patient-individualized approach to choice of tamponade.<sup>34</sup>

Despite successful treatment, PVR can recur, which results in the formation of new breaks or the reopening of treated breaks (Fig. 6.42.10). The tendency of PVR to recur has generated much interest in the use of pharmacological agents for adjuvant therapy to surgery. Fig. 6.42.1 shows that many potential pharmacological targets exist for such therapy.

Attempts to modulate the inflammatory component of PVR pathogenesis have been unsuccessful.<sup>35</sup> Randomized controlled trials investigating intraoperative intravitreal triamcinolone<sup>36</sup> and intraoperative slow-release dexamethasone implants<sup>37</sup> have failed to improve anatomical outcomes in cases with established PVR, whereas the use of postoperative oral prednisolone<sup>38</sup> did not influence the development of PVR.

A meta-analysis of the combination of adjuvant 5-fluorouracil (an antimetabolite) and low-molecular-weight heparin as an adjunct in the





**Fig. 6.42.10 Reproliferation and Failed Retinectomy for Proliferative Vitreoretinopathy.** Reproliferation of membranes along the edge of a relaxing retinectomy has resulted in elevation of the posterior edge.

treatment of PVR highlights inconsistent results,<sup>39</sup> reducing the incidence of PVR in high-risk cases undergoing vitrectomy<sup>40</sup> but failing to improve the outcome in cases with established PVR<sup>41</sup> or in preventing the development of PVR in unselected cases.<sup>42</sup>

Perioperative use of daunomycin, another antimetabolite, resulted in a weak beneficial effect in achieving anatomical success in a large randomized controlled trial.<sup>43</sup> A smaller randomized control trial investigating oral isotretinoin in established PVR showed statistically significant improvement in reattachment rates.<sup>44</sup>

## COURSE AND OUTCOME

Untreated, PVR inevitably leads to severe loss of vision, hypotony, and sometimes phthisis bulbi. Success rates of surgical treatment vary and depend on the severity of PVR and the surgical techniques employed.<sup>45,46</sup> Prior to the introduction of closed intraocular microsurgery, success rates were poor. With modern techniques, anatomical success is being achieved in an increasing number of cases. Most recent series report single surgery anatomical success rates of approximately 80% in cases with PVR C.<sup>4,29</sup>

Despite improved anatomical results, visual outcomes are often disappointing.<sup>3,47</sup> When patients have a normal fellow eye, functional vision in the operated eye may not be useful, and it is considered a “spare.”<sup>48</sup> It is notable that vision-threatening pathology has been demonstrated in over

50% of fellow eyes in PVR cases,<sup>49</sup> and this is an important consideration when deciding to operate on PVR cases.

Visual loss in PVR is a combination of photoreceptor degeneration and apoptosis, neural remodeling, and epi- and subretinal pathology.<sup>50</sup> Subretinal gliosis prevents photoreceptor regeneration.<sup>50</sup> Clinically it has been noted that two-thirds of PVR cases with poor visual recovery have cystoid macular edema,<sup>51</sup> and treatment of this with topical corticosteroids and anti-inflammatory medications or potentially intraocular corticosteroid injections may be of value in improving visual outcomes.

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# Posterior Segment Ocular Trauma

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# 6.43



**Definition:** Penetrating and/or nonpenetrating physical trauma to the globe, resulting in damage to the posterior segment.

## Key Features

- Blunt injury with or without globe rupture.
- Penetrating injury with or without foreign body.

## Associated Features

- Hemorrhage.
- Commotio retinae.
- Choroidal rupture.
- Traumatic macular hole.
- Sclopetaria.
- Retinal detachment.
- Proliferative vitreoretinopathy.
- Endophthalmitis.
- Sympathetic ophthalmia.

## INTRODUCTION

Ocular trauma is an important cause of visual loss and subsequent disability. With modern diagnostic techniques and surgical approaches, many eyes can be salvaged with retention of vision.<sup>1-4</sup> Despite advances in medical and surgical management, penetrating trauma continues to be a complicated and challenging condition.

Posterior segment trauma is broadly divided into nonpenetrating and penetrating injuries. Nonpenetrating injuries that involve the posterior segment are the result of severe, blunt, concussive blows to the globe and result in specific types of ocular damage such as commotio, choroidal rupture, traumatic macular hole, and sclopetaria.

Penetrating injuries are divided into various subcategories based on specific types of injuries. Penetrating injuries can occur secondary to blunt force trauma, lacerating injuries, or injuries associated with intraocular foreign bodies.

## OCULAR MANIFESTATIONS AND CLINICAL EXAMINATION

### History

Clinical history is essential to ascertain important details about the mechanism of injury. A careful history as to the circumstances surrounding the injury can help elucidate the type of injury (blunt trauma, penetrating injury with or without foreign body), the potential for secondary complications (clean vs. contaminated or “dirty” wound), and the potential for other associated nonocular injuries (e.g., the potential for a subdural hemorrhage in an elderly patient after a fall). Finally, a comprehensive medical history should be obtained with specific attention directed toward active medical conditions, current medications (specifically anticoagulants), drug allergies, and history of tetanus immunization.

## Clinical Examination

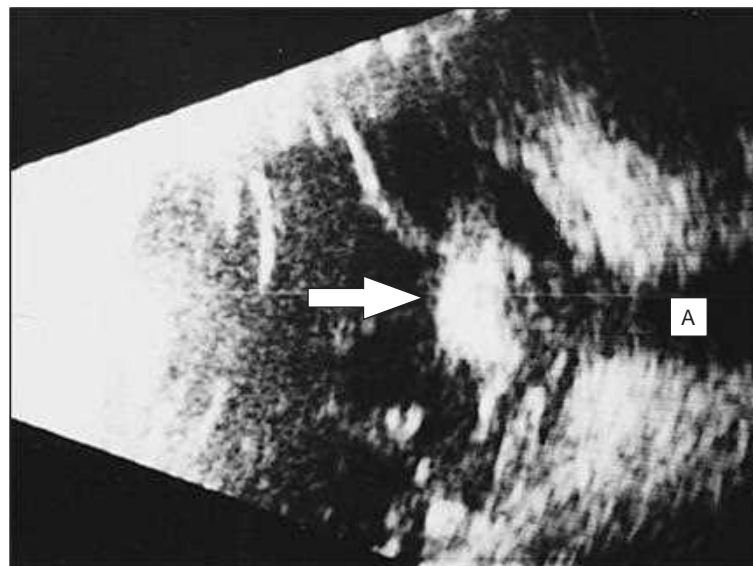
The initial clinical examination should be as comprehensive as possible while avoiding iatrogenic injury to the eye. Visual acuity may be difficult to accurately assess in the setting of severe ocular trauma. Pupillary examination should be assessed for the presence of an afferent pupillary defect, which can be an important objective assessment of the visual potential of the injured eye. Care should be taken to limit the examination of extraocular motility due to the potential extrusion of ocular contents. Ocular tonometry should be deferred in the setting of a potential ruptured globe.

Slit-lamp evaluation with minimal pressure on the globe should be performed with attention toward finding any open lacerations of the cornea or sclera. Extensive subconjunctival hemorrhage in the setting of a hypotonus globe should raise the suspicion for an occult rupture that cannot be directly visualized. Early signs of infection such as inflammation should be ascertained.

If the fundus can be visualized, then the presence of a penetrating injury with or without foreign body (IOFB) should be by ophthalmoscopy. Identification of retinal tears, retinal detachment, and choroidal hemorrhage are critical prior to surgical intervention. Retinal vasculitis and diffuse intraretinal hemorrhages can be an important harbinger of endophthalmitis. In the setting of blunt trauma, macular and peripheral evaluation are important to identify the various manifestations of nonpenetrating trauma.

## Ancillary Testing

Ancillary testing is useful in the evaluation of patients who have penetrating injuries or in patients with poor visualization of the fundus. Standard orbital plain film radiographs will delineate the presence of a radiopaque foreign body (Fig. 6.43.1). Radiolucent foreign bodies such as wood or glass will often not be visualized with plain films. Computed tomography (CT)



**Fig. 6.43.1 Radiopaque Intraocular Foreign Body (arrow).** Note the characteristic acoustic shadowing (A) behind it.



scanning of the orbits is more helpful in not only determining the presence of a radiopaque foreign body but also localizing the foreign body. It is important to order axial, coronal, and lateral, fine-section images (2-mm “cuts”) to help precisely localize the IOFB. Magnetic resonance imaging (MRI) is contraindicated in any patient with a potential magnetic IOFB. Diagnostic ultrasound can help detect and localize IOFBs that are radiolucent. Ultrasound can also help to assess the amount of liquefaction of the hemorrhage in cases where choroidal hemorrhage is present. Liquefaction of choroidal hemorrhage often occurs within 7–14 days after occurrence. It is at this time that drainage can occur most effectively.

## NONPENETRATING TRAUMA

Blunt injury to the globe can result in a variety of anterior segment manifestations that can affect the management of the posterior segment. Corneal edema can preclude an adequate view of the posterior segment. Anterior chamber hemorrhage (hyphema) can also reduce or eliminate visualization into the back of the eye. Subluxation or dislocation of the crystalline lens may require removal via a posterior approach.

### Comotio Retinae

Comotio retinae is retinal whitening/opacification that results from a blunt injury. The ocular findings will often resolve in a matter of days to weeks. Vision loss can result from commotio involving the posterior pole (historically referred to as Berlin’s edema, [Fig. 6.43.2](#)).<sup>5</sup> It is a common retinal finding after significant ocular injury occurring in up to half of all cases of significant blunt trauma.<sup>6</sup> Histopathological studies show that the findings are localized to the outer retina. These findings are supported by optical coherence tomography (OCT) that shows increased reflectivity of the inner and outer segments.

Clinical findings of commotio include the characteristic retinal whitening. Comotio may result in significant vision loss that can be transient. Healing can result in pigmentary changes and retinal thinning that may be associated with poor visual recovery if the area of involvement is macular. Areas of involvement outside of the macula can result in peripheral visual field loss and retinal pigment epithelium (RPE) changes that can mimic sectoral retinitis pigmentosa (RP), acute zonal occult outer retinitis (AZOOR), chronic central serous, and similar conditions.

Diagnostic testing in the setting of commotio should include OCT testing to identify the extent of photoreceptor involvement. Photography to document the extent of the involvement is often useful in these cases.

Management of collateral injuries is of most importance as there is no therapy for commotio. The prognosis for commotio is variable.

### Choroidal Rupture

Choroidal rupture often occurs as the result of blunt trauma ([Fig. 6.43.3](#)). It represents a tear not only in the choroid but also in the RPE and Bruch’s membrane. It is the disruption in Bruch’s membrane that results in the late complication of this condition, choroidal neovascularization. Choroidal ruptures can occur anteriorly (due to direct concussive force of the blunt trauma) or posteriorly (due to indirect blunt force).

Clinical findings of choroidal rupture acutely include the presence of a curvilinear defect of the RPE and choroid. Often this area has associated subretinal hemorrhage. The initial hemorrhage is due to the rupture of the choroid. Often this hemorrhage will clear within a few weeks. Remote from the initial injury, choroidal neovascularization can develop resulting in vision loss remote to the initial trauma.

Initial diagnostic testing in the setting of choroidal rupture can include OCT and photography. If the development of choroidal neovascularization is suspected, OCT and fluorescein angiography can be very helpful in determining the presence and extent of the abnormal vessels.

Therapy of choroidal rupture is limited. Visual acuity will often depend on the involvement of the foveal center by the rupture. The late occurring sequela of choroidal neovascularization can result in loss of vision. Patients should be made aware of this potential occurrence and should be given and instructed on use of an Amsler grid for detection of choroidal neovascularization, should it occur. Intravitreal antivascular endothelial growth factor therapy is very effective in the management of these vessels.

### Traumatic Macular Hole

Full-thickness macular hole formation can result from blunt ocular trauma. Macular hole formation can occur immediately after trauma or

may develop several weeks to months after the injury. The exact mechanism of macular hole formation in this setting is unknown, but acute anteroposterior vitreous traction is suspected. Macular hole formation can also be seen after severe blunt trauma in association with commotio and retinal hemorrhage. OCT can aid in identifying the progressive retinal changes leading to the development of the macular hole. Often, cystic intraretinal or subretinal findings can be visualized on OCT prior to the onset of the full-thickness defect. Patients with good visual acuity after their initial injury will often notice the development of a central scotoma, whereas those without good visual acuity due to associated injuries may not be able to discern any differences. Biomicroscopy and OCT testing are critical to the diagnosis of a posttraumatic full-thickness macular hole.

Pars plana vitrectomy with intravitreal gas tamponade is the primary therapy for this condition. Timing of surgery is controversial, as some traumatic macular holes close spontaneously. Traumatic macular holes may carry a poorer prognosis for surgical closure due to their size. Visual improvement may be limited due to concomitant injuries.

### Chorioretinitis Sclopetaria

Chorioretinitis sclopetaria (CRS) is a simultaneous break in the retina and the choroid that occurs as a result of a high-velocity object coming in contact with the globe without penetrating the eye ([Fig. 6.43.4](#)). The simultaneous retraction of the choroid and retina at the site reveals the bare sclera.<sup>7</sup> The site of involvement can be adjacent to the impact site or remote from the site. Remote (or indirect) areas of involvement can result in significant damage to the macula.

Clinically, visual acuity is often limited due to the mechanism and severity of the injury. Hemorrhage is often present around the area of CRS in either the preretinal or subretinal space. There is often surrounding commotio present. The sclera is often readily visible through the defect in the retina/choroid. With time, the surrounding areas develop a pigmentary response and scar formation ensues. Initially, clinicians are concerned that the area of injury may develop into a retinal detachment. Often with observation, this does not occur.

Therapy is limited. If the patient develops significant, vision-limiting vitreous hemorrhage or a retinal detachment ensues, then surgery with vitrectomy and/or scleral buckling is warranted. The prognosis is poor in cases that involve the macular area.

### Retinal Tear

Trauma is responsible for about 5% of all retinal detachments.<sup>8</sup> As such, blunt trauma can result in the precursor to retinal detachment, the retinal tear. Traumatic posterior vitreous detachment can result from compressive forces within the eye. The incidence of retinal tear formation in blunt trauma is unknown. More severe blunt trauma and predisposing factors such as myopia and the presence of lattice degeneration increase the risk of developing a retinal tear.

Patient symptoms consistent with a posterior vitreous detachment, including “flashes and floaters,” should alert the examiner to the possible presence of peripheral pathology secondary to the trauma. Clinical examination is critical in diagnosing a traumatic retinal tear. Slit-lamp biomicroscopy to determine the presence of pigmented vitreous cell should be performed. Vitreous hemorrhage is suggestive of a possible retinal tear. Indirect ophthalmoscopy should take place to thoroughly examine the peripheral retina. Depressed examination is also essential, but associated injuries should be assessed prior to proceeding with indentation of the eye wall to prevent exacerbation of anterior chamber hyphema. Additionally, concomitant injuries may prohibit depressed examination secondary to patient discomfort.

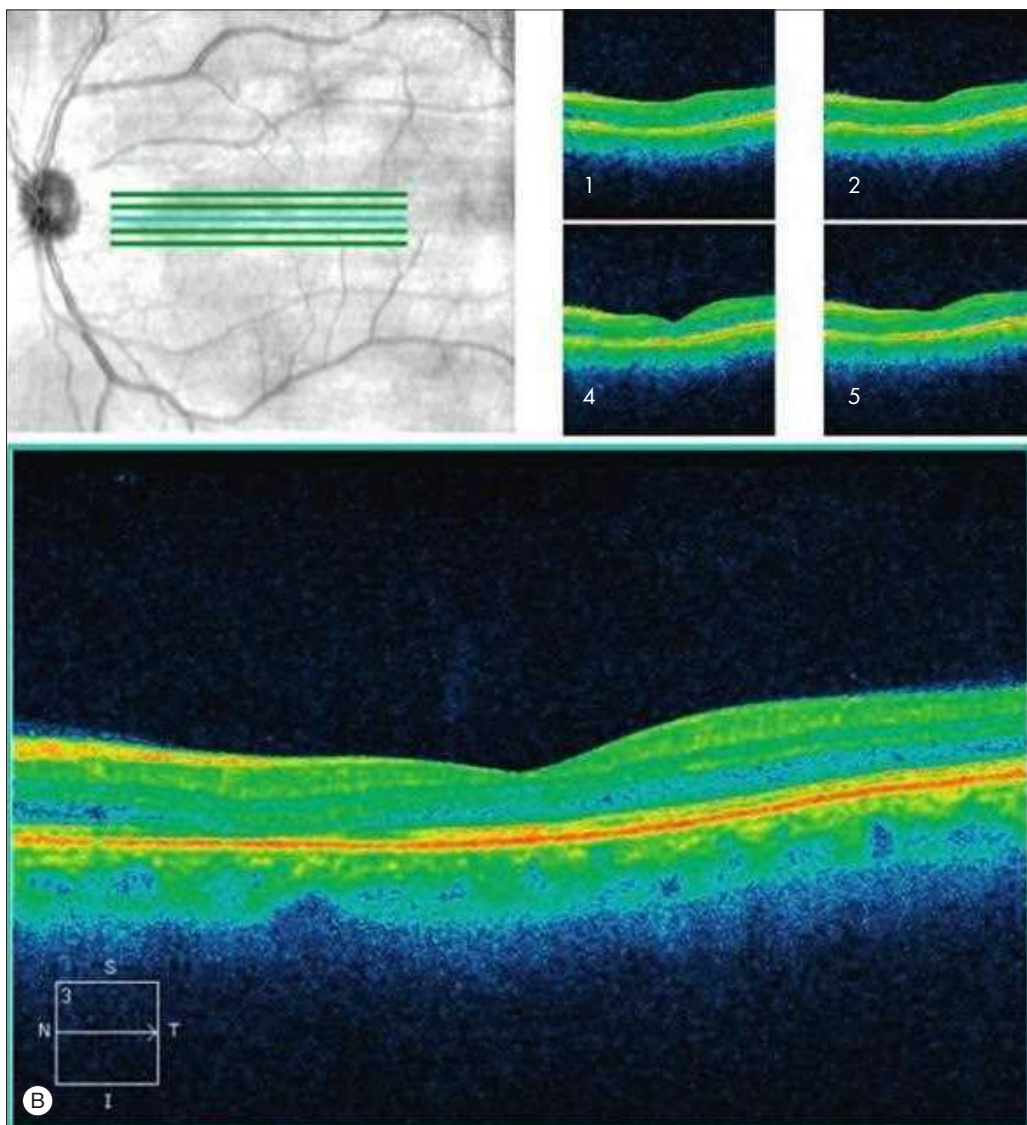
Treatment of a retinal tear with prophylactic laser therapy is essential to prevent retinal detachment. Care should be taken to differentiate a traumatic retinal tear from CRS, which is often more extensive, results in a defect of both the retina and choroid, and requires no treatment to prevent retinal detachment.

### Retinal Detachment

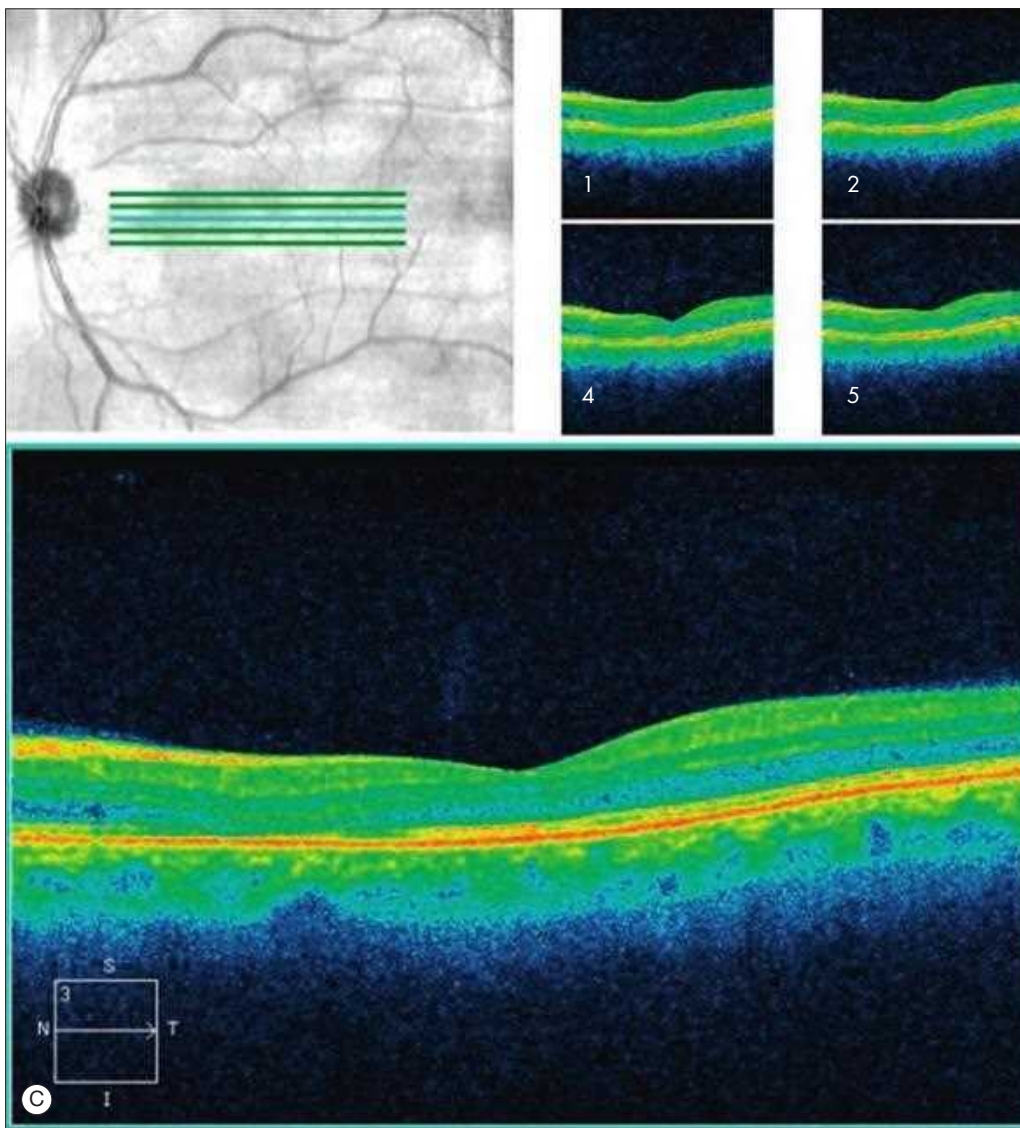
Blunt and penetrating trauma both represent significant risk factors for the development of retinal detachment. Blunt trauma can result in retinal tears secondary to a vitreous detachment (see earlier). Retinal detachment in the setting of blunt trauma can also result from a retinal dialysis (see later).



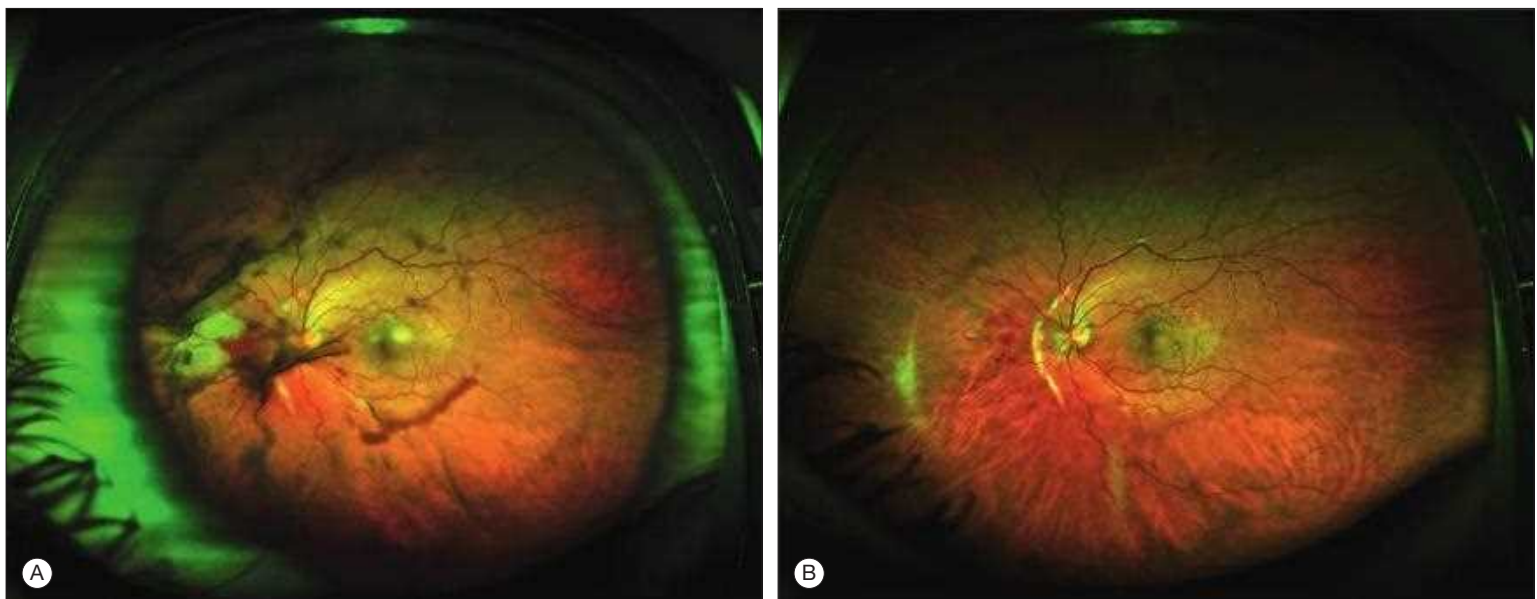
**Fig. 6.43.2** (A) Berlin's edema (commotio retinae) in a patient after blunt trauma. (B) Acute optical coherence tomography (OCT) findings demonstrate disruption of the outer retina.





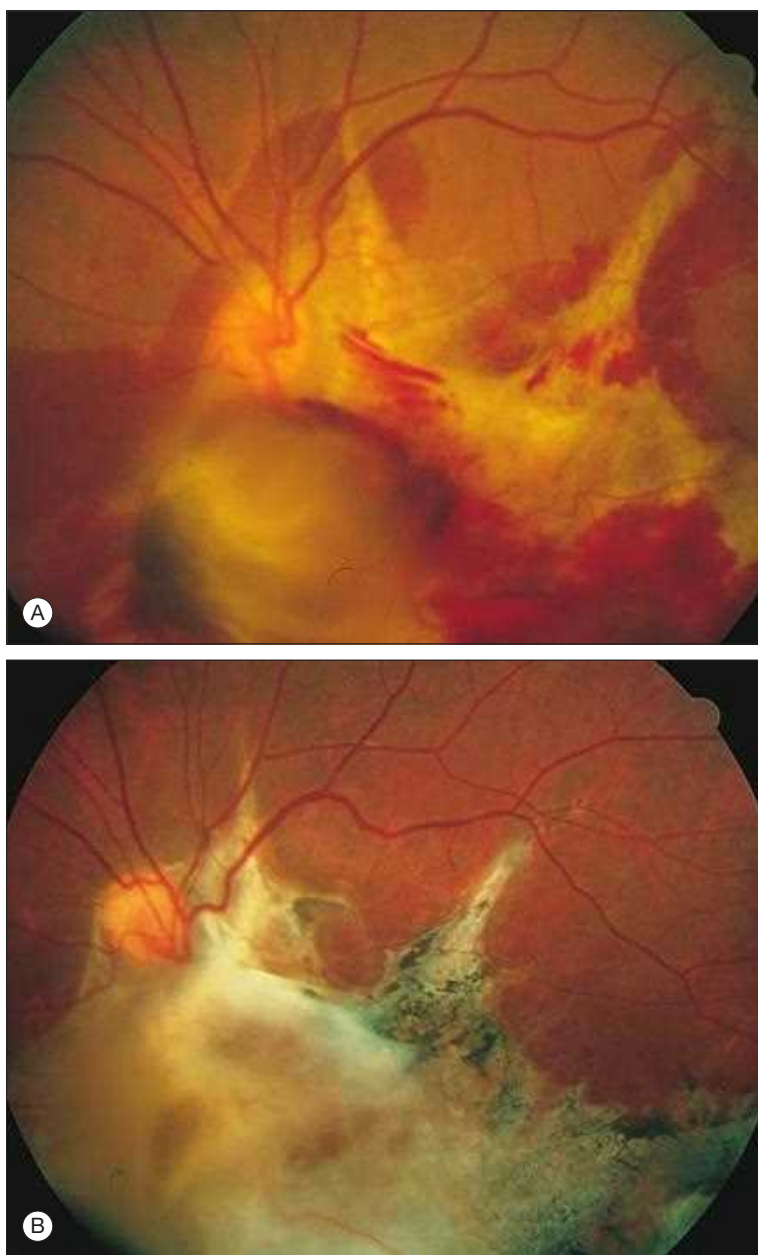


**Fig. 6.43.2, cont'd** (C) After resolution of the acute findings, the OCT shows outer retinal atrophy including photoreceptor loss. (B–C courtesy Drew Sommerville, MD; Talley Eye Care; Evansville, IN.)



**Fig. 6.43.3 Choroidal Rupture With Vitreous Hemorrhage and Commotio.** NOTE: Blunt trauma from a broken exercise band resulted in commotio and choroidal rupture nasal to the optic nerve. Vitreous hemorrhage also resulted (A). One month later, the commotio has resolved and the choroidal rupture can be well visualized (B).





**Fig. 6.43.4 Gunshot Wound to the Periocular Region.** (A) Sclopetaria manifests as subretinal and choroidal hemorrhage; also note marked disruption and necrosis of the choroid and retina. (B) After 6 months and no surgical intervention, the retina remains attached and marked chorioretinal scarring is present.

Clinically, retinal detachment in the setting of blunt trauma can occur acutely or remote from the traumatic event. In either case, a careful history of the symptoms is critical. The examination should include biomicroscopy to determine if the macula is involved by the detachment (macula/fovea—on/off). In addition, associated injuries such as commotio, choroidal rupture, and macular hole must be assessed. Injury to the anterior segment—hyphema, angle recession, traumatic cataract, and intraocular lens (IOL) dislocation—can also affect surgical planning and disposition. Ocular ultrasonography can be of benefit when visualization of the posterior segment is obscured by vitreous hemorrhage or opacities of the anterior segment.

As with other causes of retinal detachment, treatment centers on surgical repair. Most commonly scleral buckling, pars plana vitrectomy, or a combination of both is employed to repair traumatic retinal detachments. In addition, injuries to the anterior segment such as traumatic cataract or IOL dislocation may necessitate surgical management at the time of the retinal detachment (RD) repair.

## Retinal Dialysis

Retinal dialysis is a tearing of the retina at the ora serrata due to an avulsion of the vitreous base from sudden traction at the vitreous base. Not all dialyses are traumatic in nature, and a developmental abnormality may be responsible for most of the nontraumatic cases. Dialyses are most

commonly seen in the inferotemporal quadrant. When a dialysis occurs in the superior or nasal areas, trauma should be strongly suspected.

Clinical examination is critical in diagnosing a retinal dialysis. A peripheral depressed examination is almost essential to differentiate a retinal dialysis from a giant retinal tear, as a dialysis will not fold back on itself or become inverted due to the presence of the vitreous base adherent to the edge of the retina.

Treatment for a retinal dialysis without an associated retinal detachment includes observation (particularly if there is RPE hyperplasia posterior to the area of dialysis) and laser or cryotherapy. In the setting of a retinal detachment, a scleral buckle with cryotherapy is effective in repairing the detachment in over 90% of eyes. If the subretinal fluid is shallow, often a nondrainage buckle is effective. Care must be taken when performing vitrectomy surgery in cases of retinal detachment secondary to retinal dialysis in younger patients, as their vitreous may be formed and more difficult to separate during surgery.

## Retinal Pigment Epithelium Contusion/Traumatic Choroidopathy

RPE contusion occurs because of blunt trauma that results in RPE damage and leakage acutely. This leakage can cause a serous retinal detachment that resolves within 3 weeks of the initial injury. Remote from the injury, angiography can show increased transmission through the damaged RPE. Visual acuity often is normal if the foveal area is spared or minimally involved. There is no treatment for this condition.

Traumatic choroidopathy is a rare result of significant blunt trauma. Choroidal nonperfusion can result in contusion necrosis to the RPE, which can result in a serous retinal detachment. Often with such significant blunt trauma, commotio can also be present. Angiography will demonstrate multifocal areas of leakage at the level of the RPE in the acute setting. Visual prognosis is poor in these cases.

## Macular Hemorrhage

Intraretinal or subretinal hemorrhage can occur in cases of blunt ocular trauma. Intraretinal hemorrhage can be isolated or occur with other findings of trauma, including commotio or macular hole formation. Subretinal hemorrhage should suggest the possibility of a choroidal rupture. Careful follow-up observation is necessary to identify the rupture site as the hemorrhage resolves. In isolated cases of hemorrhage, observation is usually warranted, as often it will resolve without significant vision loss.

## Optic Nerve Avulsion

Optic nerve avulsion (ONA) is a visually devastating condition that results from severe blunt or penetrating trauma. Vision is profoundly affected, with most patients demonstrating no light perception vision. Absence or recession of the optic nerve head is present on examination if associated injuries permit visualization of the posterior pole. Often there will be surrounding hemorrhage around the area in question. There is no treatment for this devastating complication of trauma.

## PENETRATING TRAUMA

Management of penetrating injuries varies according to the severity, extent, and location of the injury, as well as the presence or absence of an IOFB. The general principles of management of a penetrating injury to the eye include:

- Primary closure of the wound.
- Removal of any foreign body material.
- Prevention of secondary complications from the injury (retinal detachment or infection).
- Anatomical and visual rehabilitation of the eye.
- Protection of the fellow eye (protective eyewear; enucleation in rare instances to reduce the risk of sympathetic ophthalmia).
- General rehabilitation of the patient.

## Initial Closure

In cases of penetrating eye injuries, primary closure of the globe is the first priority. Posterior penetrating injuries should be closed as meticulously as possible. A scleral laceration is often best closed utilizing either 9-0 or

8-0 nylon sutures in an interrupted fashion. Occasionally, running sutures may be required in cases that have poor potential for wound apposition with traditional suturing techniques. Prolapse of intraocular contents can occur with manipulation of the globe, so great care must be taken with surgical exploration to prevent this from occurring. Scleral lacerations extending posterior to the equator may require some gentle pressure to allow for full visualization. Very posterior lacerations (such as those that occur with “through-and-through” perforating injuries) can self-seal if given ample time. For penetrating injuries that involve the vitreous base, a prophylactic scleral buckle may reduce the risk of a subsequent retinal detachment.<sup>2</sup> In addition, this can minimize the need to reopen scarred tissues in the area of the laceration for subsequent surgeries.

## INTRAOCULAR FOREIGN BODIES

IOFBs should be removed at the time of initial closure if possible. The presence of an IOFB increases the risk of endophthalmitis. Prompt surgical removal may be associated with a decreased risk of clinical infection.<sup>9-11</sup> Intraocular foreign bodies that are metallic can be removed by either intraocular forceps or utilizing a rare earth magnet or external electromagnet (most useful for IOFBs located in anterior vitreous adjacent to the pars plana, Videos 6.43.1 and 6.43.2).



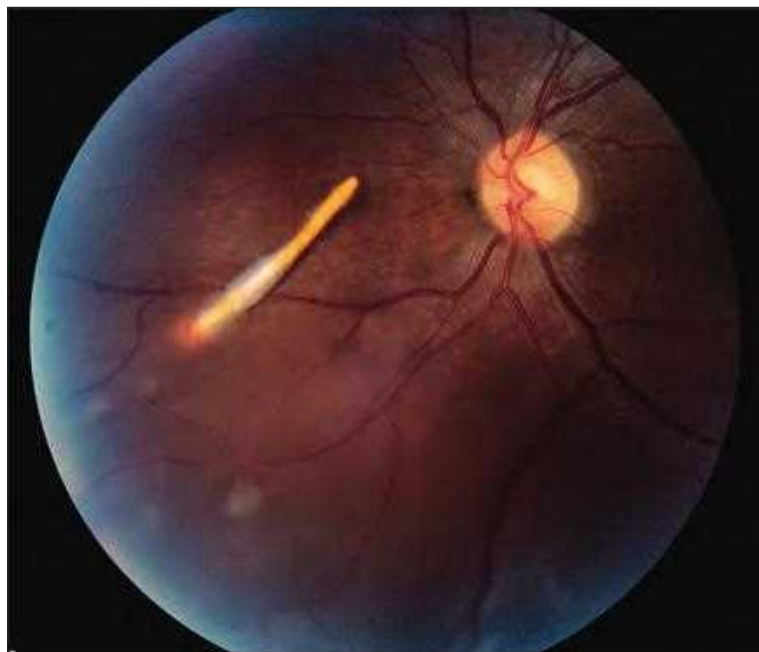
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## Metallosis

Metallosis occurs when certain types of metallic IOFBs are not removed promptly from the eye (Fig. 6.43.5). Damage occurs as a result of oxidation and other chemical reactions with the surrounding tissues.<sup>12,13</sup> Iron and copper are the two most common alloys responsible for metallosis. Iron-containing IOFBs result in siderosis. Siderosis often manifests itself months to years after the injury and can result in heterochromia, RPE degeneration (peripheral initially), and a gradually progressive loss of vision. Copper-containing alloys with less than 85% copper cause chalcosis. Chalcosis can result in a Kayser–Fleischer ring, greenish heterochromia, sunflower cataract of the anterior capsule, and refractile deposits in the macular region, often with peripheral sparing. Copper alloys of greater than 85% result in a sterile endophthalmitis. Prompt and complete removal of the IOFB is essential in the management of these sequelae.

## Secondary Infection

Aside from damage from the primary injury, endophthalmitis is the most significant consequence of a penetrating eye injury. The mechanism of injury is the greatest determining factor for the development of infection, and so a careful history should be ascertained. A variety of techniques are used for prophylaxis of infection. First, if there is an adequate view to

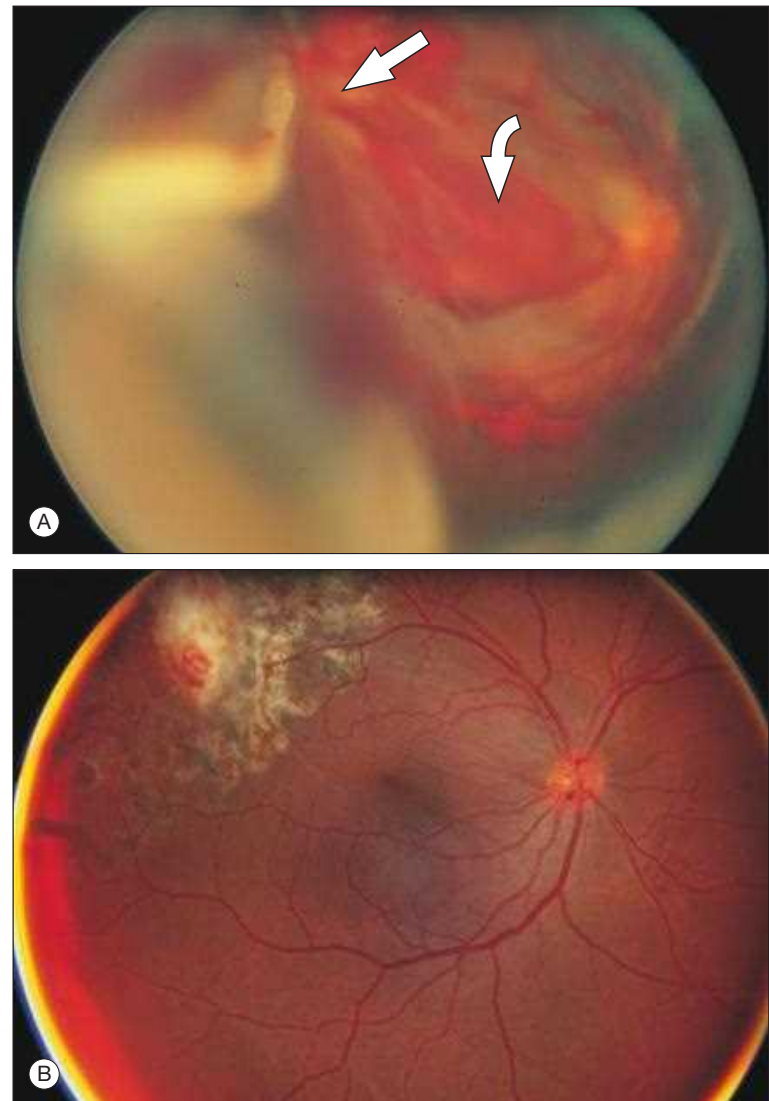


**Fig. 6.43.5 Copper Intraocular Foreign Body.** Acute presentation of a patient with a penetrating wire injury. (Courtesy Andrew Pearson, MD and Drew Sommerville, MD; University of Kentucky Department of Ophthalmology.)

the posterior segment with no contraindications to the administration of intravitreal injections, then antibiotics can be administered as a pars plana injection. This route of administration ensures that the highest concentration of antibiotics reaches the area of greatest concern for infection. If the view to the posterior segment is compromised, then intracameral antibiotics can be considered. The role of intravenous antibiotics in the setting of a ruptured globe injury is controversial because of poor ocular penetration, particularly with vancomycin. However, systemic administration of moxifloxacin has been shown to achieve minimum inhibitory concentrations in both noninjured and injured eyes.<sup>14</sup>

## Rehabilitation: Secondary Surgical Timing

Timing and approach to the surgical repair of disrupted intraocular structures after penetrating injury are dependent on the nature and severity of the initial trauma. There are two general approaches to the timing of surgery: initial closure/delayed repair and simultaneous closure/repair. The first approach involves an initial closure of the rupture site along with the placement of a scleral buckle if indicated. This is then followed 4–10 days later by a vitrectomy. The benefit of this approach is improved visualization through the cornea and reduced intraocular bleeding. The second approach of simultaneous closure and repair allows for earlier removal of blood and lens remnants from the eye, which may reduce the risk of complicated retinal detachment secondary to proliferative vitreoretinopathy (PVR, Fig. 6.43.6). It may also reduce the need for a second surgery. There are two circumstances in which delayed secondary surgery would be preferred: if there is a posterior exit wound that cannot be closed at the time of repair, and massive hemorrhagic choroidal detachments.



**Fig. 6.43.6 Hemorrhagic Retinal Detachment in a Patient After an Ice-Pick Stab Wound.** (A) Note the incarceration of the retina in the posterior impact site (arrow) and the subretinal blood (curved arrow). A localized choroidal hemorrhage is seen in the foreground on the left. (B) Postoperative appearance after vitrectomy, removal of subretinal blood, and extraction of retina from the area of incarceration (scar).



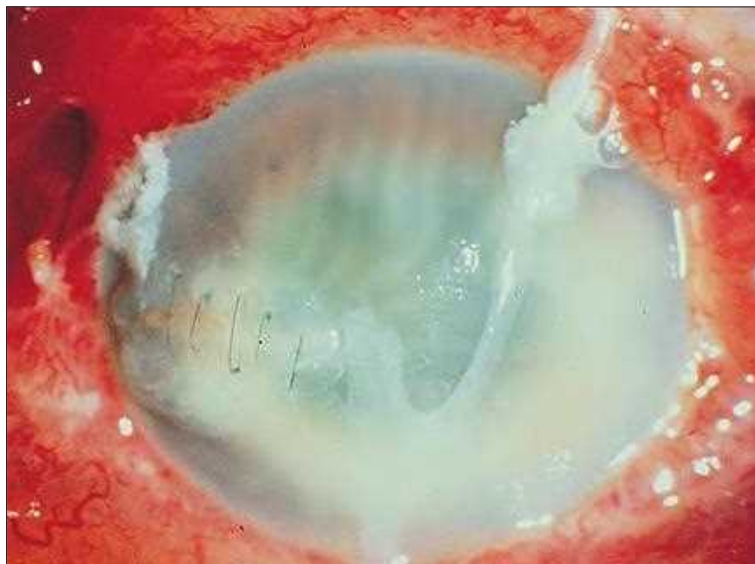
## Rehabilitation: Surgical Technique

Vitreotomy permits the rehabilitation of many eyes that previously would have been lost after penetrating injury. A three-port technique is used most commonly. In cases of poor visualization to the posterior segment, it is important to identify choroidal or retinal detachments preoperatively. This is best accomplished with ultrasonography. Placement of the infusion cannula is a critical first step. A longer infusion cannula (6 mm vs. the traditional 4 mm cannula) and more anterior placement may avoid sub-retinal or suprachoroidal placement. Placement of infusion through the anterior chamber may be necessary in cases where there are appositional choroidal detachments or a total retinal detachment with little room for traditional pars plana infusion placement. The second consideration must be given to obtaining an adequate view to the posterior segment. Anterior chamber hemorrhage and lens damage must be addressed to visualize the posterior segment. Considerable hemorrhage can occur from the injured ocular structures, further inhibiting the view. Although small-gauge surgery has improved significantly with newer generations of equipment, posterior segment trauma in the setting of both primary and secondary repair as well as removal of IOFBs may benefit from larger gauge instrumentation.

Complicated PVR may occur in eyes after penetrating injury. PVR can manifest as severe membrane formation on the surface of the retina. It is often associated with a retinal detachment. Repair of a PVR-related retinal detachment requires release of the membranes during vitrectomy, laser photocoagulation to create a chorioretinal adhesion, reattachment of the retina using gas or oil tamponade, and often the placement of a scleral buckle to support the peripheral vitreous. In cases of extensive membrane formation or in instances where a foreign body penetrates the retina causing retinal incarceration in the wound, it is necessary to perform a retinectomy to release traction on the retina and allow it to reoppose the eye wall.

## Traumatic Endophthalmitis

Endophthalmitis in the setting of penetrating trauma usually carries a poor prognosis.<sup>15,16</sup> This results from both the injury itself and the damage caused by the infection. Contributing to the poor outcome may be the delay in treatment, difficulty administering antibiotics in a standard manner, and virulence of the organisms involved (e.g., *Bacillus cereus*). Risk of traumatic endophthalmitis varies depending on the circumstances of the injury (rural injuries having a higher incidence),<sup>17</sup> retained IOFB,<sup>9-11</sup> and injury to the crystalline lens.<sup>11</sup> Endophthalmitis should be suspected when inflammation is present, including hypopyon, retinal vasculitis, and vitritis (Fig. 6.43.7). Management of traumatic endophthalmitis includes obtaining cultures from either the vitreous (preferred) or the anterior chamber. Broad-spectrum antibiotics should be administered intravitreally if possible. Vancomycin adequately covers common Gram-positive organisms



**Fig. 6.43.7 Traumatic Endophthalmitis (*Streptococcus faecalis*) at Presentation After Penetrating Trauma.** Note the marked anterior chamber fibrin, early ring infiltrate of the cornea, peripheral hypopyon, and purulent material in the area of corneal laceration.

(*Staphylococcus* and *Streptococcus*) and *Bacillus*. Cefazidime provides additional Gram-negative coverage without the risk of vascular occlusion associated with intravitreal gentamicin. The simultaneous administration of intraocular corticosteroids is controversial. If antibiotics cannot be administered intravitreally because of the presence of a retinal detachment or extensive hemorrhagic choroidal detachments, then intracameral and/or systemic antibiotics can be used. Topical antibiotics may be useful as an adjuvant.

## COURSE AND OUTCOME

### Prognosis

Prognosis is related to the severity of the injury and complications that develop secondary to the injury. Several variables are associated with the long-term prognosis:

- Initial visual acuity.
- Presence of an afferent pupillary defect.
- Severity of the initial injury (size and location of the initial wound).
- Presence of an IOFB.
- Presence of infection.
- Presence of extensive hemorrhagic choroidal detachments.
- Presence or occurrence of a retinal detachment.
- Posterior exit wound.

A scoring system has been proposed to better estimate the visual potential after an ocular injury. This scoring system helps give a more accurate estimate of the potential for visual recovery.<sup>18</sup>

### Sympathetic Ophthalmia

Sympathetic ophthalmia (SO) is a rare but potentially devastating consequence of penetrating injury.<sup>19</sup> It manifests as a bilateral granulomatous inflammatory response. SO is presumed to be caused by sensitization of the immune system to uveal antigens. The majority of cases occur between 3 weeks and 3 months of the initial injury, but patients can present years after the initial injury with symptoms of uveitis (pain, photophobia, loss of vision). Bilateral panuveitis is the most common finding. Treatment of SO involves the use of oral, topical, or periocular corticosteroids, initially often with more prolonged therapy involving immunomodulatory agents. Early enucleation (within two weeks of the initial injury) is believed to reduce the risk of developing SO and should be considered for severely traumatized eyes with no visual potential. Despite the rarity of the condition, it is important to advise the patient of this possibility after penetrating trauma.

### Additional Considerations

It is critical to emphasize the need for protective eyewear for patients who have suffered vision loss from ocular trauma. Use of polycarbonate eyewear should be prescribed and encouraged. In young children, the potential for amblyopia exists in the traumatized eye. Thus an eye with good visual potential should undergo treatment for amblyopia if the child is in the appropriate age range.

Traumatic eye injuries not only impart significant vision loss but also can have a tremendous psychological impact on patients. Depression and anxiety are commonplace in this setting. Psychological support is often necessary in helping to overcome these obstacles. In addition, patients with significant vision loss in one eye require assistance in adjusting to a monocular life. Low vision services and rehabilitation therapy are important considerations. An additional resource is the book *A Singular View: The Art of Seeing With One Eye* by Frank Brady.

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# Distant Trauma With Posterior Segment Effects

Jason Hsu, Carl D. Regillo

# 6.44

## TERSON SYNDROME

**Definition:** Intraocular hemorrhage associated with acute intracranial hemorrhage.

### Key Features

- Bilateral, multiple posterior segment hemorrhages.
- Intraretinal, preretinal, or intravitreal location.

### Associated Features

- Spontaneous or trauma-induced intracranial blood (usually subarachnoid).
- Decreased vision with good spontaneous recovery.

## PURTSCHER RETINOPATHY

**Definition:** Peripapillary retinal infarctions associated with severe trauma or various systemic conditions.

### Key Features

- Bilaterally symmetrical peripapillary cotton-wool spots.
- Bilateral retinal hemorrhages.

### Associated Features

- Severe head, chest, or long bone injury.
- Amniotic fluid embolism.
- Pancreatitis.
- Other rare systemic conditions.
- Decreased vision with variable or limited recovery.

## SHAKEN BABY SYNDROME

**Definition:** Intraocular hemorrhage that results from whiplash-like child abuse.

### Key Features

- Bilateral retinal or vitreous hemorrhage.
- No evidence for direct eye trauma.

### Associated Features

- Intracranial hemorrhage (usually subdural).
- Cerebral edema or atrophy.
- Decreased vision.
- Variable recovery as a result of ocular or central nervous system damage.

## TERSON SYNDROME

### INTRODUCTION

In 1900, Terson reported the association of vitreous hemorrhage with an acute subarachnoid hemorrhage. The syndrome that now bears his name has evolved to include cases with any type of intraocular hemorrhage present after spontaneous or trauma-induced intracranial bleeding.<sup>1</sup>

### EPIDEMIOLOGY AND PATHOGENESIS

Intraocular hemorrhage is seen in approximately 20% of patients with acute intracranial bleeding.<sup>1,2</sup> Significant vitreous hemorrhage occurs in a smaller percentage of these patients, being observed in 3%–5% of all patients with intracranial bleeding. The intracranial hemorrhage can be subdural, subarachnoid, or intracerebral in location. Subarachnoid bleeding from a cerebral aneurysm, in particular an anterior communicating artery aneurysm, is the most common underlying cause.<sup>2</sup>

The pathogenesis of Terson syndrome remains controversial. Some investigators initially assumed that the intraocular hemorrhage resulted from dissection of the subarachnoid hemorrhage down the optic nerve sheath and into the eye.<sup>1</sup> The lack of communication between the subarachnoid space of the optic nerve and vitreous renders this mechanism unlikely. Furthermore, the retinal hemorrhages are often not contiguous with the optic nerve, and autopsy studies have not shown that the optic nerve sheath hemorrhage extends to the globe.<sup>3</sup>

It is now believed that the sudden rise in intracranial pressure that occurs at the time of the intracranial bleed is the primary event that leads to intraocular bleeding.<sup>2</sup> In support of this is the observation that the amount of ocular hemorrhage correlates directly with the rapidity and magnitude of intracranial pressure elevation. How increased intracranial pressure translates into intraocular bleeding remains unclear. Potential explanations include increased orbital venous pressure translated directly through the cavernous sinus or compression of both the ophthalmic vein and adjacent retinochoroidal anastomoses due to a rapid effusion of cerebrospinal fluid or blood into the optic nerve sheath.<sup>1-4</sup> In either scenario, an acute obstruction to the retinal venous circulation results and leads to the rupture of superficial retinal vessels.

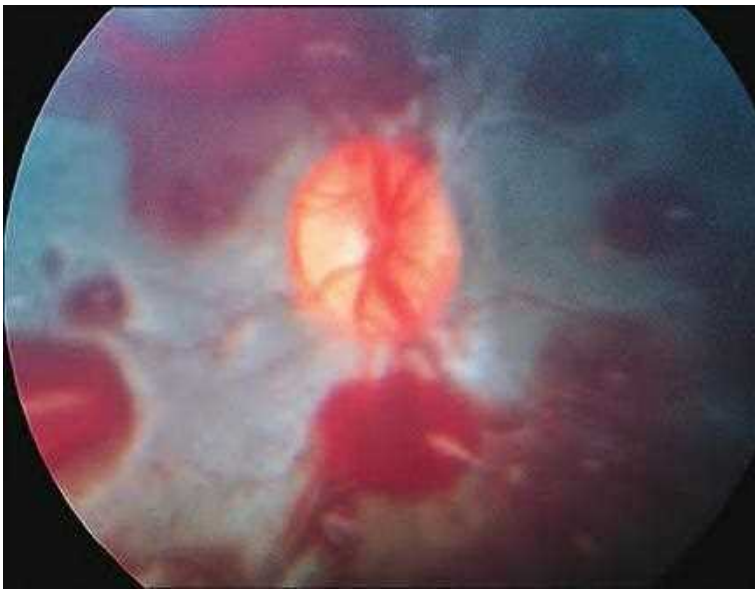
### OCULAR MANIFESTATIONS

Terson syndrome consists of multiple, usually bilateral, retinal hemorrhages in the posterior pole (Fig. 6.44.1). Visual acuity is often diminished, but this may not be easily quantified when the neurological manifestations predominate. The amount of acute vision loss is typically related to the extent of intraocular hemorrhage. Although hemorrhages can be subretinal and intraretinal, they are usually more superficial, being under the internal limiting membrane or preretinal (subhyaloid). Significant vitreous hemorrhage is possible, probably from blood that breaks through the internal limiting membrane or posterior hyaloid face into the vitreous gel. Late complications include epiretinal membrane formation, macular holes, perimacular retinal folds, and, rarely, traction or rhegmatogenous retinal detachments.<sup>5,6</sup>

### DIAGNOSIS AND ANCILLARY TESTING

The typically devastating consequences of acute intracranial hemorrhage, rather than the intraocular consequences, lead the patient to seek medical





**Fig. 6.44.1 Terson Syndrome.** Multiple superficial intraretinal hemorrhages and preretinal hemorrhage in an eye of a patient who had suffered intracranial bleeding from head trauma. (Courtesy Lon S. Poliner, MD.)

#### BOX 6.44.1 Differential Diagnosis of Terson Syndrome

- Purtscher retinopathy
- Shaken baby syndrome
- Valsalva retinopathy
- Blood dyscrasia

attention. In such patients, the diagnosis of Terson syndrome is generally obvious on ophthalmic evaluation. It may be an important diagnosis to establish because the presence of intraocular hemorrhage may be associated with a higher mortality than when no ocular involvement occurs.<sup>7,8</sup> In suspected cases without established intracranial hemorrhage, emergency neuroimaging is indicated.

### DIFFERENTIAL DIAGNOSIS

The differential diagnosis for Terson syndrome is given in [Box 6.44.1](#).

### TREATMENT AND OUTCOME

In Terson syndrome, the blood typically clears completely and the visual acuity returns to normal.<sup>1,2</sup> However, in some cases the vision remains decreased from persistent vitreous hemorrhage or epiretinal membrane formation. In such situations, vitrectomy to clear the hemorrhage or remove membranes can improve the visual outcome.<sup>7,9</sup> Timing of vitrectomy does not seem to influence final outcomes, although the rare associated retinal detachment requires urgent surgical intervention.<sup>10</sup>

Occasionally some vision loss may persist as a result of subretinal hemorrhage that has disrupted the retinal pigment epithelium (RPE) or direct damage to the outer retina in the foveal area.

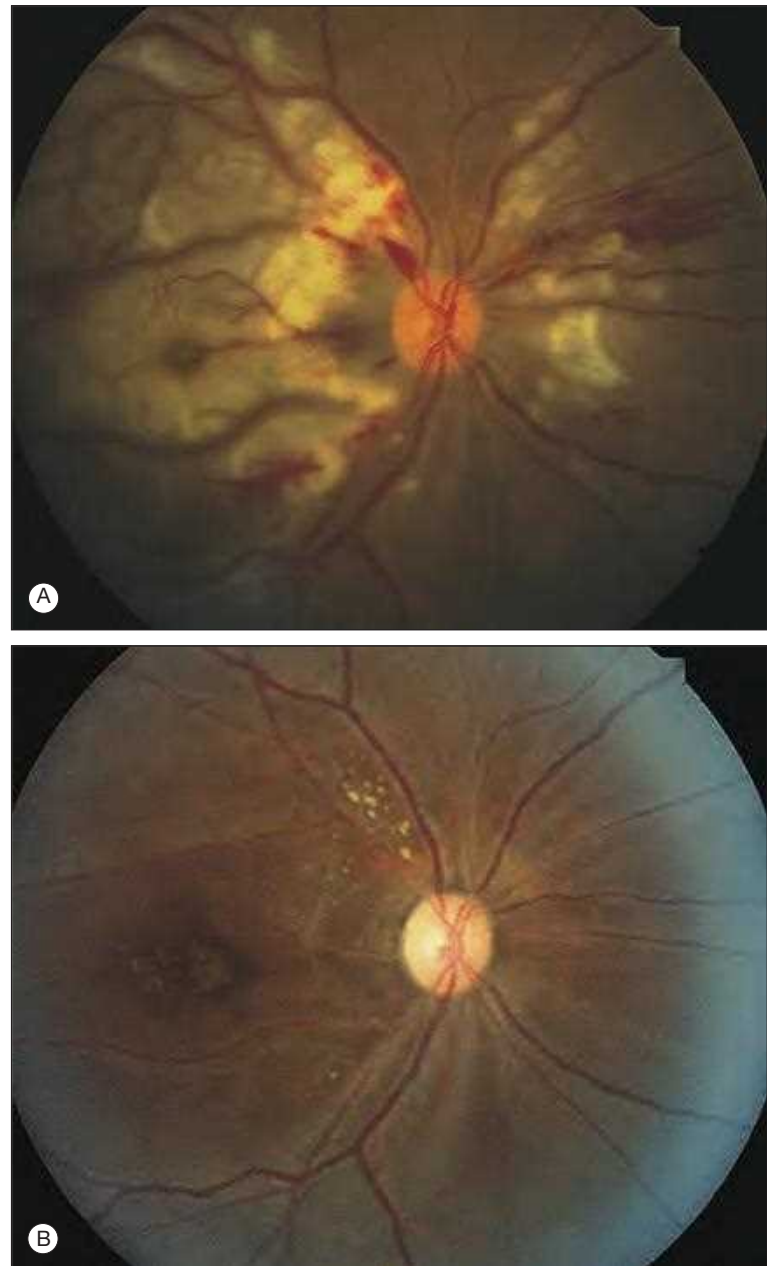
## PURTSCHER RETINOPATHY

### INTRODUCTION

In 1910, Purtscher described the occurrence of bilateral patches of retinal whitening and hemorrhage around the optic disc in patients who suffered massive head trauma.<sup>11</sup> Subsequently, this appearance was observed with other trauma, along with a variety of nontraumatic systemic diseases such as acute pancreatitis, systemic lupus erythematosus, thrombotic thrombocytopenic purpura, and chronic renal failure.<sup>12–14</sup>

### EPIDEMIOLOGY AND PATHOGENESIS

Clinical and experimental data suggest that Purtscher retinopathy results from occlusion of small arterioles by intravascular microparticles generated



**Fig. 6.44.2 Purtscher Retinopathy Associated With Thrombotic Thrombocytopenic Purpura.** (A) At presentation. (B) After 4 months of follow-up. Peripapillary retinal whitening and hemorrhage slowly resolved to leave macular pigment mottling and optic disc pallor. Visual acuity remained unchanged in the counting fingers range. (Copyright 1997, American Medical Association. With permission from Power MH, Regillo CD, Custis PH. Thrombotic thrombocytopenic purpura associated with Purtscher retinopathy. *Arch Ophthalmol* 1997;115:128–9.)

by the underlying systemic condition.<sup>1,12,13,15,16</sup> These microparticles may consist of fibrin clots, platelet-leukocyte aggregates, fat emboli, air emboli, or other particles of similar size that block the arterioles in the peripapillary retina. In experimental animal studies, fibrin clots 0.15–1.0 mm in size injected into the ophthalmic artery produced a Purtscher-like fundus.<sup>15</sup>

### OCULAR MANIFESTATIONS

Patients experience acute, painless loss of central vision in one or both eyes that is often marked. Ophthalmoscopy reveals multiple, variably sized cotton-wool spots, inner retinal whitening (“Purtscher flecken”), and intraretinal hemorrhages around the optic nerve ([Fig. 6.44.2](#)). Some degree of asymmetry is often seen, but a unilateral picture is uncommon. Acutely, the optic nerve and peripheral retina usually appear normal, although disc pallor often develops over time (see [Fig. 6.44.2B](#)).

**BOX 6.44.2 Systemic Conditions Associated With Purtscher and Purtscher-Like Retinopathy**

- Severe head, chest, or long bone trauma
- Acute pancreatitis
- Systemic lupus erythematosus (SLE)
- Fat embolism syndrome
- Thrombotic thrombocytopenic purpura (TTP)
- Hemolysis, elevated liver enzymes, low platelets (HELLP) syndrome
- Chronic renal failure
- Amniotic fluid embolism
- Scleroderma
- Dermatomyositis

**DIAGNOSIS AND ANCILLARY TESTING**

Classically, Purtscher retinopathy occurs in conjunction with severe head or chest trauma. It can also be seen after extensive long bone fractures.<sup>14</sup> For trauma-related cases, the diagnosis is apparent after fundus examination and no further evaluation is needed. However, for cases associated with a systemic medical condition, the underlying cause may not be readily apparent. Such patients may present to the ophthalmologist first if the ocular symptoms predominate.<sup>13</sup> Therefore, a Purtscher-like fundus appearance without recent trauma or known causative medical condition requires that a comprehensive medical evaluation be performed in conjunction with an internist. Fluorescein angiography shows areas of capillary dropout corresponding to the patches of retinal whitening and blocked fluorescence from intraretinal blood.<sup>13</sup> Angiographic evidence for retinal capillary nonperfusion around the fovea may be present in cases with decreased vision. Optical coherence tomography (OCT) of the Purtscher flecken demonstrates hyperreflectivity affecting the inner plexiform, inner nuclear, and outer plexiform layers consistent with deep capillary plexus ischemia.<sup>17</sup>

**SYSTEMIC ASSOCIATIONS**

Systemic diseases associated with Purtscher-like retinopathy are listed in [Box 6.44.2](#).

**PATHOLOGY**

Histopathologically, evidence exists for retinal capillary obliteration and inner retinal atrophy in areas of clinically observed retinal whitening. These findings are relatively nonspecific, being consistent with cotton-wool spots from a variety of causes.<sup>12</sup>

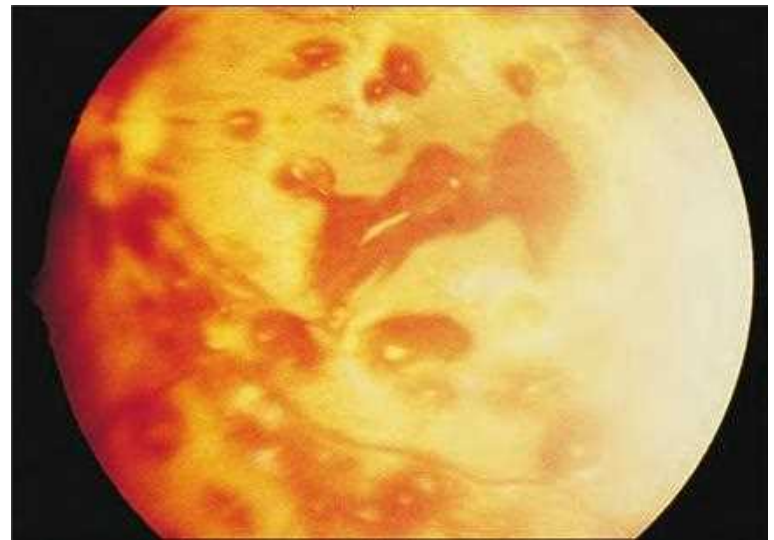
As noted clinically, the pathology is confined mainly to the retina posterior to the equator. Optic atrophy is typically present in varying degrees.

**TREATMENT AND COURSE**

No known treatment exists for Purtscher retinopathy. Although retinal whitening and hemorrhages disappear over weeks or months, usually no significant vision recovery occurs due to infarction of the macula or optic nerve. Macular pigmentary alterations and optic atrophy are typical late findings. Medical or surgical therapy directed at the underlying condition may help prevent additional retinal or optic nerve damage by reducing the potential for new emboli to form.

**SHAKEN BABY SYNDROME****INTRODUCTION**

In the 1970s, radiologist John Caffey proposed a whiplash-like mechanism of child abuse to explain the association of ocular and intracranial bleeding in infants who lacked external signs of head trauma.<sup>18</sup> These are now recognized as hallmark findings of shaken baby syndrome. Unfortunately, this syndrome represents a common form of child abuse that often results in significant morbidity and mortality. As the name implies, it is encountered almost exclusively in children under 2 years of age, with most being younger than 12 months.<sup>19</sup>



**Fig. 6.44.3 Shaken Baby Syndrome.** Numerous superficial retinal hemorrhages (many with white centers) in the posterior pole of an infant who had been the subject of shaking abuse. (Courtesy Dennis P. Han, MD.)

**EPIDEMIOLOGY AND PATHOGENESIS**

The age predilection is likely due to anatomical features that make the infant more likely to suffer from intracranial and intraocular bleeding as a result of shaking.<sup>18</sup> Compared to older children or adults, an infant's head is proportionately larger and heavier relative to the body and is not as well stabilized by neck muscles. The average adult is also able to generate significantly larger acceleration-deceleration forces when shaking an infant than when shaking a larger person.

Intracranial bleeding in this setting may result from shearing of the delicate vessels that bridge the cerebral cortices and venous sinuses when the brain quickly shifts within the cranium. Direct contusion may also occur. Blood, edema, and intracranial pressure elevation often result in permanent neurological damage.

The pathogenesis of the ocular hemorrhage is not well understood. Although a mechanism similar to Terson syndrome may be one explanation, it is likely that the movement of the vitreous within the globe contributes to secondary traction on the internal limiting membrane and superficial retinal vessels. Increased venous pressure transmitted to the retina (such as in Valsalva retinopathy) may also occur, especially with a firm grip on the chest with shaking or even from choking of the victim.

**OCULAR MANIFESTATIONS**

The most common ocular finding in about 85% of patients is intraocular hemorrhage in various locations—subretinal, intraretinal, preretinal (subhyaloid), and intravitreal.<sup>19–22</sup> Intraretinal and preretinal hemorrhages predominate ([Fig. 6.44.3](#)), with most concentrated in the posterior pole and usually being bilateral. In many cases, the amount of intraocular blood correlates with the degree of acute neurological damage.<sup>23,24</sup> Cotton-wool spots, white-centered hemorrhages, macular edema, papilledema, retinosis, hemorrhagic posterior vitreous detachment, macular holes, and RPE tears are less common findings.<sup>1,18,25–27</sup> After the abuse has stopped, hemorrhages and some of the other acute changes resolve within several months. Late manifestations include perimacular retinal folds, chorioretinal atrophy or scarring, optic atrophy, neovascularization, and retinal detachment.<sup>19,28–30</sup>

**DIAGNOSIS AND ANCILLARY TESTING**

The diagnosis is made when the ocular findings above are present in conjunction with certain systemic features and a history of shaking abuse. As a history of abuse may be difficult to elicit with certainty, the clinician must maintain a high index of suspicion based on the clinical findings. The hallmark nonocular sign is intracranial hemorrhage. Unlike Terson syndrome, this is usually subdural and often involves both sides of the brain.<sup>18,20,31</sup> Other findings include subarachnoid or intracerebral blood, cerebral edema, and cerebral atrophy. Elevated intracranial pressure is often present. A variety of neurological symptoms can occur, ranging from

**BOX 6.44.3 Causes of Retinal Hemorrhages in Infancy**

- Birth trauma (neonates only)
- Shaken baby syndrome
- Spontaneous intracranial hemorrhage (Terson syndrome)
- Acute hypertension
- Direct eye, head, or chest trauma (accidental or nonaccidental)
- Cardiopulmonary resuscitation
- Systemic infections and meningitis
- Viral retinitis
- Hematological disorders (e.g., malignancies, coagulopathies)
- Systemic (or retinal) vasculitis

irritability and lethargy to seizures, coma, and death. Neuroimaging is used to diagnose the intracranial pathology. Cerebrospinal fluid and subdural aspirations may be needed to confirm blood in the central nervous system.

Extracranial signs of abuse may also be evident and help confirm the diagnosis. From shaking injury alone, bruises or fractures that involve the trunk or limbs can be seen. Cervical cord hematomas have also been described and are thought to be strongly suggestive of whiplash-like injury.<sup>31</sup> However, with shaking as the only mechanism of abuse, there is often a paucity of overt extracranial findings.

OCT may show areas of focal vitreous separation in the macula, perimacular folds with vitreous attachment at the apices, epiretinal membrane, retinoschisis, lamellar or full-thickness macular hole, and even foveal detachment.<sup>32–34</sup> These findings appear to be consistent with shearing forces at the vitreoretinal interface induced by shaking. Fluorescein angiography has demonstrated areas of peripheral nonperfusion in some cases.<sup>35</sup> However, the clinical implications of this finding are unclear given that some of these patients were observed and never developed neovascularization.

**DIFFERENTIAL DIAGNOSIS**

Intraocular hemorrhages in infancy, although highly indicative of shaken baby syndrome, are not specific for child abuse as they can be seen in other conditions (Box 6.44.3).<sup>19</sup> Direct head trauma or spontaneous subarachnoid hemorrhage can result in intraocular bleeding as described before in Terson syndrome. However, some studies suggest that intraocular hemorrhage may be uncommon in children with intracranial hemorrhage from nonabusive mechanisms, such as accidental or surgical trauma.<sup>36</sup> Retinal hemorrhages can also be seen after vaginal delivery and cardiopulmonary resuscitation. Finally, several systemic conditions, including arterial hypertension, hematological disorders (e.g., leukemia), sepsis, meningitis, and vasculitis, can cause intraretinal hemorrhage.

**PATHOLOGY**

As observed clinically, the most common histopathological finding is intraocular hemorrhage with blood observed in all retinal layers, between the retina and the RPE, and in the vitreous.<sup>21,22</sup> Intraorbital optic nerve sheath hemorrhage is observed frequently and may lead to optic disc edema or optic atrophy.<sup>19,21,22</sup> Intraretinal edema, retinal folding, and RPE alterations are other not uncommon findings. Other pathological globe changes are unusual in shaken baby syndrome alone.

**TREATMENT, COURSE, AND OUTCOME**

Some degree of permanent visual loss is common, with little that can be done therapeutically to alter the visual outcome. Irreversible damage to the macula, optic nerve, and/or occipital cortex is responsible for the decreased vision.<sup>18,19,28,29</sup> Promising signs of potential for visual function are good pupillary reflexes, clear ocular media, retinal findings that are limited to intraretinal hemorrhages, and a normal optic disc.<sup>18</sup> In patients who have vitreous hemorrhage obscuring the macula, vitrectomy to clear the blood can be performed. In this setting, electroretinography should be done preoperatively, as surgery is unlikely to be beneficial if there is no significant bright flash response.<sup>18</sup> Even in cases where the visual pathway is relatively well preserved, the patient's overall function may still be very limited due to severe neurological damage.

**MISCELLANEOUS CONDITIONS****WHIPLASH INJURY**

A whiplash injury to the head in adults produces a unique ocular problem called whiplash maculopathy.<sup>37</sup> In this disorder, the patient usually reports bilateral, mild blurred vision that begins immediately after a significant head and neck flexion–extension injury. Automobile accidents with rapid deceleration are the most common cause. Visual acuity is found to be slightly decreased, rarely worse than 20/30, and ocular examination is notable only for a faint gray haze to the foveal retina accompanied by a small depression. A shallow posterior vitreous separation may also be seen. Fluorescein angiography is usually normal. OCT may demonstrate disruption of the inner segment–outer segment junction.<sup>38</sup> Within days, the vision returns to normal and the gray retinal discoloration fades, but the small foveal depression appears to persist indefinitely. Similar foveal changes can be seen after direct eye trauma with mild commotio retinae of the central macula and after sun gazing (solar retinopathy).

**FAT EMBOLISM SYNDROME**

Distinct posterior segment changes are also seen in fat embolism syndrome. A variety of systemic and ocular signs can develop within a few days of a person sustaining significant fractures of medullated bones. Retinal changes are observed in up to 60% of patients who meet the diagnostic criteria of fat embolism syndrome but in only about 5% of patients who present with long bone fractures with or without other systemic signs.<sup>14</sup>

The classic eye findings are bilateral cotton-wool spots and intraretinal hemorrhages.<sup>1,14</sup> Although the syndrome may resemble Purtscher retinopathy, the white retinal infarcts and hemorrhages are usually smaller, less numerous, and more peripheral, with most patients being asymptomatic or having minor visual complaints.<sup>12</sup>

The associated systemic manifestations of fat embolism syndrome include petechial rash, central nervous system alterations, respiratory compromise, fever, tachycardia, anemia, and elevated erythrocyte sedimentation rate. The condition is fatal in 20% of cases.<sup>1</sup> The ophthalmologist is rarely involved during the acute phase of fat embolism syndrome, as ocular symptoms are usually minimal. However, some patients notice persistent paracentral scotomata, and the ophthalmologist may be in a position to evaluate these and other ocular symptoms at some point during or after the acute phase of the syndrome.<sup>14</sup>

No treatment is currently available for ocular manifestations associated with fat embolism syndrome.

**VALSALVA RETINOPATHY**

Valsalva retinopathy occurs when increased intrathoracic or intra-abdominal pressure is transmitted to the eye, resulting in intraocular bleeding. The hemorrhage is usually unilateral or bilaterally asymmetrical and located in the macula. Subinternal limiting membrane hemorrhage is most common, but subretinal, retinal, and/or vitreous hemorrhaging may also occur. Coughing, vomiting, sneezing, straining at stool, lifting, and sexual intercourse are all possible causes. Valsalva retinopathy typically clears without sequelae. The neodymium:yttrium–aluminum–garnet and argon laser have been used to disrupt preretinal hemorrhage in selected cases to speed the clearance.<sup>39,40</sup> In most cases, laser or surgical intervention is unnecessary.

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# Retinal Toxicity of Systemically Administered Drugs

6.45

Alexander L. Ringeisen, Mihai Mititelu

**Definition:** Retinal injury resulting from systemically administered drugs.

## Key Features

- Retinal pigmentary epithelial irregularities.
- Atrophy of the retina, retinal pigment epithelium, and/or choroid.
- Bullseye maculopathy.
- Crystalline deposition.
- Macular edema.

## Associated Features

- Rheumatoid arthritis.
- Collagen vascular diseases.
- Psychiatric illness.
- Acquired immunodeficiency syndrome.
- Malignancy.

## INTRODUCTION

The toxic retinopathies form a diverse group of conditions that result from retinal damage caused by systemically administered drugs. Although they are relatively rare, these conditions should be considered whenever an “unusual” retinopathy is evaluated, particularly when features of bilateral pigmentary disturbance or retinal crystal deposition are present. Adequate knowledge of systemic medication use in a patient with an unusual retinopathy can lead to prompt recognition of a toxic retinopathy. This may minimize an otherwise extensive workup and spare the patient from future exposure to the noxious agent.

## CHLOROQUINE AND HYDROXYCHLOROQUINE

Chloroquine and its derivative hydroxychloroquine (HCQ) have historically been used for prophylaxis and treatment of malaria, but currently are more commonly used to treat connective tissue diseases. The two drugs differ in their therapeutic and toxic dose ranges but can produce identical retinopathies. The exact mechanism of retinopathy remains to be elucidated, but in animal models, the ganglion cells show the earliest histological evidence of toxicity, followed by other elements of the retina (particularly the outer retina) and the retinal pigment epithelium (RPE).<sup>1</sup>

Patients with retinopathy may be asymptomatic. When symptoms do occur, the earliest complaints are usually difficulty with night vision, reading, or with other fine visual tasks caused by central or paracentral scotomas. The earliest scotomas are subtle, usually within 10° of fixation, and are more common superiorly than inferiorly to fixation.<sup>2</sup> With time, the scotomas enlarge, multiply, and may involve fixation, ultimately reducing visual acuity.

The fundus appearance may remain entirely normal even after scotomas have developed. The earliest fundus findings are irregularity in the macular pigmentation and blunting of the foveal reflex. With time, the central irregular pigmentation may become surrounded by a concentric zone of hypopigmentation, usually horizontally oval and more prominent inferior to the fovea (Fig. 6.45.1).<sup>3</sup> This paracentral depigmentation results in a bullseye maculopathy, which is a classic finding of advanced stage

HCQ toxicity. With continued exposure to the drug, or even on cessation of systemic therapy in the presence of advanced retinopathy, there may be progressive, generalized pigmentary changes. The end-stage appearance may be indistinguishable from that of a cone-rod dystrophy, with bullseye maculopathy, peripheral pigment irregularity and bone spicule formation, vascular attenuation, and optic disc pallor.

Based on improved recognition and the availability of new screening tools, the American Academy of Ophthalmology (AAO) published revised screening recommendations in 2016.<sup>4</sup> The goal of screening is to detect early toxicity prior to development of significant damage, since retinal changes are not reversible and may in fact progress after discontinuation of the drug. The overall prevalence of toxicity after 5 years of use is 75%, although it varies greatly with the duration of therapy and daily dose.<sup>5</sup> Screening should include a baseline examination for all patients starting these drugs with annual screening starting after 5 years of use. Patients with coexisting renal disease or concomitant tamoxifen use are considered at high risk of developing toxicity and may be screened more often based on the provider's clinical suspicion. The AAO recommends that all patients using HCQ keep daily dosage below 5.0 mg/kg real weight. A lower limit is advisable in patients who are at high risk as described earlier. Pre-existing maculopathy is considered a contraindication to treatment with HCQ because underlying abnormalities may mask early toxicity; therefore, these patients should try alternative therapy or have a comprehensive initial examination to establish the baseline.<sup>4</sup>

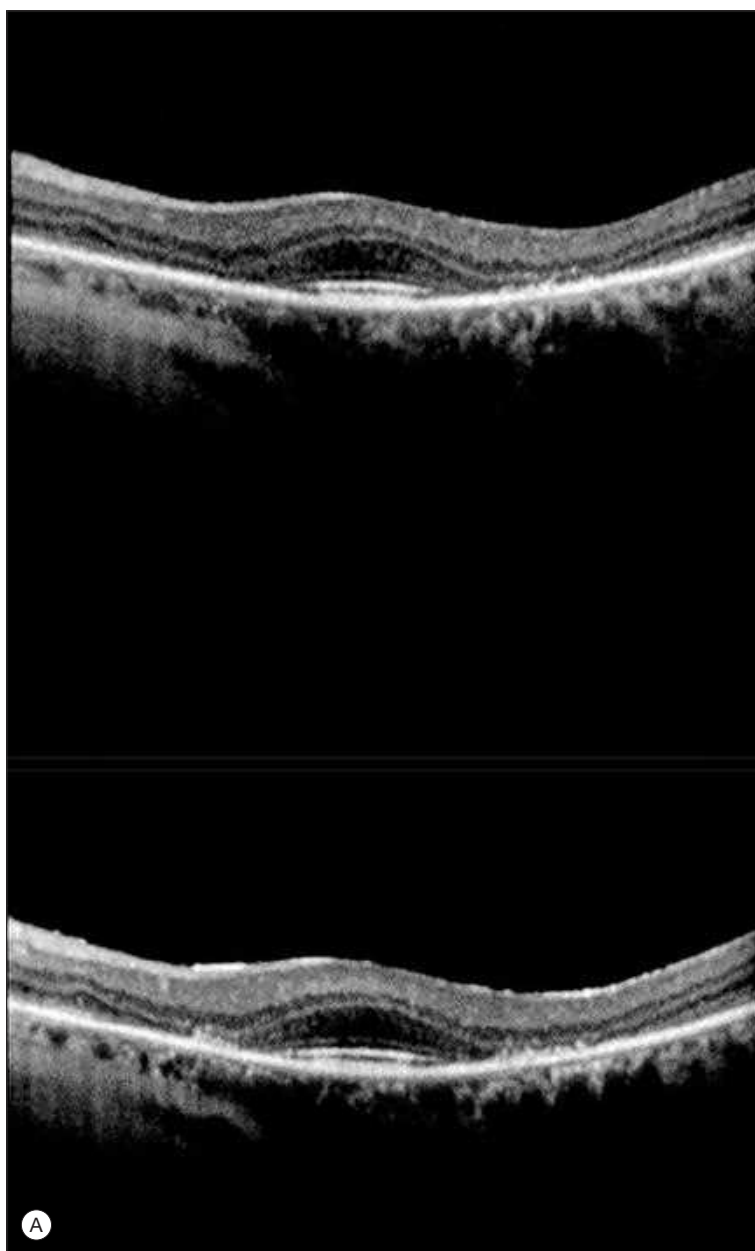
The 2016 AAO guidelines recommend baseline and follow-up screening examinations to include visual acuity testing, dilated fundus examination, spectral-domain optical coherence tomography (SD-OCT) testing, and functional assessment with Humphrey 10–2 test.<sup>4</sup> Multifocal electroretinogram (mf-ERG) and/or fundus autofluorescence (FAF) testing may be used as adjunct testing when available on an as-needed basis. SD-OCT can reveal evidence of early disruption of the parafoveal inner segment–outer segment (IS-OS) junction with thinning of the outer nuclear layer. In late stages, there is complete loss of the ellipsoid zone throughout the fovea.<sup>6</sup> Fundus autofluorescence can highlight mild increased autofluorescence in a pericentral ring around the fovea, while a complete loss of autofluorescence may be seen in severe cases.<sup>7</sup> Multifocal electroretinogram shows pericentral loss of amplitude and delayed implicit time.<sup>8</sup> Changes on Humphrey 10–2 field, even if subtle, should be evaluated by objective testing. Fundus photography, Amsler grid testing, time-domain OCT, fluorescein angiography, full-field electroretinography (ff-ERG), color vision testing, and electro-oculogram are not recommended for screening. Dilated retinal examinations should be done at each visit but are not sufficient for screening independently.

If subjective visual complaints or objective findings are suggestive of toxicity, discontinuation of the drug should be discussed with the patient and the prescribing physician. Discontinuation could lead to worsening of the underlying autoimmune disease and require use of different agents, whereas retinal changes may continue to progress chronically despite cessation of the therapeutic agent.

## SILDENAFIL

Sildenafil is an inhibitor of type-5 phosphodiesterase that is used to treat male impotence. Visual symptoms are correlated to serum concentrations of the medication and include subjective visual phenomena, including a bluish discoloration of vision and increased sensitivity to light.<sup>9</sup> Some studies have reported reversible mild reductions in ERG a- and b-wave amplitudes, increased choroidal thickness, increased error rates along the





**Fig. 6.45.1 Chloroquine and Hydroxychloroquine Maculopathy.** Spectral domain optical coherence tomography exhibits loss of ellipsoid zone and thinning of the outer retina in the parafoveal region ("flying saucer" sign) (A–B). Fundus autofluorescence shows an increased signal in the parafoveal region, which denotes abnormal retinal pigment epithelium metabolism (B). (Courtesy Mihai Mititelu, MD, MPH.)

blue–green axis in Farnsworth-Munsell 100 (FM) hue testing, and higher rod response and sensitivity shortly after ingestion.<sup>10,11</sup> Anecdotal reports of ischemic optic neuropathy, branch retinal vein occlusion, serous macular detachment, and central serous chorioretinopathy have been described. Attributing ocular changes to sildenafil is difficult, as such changes may be compounded by high exertion during sexual activity, interactions with nitrates, and other ocular comorbidities.<sup>12</sup> Current recommendations suggest sildenafil be used with caution in the setting of retinitis pigmentosa and nonischemic optic neuropathy.

## THIORIDAZINE

Thioridazine is a phenothiazine antipsychotic drug that has been used in high doses in the past. At these doses, a subacute, dramatic form of retinopathy could appear<sup>13,14</sup> with extensive geographic areas of depigmentation, loss of choriocapillaris, and optic atrophy. At the lower doses (<800 mg/d) used today, this dramatic type of retinopathy rarely, if ever, occurs.

A variant referred to as nummular retinopathy has been described in patients taking chronic doses of thioridazine. These patients are much less likely to have symptoms. Multiple large round areas of depigmentation and atrophy develop posterior to the equator, with relative sparing of the macula (Fig. 6.45.2). Over time, the areas of atrophy may enlarge and become confluent. Fluorescein angiography demonstrates loss of pigment epithelium and choriocapillaris within the areas of depigmentation.<sup>15,16</sup> Visual field changes are nonspecific, but most characteristically show paracentral scotomas or ring scotomas.

The manufacturers' current recommendation is that the dose be titrated to a minimal effective dose of 300 mg/day or less, with an absolute maximum of 800 mg/day for limited periods. Cases of retinopathy among patients treated according to these guidelines remain rare.

## NIACIN

Niacin (nicotinic acid, vitamin B<sub>6</sub>) is used at pharmacological doses to lower serum cholesterol, and rarely maculopathy may develop in patients taking 1.5 g or more daily.

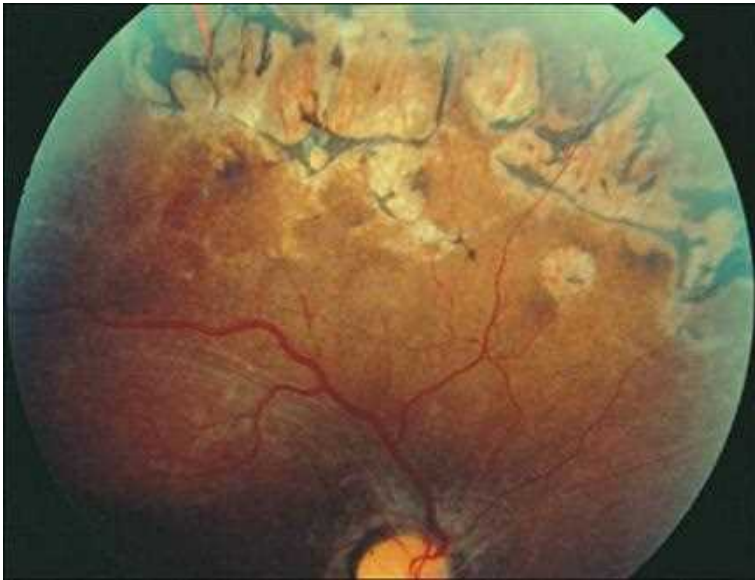
Affected patients develop central visual changes weeks or months after the initial administration of the drug. Reduction in visual acuity is usually mild to moderate.<sup>17,18</sup> Patients develop a bilateral maculopathy that has the clinical appearance of cystoid macular edema, but there is no dye leakage or accumulation with fluorescein angiography. OCT reveals the presence of cystoid spaces in the inner nuclear and outer plexiform layers (Fig. 6.45.3).<sup>19</sup> The subjective and objective findings improve after the medication is withdrawn, but if left untreated, chronic macular edema may lead to retinal and retinal pigment atrophy causing permanent vision loss.

## CANTHAXANTHINE

Canthaxanthine is a carotenoid drug that, when taken orally, causes bronzing of the skin. Although it has been used for treatment of certain dermatological disorders such as vitiligo, its main use has been as an artificial tanning agent. The risk of retinopathy is dose related. At cumulative doses

of greater than 30 g, the majority of patients are found to have retinopathy. Patients who have canthaxanthine retinopathy are usually asymptomatic. The fundus appearance is bilateral wreath formation of highly refractile yellow crystals found in the inner retinal layers that surround the fovea (Fig. 6.45.4).<sup>20</sup>

Although the patients are usually asymptomatic, central perimetry demonstrates reduced sensitivity in patients who have retinopathy. After cessation of drug therapy, visual field testing may return to normal as the number of visible crystals decreases slowly over many years.<sup>21</sup>



**Fig. 6.45.2 Thioridazine Retinopathy Associated With Chronic Use (Nummular Retinopathy).** (From Weinberg DV, D'Amico DJ. Retinal toxicity of systemic drugs. In: Albert DM, Jakobiec FA, editors. Principles and practice of ophthalmology. Philadelphia: WB Saunders; 1994. p. 1042–50.)

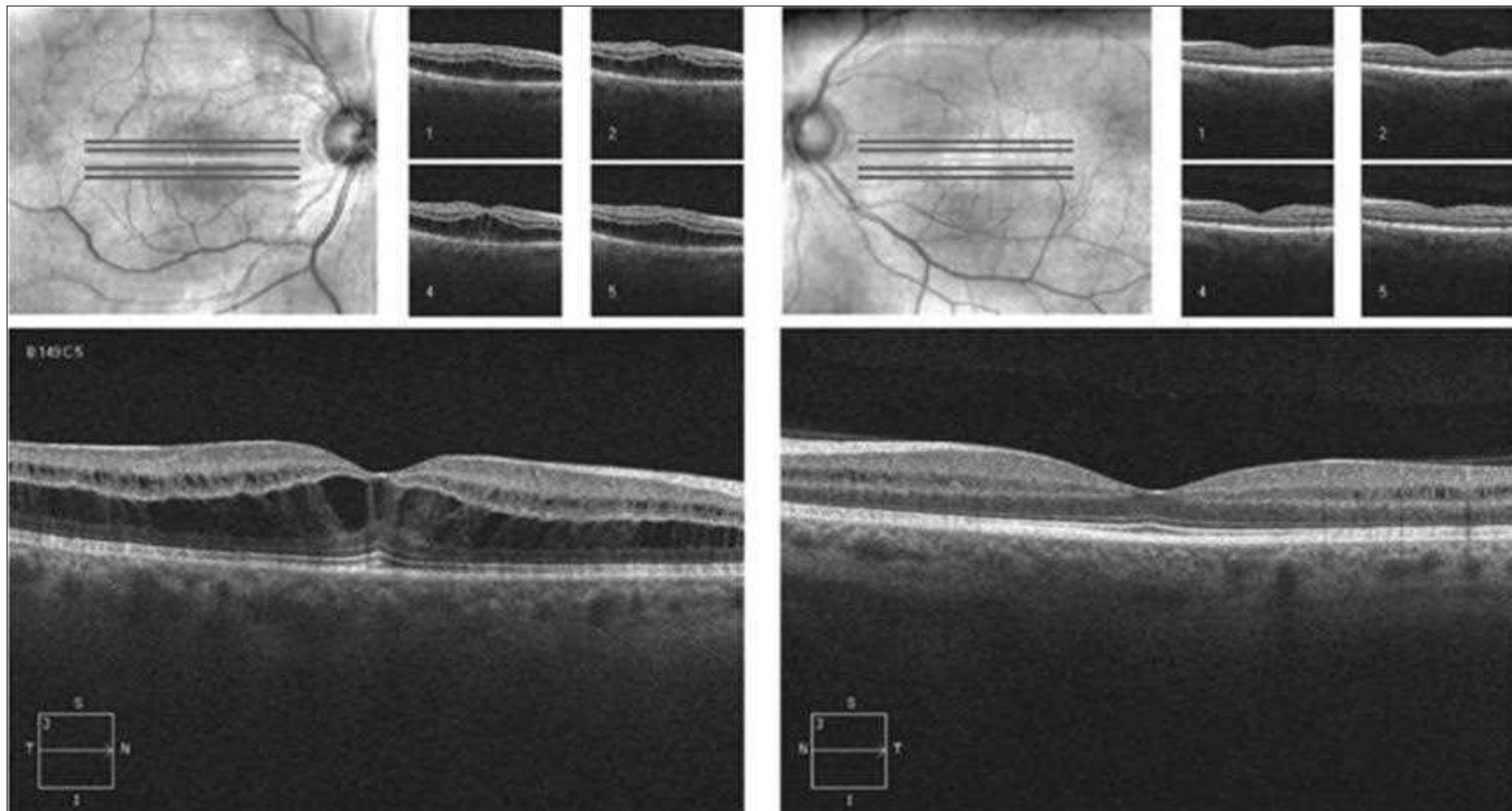
## TAMOXIFEN

Tamoxifen is a nonsteroidal estrogen antagonist that is used in the treatment of breast cancer. Retinopathy was first described among women treated with more than 180 mg/day for longer than a year.<sup>22</sup> These patients usually had a symptomatic decrease in vision and characteristic fundus findings were small, white, refractile deposits in the inner retina, particularly in the perimacular area. Associated pigmentary irregularity occurred (Fig. 6.45.5).<sup>23</sup>

Currently, the drug is used at much lower doses, typically 20 mg/day. Fluorescein angiography demonstrates window defects and/or cystoid macular edema. OCT studies have revealed a foveolar cystoid space and loss of photoreceptors without macular thickening (see Fig. 6.45.5).<sup>24,25</sup> Many of the cases of low-dose tamoxifen retinopathy have been asymptomatic, but mild to moderate reduction of visual acuity has been reported in others. Conflicting data exist in the literature as to the incidence and significance of retinopathy in asymptomatic patients.<sup>26–30</sup> Although mild crystal deposition with or without macular edema may be possible with low doses, it is probably uncommon. This is supported by the large number of patients treated with this drug and the relative paucity of well-documented cases in the literature. There is lack of consensus in the literature as to whether routine screening of asymptomatic patients using lower doses of tamoxifen is necessary. Cessation of medication should be considered if visual function is affected but only after discussion with the patient's oncologist.

## FINGOLIMOD

Fingolimod is a US Food and Drug Administration (FDA)–approved oral drug for relapsing multiple sclerosis<sup>31</sup> and is associated with macular edema in a subset of patients. Incidence of macular edema is about 0.2% with 0.5 mg/d dose and increases with higher doses and in the presence of comorbidities such as pre-existing uveitis and diabetes. Patients may complain of blurred vision or have minimal or no symptoms. OCT reveals intraretinal cystic spaces, and dye leakage is seen on fluorescein angiography. According to the prescribing information, patients starting fingolimod should have a comprehensive baseline examination followed by repeat examination after 3 or 4 months. If macular edema develops, discontinuation of fingolimod should be considered in consultation with



**Fig. 6.45.3 Spectral-Domain Optical Coherence Tomography Demonstrating Cystoid Spaces in the Outer and Inner Nuclear Layers and Possibly the Ganglion Cell Layer in the Right Eye and in the Inner Nuclear Layer in the Left Eye.** (From Courtney RJ and Singh RP. Spectral domain optical coherence tomography features in niacin maculopathy. Eye [Lond] 2014;28:629–32. Figure 2.)



the neurologist.<sup>32</sup> Should the patient and prescribing physician wish to continue fingolimod, treatment of the macular edema has been successfully reported using topical nonsteroidal anti-inflammatory drugs and sub-Tenon's triamcinolone.<sup>33,34</sup>

## PACLITAXEL

Paclitaxel (in both its free and albumin bound versions) and docetaxel are related drugs used as chemotherapeutic agents. They can cause cystoid macular edema without dye leakage on fluorescein angiography (Fig. 6.45.6). It is believed that the macular edema occurs secondary to damage to Müller cells.<sup>35</sup> Discontinuation of the medication (and replacement with a different chemotherapeutic agent) usually leads to resolution of the cystoid macular edema (CME).<sup>36</sup>

## DEFEROXAMINE

Deferoxamine mesylate is a chelating agent used to reduce iron levels in patients with transfusion-dependent anemia and to treat aluminum toxicity in patients receiving chronic renal dialysis. The onset of visual symptoms

from deferoxamine toxicity may be relatively acute or occur after long exposure. The incidence may be higher in dialysis patients and in older individuals.<sup>37</sup> Patients usually complain of blurred vision, nyctalopia, color vision abnormalities, or visual field restriction. At the time of onset, the fundus may appear normal or subtle pigment mottling may be found. The spectrum of changes varies widely and may include RPE window defects, bullseye lesions, vitelliform maculopathy, and late hyperfluorescence of the macula.<sup>38,39</sup> Color vision is frequently abnormal, typically with a tritan dyschromatopsia. Visual field testing usually shows central or cecentral scotomas and, less commonly, peripheral restriction. Electroretinography may show decreased amplitude and prolonged implicit times. Visually evoked potentials may also show low voltage and delayed conduction times. Where available, fundus autofluorescence is an effective method for screening patients at risk for deferoxamine retinal toxicity.<sup>40</sup> If deferoxamine is withdrawn promptly, partial or complete functional recovery is usually seen. The maculopathy may progress, however, and develop into coarse macular pigmentary changes and occasionally peripheral pigmentary clumping as well.

## DIDANOSINE

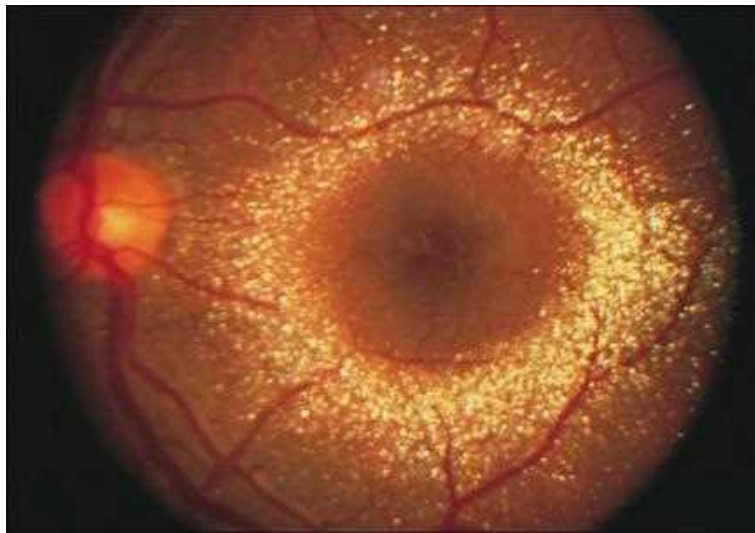
Didanosine (2',3'-dideoxyinosine) is an antiretroviral drug used for the treatment of human immunodeficiency virus infection. A peripheral retinal degeneration has been observed in children and adults treated with this drug.<sup>41,42</sup> Fundus findings consist of small, sharply demarcated areas of retinal and RPE atrophy around the midperiphery. This degeneration may progress with continued exposure to the drug. ERG may exhibit signs of rod and cone dysfunction. Central visual acuity is usually preserved with restriction of peripheral visual field.<sup>41,43,44</sup> Cessation of the medication should be considered once retinopathy is detected.<sup>42</sup>

## CLOFAZIMINE

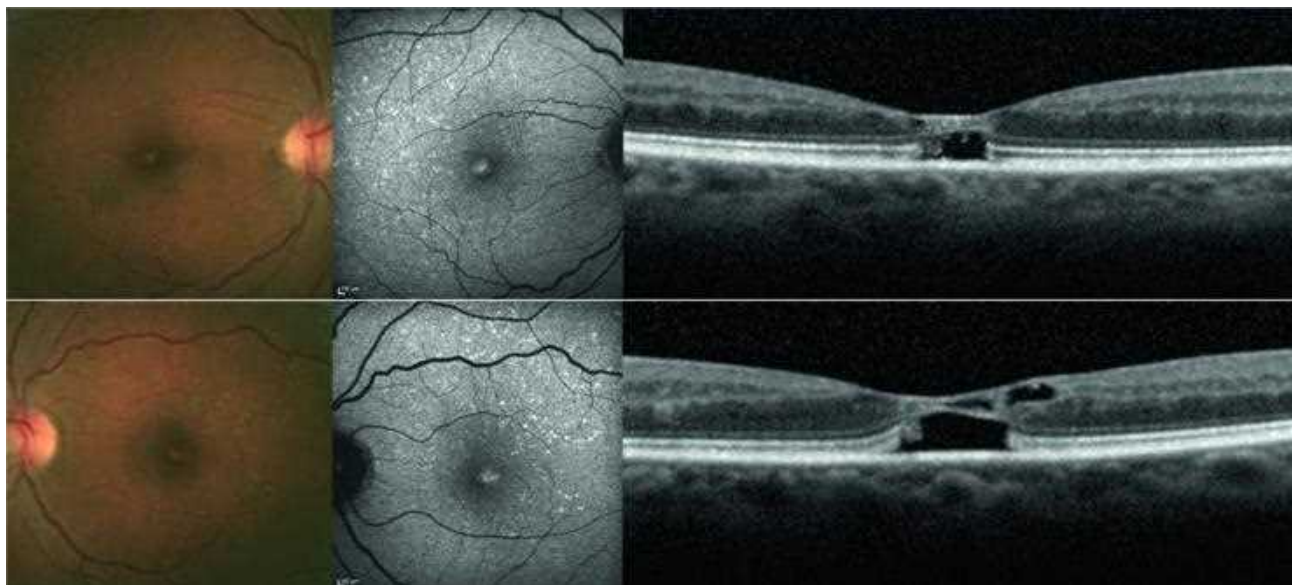
Clofazimine is an iminophenazine dye with antimycobacterial and anti-inflammatory activity. Retinal toxicity in the form of a bullseye maculopathy has been reported in patients who were given clofazimine for treatment of *Mycobacterium avium* complex infections associated with acquired immunodeficiency syndrome. In contrast to other bullseye maculopathies, the pigment changes in these patients were more extensive and extended outside the major vascular arcades.<sup>45,46</sup>

## THIAZOLIDINEDIONES

Thiazolidinediones are oral antidiabetic agents that include rosiglitazone and pioglitazone. They are known to cause excess fluid retention in some patients. A case series suggested a possible link between use of these

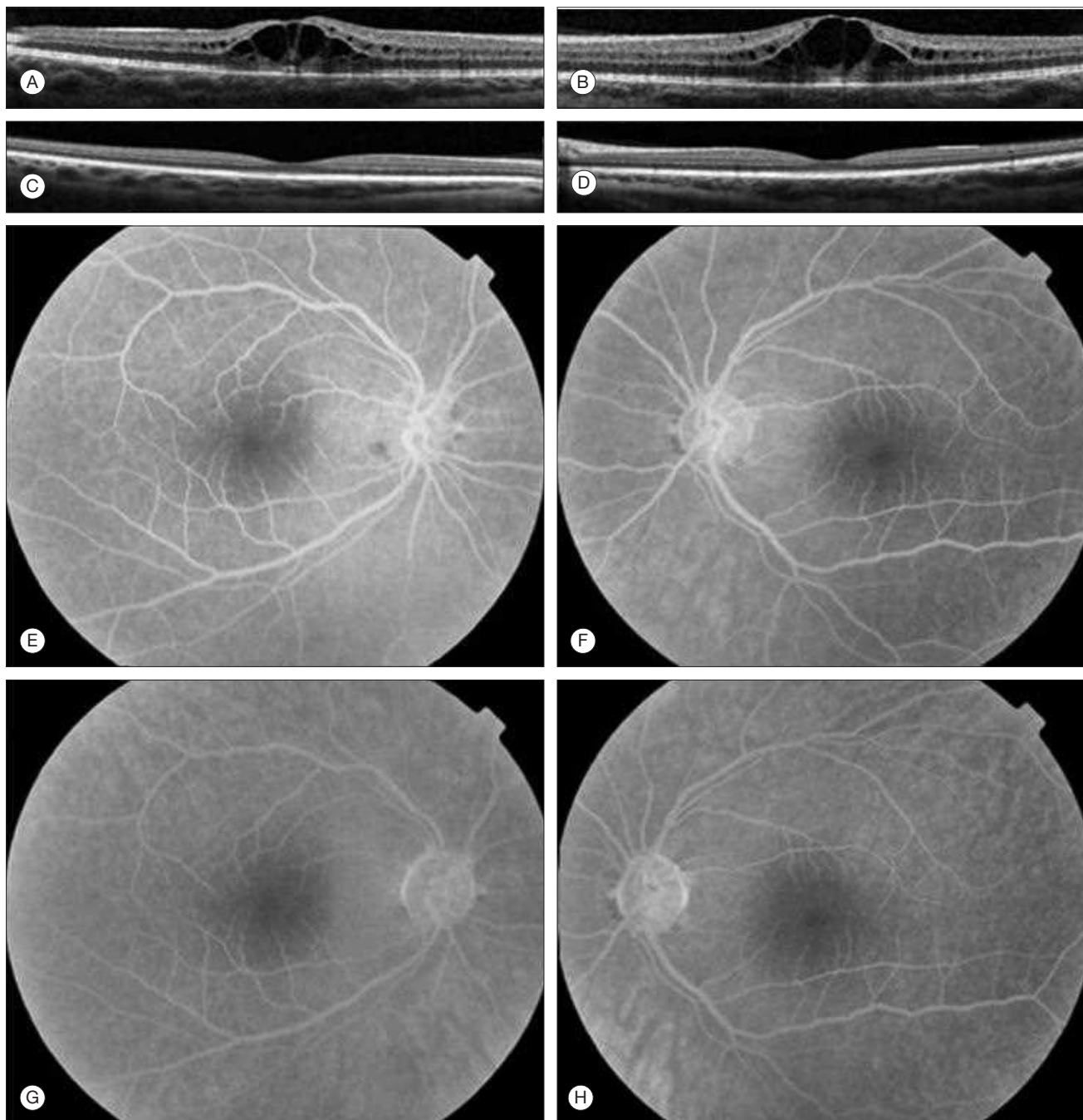


**Fig. 6.45.4 Canthaxanthine Retinopathy.** Large yellow crystals are distributed in a prominent macular ring. (From Weinberg DV, D'Amico DJ. Retinal toxicity of systemic drugs. In: Albert DM, Jakobiec FA, editors. Principles and practice of ophthalmology. Philadelphia: WB Saunders; 1994. p. 1042–50.)



**Fig. 6.45.5 Tamoxifen Retinopathy. Pseudocystic Foveal Cavitation in Tamoxifen Retinopathy.** (Top left) Color fundus photograph of the right eye demonstrates yellow spots in the posterior pole, (top middle) corresponding to punctate hyperautofluorescent foci on autofluorescence imaging. There is an absence of normal hypoautofluorescence in the fovea. (Top right) Spectral-domain optical coherence tomography imaging demonstrates foveal cavitory spaces. (Bottom) Similar findings are present in the left eye, with more pronounced cavitation. (From Doshi RR, Fortun JA, Kim BT. Pseudocystic foveal cavitation in tamoxifen retinopathy. Am J Ophthalmol 2014;157:1291–1298.e3. Figure 1.)





**Fig. 6.45.6 Paclitaxel Toxicity.** Paclitaxel causes cystoid macular edema evident on optical coherence tomography (A–B) which resolved 7 weeks after discontinuation of paclitaxel therapy (C–D). Initial presentation shows cystoid macular edema with or without dye leakage on fluorescein angiography (E–H). (From Padrón Pérez N, Rubio Caso MJ, Arias Barquet L, et al. Bilateral cystoid macular edema in a patient with taxane-based chemotherapy. *Can J Ophthalmol* 2013;48:e3–e4. Figure 1.)

drugs and diabetic macular edema, especially in patients with generalized fluid retention. In such cases, cessation of medication leads to prompt resolution of diabetic macular edema.<sup>47</sup> Later, more robust studies have been mixed in identifying a causal relationship between thiazolidinediones and the development of macular edema.<sup>48,49</sup>

## IMATINIB

Imatinib is a tyrosine kinase inhibitor that is used in the treatment of chronic myelogenous leukemia. It leads to generalized fluid retention throughout the body and may cause macular edema.<sup>50–52</sup> Cessation of drug therapy and replacement with different chemotherapeutic drug typically results in resolution of macular edema with subsequent vision improvement.

## MITOGEN-ACTIVATED PROTEIN KINASE INHIBITORS AND IMMUNE CHECKPOINT INHIBITORS

Oncological agents such as mitogen-activated protein kinase (MEK) inhibitors and immune checkpoint inhibitors target extracellular signaling and have become common in the treatment of cancers, including cutaneous

metastatic melanoma, non–small-cell lung cancer, and lymphoma among others. MEK inhibitors (trametinib, cobimetinib) and immune checkpoint inhibitors (ipilimumab, pembrolizumab) have been implicated in cases of bilateral serous retinal detachments with or without uveitis. Specifically, central serous-like chorioretinopathy has been reported with use of various MEK inhibitors (presumably due to toxicity to the RPE), whereas rare cases of Vogt–Koyanagi–Harada–like syndrome have been described in genetically predisposed patients receiving immune checkpoint inhibitors. Discontinuation of the chemotherapeutic agent is associated with spontaneous resolution of the serous detachments.<sup>53–55</sup>

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# Anatomy of the Uvea

Monica Evans

## 7.1

**Definition:** The uvea is a pigmented, vascular structure consisting of the iris, ciliary body, and choroid.

### Key Feature

- Supplies blood to most of the eye from anterior and posterior ciliary branches of the ophthalmic artery.

### Associated Features

- Produces aqueous humor in the ciliary processes.
- Controls near accommodation by contraction of ciliary muscles, which relax the zonular fibers to the lens.
- Increases aqueous outflow by contraction of ciliary muscles, which open the trabecular meshwork.

## INTRODUCTION

The uveal tract is the vascular coat of the eye, lying between the sclera and the neuroepithelium. It consists of the iris, ciliary body, and choroid. The former represents the anterior part, the latter the posterior part, and the ciliary body forms the middle part. The uvea contains nerves, supporting connective tissue, and a variable number of melanocytes that are responsible for its distinctive color. The uvea is supplied anteriorly by long posterior ciliary arteries and the anterior ciliary arteries. Posteriorly the uvea is supplied by several posterior ciliary arteries that enter the choroid around the optic nerve.

The choroidal vasculature is responsible for approximately 80% of blood supplies in the eye. A unique feature about the human retina is the presence of two blood–retina barriers: the inner and outer blood–retina barriers that are formed by tight junctions between adjacent endothelial or retinal pigment epithelial cells. The outer blood–retina barrier separates the neural retina from a network of fenestrated vessels called choriocapillaris, which is the major blood supplier for the neural retina. This barrier plays many essential roles in the maintenance of normal physiological processes in the retina, through the transport of nutrients, water, and ions and the removal of metabolic wastes.<sup>1</sup>

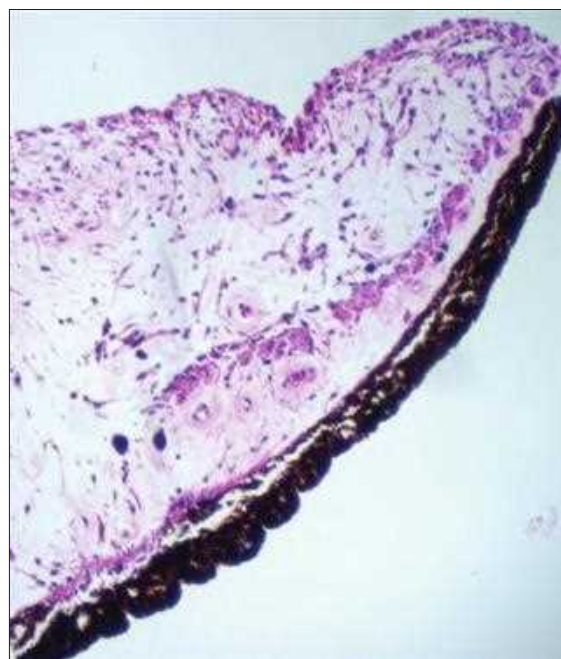
Pathological changes involving the uvea primarily include vascular, inflammatory, and neoplastic diseases. Both primary and metastatic tumors are found in the iris, ciliary body, and choroid. Inflammatory changes are clinically recognized as uveitis and are divided into anterior, posterior, intermediate, and pan uveitis.

## IRIS

The iris forms a diaphragm in front of the crystalline lens. The iris controls the amount of light transmitted into the eye by changes in the pupillary size. The vascular supply to the iris originates in the anterior and long posterior ciliary arteries. Histologically, the iris is made up of three layers:

- An anterior layer is composed of fibroblasts, melanocytes, and collagen, and its anterior surface is folded into many ridges and crypts.
- A middle stromal layer contains fibroblasts, melanocytes, and collagen.
- A posterior layer is composed of the dilator muscle and pigment epithelium (Fig. 7.1.1).

The stroma, or middle layer, makes up the bulk of the iris and contains blood vessels, nerves, melanocytes, and clump cells in a loose extracellular



**Fig. 7.1.1 Normal Iris. Pupillary zone.** Note the sphincter muscle.

matrix of collagen and mucopolysaccharides.<sup>2</sup> The iris color is determined by the number and degree of melanin granules in the superficial stromal melanocytes.<sup>3</sup> Uveal melanosomes originating in the iridal stroma contain both black (eumelanin) and red (pheomelanin) pigment. Eumelanin/pheomelanin ratio varies with iris color, with lower ratios being observed for lighter color (hazel, blue) irides.<sup>4</sup>

Unlike the anterior surface, the posterior epithelium is velvety smooth and uniform. It consists of two layers of densely pigmented cells, which are arranged apex to apex.<sup>5</sup>

The dilator muscle of the pupil extends from the region of the sphincter muscle to the base of the iris and is located in the posterior portion of the iris. The sphincter muscle is located in the posterior iris stroma in the pupillary zone and consists of a circular band of smooth muscle fibers (Fig. 7.1.2). The dilator muscle is innervated by parasympathetic nerves and the sphincter muscle by the sympathetic nervous system.

## CILIARY BODY

The ciliary body extends from the base of the iris and becomes continuous with the choroid at the ora serrata. It is approximately 6–6.5 mm in anteroposterior dimension. It consists of an anterior portion called the pars plicata and a posterior portion called the pars plana. The pars plicata contains approximately 70 finger-like projections called ciliary processes, which are covered by the ciliary body epithelium (Fig. 7.1.3). The pars plicata is the flat part of the ciliary body and ends at the ora serrata. The ciliary processes are thin and finger-like in children (Fig. 7.1.4). With age they become thickened and reveal hyalinization of the stroma (Fig. 7.1.5). The stroma of these areas is filled with fibrous connective tissue, rich vascular networks, melanocytes, and bundles of smooth muscle.

The smooth muscle of the ciliary body can be divided into three groups of fibers: the outer longitudinal portion that attaches anteriorly to the scleral spur and trabecular meshwork fibers, a middle oblique portion, and the inner circular portion.<sup>6</sup> Accommodation is the result of a parasympathetic stimulus that is followed by contraction of the ciliary muscle, which decreases the zonular tension on the crystalline lens. This allows the lens



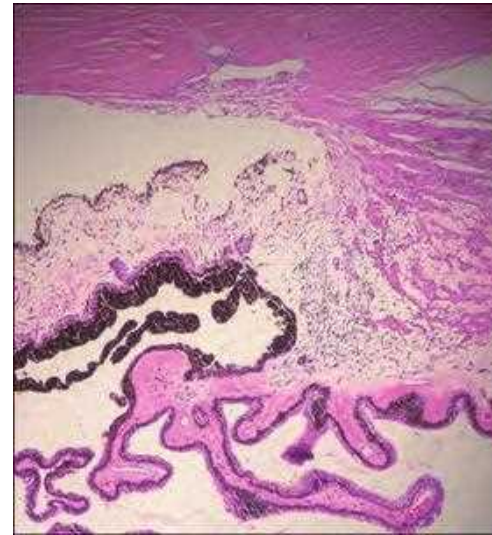
**Fig. 7.1.2** Trichrome Stain of the Anterior Segment Showing the Normal Anatomy of the Iris, Angle, and Ciliary Body. Note the dilator and sphincter muscle of the iris and ciliary body muscle (red). The ciliary body appears with hyalinization of the stroma (blue).



**Fig. 7.1.3** Gross Appearance of Inner Surface of Iris, Ciliary Body, Posterior Lens Capsule, and In-the-Bag Intraocular Lens. Note the ciliary processes.



**Fig. 7.1.4** Ciliary Body of a Child, Revealing Thin and Finger-Like Ciliary Processes.



**Fig. 7.1.5** Ciliary Body of an Adult, Revealing Marked Hyalinization of the Stroma.

to move forward and assume a more spherical shape, increasing the dioptric power of the eye.

The innermost part of both pars plana and pars plicata is covered by a bilayer epithelium: the outer pigmented epithelium cells and the inner nonpigmented cells. The cells of these two layers are arranged apex to apex with tight junctions between them. The zonula occludens near the apices of the nonpigmented epithelial cells form the blood–aqueous barrier. The principal source of aqueous humor is the nonpigmented ciliary epithelium of the pars plicata. Production of the vitreous mucopolysaccharide has been attributed to the nonpigmented ciliary epithelium of the pars plana.

## CHOROID

The choroid is the principal vascular and pigmented tissue that forms the middle coat of the posterior part of the eye. It extends from the ora serrata to the optic nerve.<sup>7</sup> The choroid is the most vascular tissue in the eye, and it has been implicated in the pathophysiology of a variety of ocular diseases.<sup>8</sup> It is attached to the sclera by connective tissue strands and especially posteriorly by numerous blood vessels and nerves that enter the choroid from the sclera. Small amounts of choroidal tissue may extend into the scleral canals through which ciliary vessels and nerves enter the eye. It varies in thickness from 0.1 mm anteriorly to 0.22 mm posteriorly. Choroidal thickness maps using a spectral-domain optical coherence tomographic instrument show that thinner choroidal area spreads around the optic disc and the peripapillary choroid increases in thickness the farther it is away from the optic nerve. The peripapillary choroid in the inferior quadrant is significantly thinner compared with all other quadrants.<sup>9,10</sup>

Histologically, the choroid reveals four layers: the lamina fusca, the stroma, the choriocapillaris, and Bruch's membrane. Bruch's membrane can be divided into five components: the basement membrane of the retinal pigment epithelium, an inner collagenous zone, an elastic layer, the outer collagenous zone, and the basement membrane of the endothelium of the choriocapillaris. The choriocapillaris, a highly vascularized layer, is the capillary layer of the choroid and provides nutrition to the retinal pigment epithelium and outer retinal layers (photoreceptor cell and outer plexiform layers and the outer aspect of the inner nuclear layer). It appears to have a finely spotted appearance and to be arranged in polygonal structures that might be associated with clusters of choriocapillaris lobules of 200- to 250- $\mu$ m diameter and approximately 20- $\mu$ m thickness with a central arteriolar feeder and an array of draining venuoles.<sup>11,12</sup> The endothelial cells lining the choriocapillaris are fenestrated and are joined by gap junctions. The stroma of the choroid contains larger arteries and veins. These vessels are not fenestrated. The lamina fusca is the transition zone between sclera and choroid. It consists of a delicate meshwork of elastic fibers, fibrocytes, and melanocytes, traversed by long posterior ciliary nerves and vessels.

There are various studies that can be used to visualize the choroid vascular structures. Fluorescein angiography (FA) and indocyanine green angiography (ICGA) are both invasive tests that require intravenous administration of dye and imaging for 10–30 minutes. Fluorescein is typically used to visualize the retinal vasculature, whereas ICGA is used to see the choroidal vasculature.<sup>13</sup> Optical coherence tomography angiography (OCTA) is a new noninvasive imaging technique that employs motion contrast imaging to high-resolution volumetric blood flow information,

generating angiographic images in a matter of seconds. OCTA can show images from the internal limiting membrane (ILM) to the choroid to visualize the individual vascular plexus and segment the inner retina, outer retina, choriocapillaris, or other area of interest.<sup>8</sup>

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# Mechanisms of Uveitis

Igal Gery, Chi-Chao Chan

# 7.2

**Definition:** Uveitis represents a complex intraocular inflammatory process that can involve not only the uveal tract but also the retina, vitreous, optic nerve, cornea, and sclera.

## Key Feature

- Inflammation, including leukocytic infiltration, and exudate in the anterior chamber and/or vitreous, as well as inflammation in the uvea and retina.

## Associated Features

- Idiopathic in many instances.
- When an underlying cause is identified, the causative agents and/or mechanisms include infection, trauma, and autoimmunity.

## INTRODUCTION

The term uveitis is used for a group of conditions in which inflammation affects various components of the uveal tract (i.e., the iris, ciliary body, and choroid). In addition, diseases in which adjacent uveal tissues such as the retina and vitreous are affected are also often included under the term uveitis. Some uveitic conditions are caused by infection, whereas all other noninfectious uveitis are assumed to be initiated by immune processes, in particular autoimmunity.<sup>1</sup>

The human immune response has been extensively investigated in the last four decades. This chapter focuses on issues of the immune response related mostly to ocular inflammation; additional information on the immune system is available in numerous reviews and books.<sup>2</sup> The physiological function of the immune system is defense against infection, but in certain situations immune responses are harmful, causing pathological outcomes such as allergy or autoimmune disease. The major outcome of both physiological and pathological immune responses is inflammation, with ensuing local tissue damage that is detrimental to the nondividing cells (the retina and optic nerve) of the vision process. Therefore, this chapter emphasizes posterior uveitis.

## INNATE AND ADAPTIVE IMMUNITIES

Defense against infection is mediated by two systems. There is an early innate immunity that clears the infection or keeps it in check until the second system, antigen-specific adaptive immunity, develops. The two systems consist of both cellular and humoral components. The cellular component of the innate immunity includes several populations of phagocytes, natural killer (NK) cells, and NKT cells.<sup>3</sup> The molecules that participate in innate immunity include components of the complement cascade, the acute phase response proteins, and numerous cytokines and chemokines. In addition to directly confronting infective agents, phagocytic cells of the innate immunity system provide specific stimuli to the adaptive immunity, mainly by the release of proinflammatory cytokines such as interleukin (IL)-1 and tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), and by triggering antigen-presenting cells (APCs) via their toll-like receptors (TLRs). TLRs, which are located mainly on phagocytes, detect microbial products and trigger the expression of genes, in particular those of proinflammatory cytokines, such as interferons, and chemokines and costimulatory molecules.

The system of adaptive immunity differs from that of innate immunity by being antigen specific and including a memory component. The

cellular component of the adaptive immunity consists of two families of lymphocytes, B and T cells. B cells respond by producing specific antibodies, whereas T cells respond by acquiring the features of effector cells, then either produce cytokines that activate other cells or become cytotoxic, capable of lysing cells that express the target antigen.

All components of both the innate and adaptive immune systems are involved in the pathogenic processes of ocular inflammation.

## CELLS OF THE IMMUNE SYSTEM

### Nonlymphocytic Leukocytes

Nonlymphocytic leukocytes are derived from bone marrow myeloid cells. The primary function of these leukocytes is to identify, ingest, and destroy microbes. These cells belong to two major families, the granular and non-granular leukocytes. The granulocytes are characterized by the presence of granules in their cytoplasm and are divided into three subpopulations: neutrophils (polymorphonuclear leukocyte, PMN), basophils, and eosinophils. PMNs are crucial in the defense against bacterial infection and are the first cells to be recruited into infected tissues. In addition, these granulocytes, mainly PMNs, are the hallmark of acute inflammation. These cells are often found in uveitic conditions such as Behçet's disease and other acute uveitides and are a major component in many animal models of uveitis.<sup>4</sup> Basophils and eosinophils also play specific roles in the allergic reaction,<sup>5</sup> whereas eosinophils specifically participate in the response against helminths.<sup>6</sup>

The agranulocytes include macrophages, their circulating precursors, the monocytes, and the dendritic cells. Agranulocytes play central roles in both innate and adaptive immunity. Macrophages are found in normal tissues and are major participants in inflammation, in particular of the chronic type. These cells are also capable of forming "giant cells" following fusion of many macrophages that phagocytosed foreign bodies or insoluble antigens. Giant cells characterize certain chronic forms of uveitis (granulomatous uveitis) such as Vogt-Koyanagi-Harada (VKH) disease, sympathetic ophthalmia, or sarcoidosis.<sup>4</sup> A major function of macrophages is to serve as APCs (detailed later).

Another population of cells specific to the eye and the brain are the microglia. These bone marrow-derived cells resemble macrophages in many aspects, and their main function is assumed to be removal of apoptotic cells, both during development and following apoptotic events such as light damage or retinal degeneration due to genetic defects.<sup>7</sup>

### B Cells

The main function of this population of lymphocytes is to produce antibodies, the major humoral component of adaptive immunity. Antibodies play minor roles in the pathogenesis of immune-mediated uveitis except for autoimmune retinopathy<sup>8</sup> and phacoanaphylactic endophthalmitis.<sup>9</sup> B cells are also capable of presenting antigens to T cells, and in this capacity they may play an important role in the process of sensitization and/or activation of pathogenic T cells. Certain B cells may also function in regulation of immune responses and are accordingly named B-regulatory (Breg) cells.<sup>10</sup>

### T Cells

The population of T cells comprises several subsets of lymphocytes that mature in the thymus and are responsible for four major functions of the antigen-specific immune response:

- Mediation of cellular or delayed-type hypersensitivity.
- T-cell cytotoxicity.

- Immunoregulation.
- Providing help to antibody-producing B cells.

All T cells express a receptor, TCR, which determines their antigen specificity. The two major subsets of T cells are designated according to their function as helper (Th) and cytotoxic (Tc or CTL) cells and are identified by expressing markers designated CD4 or CD8, respectively. These two major populations are further divided into subpopulations according to their function and the cytokines they produce.

Five subpopulations of Th cells have been identified so far, Th1, Th2, Th9, Th17, Th22, classified mainly according to the signature cytokines they produce and their function in the immune response.<sup>11</sup> Of particular importance are the Th1 and Th17 subpopulations, with the signature cytokines interferon (IFN)- $\gamma$  and interleukin (IL)-17, respectively. Th1 and Th17 are involved in protection against microbial and parasitic infection and are also responsible for initiation of pathogenic autoimmune diseases in various organs, including the eye.<sup>11</sup> In addition to subsets of T cells with effluent functions, data collected in recent years have revealed that Th cells also perform immunoregulatory functions and are responsible to a large extent for the process of peripheral tolerance (see later). The data indicate that different populations of T cells are involved in this activity, with the majority of these cells carrying the surface markers of CD4 and CD25. Another marker, the transcription factor FoxP3, was found to be closely related to the regulatory activity of these cells.<sup>12</sup>

## Mast Cells

Mast cells are bone marrow-derived cells that reside in many tissues, including those of the eye, and perform multiple functions, such as being the major cells involved in the allergy reaction. Mediators released by mast cells induce leakage of blood vessels, and thus mast cells are assumed to promote the uveitogenic process.<sup>13</sup>

## NK and NK T Cells

The large population of NK cells is a component of the innate immunity system, and their function is to kill cells that acquire abnormal antigenicity mainly due to viral infection. The killing capacity of NK cells is enhanced by innate immunity molecules, IFN- $\alpha$ , and IFN- $\beta$ .

NK T (NKT) cells are a unique T-lymphocyte sublineage that expresses surface markers of both NK and T cells.<sup>3</sup> The function of these cells is complex, as they can promote or suppress immune responses, including those involved in the development of experimental autoimmune uveitis (EAU).<sup>14</sup>

## Antigen-Presenting Cells

APCs play a major role in the immune system by enabling T cells to recognize their target antigen. Since TCRs recognize only short peptides, in combination with major histocompatibility complex (MHC) molecules, APCs are essential for cleaving the antigenic protein and providing its peptides in complex with MHC molecules. The populations of APCs include dendritic cells, macrophages, and B cells. Enhanced expression of MHC is shown in ocular resident cells in eyes with uveitis.<sup>15</sup>

## MOLECULES OF THE IMMUNE SYSTEM INVOLVED IN UVEITIS

Immune responses are mediated by molecules that are released by or expressed on the cellular surface. These are detailed in the subsections that follow.

### Antibodies

Antibodies are produced and released by B cells and mediate immunopathogenic processes of types I, II, and III (see later). With the exception of a rare ocular condition, autoimmune retinopathy and phacoanaphylactic endophthalmitis,<sup>8,9</sup> antibodies seem to play minor roles in the pathogenesis of uveitis.

### Cytokines

Cytokines are proteins that are produced by lymphoid and a variety of other cells. These molecules are responsible for communication between

cells of the immune system and are the principal mediators of inflammation and immune reactions.<sup>2</sup> Most known cytokines are designated by the term interleukin (IL). As of 2017, there are 41 well-defined ILs, and the list will certainly get longer.

Analysis of cytokines in mouse eyes with immune-mediated inflammation revealed that the great majority of the 34 tested cytokines were upregulated at the peak of disease, indicating the involvement of a large number of molecules in the pathogenic process.<sup>16</sup> Cytokines, in particular IFN- $\gamma$ , IL-17, TNF- $\alpha$ , and IL-1, play pivotal roles in the inflammatory process by affecting a large spectrum of cells that express the corresponding specific receptors. Thus they initiate a complex sequence of events that includes activation of the same and other cells and the production of numerous additional molecules, including other cytokines, chemokines, and adhesion molecules. In contrast to these proinflammatory cytokines, there are cytokines, in particular IL-4, IL-10, IL-35, and TGF- $\beta$ , that may exert an opposite effect (i.e., inhibition of immune responses).

## Chemokines and Chemokine Receptors

Chemokines are a family of low-molecular-weight (8–10 kDa) cytokines that exert the capacity of chemoattraction for cells that express receptors with specificity toward the corresponding chemokines. Together these two families of molecules are responsible for the cell migration of the inflammatory process. Chemokines are divided into four groups, on the basis of the number and location of their N-terminal cysteine residues. Chemokine receptors are divided according to their specific interaction with chemokines of one of the four subfamilies. The receptors exhibit overlapping specificity for chemokines of the same subfamily, however. All receptors act by coupling to G-proteins that activate enzymes, including those that stimulate cellular locomotion. Numerous chemokines and chemokine receptors participate in the uveitic process.<sup>16,17</sup>

## Adhesion Molecules

These molecules are expressed on the surface of cells of the immune system and other cells and are responsible for promoting adhesive interactions with other cells or with the extracellular matrix. This family of molecules, which includes the selectins, integrins, and members of the immunoglobulin superfamily, is crucial for cell migration and activation during the inflammatory process (see later). Enhanced expression of adhesion molecules has been demonstrated in the resident cells of uveitic eyes.<sup>18</sup>

## Other Molecules

Other molecules that participate in the immunopathogenic process of uveitis include mainly members of the complement cascade. Certain members of this group are chemotactic for leukocytes and were found to play major roles in the development of experimental uveitis.<sup>19</sup>

The involvement of certain molecules in inflammatory processes in the eye is detailed later. An increasing number of these molecules have become targets for the treatment of uveitis.

## TOLERANCE AND AUTOIMMUNITY

Apart from protection against invading pathogens, the immune system is required to avoid developing pathogenic immune response against self-antigens (i.e., autoimmunity). In normal conditions, this requirement is well met by using multiple mechanisms that together prevent development of pathogenic autoimmunity. Disease may develop, however, when one or more of these mechanisms fail. These mechanisms include central and peripheral tolerance, anergy, immunoregulation, and ignorance.

### Central Tolerance

Central tolerance is the major mechanism for prevention of autoimmunity. This process takes place in the thymus, the organ in which immature lymphocytes that originated in the bone marrow undergo two selection processes before migrating into the periphery. Firstly, thymocytes are positively selected in the thymic cortex, according to their capacity to interact with self MHC molecules. Next, the positively selected lymphocytes migrate into the thymic medulla, where self-antigens are expressed, and induce apoptosis in thymocytes with high affinity toward these autoantigens. The negative selection process is extremely effective, and trace amounts of tissue-specific antigens were found to eliminate large numbers of thymocytes specific to these antigens.<sup>20,21</sup>



It is of note that uveitogenic antigens can be found in thymi of both human donors and mice.<sup>20,22</sup> Importantly, the level of expression of individual uveitogenic antigens in the thymus of mice of different strains was found to be inversely related to susceptibility to induction of EAU by these antigens.<sup>23</sup> These observations—and the finding that the level of thymic expression of tested retinal antigens varied among individual human donors<sup>22</sup>—suggest, therefore, that susceptibility to uveitis is determined at least in part by the level of thymic expression of uveitogenic antigens.

Negative selection is, however, an incomplete process, and lymphocytes with low affinity toward autoantigens do escape deletion.<sup>24</sup> Several mechanisms are in place to prevent these cells from initiating pathogenic autoimmunity. These are described in the following subsections.

## Peripheral Tolerance

Peripheral tolerance is an incompletely defined process and includes at least three different mechanisms:

- Elimination of autoantigen-specific lymphocytes by apoptosis following exposure to high levels of the target protein.
- Induction of anergy in the self-specific lymphocytes following exposure to the antigen in the absence of costimulation.
- Suppression by T-regulatory cells.

The existence, features, and activity of T-regulatory cells have been well studied in recent years (see earlier) and their capacity to inhibit autoimmune uveitis has been established in the animal model of EAU.<sup>25</sup>

## Ignorance

This poorly studied mechanism probably plays a major role in preventing pathogenic autoimmunity against partially sequestered antigens such as most ocular proteins. Lymphocytes specific against ocular- and other organ-specific antigens are readily found in normal humans,<sup>24</sup> and immune ignorance is assumed to be responsible at least in part for the absence of pathogenic autoimmunity in these cases. The generally accepted explanation for the inactivity of self-specific lymphocytes is their naïve status.

## MECHANISMS THAT TRIGGER AND PROMOTE UVEITOGENIC PROCESSES

Uveitis develops in only a small proportion of humans, and accumulating data have identified several mechanisms that trigger and promote the development of this pathogenic process. These mechanisms include genetic makeup and environmental factors such as trauma and microbial infection.

## Genetic Background

The possible involvement of genetic factors in the pathogenesis of uveitis has been indicated in studies with twins, familial aggregation, and in particular by the associations between several uveitic conditions and certain human leukocyte antigen (HLA) alleles.<sup>22,26</sup> The observations in humans were confirmed in studies with experimental animals in which associations were found between the susceptibility to the induction of EAU and the genetic makeup of the animal. The data with well-defined mouse strains show that the susceptibility to EAU is affected by both MHC and non-MHC genes.<sup>27</sup>

## Trauma

The role of trauma as the trigger mechanism for development of pathogenic autoimmunity in the eye is indicated by two severe inflammatory eye diseases that develop following trauma, namely, sympathetic ophthalmia<sup>9</sup> and phacoanaphylactic endophthalmitis.<sup>28</sup> The original notion about the pathogenesis of these conditions had been that the damage releases sequestered antigens from the uvea or lens, respectively, and initiates specific autoimmune responses that selectively affect these tissues. More recent studies have suggested, however, that release of sequestered antigen by itself does not trigger an immune response and that additional mechanisms are involved in the initiation of the immunopathogenic response. These mechanisms include microbial contamination that often accompanies the trauma and the accumulation of necrotic products at the site. Necrotic cells promote immunopathogenicity by stimulating danger signals and proinflammatory processes.<sup>29</sup> It is of note that in contrast to

the proinflammatory activity of cells dying by necrosis, cells undergoing apoptosis stimulate anti-inflammatory activity.<sup>29</sup>

## Microbial Infection

Microbial infection is assumed to trigger pathogenic autoimmunity by two different mechanisms: molecular mimicry and non-antigen-specific stimulation of the immune response by microbial molecules.

The notion of molecular mimicry being a trigger for autoimmunity was proposed following the finding of identity between short stretches of sequence of uveitogenic antigens, such as arrestin (S-antigen), and certain microbial products.<sup>30</sup> Furthermore, immunization of experimental animals with the microbial molecules induced inflammatory changes similar to those induced by the ocular antigen.<sup>30</sup> It is possible, therefore, that effector cells specific against microbial products could initiate pathogenic responses following recognition of the tissue antigens that cross-react with the microbial components.<sup>31</sup> This notion was further promoted by the finding that naïve lymphocytes, specific against a retinal antigen, are activated by components of the intestinal flora to acquire pathogenicity and induce uveitic changes in the mouse eyes.<sup>32</sup> Moreover, the experimental system used in this study indicated that the intestinal flora is crucial for development of spontaneous EAU in these mice.<sup>32</sup>

Another likely mechanism for triggering pathogenic autoimmunity is via stimulation of the innate immunity by microbial products that activate the immune response through the TLR system. Numerous microbial molecules, such as endotoxin, bacterial DNA, or viral RNA, are potent ligands for TLRs that are expressed on macrophages and other APCs.<sup>33,34</sup> The activity of these TLR-ligands is the basis for their “adjuvant” capacity.

As all mechanisms mentioned here are capable of promoting pathogenic autoimmunity, it seems likely that uveitic conditions develop as a result of synergy between the different mechanisms.

## MECHANISMS OF INFLAMMATION

### Types of Immunopathogenic Processes

Disease-inducing immunological processes have been classified into four types, according to the pathogenic mechanisms involved.<sup>2</sup>

*Type I* pathogenic response, known as immediate hypersensitivity, is mediated by antibodies of the IgE type that are attached to mast cells. When the antibodies are exposed to their specific antigen, the mast cells are activated and release the contents of their granules, including mediators such as histamine, several enzymes, prostaglandins, leukotrienes, and certain cytokines. In the eye, this type of response is involved in reactions such as hay fever and allergic conjunctivitis.<sup>5</sup>

*Type II* response is mediated by antibodies against cellular or matrix antigens that cause damage by one of three mechanisms: (1) activation of the complement cascade and enhanced opsonization, (2) recruitment of damaging neutrophils and macrophages, or (3) interference with functions of receptors or other molecules with specific functions. The latter mechanism is thought to be the pathogenic mechanism for Grave's disease and myasthenia gravis.<sup>35</sup>

*Type III* reaction, known also as immune complex disease, is induced by antigen-antibody complexes that initiate pathogenicity mainly by triggering the complement cascade. The systemic disease that is the hallmark for type III immunopathogenesis is serum sickness, and its experimental local model is the Arthus reaction. It is assumed that immune complexes play a major role in the pathogenesis of phacoanaphylactic endophthalmitis.<sup>28</sup>

*Type IV* immunopathogenic reaction, also named delayed hypersensitivity or cell-mediated inflammation, is induced by Th1 or Th17 lymphocytes. These cells are responsible for eradication of certain microbes and parasites, but they elicit the same processes when the targets are autoantigens. The pathogenic processes of this immune reaction have been well dissected and are detailed later. Type IV reactions were identified as the immunopathogenic mechanism in the majority of animal models for uveitic conditions, and it is assumed that they are also responsible for most cases of intraocular inflammation in humans.<sup>11,36</sup>

## IMMUNOPATHOGENIC PROCESSES OF UVEITIS IN HUMANS

It is generally assumed that processes similar to those described in experimental animals take place in humans during the development of noninfectious uveitis due to autoimmunity.<sup>11,36</sup> This notion is supported by the

finding of lymphocytes specific to ocular antigens in the blood of uveitic patients<sup>24</sup> and by the similarity in the histopathological changes<sup>4,11</sup> and in the susceptibility to immunosuppressive agents between uveitic patients and animals with EAU.<sup>11,36</sup> As mentioned earlier, small numbers of T cells with specificity toward ocular self-antigens normally escape deletion in the thymus, but the mechanism for their activation remains unclear. The finding of activation of autoreactive T cells by the gut flora<sup>32</sup> provides a new potential mechanism for the activation process, but the relatively rare occurrence of uveitis indicates that additional mechanisms are required for disease development. One such mechanism could be the adjuvant effect of systemic microbial infection mentioned earlier.<sup>33,34</sup> The finding that “licensing” in lymphoid organs is also required for autoreactive cells to initiate the pathogenic process in the target organ<sup>37,38</sup> emphasizes the complexity of the pathogenic autoimmunity.

## MECHANISMS THAT INHIBIT INFLAMMATION IN THE EYE

Ocular tissues that participate in the vision process have limited capacity for regeneration and therefore are highly susceptible to the damaging effects of inflammation. To protect against these detrimental effects, the eye is equipped with several mechanisms that together provide the eye with an immune privilege environment in which immune responses, in particular of the cellular type, are inhibited.<sup>39,40</sup> These mechanisms include:

- Poor supply of lymphatics.
- Low expression of MHC molecules.
- The presence of immunosuppressive molecules such as TGF- $\beta$ , VIP,  $\alpha$ -MSH, or Fas ligand.
- The phenomenon of anterior chamber–associated immune deviation (ACAID), in which antigenic challenge at the anterior chamber induces specific and selective suppression of Th1 and Th17-mediated cellular immunity against the eliciting antigen.<sup>39–42</sup>

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# General Approach to the Uveitis Patient and Treatment Strategies

7.3

Russell W. Read

**Definition:** Uveitis is an inflammatory process that in strict definition targets the uveal tract (iris, ciliary body, choroid) primarily and other ocular structures secondarily. In common use, uveitis may refer to any form of intraocular inflammation.

**Key Feature**

- Evidence of inflammation within the eye.

**Associated Features**

- Pain, redness, photophobia, blurred vision, floaters.
- Inflammatory cells localized to intraocular structures (e.g., keratic precipitates, iris nodules, retinal vasculitis, chorioretinal infiltrates).
- Peripheral anterior synechiae, posterior synechiae, or both.
- Optic disc edema, macular edema, or both.
- Retinitis and/or retinal vasculitis.
- Secondary cataract and glaucoma.

**INTRODUCTION**

Uveitis is not a single condition but rather a category that encompasses multiple distinct conditions united by the common feature of inflammation of the uveal tract (iris, ciliary body, choroid). This inflammation may be primary or due to inflammation of adjacent structures. Uveitis is under-recognized as a cause of blindness as it is estimated to be responsible for 10%–15% of blindness<sup>1</sup> and is a leading cause of blindness in the United States.<sup>1,2</sup>

**CLASSIFICATION**

The Standardization of Uveitis Nomenclature (SUN) consensus conference workshop emphasizes an anatomical approach to uveitis classification (Table 7.3.1).<sup>3</sup> Additional descriptors are used to define the disease beyond anatomical location. These additional features include time frame of onset (sudden versus insidious); duration (limited – less than 3 months’ duration versus persistent – greater than 3 months’ duration); course (acute, recurrent, or chronic); laterality (unilateral versus bilateral); and granulomatous

versus nongranulomatous appearance. This additional information allows one to focus their differential diagnosis using a technique described under “Differential Diagnosis” later.

**EPIDEMIOLOGY**

Uveitis occurs at between 52 and 341 per 100 000 person-years in the United States.<sup>10,11</sup> Anterior uveitis is by far the most common anatomical subtype, accounting for up to 92% of cases outside uveitis referral centers,<sup>6,8</sup> with the other anatomical categories less frequently represented in community practices (see Table 7.3.1). The most common etiologies ascribed for anterior uveitis are idiopathic (38%–56%), seronegative spondyloarthropathies (21%–23%), juvenile arthritis (JA; 9%–11%), and herpetic keratouveitis (6%–10%). The majority of intermediate uveitis is idiopathic. Toxoplasmosis is the most common cause of posterior uveitis, and the most common categories of panuveitis are idiopathic (22%–45%) and sarcoidosis (14%–28%).<sup>6,9,12</sup> There is a much higher incidence of uveitis in older individuals than previously reported, with an average incidence of 340.9/100 000 persons per year in the US Medicare population of individuals age 65 years and over.<sup>10</sup>

**OCULAR MANIFESTATIONS**

The clinical manifestations of uveitis vary depending on the primary site of involvement in the eye, the course of the disease, and the presence of complications. The symptoms of acute anterior uveitis typically include pain, redness, photophobia, and blurred vision, developing over a period of hours to days. In contrast, chronic anterior uveitis (more recently termed insidious onset by the SUN nomenclature) may present with little pain or photophobia but still with blurring of vision. Intermediate and posterior uveitis typically presents with floaters or impaired vision while patients with panuveitis may present with any or all the above.

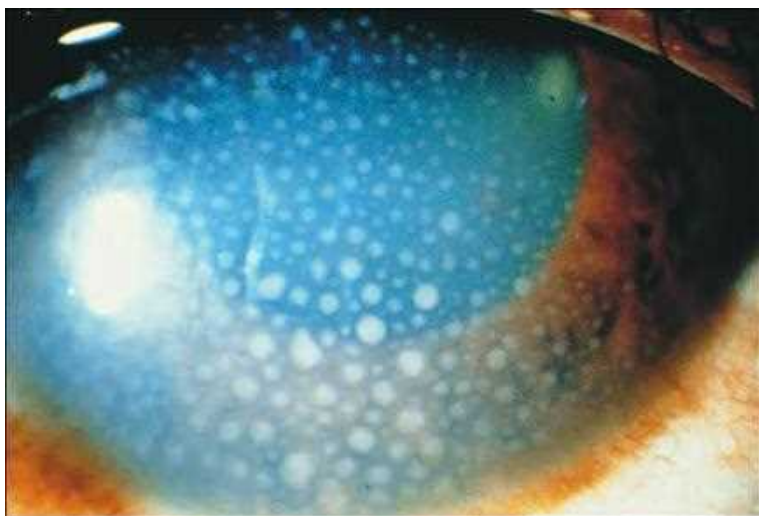
Approach to the uveitis patient must be comprehensive. The importance of a careful, complete history (including family, social, travel, and medication histories) and review of systems cannot be overemphasized. Since any intraocular or adjacent structure may yield physical examination findings that help the clinician in the development of a differential diagnosis, the ocular examination must be similarly comprehensive. The conjunctiva may show ciliary flush (perilimbal injection characteristic of anterior uveitis, Fig. 7.3.1) or nodules (e.g., in sarcoidosis), the latter of which can

TABLE 7.3.1 Classification, Clinical Features, and Epidemiology of Uveitis

Anatomical Category	Clinical Features	Percent of Cases <sup>2</sup>	Includes <sup>3,4</sup>
Anterior	<ul style="list-style-type: none"><li>• Anterior chamber cell</li><li>• Keratic precipitates</li><li>• Iris nodules</li><li>• Posterior and peripheral anterior synechiae</li></ul>	25% <sup>5</sup> –92.2% <sup>6</sup>	<ul style="list-style-type: none"><li>• Iritis</li><li>• Iridocyclitis</li><li>• Anterior cyclitis</li></ul>
Intermediate	<ul style="list-style-type: none"><li>• Vitreous cell</li><li>• Peripheral retinal vascular sheathing</li><li>• Pars plana exudate</li></ul>	1.3% <sup>6</sup> –26% <sup>7</sup>	<ul style="list-style-type: none"><li>• Pars planitis</li><li>• Posterior cyclitis</li><li>• Hyalitis</li></ul>
Posterior	<ul style="list-style-type: none"><li>• Choroiditis</li><li>• Retinitis</li><li>• Retinal vascular sheathing</li><li>• Papillitis</li></ul>	4.7% <sup>8</sup> –38.4% <sup>9</sup>	<ul style="list-style-type: none"><li>• Choroiditis (focal, multifocal, diffuse)</li><li>• Chorioretinitis</li><li>• Retinochoroiditis</li><li>• Retinitis</li><li>• Neuroretinitis</li></ul>
Panuveitis	<ul style="list-style-type: none"><li>• All of the above</li></ul>	0.8% <sup>6</sup> –38% <sup>5</sup>	



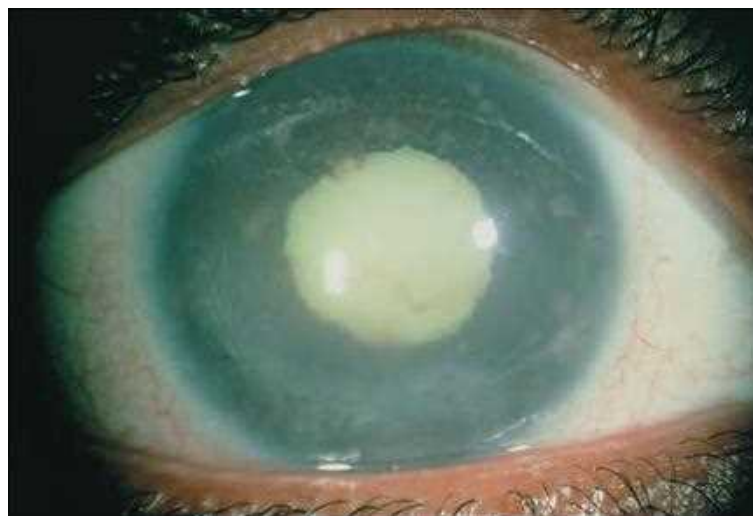
**Fig. 7.3.1 HLA-B27-Related Acute Anterior Uveitis.** This severe case of anterior uveitis demonstrates fibrin clot formation and hypopyon in the anterior chamber.



**Fig. 7.3.2 Keratic Precipitates in Anterior Uveitis.** These keratic precipitates are granulomatous in appearance, as would be expected with entities such as sarcoidosis, Vogt-Koyanagi-Harada syndrome, and sympathetic ophthalmia.

be biopsied for diagnosis. The cornea may reveal keratic precipitates (collections of inflammatory cells on the endothelial surface, Fig. 7.3.2), the granulomatous or nongranulomatous character of which can further direct the differential (see Fig. 7.3.2). Keratic precipitates are normally concentrated in Arlt's triangle due to the aqueous convection currents in the anterior chamber. Keratic precipitates outside Arlt's triangle are more typical of Fuchs' heterochromic iridocyclitis or herpetic keratouveitis. Keratic precipitates are usually white when fresh and become more pigmented and shrunken ("crenated") with time. Other corneal features that may indicate herpetic disease include epithelial dendrites, geographic ulcers, or stromal scarring. Chronic uveitis may result in calcium deposition at the level of Bowman's membrane, a finding termed *band keratopathy*.

The hallmark finding in anterior uveitis is the presence of leukocytes in the aqueous humor. Breakdown of the blood-ocular barrier also results in protein leakage into aqueous, which is termed *flare*. Both are graded on a scale of 0–4+. Although a plethora of grading scales have been proposed, the SUN consensus scale has been agreed to by uveitis specialists and should be used.<sup>3</sup> With severe anterior uveitis, fibrin and hypopyon formation may be seen (see Fig. 7.3.1). Eyes with long-standing uveitis may have persistent flare that will not resolve no matter the intensity of treatment. Although this does not represent active inflammation, the presence of flare (protein) in the anterior chamber may predispose to the development of anterior or posterior synechiae. The development of 360° of posterior synechiae results in pupillary seclusion, iris bombé, and angle-closure glaucoma. Nodules in the iris (Koeppe nodules at the pupillary border; Busacca nodules within the iris stroma) or angle may be seen in granulomatous



**Fig. 7.3.3 Chronic Granulomatous Uveitis.** This patient demonstrates several features of chronic granulomatous uveitis, as may be seen with sarcoidosis, including iris nodules, posterior synechiae, and cataract formation.

uveitis (Fig. 7.3.3). Unilateral disease, elevated intraocular pressure (IOP), and sectoral iris atrophy are suggestive of herpetic disease.

Cataract is a common complication of long-standing uveitis and chronic corticosteroid therapy. Most such cataracts are posterior subcapsular in location. Posttraumatic or postsurgical cases of uveitis need to be checked carefully for capsular integrity, retained lens material, or intraocular lens (IOL) malposition.

The vitreous may show cellular infiltration, snowball opacities, fibrosis with resultant traction on the retina, or cyclitic membrane formation. It is important to determine where cells are present in the vitreous cavity. In cases of iridocyclitis, cells are found in the anterior vitreous cavity whereas with intermediate, posterior, or panuveitis, cells are distributed either throughout the vitreous or posteriorly alone.

Edema of the optic nerve, macula, or both may occur in any form of uveitis. Sheathing of retinal vessels with perivascular exudate may be seen in the periphery with intermediate uveitis or more posteriorly with posterior uveitis/retinal vasculitis. Lesions, presumably representing infiltration of inflammatory cells into the choroid, may develop, producing creamy white to yellow spots deep to the retina. More diffuse thickening of the choroid may be detectable with ultrasonography or enhanced depth imaging on optical coherence tomography (OCT). Retinal whitening indicates edema from inflammatory or infectious involvement. Hemorrhage may be present. Disruption of Bruch's membrane by inflammatory insult may lead to choroidal neovascularization. Once edema and inflammation resolve, atrophy of the retina, choroid, or both may become evident. Retinal atrophy increases the risk of retinal tears and rhegmatogenous detachment. Peripheral examination with scleral depression may reveal collections of inflammatory cells and fibrosis over the pars plana (so-called snowbanking).

In acute anterior uveitis, IOP is usually reduced due to an inflammation-induced reduction in aqueous production. With therapeutic reduction of inflammation, this is reversible. Persistent reduction in IOP may occur if chronic uveitis produces ciliary body atrophy or cyclitic membrane-induced ciliary body detachment. Potentially irreversible hypotony and eventual phthisis bulbi may occur. Elevation of IOP in uveitis results from aqueous outflow obstruction by any of a number of mechanisms, including plugging of the trabecular meshwork with inflammatory cells, swelling of meshwork fibers (trabeculitis), peripheral anterior synechiae formation, pupillary block from extensive posterior synechiae, and corticosteroid-induced IOP elevation. Gonioscopy should be performed regularly in patients with chronic uveitis to monitor for peripheral anterior synechiae formation and angle closure.

## DIAGNOSIS AND ANCILLARY TESTING

As previously mentioned, the approach to uveitis must be comprehensive (Box 7.3.1) since it may be associated with any of multiple systemic conditions, some of which may be curable (e.g., bacterial uveitis such as syphilis). Even if the disease is not curable, attention to the systemic component may be required to prevent life-threatening complications (e.g., systemic vasculitis).

**BOX 7.3.1 History Taking in Uveitis****Present Illness**

Onset, course, laterality, ocular symptoms, associated systemic symptoms

**Past Ocular History**

Previous episodes, past therapy and response, previous or antecedent ocular trauma or surgery

**Medical History**

Systemic illnesses, prodromal syndromes, medications

**Social History**

Age, race/ethnicity, gender, birthplace, travel, dietary habits, sexual history, intravenous drug abuse

**Family History**

Medical illnesses, ocular disease, history of uveitis, contagious diseases (e.g., tuberculosis), maternal infections

**Review of Systems**

General – fever, weight loss, malaise, night sweats

Musculoskeletal – arthralgias, lower back pain, joint stiffness

Dermatological – rashes, sores, alopecia, vitiligo, poliosis, tick/insect bites

Neurological – tinnitus, headache, meningism, paresthesias, weakness/paralysis, altered mental status

Respiratory – shortness of breath, cough, sputum production

Gastrointestinal – diarrhea, bloody stools, oral aphthous ulcers

Genitourinary – dysuria, discharge, genital ulcers, balanitis, epididymitis

**DIFFERENTIAL DIAGNOSIS**

Once a complete history and ocular examination with a targeted extraocular physical examination have been performed, a differential diagnosis is developed that directs a targeted diagnostic plan. One method of developing and narrowing the differential has been described as naming and meshing.<sup>13</sup> The clinical manifestations are given as specific a set of descriptors as possible using the previously mentioned classification schemes. As an example, rather than the simplistic “anterior uveitis,” a much more useful descriptor would be sudden-onset unilateral nongranulomatous anterior uveitis or insidious-onset bilateral granulomatous uveitis. Once named, this description is matched against a list of uveidities that most closely fit with those clinical characteristics (Table 7.3.2), keeping in mind other important factors such as demographics, ethnicity, and exposures. In the preceding examples, HLA-B27–associated sudden-onset anterior uveitis and sarcoidosis, respectively, most closely mesh with the descriptors. However, if the first example occurred in a Turkish national, then Behçet’s would be included in the differential as well. Once a list of potential uveitic entities has been developed, testing can be performed.

Although no definitive rules govern when a laboratory workup should be performed and what it should entail, a common practice among uveitis specialists is not to test in first episodes of unilateral nongranulomatous anterior uveitis unless specific findings on history or physical examination suggest a specific diagnosis. For any other form of uveitis, most uveitis specialists will perform a workup. A targeted approach is preferred wherein tests are ordered only for the most likely entities based on the differential generated through the naming and meshing process.<sup>9</sup> Certain entities should be tested for in virtually every uveitis patient (syphilis, tuberculosis, and sarcoid, since they may cause essentially any form of uveitis). Table 7.3.2 lists the most commonly used laboratory investigations in the workup of uveitis patients as well as the diseases for which they are useful. These tests are discussed further in the respective chapters for individual uveitic entities.

Beyond laboratory and radiographic testing, other useful ancillary tests in uveitis include angiography, both fluorescein and indocyanine green (to assess cystoid macular edema, serous retinal detachments, retinal and choroidal vascular involvement, and choroidal perfusion), ultrasonography (measurement of choroidal thickness, presence of posterior scleritis, and to rule out posterior segment pathology in eyes with media opacities), and OCT (to assess cystoid macular edema and choroidal thickening with enhanced depth imaging in addition to expanding functions like OCT angiography and en face OCT). Diagnostic vitrectomy and/or retinochoroidal biopsy can be of help in suspected cases of infectious uveitis, intraocular neoplasm, or disease nonresponsive to treatment. Specimens can be sent for histology, culture, antibody testing, electron microscopy, polymerase chain reaction (PCR) testing, and more recently, DNA deep sequencing.<sup>15</sup>

**TABLE 7.3.2 Differential Diagnosis and Laboratory Investigations for Uveitis**

Type of Uveitis	Most Common Etiologies	Laboratory Tests
Acute Anterior	Seronegative spondyloarthropathies	HLA-B27, sacroiliac films
	Behçet’s syndrome	HLA-B51
	Herpetic (HSV, VZV, CMV)	Aqueous tap for PCR
	Glaucomatocyclitic crisis	
	Poststreptococcal	Antistreptococcal lysin-O titer
	Tubulointerstitial nephritis and uveitis syndrome	HLA-DRB1*0102, <sup>14</sup> urinalysis, β2 microglobulin
Chronic Anterior	Juvenile idiopathic arthritis	Antinuclear antibodies (ANA)
	Sarcoidosis	Chest X-ray/CT, biopsy, angiotensin-converting enzyme, serum lysozyme
	Fuchs heterochromic iridocyclitis	
	Syphilis	Rapid plasma reagin (RPR), treponema pallidum antibodies
	Tuberculosis	PPD, QuantiFERON TB Gold, T-SPOT, TB, chest X-ray
Intermediate	Herpetic	Aqueous tap for PCR
	Pars planitis	
	Sarcoidosis	See above
	Lyme disease	ELISA, Western blot
Posterior	Multiple sclerosis	MRI of brain, CSF analysis
	Toxoplasmosis	ELISA
	Toxocariasis	ELISA
	Sarcoidosis	See above
	Syphilis	See above
	Tuberculosis	See above
	Viral (HSV, VZV, CMV)	Aqueous/vitreous tap/biopsy for PCR
	Birdshot choroidopathy	HLA-A29
	Serpiginous choroidopathy	
	Ocular histoplasmosis	
Panuveitis	Multifocal choroiditis/panuveitis	
	VKH disease	Fluorescein angiography, ultrasound, OCT with EDI
	Sympathetic ophthalmia	Same as for VKH, plus history
	Sarcoidosis	See above
	Toxoplasmosis	See above
	Toxocariasis	See above
	Syphilis	See above
	Tuberculosis	See above
	Endophthalmitis	Vitreous culture

See subsequent chapters for detailed description of each entity. CMV, Cytomegalovirus; CSF, cerebrospinal fluid; CT, computed tomography; EDI, enhanced depth imaging; ELISA, enzyme-linked immunosorbent assay; HLA, human leukocyte antigen; HSV, herpes simplex virus; MRI, magnetic resonance imaging; OCT, optical coherence tomography; PCR, polymerase chain reaction; PPD, purified protein derivative; TB, tuberculosis; VKH, Vogt-Koyanagi-Harada; VZV, varicella-zoster virus.

**TREATMENT**

The goal of the treatment of eye disease is to protect and preserve visual function. In uveitis, treatment must be directed toward potentially two separated but intimately related processes: elimination of infection (if present) and suppression of the host inflammatory response. Up to 90% of uveitis is noninfectious, so the latter is most commonly the sole target, but the former must never be removed from consideration when planning treatment. Once the decision is made to treat, any and all means of immunosuppression must be considered in the pursuit of that goal. Therapy may be administered via any of multiple routes (topical, periocular, intraocular, systemic) using any of the multiple therapeutic categories of anti-inflammatories now available. If the ophthalmologist is not comfortable or familiar with therapy beyond that applied to the eye or systemic corticosteroids, then they must refer or collaborate with someone who is. The most common anti-inflammatory medications used in the treatment of uveitis are outlined in Table 7.3.3. Therapies for specific types of uveitis are detailed in subsequent chapters.



TABLE 7.3.3 Anti-inflammatory Therapy in the Treatment of Uveitis

Drug Class	Medication	Mechanism of Action	Side Effects	Comments
Glucocorticoids	Prednisone, methylprednisolone sodium succinate, triamcinolone acetonide, dexamethasone, fluocinolone acetonide, difluprednate, prednisolone acetate, prednisolone sodium phosphate, loteprednol etabonate, rimexolone	Engagement of cytosolic corticosteroid receptor with transportation into nucleus and subsequent myriad effects, including inhibition of cyclo-oxygenase and lipoxygenase pathways, decreased production of vasoactive amines and interleukins, decreased circulating monocytes, decreased macrophage activity, decrease in complement levels. Pleiotropic effects are the basis of the significant side effects	<b>Topical</b> – elevated IOP, cataract, increased susceptibility to infection, corneal or scleral thinning/perforation <b>Periocular</b> – same as topical, as well as ptosis, scarring of Tenon's capsule, scleral perforation, hemorrhage, abscess <b>Systemic</b> – same as topical, as well as weight gain, fluid retention, electrolyte disturbances, osteoporosis, aseptic necrosis of hip, hypertension, impaired glucose tolerance, mental status changes, impaired wound healing, menstrual irregularities, others	Most versatile agent but also one with most potential side effects, especially with chronic use May be used topically, intraocularly, periocularly, orally, intravenously
Antimetabolites	Methotrexate	Increase in extracellular adenosine, increase in intracellular cAMP result in immunosuppression <sup>36</sup>	Hepatotoxicity, GI upset, pneumonitis, stomatitis, bone marrow suppression, teratogenicity, increased risk of infection	Given weekly, orally or subcutaneously
	Mycophenolate mofetil	Inhibits lymphocyte purine synthesis by inhibition of inosine monophosphate dehydrogenase	Diarrhea, nausea, bone marrow suppression, teratogenicity, increased risk of infection	Daily oral use
	Azathioprine	Alters purine metabolism	GI upset, hepatitis, bone marrow suppression, teratogenicity, increased risk of infection	Daily oral use
T-cell inhibitors	Cyclosporine	Inhibits T cells via inhibition of calcineurin by binding to cyclophilin	Renal toxicity, hypertension, hirsutism, tremor, teratogenicity, increased risk of infection	Daily oral use
	Tacrolimus	Inhibits T cells via inhibition of calcineurin by binding to FK binding protein	Renal toxicity, hypertension, neurotoxicity, hepatitis, diabetes	Daily oral use
	Abatacept	Decoy receptor that blocks activation of T cells by preventing binding to costimulatory molecules on antigen-presenting cells	Increased risk of infection, headache, upper respiratory tract infection, sore throat, and nausea	Has shown efficacy in JA-associated uveitis Intravenous infusion every 4 weeks after initial loading schedule or subcutaneous weekly
B-cell inhibitors	Rituximab	Monoclonal antibody that binds to CD20 resulting in depletion of circulating and tissue-based B cells	Increased risk of infection, severe skin and mouth reactions, PML, nausea, diarrhea, headache, muscle spasms, anemia, peripheral edema	Varies; for RA, two infusions given two weeks apart every 24 weeks
Alkylating agents	Cyclophosphamide	Lymphotoxicity, crosslinks DNA	Hemorrhagic cystitis, sterility, increased risk of malignancy, bone marrow suppression, teratogenicity, increased risk of infection	Daily oral or monthly intravenous infusion
	Chlorambucil	Lymphotoxicity, crosslinks DNA	Sterility, increased risk of malignancy, bone marrow suppression, teratogenicity, increased risk of infection	Daily oral or short-term high-dose regimen <sup>16</sup> Alkylating therapy has the greatest potential to induce a long-term drug-free remission
Cytokine inhibitors	Adalimumab, certolizumab pegol, golimumab, infliximab, and etanercept	Inhibits TNF- $\alpha$ via an anti-TNF- $\alpha$ antibody (all but etanercept) or via a decoy receptor (etanercept)	GI upset, headache, development of antinuclear antibodies (ANA), possible lupus-like syndrome, increased risk of infection (especially TB), exacerbation of multiple sclerosis, worsening of heart failure	Varies depending on agent Intravenous infusion, subcutaneous injection (weekly to monthly depending on agent) <sup>17</sup>
	Anakinra	IL-1 receptor antagonist	Increased risk of infection, headache, nausea, diarrhea, sinusitis, arthralgia, flu-like symptoms, abdominal pain	Daily subcutaneous injection
	Tocilizumab	Monoclonal antibody against IL-6	Increased risk of infection, GI perforation, headache, hypertension, increased ALT	Efficacy for uveitis reported <sup>18</sup> Intravenous infusion every 2–4 weeks
Lymphocyte migration inhibitors	Natalizumab	Monoclonal antibody against $\alpha$ 4-integrin, an adhesion molecule involved in lymphocyte migration into bowel and central nervous system	Increased risk of infection, including PML	Monthly intravenous infusion
	Fingolimod	Sphingosine-1-phosphate receptor modulator; inhibits release of lymphocytes from lymph nodes into circulation	Decreased heart rate, increased risk of infection, macular edema	Daily oral use
Interferon	Interferon- $\alpha$ , $\beta$ interferon	Both bind to same interferon receptor and mediate multiple biological effects	Myalgias, fever, depression	Successful reports in Behçet's, <sup>19</sup> macular edema <sup>20,21</sup> Subcutaneous, schedule varies but up to once daily
Complement inhibitors	Eculizumab	Monoclonal antibody against complement component C5	Increased risk of infection, headache, nasopharyngitis, back pain, nausea, hypertension	No human data in uveitis, animal studies show efficacy in experimental uveitis <sup>22</sup> Use is restricted to registered healthcare professionals Intravenous infusion

\*While commercially available in the United States, many of these agents have little or no human uveitis data available. None should be used by individuals without experience in their use and monitoring.

ALT, Alanine aminotransferase; cAMP, cyclic adenosine monophosphate; GI, gastrointestinal; IOP, intraocular pressure; JA, juvenile arthritis; PML, progressive multifocal leukoencephalopathy; RA, rheumatoid arthritis; TB, tuberculosis; TNF- $\alpha$ , tumor necrosis factor alpha.

## Mydriatic and Cycloplegic Agents

Anterior uveitis results in irritation of the ciliary muscle, causing spasms that produce the stereotypical photophobia. Cycloplegics act by preventing ciliary muscle contraction, reducing pain. The release of fibrin and other serum components into the anterior chamber during anterior uveitis may result in adhesions forming between the iris and anterior lens capsule (posterior synechiae) and the peripheral iris and angle (peripheral anterior synechiae). Depending on the duration of action and frequency of instillation, mydriatics result in movement of the iris, reducing the opportunity for synechiae formation. In addition, cycloplegia shifts the lens–iris diaphragm posteriorly, deepening the angle and reducing the opportunity for peripheral anterior synechiae to form. Sometimes posterior synechiae still form even with the use of mydriatic/cycloplegic agents, but at least use of these agents should result in a dilated pupil that still allows fundus examination. Multiple agents are available, including (in order of increasing duration) tropicamide, cyclopentolate, homatropine (no longer widely available), scopolamine, and atropine. Each has advantages and disadvantages. Shorter-acting agents tend to keep the pupil moving more than longer-acting agents, though they require patient compliance with multiple drops per day. Longer-acting agents may be used less frequently, reducing the dependency on compliance, but may result in synechiae formation in a dilated state, which may be unappealing to patients.

## Nonsteroidal Anti-inflammatory Drugs

As a primary treatment modality for ocular inflammatory diseases, nonsteroidal anti-inflammatory drugs (NSAIDs) are generally ineffective, other than oral agents in some cases of non-necrotizing scleritis. NSAIDs may provide some utility as an adjunct to other forms of therapy (especially topically in cystoid macular edema) or for prophylaxis against recurrent disease. Oral NSAIDs and oral corticosteroids should not be used concurrently because of the increased risk of gastric ulceration.

## Corticosteroids

Corticosteroids remain the most effective, most rapidly acting anti-inflammatory agents and thus are the first line of therapy in most cases of noninfectious uveitis. Corticosteroids produce broad suppression of the immune system by a number of mechanisms (see [Table 73.3](#)) but also may produce significant side effects. Corticosteroids may be given locally (topical, periocular, intraocular) or systemically (oral or intravenous).

### Topical

Topically applied corticosteroids penetrate the posterior segment of phakic eyes poorly, thus topical administration is useful primarily in patients with anterior uveitis and for the anterior component of panuveitis. A basic paradigm for the use of any corticosteroid, including topical formulations, is “use enough, soon enough.” In other words, early, aggressive use is required. To accomplish this, barring other considerations such as cost and availability, the most potent agent that can be safely used should be. Multiple agents exist in topical ophthalmic formulation, including (in order of decreasing clinical potency) difluprednate, prednisolone acetate, prednisolone sodium phosphate, rimexolone, loteprednol etabonate, and fluorometholone. Each has unique pharmacological and pharmacokinetic properties that may provide advantages and disadvantages in certain clinical scenarios. Patients with a history of corticosteroid-response IOP elevation should be monitored carefully and appropriate measures taken to control IOP while on corticosteroids.

### Periocular

The periocular route is a reasonable choice for unilateral disease or bilateral disease in a patient who has contraindications to—or refuses to take—systemic corticosteroids, and it may be particularly effective for cystoid macular edema. Injection is performed via a superior sub-Tenon’s capsule or inferior transseptal approach and requires only topical anesthesia. Longer-acting agents (e.g., triamcinolone acetonide) are preferred and may be given every 3–4 weeks until the desired effect is achieved or a plateau in effect is reached. Periocular injections of corticosteroids should not be used acutely in cases of infectious uveitis (e.g., acute retinal necrosis syndrome, toxoplasmosis) and should be used with caution in patients who have a history of corticosteroid-induced IOP elevation due to the extended duration of effect of depot formulations such as triamcinolone acetonide.

### Intravitreal

Corticosteroids can be delivered intravitreally by injection of a suspension (triamcinolone acetonide), degradable implant (dexamethasone intravitreal implant), or by surgical implantation of a sutured sustained-release device (fluocinolone acetonide). Duration of effect varies with intravitreal injections having a shorter duration (up to several months) as compared to the sustained-release implant (2.5 years). As with any form of corticosteroid, cataract formation and elevation in IOP are potential adverse effects but can usually be managed by standard means. Finally, though rare, endophthalmitis may occur due to the invasive nature of the procedure.

### Systemic

Systemic corticosteroids (oral or intravenous) have the broadest utility and are useful in all forms of uveitis. Initiating therapy at a high dose followed by tapering once an effect is achieved is more effective and reduces the overall burden of exposure compared to beginning at a lower dose with subsequent increases because of poor response. A pulse of oral corticosteroids can be given with no taper if the duration is less than two weeks, but therapy beyond this period necessitates a tapering schedule due to adrenal suppression. Patients on long-term corticosteroid therapy should receive calcium and vitamin D supplementation, as well osteoporosis monitoring and prophylaxis. Oral therapy is most commonly accomplished using prednisone (1 mg/kg/day, maximum of 60 mg/day of prednisone) while intravenous therapy may consist of methylprednisolone 1 gram per day for 3 days, followed by an oral prednisone taper. Too rapid a taper may result in rebound disease and a mistaken assumption that oral prednisone is not effective. Conversely, too slow a taper results in prolonged exposure to higher than needed doses and increases the incidence of side effects. In no case should a patient be maintained on chronic oral prednisone at a dose greater than 7.5 mg per day. If a dose greater than this is required for disease control or if disease is not controlled at the maximum dose within 4 weeks, then institution of immunosuppressive therapy is necessary.

## Immunosuppressive Therapy

Immunosuppressive therapy plays a vital role in the treatment of noninfectious uveitis, allowing one to achieve control of disease in patients who have not responded adequately to—or who develop side effects from—corticosteroid therapy.<sup>23</sup> These agents are safe and effective, and counseling of any other nature is a disservice to patients. However, only individuals comfortable in monitoring the side effects of these medications should assume primary control over therapy. If the individual ophthalmologist is not comfortable in that role, then referral to a uveitis specialist should occur. If a uveitis specialist is not available, then partnership with a rheumatologist or hematologist/oncologist can be fruitful. Prompt, accurate communication between ophthalmologist and the prescribing specialist ensures that such therapy is successful by monitoring for complete control of uveitis, reduction of the risk of ocular complications, and avoidance of adverse events.

A variety of immunosuppressive medications exist, and [Table 73.3](#) summarizes the most commonly used agents, their mode of action, and their potential side effects. Little comparative effectiveness data exists to guide the selection of a specific agent for a specific condition. Rather, most specialists chose an agent based on familiarity, side-effect profile, and comorbidities of the patient. Antimetabolites are a frequent first choice. If these agents are incompletely successful, then an additional agent is added to the regimen, currently a biological agent—TNF inhibitor being the most common, though additional antimetabolites or a T-cell inhibitor are viable alternatives. If the initial agent chosen provides minimal or no benefit, then a trial of a separate antimetabolite may be warranted. If a combination of agents (e.g., antimetabolites, T-cell inhibitors, biologics) is unsuccessful, then advancing to alkylating agents may be warranted. While they carry the potential for significant toxicity, alkylating agents are the medications most likely to induce a long-term drug-free remission.

## COURSE AND OUTCOME

Uveitis may cause visual loss and blindness due to a variety of causes, including secondary complications such as cataract, glaucoma, choroidal neovascularization, cystoid macular edema, optic neuropathy, and others. Cataract extraction can be safely accomplished in uveitic eyes, but should ideally be performed only after quiescence has been achieved, by whatever means necessary, for 3–4 months. This does not mean that the patient has to be off therapy and under control for that period, rather that they are under control using whatever medication regimen is required.

Small-incision ultrasonic phacoemulsification is the preferred technique due to less manipulation of the eye. Eyes with significant vitritis often benefit from combined cataract extraction and pars plana vitrectomy.<sup>24</sup> With the exception of patients with chronic juvenile arthritis–associated uveitis, if quiescence is achieved and maintained, most eyes tolerate a posterior chamber intraocular lens (PCIOL).<sup>25</sup> Eyes with a proclivity to form posterior synechiae or patients in whom compliance has been an issue should be considered for aphakia. Patients with inflammation centered around the pars plana region tend to have a higher complication rate than those with other types of uveitis.<sup>26</sup>

Ocular hypertension and glaucoma may occur in uveitic eyes via a variety of mechanisms, as previously discussed. Medical therapy is the reasonable first line agent for IOP control. Any of the modern agents are acceptable, though prostaglandin analogs may worsen cystoid macular edema.<sup>27</sup> Previous concerns about exacerbating uveitis with these agents is probably not warranted for certain agents.<sup>28</sup> In cases of pupillary block, iridectomy should be performed. Laser iridectomy is easier to perform than surgical iridectomy and if made large enough and with argon laser pretreatment, may remain patent. However, with closure, surgical iridectomy should be performed. If filtering surgery is necessary, the use of antimetabolites (e.g., mitomycin) or aqueous drainage devices greatly increases the success rate in these patients.<sup>29,30</sup>

Uveitis is frequently complicated by cystoid macular edema (CME), which can result in irreversible visual loss. The first goal in treatment of CME is control of the underlying inflammatory disease. If the uveitis is controlled, then periocular, intravitreal, or systemic corticosteroids may be successful. Therapeutic vitrectomy may also be beneficial in some cases. Various other agents have been tried for uveitic CME with varying success, including acetazolamide,<sup>31</sup> octreotide,<sup>32</sup> interferon,<sup>20</sup> and tocilizumab.<sup>33</sup>

Retinal detachment may occur in uveitis as a serous detachment (e.g., with Vogt–Koyanagi–Harada [VKH] syndrome, which should respond to anti-inflammatories), as a rhegmatogenous detachment (e.g., from the retinal atrophy induced by acute retinal necrosis syndrome), or as a

tractional detachment from fibrosis due to any number of uveitic conditions, both of which require surgical intervention.

Chronic uveitis may lead to hypotony through aqueous hyposecretion as a result of damage to the aqueous-producing nonpigmented ciliary epithelium or by cyclitic membrane formation with ciliary body detachment. The reduction in aqueous production leads to decreased nutrient supply to anterior segment structures and further complications such as corneal edema. Cyclitic membranes may be removed surgically, which may allow reattachment of the ciliary body and return of normal aqueous production, depending on the time frame of detachment. Attempts to increase aqueous production pharmacologically, while initially promising, have over the long term been generally disappointing.<sup>34</sup> Some benefit may be gained by injection of intravitreal viscoelastics.<sup>35</sup> Chronic hypotony may result in phthisis bulbi. This and other dire consequences of uveitis are the result of inadequate control of inflammation. Thus elimination of inflammation as early as possible in the course of uveitis is vital to preserve visual function.

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# Herpetic Viral Uveitis

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# 7.4

## HERPES SIMPLEX AND VARICELLA ZOSTER

### HERPETIC ANTERIOR UVEITIS

**Definition:** Chronic recurrent unilateral anterior uveitis caused by herpes simplex virus (HSV) or varicella zoster virus (VZV).

#### Key Features

- Ocular hypertension.
- Iris atrophy.
- Minimal or no vasculitis and vitritis.

#### Associated Features

- Keratitis.
- Pigmented keratic precipitates.

### VARICELLA-ZOSTER AND HERPES SIMPLEX VIRUS-INDUCED ACUTE RETINAL NECROSIS

**Definition:** A necrotizing retinitis caused by infection with VZV or HSV (rarely cytomegalovirus) in an immunocompetent host.

#### Key Features

- Severe uveitis or vitritis.
- Retinal vasculitis.
- Retinal necrosis.

#### Associated Features

- Keratic precipitates.
- Optic neuritis.
- Retinal detachment.

### PROGRESSIVE OUTER RETINAL NECROSIS

**Definition:** A necrotizing retinitis caused by infection with VZV or HSV in an immunocompromised host.

#### Key Features

- Multifocal lesions.
- Retinal necrosis.
- Minimal or no vasculitis and vitritis.

#### Associated Features

- Rapid progression.
- Poor prognosis.

## HERPES SIMPLEX VIRUS AND VARICELLA-ZOSTER VIRUS

### INTRODUCTION

HSV (represented by HSV-1 and HSV-2 serotypes) and VZV are members of *Herpesviridae*, a family of double-stranded DNA viruses

### EPIDEMIOLOGY AND PATHOGENESIS

HSV types 1 and 2 are ubiquitous, infecting the majority of world's population. HSV is the leading cause of herpetic anterior uveitis. It is the second leading cause (following VZV) of acute retinal necrosis (ARN), being more frequent in younger adults and children, however.<sup>1</sup> Following primary infection, the virus enters a dormant stage in the trigeminal ganglion. Episodes of reactivation lead damage of downstream tissues innervated by the trigeminal nerve.

Varicella (chickenpox) is a syndrome that occurs in the course of the primary infection with VZV. Following the primary infection, the virus establishes life-long latency in the sensory ganglia. Prior to the introduction of the varicella vaccine in 1995, infection with VZV was nearly universal in the United States. Herpes zoster (HZ) or shingles is a secondarily reactivated infection.<sup>2</sup> Herpes zoster ophthalmicus (HZO) is an outbreak of HZ occurring along the ophthalmic branch of the trigeminal nerve. VZV uveitis may be associated with HZO, but frequently it is seen in isolation. Progressive outer retinal necrosis (PORN) is a severe rapidly progressive retinitis caused by VZV.

### OCULAR PRESENTATION

Although considerable effort was spent attempting to delineate differentiating clinical features of HSV and VZV uveitis, there are no clear boundaries distinguishing HSV and VZV-associated syndromes.<sup>1,3</sup> Here we discuss HSV and VZV-associated disease in the context of their shared syndromes.

Herpetic anterior uveitis is typically a unilateral condition. It can demonstrate robust anterior chamber cell and flare. Frequently there is evidence of concurrent or previously healed keratitis. Eye pressure can be elevated, sometimes severely, even with a gonioscopically open anterior chamber angle. Pigmented keratic precipitates (KP) are common. In some cases the iris is severely affected, displaying sectoral atrophy.<sup>4,5</sup>

ARN syndrome presents with panuveitis with the vitreous frequently showing marked inflammatory cell and haze. The retina shows discrete areas of whitening, typically located in the far to midperiphery, that represent retinal necrosis, the hallmark of this infection. The retinitis spreads rapidly in a circumferential fashion in the absence of treatment. Associated occlusive retinal vasculitis involving the arteries leads to areas of nonperfusion and ischemia.<sup>6</sup> Involvement of the optic nerve is common (Fig. 7.4.1, Table 7.4.1). Rhegmatogenous retinal detachment originating in the areas of retinal necrosis is very common, occurring in up to 75% of affected eyes.<sup>1,7</sup> Epiretinal membranes and proliferative vitreoretinopathy are other complications. Viral meningoencephalitis may develop. There is a high risk of the fellow eye involvement, especially in the first three months. It is important to recognize that HSV/VZV retinitis encompasses a spectrum of disease severity. The ARN is the canonical presentation, but non-necrotizing disease has been described.<sup>8,9</sup>

PORN is an aggressive form of herpetic retinitis. The majority of cases are secondary to VZV in patients with advanced acquired immune deficiency syndrome (AIDS) with CD4-positive T lymphocyte count less than 50. PORN is characterized by multifocal deep retinal lesions that can be in all three retinal zones. These lesions rapidly progress to full-thickness

retinal necrosis and become confluent, leading to profound vision loss. Retina in immediate proximity to vessels clinically appears free of retinitis, producing a so-called cracked mud. Involvement of the optic nerve, including retrobulbar optic nerve damage, is common. Characteristically, there is relative paucity of inflammatory response. Unlike in ARN, retinal vasculitis is seen infrequently and tends to be mild. Retinal detachment is common<sup>10,11</sup> (see Table 7.4.1).

Characteristic features can aid in clinical diagnosis of herpetic uveitis, but laboratory diagnosis should be sought in ambiguous cases. Presently polymerase chain reaction (PCR) techniques have supplanted other modalities as they demonstrate a marked superiority in terms of sensitivity and specificity.<sup>12</sup> In cases of ARN, aqueous samples provide detection rates similar to vitreous samples.<sup>13,14</sup> Quantitative PCR offers additional diagnostic utility by reliably detecting even a low viral load and enabling the monitoring treatment response over time. Goldmann–Witmer coefficient (GWC) is a measure of local ocular antibody production in response to the pathogen. This test may be more beneficial later in the course of the disease, once sufficient antibody response to the pathogen has mounted.

## DIFFERENTIAL DIAGNOSIS

In the case of isolated anterior uveitis, the differential diagnosis includes HLA-B 27 related anterior uveitis, sarcoidosis, tuberculosis, syphilis, Posner–Schlossman syndrome, and Fuchs’ heterochromic iridocyclitis. The differential diagnoses of ARN and PORN are similar, including syphilitic retinitis, ocular toxoplasmosis, cytomegalovirus (CMV) retinitis, Behçet’s disease, ocular lymphoma, sarcoidosis, collagen vascular diseases, and endophthalmitis.

## PATHOLOGY

Histopathology of ARN demonstrates inflammatory infiltrates involving all ocular tissues. Occlusive retinal vasculitis is observed. Marked

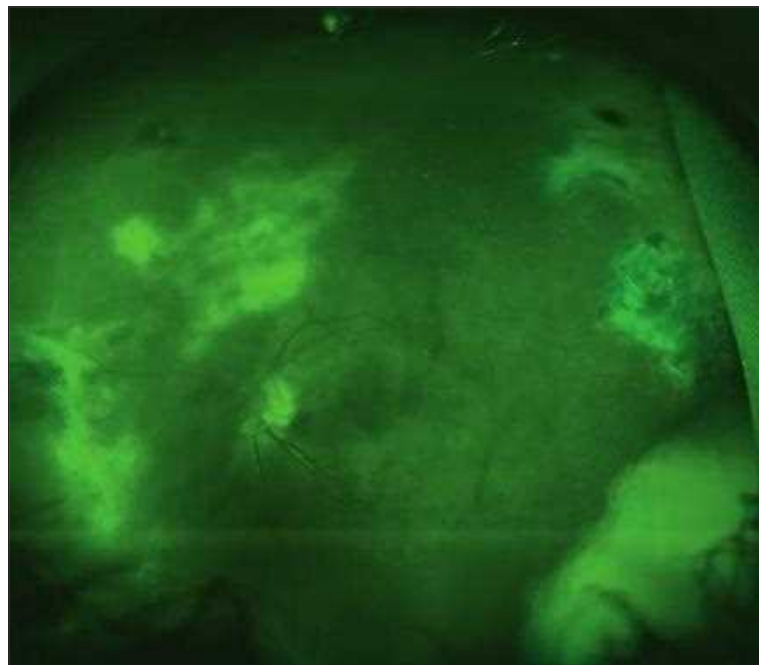


Fig. 7.4.1 Acute Retinal Necrosis—Subacute Stage.

necrosis is present in the retina as well as the optic nerve. Intranuclear inclusion bodies are present in the retina and retinal pigment epithelium (RPE). Electron microscopy demonstrates herpes viral particles.<sup>15,16</sup>

PORN demonstrates areas of severe retinal necrosis with mild to moderate inflammatory cell infiltration. The optic nerve is affected by necrosis and inflammation. Intranuclear inclusion bodies can be seen but are variable, and electron microscopy may demonstrate herpes virus particles within retina cells.<sup>10,17</sup>

## TREATMENT

Herpetic anterior uveitis is typically managed with systemic antivirals, oral acyclovir (800 mg five times daily) or valacyclovir (1 g three times daily), in combination with topical corticosteroids. The latter should not be used with antiviral coverage during the acute phase. Chronic maintenance therapy with a low-dose corticosteroid is often required.

Historically, the therapy of choice for ARN was intravenous acyclovir (10 mg/kg 3 times a day induction therapy for a week) followed by oral acyclovir (800 mg 5 times a day for at least 6 weeks) as maintenance. Oral acyclovir is insufficient for induction, but it is frequently employed for prophylaxis for one to three months and indefinitely in some patients. Valacyclovir (used as 1–2 g orally, three times daily), famciclovir (500 mg orally, three times daily), and valganciclovir (900 mg orally, twice daily) are newer oral outpatient alternatives to intravenous acyclovir. Systemic corticosteroids may be used to minimize the intraocular inflammation. Oral antiplatelet agent aspirin is occasionally employed to limit retinal vascular complications. Intravitreal injection of foscarnet (2.4 mg/0.1 mL) or ganciclovir (2 mg/0.1 mL) can be used in addition to systemic therapy.<sup>18</sup> Utility of prophylactic vitrectomy with or without intraoperative acyclovir lavage in preventing retinal detachment was demonstrated but is not universally accepted.<sup>7</sup> Similarly, prophylactic laser barricade of the uninvolved retina is used by some practitioners.<sup>14,18</sup>

PORN is frequently refractory to therapy. Single antiviral agent systemic therapy almost always fails. Combinations of acyclovir and/or foscarnet and/or ganciclovir given intravenously have been reported as effective in halting disease progression.<sup>19</sup> Augmentation with intravitreal injection of antivirals appears to offer further advantage.<sup>20</sup> Use of prophylactic laser barricade applied proximally to the affected areas of the retina may lessen incidence of retinal detachment. Retinal detachment usually requires vitrectomy and use of silicone oil or in some cases gas tamponade.

## COURSE AND OUTCOME

Overall, herpetic anterior uveitis carries a favorable prognosis. Secondary glaucoma, cataract, keratitis, and cystoid macular edema are common complications. The disease tends to have a relapsing course.

Because of its aggressive, rapidly progressive course and frequent occurrence of optic nerve involvement and retinal detachment, ARN carries a guarded visual prognosis. Retinal detachment occurs in 70% of untreated cases and in 50% with antiviral treatment. Less than half of patients retain ambulatory vision in their affected eyes.

Original reports of PORN supported a universally poor prognosis with loss of vision to no light perception. The modern approach with use of systemic and intravitreal newer generation antivirals and HIV therapy appears to have improved the prognosis, with up to half of patients retaining ambulatory vision. Retinal detachment develops in 70% of affected eyes. Survival of patients is influenced by the status of the underlying systemic disease, most commonly AIDS.

TABLE 7.4.1 Posterior Segment Findings in ARN, PORN, CMVR, and EBV Choroiditis

	Vascular Changes	Retinal Changes	Vitreous	Retinal Pigment Epithelium Changes	Optic Nerve Changes
ARN	Occlusive vasculitis, prominent sheathing	Confluent areas of whitening/necrosis, hemorrhages	Marked vitritis	Pigmentary clumping and mottling (late finding)	Optic neuropathy, optic atrophy (late)
PORN	Paucity of vasculitis, perivascular sparing of the retina	Multifocal retinal whitening/necrosis that appears to involve outer retina	Mild inflammation	Pigmentary clumping and mottling (late finding)	Optic neuropathy, optic atrophy (late)
CMVR	Occlusive retinal vasculitis, prominent sheathing, “frosted branch” angiitis	Macular edema, areas of white retinal necrosis or granular retinitis, abundant intraretinal hemorrhages	Variable, usually mild, inflammation	Granular RPE atrophy	Optic neuritis
EBV			Vitritis present	Multifocal choroiditis, punched-out areas	

ARN, Acute retinal necrosis; CMVR, cytomegalovirus retinitis; EBV, Epstein–Barr virus; PORN, progressive outer retinal necrosis; RPE, retinal pigment epithelium.



## CYTOMEGALOVIRUS

### CYTOMEGALOVIRUS RETINITIS

**Definition:** A necrotizing retinitis caused by infection with cytomegalovirus (CMV) in an immunocompromised host.

#### Key Features

- Retinal vasculitis.
- Retinal necrosis.
- Progression to bilateral disease if untreated.

#### Associated Features

- Optic neuropathy.
- Mild vitritis.
- Atrophic healed retina.

### CYTOMEGALOVIRUS-ASSOCIATED ANTERIOR UVEITIS

**Definition:** A chronic recurrent unilateral anterior uveitis caused by CMV.

#### Key Features

- Ocular hypertension.
- Nodular keratic precipitates.
- Low-grade anterior chamber inflammation.

#### Associated Features

- Corneal endotheliitis.
- Iris atrophy.
- Paucity of posterior synechiae.

## INTRODUCTION

CMV is a member of the *Herpesviridae* family. Primary infection is very common in the general population and is frequently asymptomatic. However, CMV causes severe infections in immunocompromised patients.

## EPIDEMIOLOGY AND PATHOGENESIS

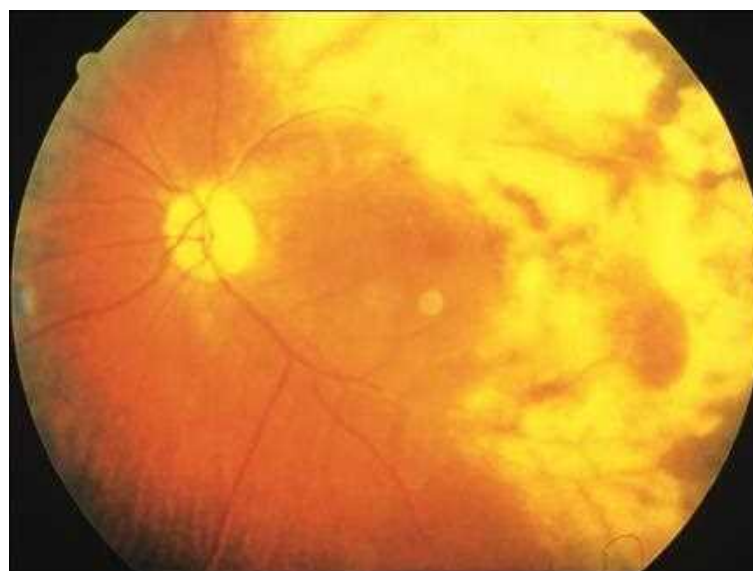
Primary CMV infection typically occurs following mucous membrane contact with contaminated bodily fluids. Latency is established following the original infection. The infection affects both genders equally and is very common in both children and adults, ultimately with the majority of adult population demonstrating evidence of exposure. CMV can reactivate in the setting of immunosuppressed states (particularly T-cell dysfunction) leading to involvement of a variety of organ systems. CMV retinitis (CMVR) is tightly linked to the AIDS epidemic, with the majority of patients having CD4+ lymphocyte counts of less than 50.

CMV has also been established as an etiological agent of anterior uveitis. It appears to be the cause of at least some cases of Posner–Schlossman glaucomatocyclitic crisis syndrome and occasionally can produce ocular findings of Fuchs' heterochromic iridocyclitis.<sup>21</sup> CMV-associated anterior uveitis typically affects healthy adults.

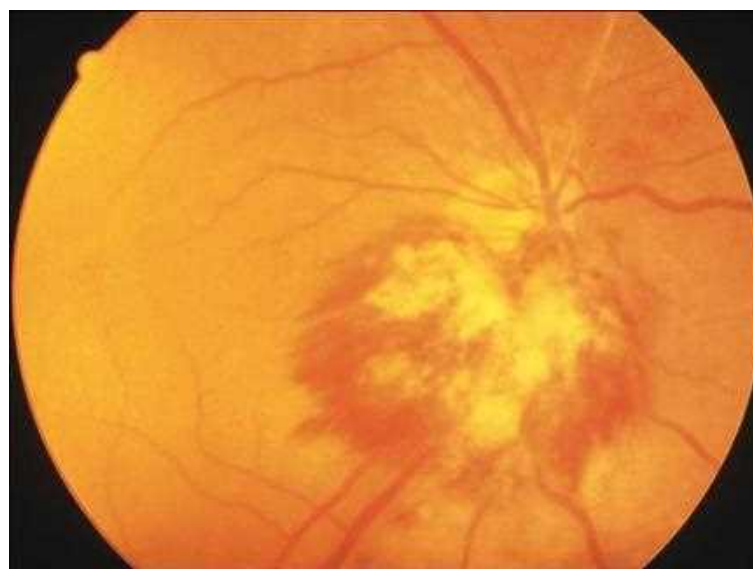
## OCULAR MANIFESTATIONS

Symptoms of CMVR include photopsia, loss of vision, and floaters. Eye pain is uncommon, and disease can be asymptomatic. CMVR typically starts as a solitary white retinitis lesion with a granular border (Figs. 7.4.2 and 7.4.3). Vasculitis is usually prominent resulting in ischemia and hemorrhages (see Table 7.4.1). If there is direct involvement of the optic nerve, a concurrent central nervous system infection is common. Associated inflammation is usually mild.<sup>22</sup> Stellate KP may be observed. When first presenting in one eye, CMVR subsequently involves the other.<sup>23</sup>

CMV-associated anterior uveitis has a chronic recurrent course characterized by episodes of elevated eye pressure concurrent with active



**Fig. 7.4.2** Cytomegalovirus Retinitis Involving the Posterior Pole, Threatening the Fovea.



**Fig. 7.4.3** Cytomegalovirus Affecting the Optic Nerve Head and the Peripapillary Retina.

inflammation marked by mild anterior chamber cell and flare. Corneal edema is frequently observed.<sup>24</sup> Nummular areas of corneal endotheliitis associated with characteristic nodular medium KP may be present.<sup>25</sup> Iris atrophy is frequently present. Between episodic recurrences, the anterior chamber may appear quiet, and intraocular pressure (IOP) tends to normalize.

## DIAGNOSIS

CMVR can be diagnosed on clinical grounds, especially in patients at high risk for the disease, such as those with AIDS. PCR of ocular fluid offers the highest utility when laboratory confirmation is necessary. Both aqueous and vitreous samples are adequate substrates for PCR.<sup>26,27</sup>

Diagnosis of CMV-associated anterior uveitis is made clinically and can be confirmed by PCR of aqueous fluid, but its sensitivity is limited. Quantitative PCR techniques have an advantage of circumventing false-positive results stemming from detection of CMV latently infecting leukocytes.

## DIFFERENTIAL DIAGNOSIS

CMVR can be mimicked by ARN, toxoplasma retinitis, syphilitic retinitis, tuberculosis, Behçet's disease, and, rarely, ocular lymphoma or leukemia, endogenous bacterial or fungal endophthalmitis, and sarcoidosis. HSV and VZV anterior uveitis, HLA-B27-associated disease, and Fuchs' heterochromic iridocyclitis can be considered in the differential diagnosis of CMV-associated anterior uveitis.

## **PATHOLOGY**

Histologically, CMVR is characterized by extensive coagulative necrosis with display of cytomegalic cells in all layers of the retina and RPE. Inclusion bodies can be observed within both the nuclei and cytoplasm of affected cells. Herpetic viral particles can be demonstrated by electron microscopy.<sup>28,29</sup>

In vivo confocal microscopy studies of endotheliitis lesions associated with CMV anterior uveitis demonstrate enlarged endothelial cells with a highly reflective intranuclear material surrounded by a hyporeflective halo. These “owl’s eye” cells are thought to represent CMV cytomegalic cells.<sup>30</sup>

## **TREATMENT**

CMVR is treated with systemic or intravitreal administration of antiviral agents. Systemic therapy can control the disease at extraocular sites and prevent involvement of the fellow eye but has adverse effects of medication. Oral ganciclovir tends to be less effective. Valganciclovir offers improved bioavailability and can be used both for induction and maintenance therapy. It is typically started at 900 mg bid. Bone marrow suppression with neutropenia is a serious side effect.<sup>31</sup> Intravitreal ganciclovir injections of 2 mg weekly are a therapeutic alternative.<sup>32</sup> Vitrasert, a no-longer-manufactured, surgically implanted ganciclovir slow-release intraocular device offered local antiviral action for up to eight months. Foscarnet and cidofovir are other therapeutic options. Renal toxicity is a common and serious side effect of both agents. When injected intravitreally, foscarnet is administered as 2.4 mg once or twice a week.<sup>33</sup> Intravitreal cidofovir is administered as a 20-µg dose given every 5 weeks. Both local and systemic use of cidofovir is associated with ocular toxicity, including iritis and hypotony.

Therapy with systemic and topical ganciclovir, oral valganciclovir, intravitreal ganciclovir, and ganciclovir implant for CMV anterior uveitis has been reported. These medications may be helpful in treatment of acute episodes of uveitis and may extend the time interval between relapses.<sup>34,35</sup> Glaucoma medications and topical corticosteroids are employed to control intraocular pressure and inflammation.

## **COURSE AND OUTCOME**

Medications to treat CMV are virustatic and not virucidal, therefore treatment of CMVR must be indefinite in an immunodeficient patient. Moreover, drug resistance develops during the course of maintenance therapy, leading to clinical disease reactivation that requires reinduction with escalating doses of medication or switching to a new antiviral agent. Development of CMVR is an independent risk factor for death in patients with AIDS. Use of highly active antiretroviral therapy (HAART) has dramatically altered the course of the disease. The incidence of retinal detachment has been significantly reduced, and the retinitis itself appears to have a milder course in patients receiving HAART.<sup>36,37</sup> Reconstitution of immune repertoire allows eventual discontinuation of maintenance therapy for CMV in many patients. Chronic anterior and intermediate uveitis, termed immune recovery uveitis (IRU), may develop as a response to viral antigens.<sup>38</sup>

CMV anterior uveitis tends to have a chronic course with episodic flares. The quiescent interval is variable, from weeks to many months. Cataract formation and persistence of IOP elevation outside the flare episodes are frequently encountered and may require surgery. In cases associated with corneal endotheliitis, corneal edema and cell loss may affect visual function. Overall visual prognosis is favorable.<sup>34,39</sup>

## **EPSTEIN–BARR VIRUS**

### **INTRODUCTION**

Epstein–Barr virus (EBV) is a double-stranded DNA virus of the *Herpesviridae* family. It is believed to be an uncommon cause of uveitis.

## **EPIDEMIOLOGY AND PATHOGENESIS**

It is transmitted through exchange of saliva or blood transfusions. By adulthood, most people have acquired an infection with the virus. EBV is the causative agent of infectious mononucleosis, and it is also associated with Burkitt’s lymphoma and other B-cell malignancies seen in immunosuppressed patients.

## **OCULAR MANIFESTATIONS**

EBV uveitis can manifest as iritis, whereas posterior segment involvement may include multifocal choroiditis characterized by punched-out areas of pigment epithelial changes and vitritis (see [Table 74.1](#)).<sup>40</sup>

## **DIAGNOSIS AND ANCILLARY TESTING**

Immunoglobulin M (IgM) and IgG antibodies in the serum can be detected and followed. In addition, EBV-related antigen can be quantified in the serum. PCR techniques have been successful in detecting viral DNA in ocular fluids.<sup>41</sup>

## **DIFFERENTIAL DIAGNOSIS**

The diagnostic entities that may mimic EBV chorioretinitis include presumed ocular histoplasmosis syndrome (POHS), recurrent multifocal choroiditis, multiple evanescent white dot syndrome (MEWDS), acute retinal pigment epitheliitis, and birdshot choroidopathy.

## **TREATMENT AND OUTCOME**

In general, EBV-related chorioretinitis appears to be fairly self-limiting. For severe systemic disease, valacyclovir therapy may be of some value.<sup>42</sup>

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# Nonherpetic Viral Infections: West Nile, Chikungunya, Zika, Ebola, HTLV 1, Measles, Rubella

7.5

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**Definition:** Nonherpetic viral intraocular inflammations include a diverse group of viral infections—those transmitted by mosquitos or body fluids or nasopharyngeal secretions. Some of these are evolving infectious uveitides; Ebola, chikungunya, and Zika viruses induced ocular inflammations. Well-established uveitis entities are those caused by West Nile virus, human T-cell lymphotropic virus type 1 (HTLV 1), measles, and rubella.

## Key Features

- West Nile virus is a single stranded RNA virus of the *Flaviviridae* family. Its ophthalmic presentations are uveitis and multifocal round and creamy chorioretinal lesions.
- Chikungunya is a single stranded RNA virus of the *Togaviridae* family, and its ocular manifestations are retinitis, uveitis, optic neuritis, conjunctivitis, scleritis, and epithelial keratitis.
- Zika virus is a neurotropic flavivirus; its clinical presentations are microcephaly, optic disc anomalies, uveitis, and chorioretinal changes.
- Ebola virus is a member of *Filovirida*, known to cause severe hemorrhagic fever. Its ophthalmic manifestations are subconjunctival hemorrhage, uveitis, and retinitis.
- HTLV 1 is a retrovirus, and it is endemic in southwest Japan, the Caribbean, and Central and South America. Ophthalmologically it presents with intermediate uveitis, retinal phlebitis, and T-cell leukemia or lymphoma.
- Measles virus is a paramyxo RNA virus. Its congenital infection manifests as cataract and pigmentary retinopathy. Acquired infection presents with retinopathy, small hemorrhages, stellate macula lesions, and optic disc swelling.
- Rubella virus belongs to *Rubivirus* and family of *Togaviridae*. Congenital infection presents with a salt-and-pepper fundus appearance. Acquired infections manifests with conjunctivitis, keratitis, iritis, and in some with features of Fuchs' cyclitis.

## WEST NILE VIRUS

### INTRODUCTION

The West Nile virus (WNV) is a single-stranded, enveloped RNA virus that is a member of the *Flaviviridae* family.<sup>1</sup> Wild birds are the primary natural hosts, and the virus is most commonly transmitted to humans through the bite of the *Culex* mosquito. Only a minority of infected individuals experience symptoms, which most often include fever, malaise, rash, and lymphadenopathy. Less than 1% of those infected experience neuroinvasive disease, including neurological deficits, aseptic meningitis, and, rarely, death.<sup>2</sup>

### EPIDEMIOLOGY

WNV has been a known cause of febrile illness and sporadic encephalitis since its discovery in 1937 in Uganda, but it was not detected in the

Western Hemisphere until an outbreak of encephalitis in New York City in 1999.<sup>3,4</sup> Subsequently, it spread rapidly across the continental United States and remains the most common cause of neuroinvasive arboviral disease in the United States.<sup>3,5</sup> In 2015, 2175 cases of WNV were reported to the Centers for Disease Control and Prevention (CDC).<sup>5</sup>

## OCULAR MANIFESTATIONS

Ocular manifestations include chorioretinitis with lesions either scattered or in linear arrays, uveitis without focal chorioretinal lesions, occlusive retinal vasculitis, congenital chorioretinal scarring, and optic neuritis.<sup>1</sup> The classic chorioretinal lesions of WNV are round, multifocal, and creamy. Multimodal imaging of the active lesions will show central hypofluorescence with surrounding staining on fluorescein angiogram (FA), dense hypocyanescence corresponding with the center of the lesion on indocyanine green (ICG) angiography, hyperautofluorescence on fundus autofluorescence (FAF) imaging, and deep retinal hyperreflective lesions extending from the outer nuclear layer to the retinal pigment epithelium (RPE) on optical coherence tomography (OCT).<sup>4</sup> Patients usually have a mild vitritis and variable anterior chamber inflammation. The lesions generally become more pigmented over time (Fig. 75.1) and have a benign, self-limited course although there are reports of permanent visual deficits in patients with subfoveal lesions or those who later develop choroidal neovascular membranes.<sup>1,2</sup> Patients with optic neuritis and occlusive retinal vasculitis are more likely to have permanent visual deficits.<sup>2</sup>

## DIAGNOSIS

WNV is diagnosed by detection of WNV-specific IgM in the serum or cerebrospinal fluid (CSF). It is important to remember that there is cross-reactivity amongst flaviviruses and patients who have been recently vaccinated for yellow fever may have a false-positive result.<sup>1</sup>

## TREATMENT

Currently, there is no treatment for WNV other than supportive measures. Anterior segment inflammation has been treated successfully with topical corticosteroids and cycloplegic agents. Case reports have demonstrated good anatomic response to intravitreal bevacizumab for the treatment of macular edema and late choroidal neovascularization.<sup>6,7</sup>

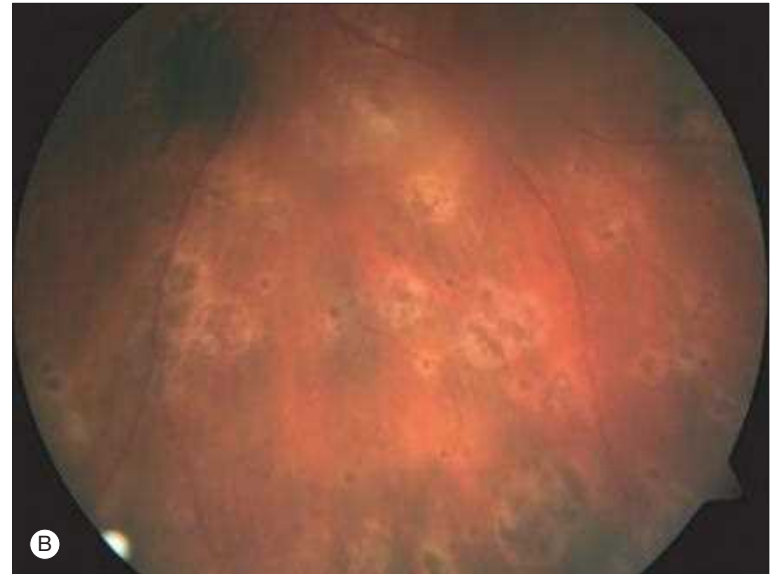
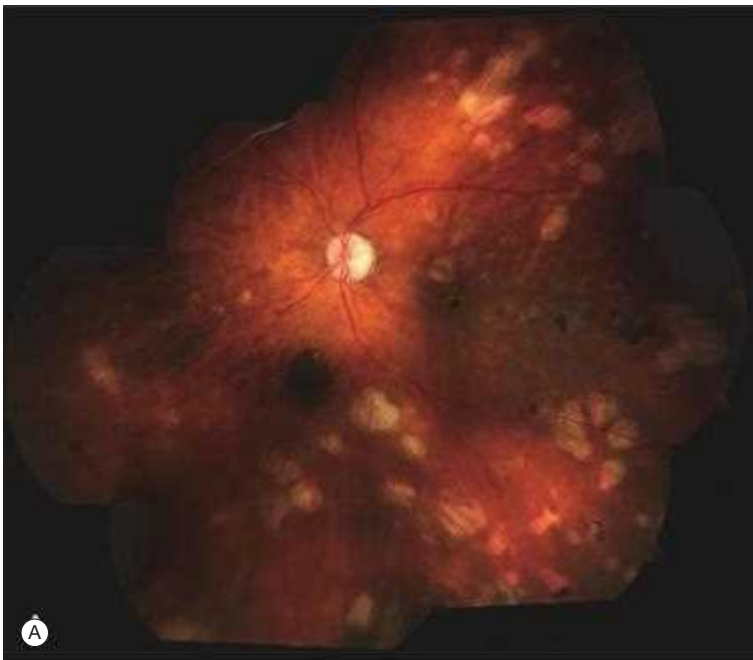
## CHIKUNGUNYA

### INTRODUCTION

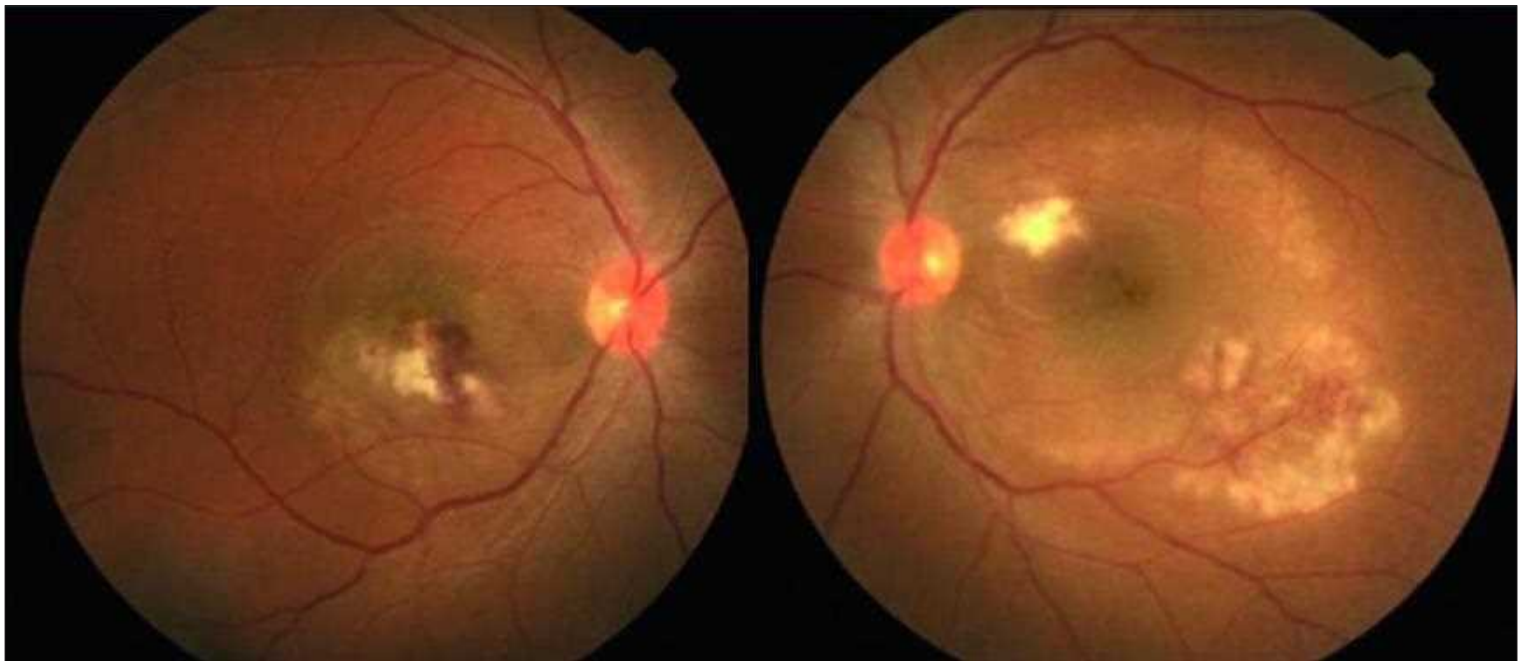
Chikungunya is a single-stranded RNA virus from the *Togaviridae* family that is transmitted by the *Aedes* mosquito.<sup>8,9</sup> Chikungunya fever is characterized by fever, severe arthralgia, and skin rash.<sup>8</sup> The illness is generally self-limited, but severe complications can occur, especially in the elderly and those with chronic medical problems.<sup>10</sup>

### EPIDEMIOLOGY

Chikungunya virus has long been endemic in Africa, Southeast Asia, and parts of the Indian subcontinent.<sup>9</sup> The first report of local transmission of



**Fig. 7.5.1** An 87-Year-Old Woman Presented With Encephalitis and Tested Positive for West Nile Virus. (A) The healed lesions are seen several months after infection. (B) The lesions have variable pigmentation and atrophy, many with central hyperpigmentation surrounded by atrophy. (Courtesy Sunil Srivastava, MD.)



**Fig. 7.5.2** A 43-Year-Old Man With Bilateral Chikungunya Retinitis Characterized by Bilateral Retinal Whitening and Hemorrhages in the Posterior Pole. (Courtesy Padmamalini Mahendradas, DO, DNB.)

chikungunya in the Western Hemisphere was not until December 2013.<sup>10</sup> Now it is endemic in tropical areas of the Americas, including Central America and the Caribbean.<sup>9</sup>

## OCULAR MANIFESTATIONS

A wide array of ocular manifestations have been associated with chikungunya virus, including nongranulomatous anterior uveitis, optic neuritis, retinitis, panuveitis, choroiditis, conjunctivitis, episcleritis, scleritis, and epithelial keratitis.<sup>9</sup> Ocular manifestations may be present during or occur several weeks after the febrile illness, and iridocyclitis and retinitis are the most common ocular manifestations associated with chikungunya virus.<sup>11</sup> Chikungunya retinitis is characterized by minimal vitritis, retinal hemorrhage, retinal whitening, and edema, most commonly in the posterior pole (Fig. 7.5.2).<sup>11</sup>

## DIAGNOSIS

During the first 7 days of infection, serum polymerase chain reaction (PCR) is the preferred method of diagnosis. After the first 7 days of infection, virus-specific IgM antibodies can be detected in serum.<sup>12</sup>

## TREATMENT

Currently, there is not an approved antiviral agent with activity against chikungunya, so the treatment remains largely supportive.<sup>9,11</sup> Anterior uveitis may be treated with topical corticosteroids.<sup>9</sup> Some reports suggest that systemic corticosteroids are beneficial in the treatment of optic neuritis, posterior uveitis, and keratouveitis, whereas others describe resolution of retinitis with systemic acyclovir and corticosteroids.<sup>9,11</sup> More studies are needed to determine whether such treatments are effective in improving the visual outcome.

## ZIKA

### INTRODUCTION

Zika virus is a neurotropic flavivirus transmitted most frequently by the *Aedes aegypti* mosquito.<sup>13,14</sup> Infected mothers can transmit the virus to fetuses, and sexual transmission has also been confirmed. Viral RNA has been identified in the sperm of infected men, although the duration of the risk of sexual transmission after infection is unknown.<sup>15</sup> Infection is characterized by fever, arthralgia, and rash.<sup>13</sup>

### EPIDEMIOLOGY

Zika virus was first identified in humans in Nigeria in 1953.<sup>15</sup> The first reported outbreak outside of Africa was not until in 2007 on Yap Island in the Federated States of Micronesia.<sup>14,15</sup> In 2015, an outbreak in Brazil reached epidemic proportions, and 6 months later an increase in the number of infants born with microcephaly alerted health officials to the association between maternal Zika infection and congenital central nervous system malformations.<sup>14,15</sup>

### OCULAR MANIFESTATIONS

Many ocular abnormalities have been documented in infants with microcephaly secondary to presumed congenital Zika infection. Changes in the vasculature, including tortuosity and hemorrhagic retinopathy; optic disc anomalies, including hypoplasia, severe cupping, and pallor; and macular changes, including pigment mottling, torpedo-like maculopathy, and sharply demarcated circular areas of chorioretinal atrophy; have all been described.<sup>14,16,17</sup> Infants with smaller cephalic diameters and those whose mothers were symptomatic in the first trimester are more likely to have ocular abnormalities.<sup>14</sup>

Infected adults may also have ocular involvement. Over 50% of infections are associated with nonpurulent conjunctivitis.<sup>15</sup> Case reports have also described anterior and posterior uveitis associated with Zika infection. Merle et al. described two patients with confirmed Zika infection who presented with bilateral hypertensive acute anterior uveitis. Zika RNA was detected in the aqueous humor of one of the four affected eyes.<sup>18</sup> Furtado et al. reported a case of bilateral normotensive anterior uveitis associated with Zika infection. Viral RNA was detected in the aqueous humor of one of the affected eyes.<sup>19</sup> Posterior involvement has also been reported in the form of a mild vitritis with mid-peripheral yellow-white chorioretinal lesions in one patient and unilateral acute idiopathic maculopathy in two others.<sup>13,20,21</sup>

### DIAGNOSIS

Within the first 7 days of infection, viral nucleic acid can be detected in serum by RT-PCR. After the first week, IgM antibodies can be detected by enzyme-linked immunosorbent assay (ELISA).<sup>15</sup>

### TREATMENT

Treatment is supportive and guided by symptoms. Anterior uveitis has shown response to topical corticosteroids and elevated intraocular pressure can be treated with aqueous suppressants.<sup>18,19</sup> Patients with acute idiopathic maculopathy have shown complete recovery without treatment.<sup>13,21</sup>

## EBOLA

### INTRODUCTION

Ebola virus is a member of the family *Filoviridae*.<sup>22</sup> It causes a severe hemorrhagic fever characterized by a maculopapular rash, fever, vomiting, diarrhea, myalgias, respiratory symptoms, and abdominal pain. It causes severe laboratory abnormalities, including transaminitis, prolonged clotting times, leukopenia, and thrombocytopenia. It is fatal about 50% of the time due to hemorrhagic complications and multiple organ failure.<sup>22,23</sup> Wild animals, particularly fruit bats, are the natural virus hosts, and human infection occurs via close contact with the blood or bodily fluids of infected animals. Ebola is highly contagious, and human-to-human transmission occurs through direct contact with the blood or bodily fluids of infected individuals.<sup>23</sup>

## EPIDEMIOLOGY

Ebola virus first appeared in humans in 1976 in two simultaneous outbreaks in South Sudan and the Democratic Republic of Congo.<sup>23</sup> An outbreak in West Africa in 2014 was the largest to date and affected Guinea, Liberia, and Sierra Leone most severely.<sup>23</sup>

### OCULAR MANIFESTATIONS

During acute infection, conjunctival injection and subconjunctival hemorrhages may occur.<sup>22</sup> Uveitis is the most common ocular complication during convalescence and may include anterior, intermediate, posterior, and panuveitis.<sup>22,24,25</sup> Ebola virus has been detected in the aqueous humor of a patient 14 weeks after the onset of infection and 9 weeks after the clearance of viremia.<sup>26</sup> That patient developed a unilateral hypertensive anterior uveitis that rapidly progressed to scleritis and panuveitis, which was treated successfully with topical, periocular, and oral corticosteroids.<sup>26</sup> Uveitis relapses have been documented up to 13 months after blood tests negative for Ebola virus, suggesting a need for long-term monitoring in Ebola survivors.<sup>24</sup>

### DIAGNOSIS

Diagnosis of Ebola is made by detection of viral RNA, IgM antibodies, or viral antigens.<sup>22</sup> Samples from infected patients are an extreme biohazard risk and must be handled in a biosafety level 4 laboratory.<sup>22,23</sup>

### TREATMENT

There is no proven treatment for Ebola virus. Thus treatment is largely supportive and consists of oral and intravenous hydration in addition to managing end-organ complications.<sup>23</sup> Uveitis has been successfully treated with topical, oral, and periocular corticosteroids and cycloplegic agents.<sup>22</sup>

## HUMAN T-CELL LYMPHOTROPIC VIRUS TYPE 1

### INTRODUCTION

Human T-cell lymphotropic virus type 1 (HTLV-1) was the first retrovirus discovered to cause human disease.<sup>27</sup> Perinatal infection with HTLV-1 is considered a risk factor for adult T-cell leukemia and for a degenerative neurological disorder known as tropical spastic paraparesis.<sup>28</sup>

### EPIDEMIOLOGY/PATHOGENESIS

In certain populations, infection with HTLV-1 is considered endemic, such as in areas of southwest Japan. It is also common in the Caribbean and parts of Central and South America.<sup>27</sup> It is transmitted via breastfeeding, sexual contact, or blood exposure.<sup>28</sup> In one study, 0.79% of people tested were seropositive for the HTLV antigens.<sup>29</sup> The interaction of HTLV-1-disregulated cells with various kinds of normal lymphocytes and vascular endothelial cells may determine the type of HTLV-1-associated disease manifestation.<sup>30,31</sup>

### OCULAR MANIFESTATIONS

Ocular manifestations include vitritis and uveitis/vasculitis.<sup>32</sup> Most patients present with an intermediate uveitis with prominent vitreous opacities.<sup>27</sup> A vasculitis composed of gray-white granular deposits scattered on the retinal veins and arteries may be characteristic of HTLV-1-associated retinal disease. Other manifestations include T-cell conjunctival and intraocular lymphomas, interstitial keratitis, Sjögren's syndrome, optic neuritis, and retinal choroidal degeneration.<sup>33</sup> A single episode of uveitis with resolution over a few weeks occurs in the majority of patients. Only a few patients suffer poor visual outcomes from either corticosteroid-induced cataracts or a retinal choroidal degeneration. HTLV-1 associated lymphomas are aggressive, and therapy is often not successful.

### DIAGNOSIS

Tests for viral DNA, including PCR techniques, have proved the presence of the HTLV-1 virus. Serum antibodies against the HTLV-1 proteins have also been used to make the diagnosis of systemic HTLV-1 infection.



## TREATMENT

The intraocular inflammation may respond to corticosteroid therapy.<sup>34</sup> Systemic disease is difficult to treat but may respond to chemotherapy, daclizumab, and antiretroviral treatment with 5-azacytidine.<sup>35,36</sup>

## MEASLES VIRUS

### INTRODUCTION

The measles virus is another RNA virus classified as a paramyxovirus. Infection with the virus is usually self-limited but can be associated with subacute sclerosing panencephalitis (SSPE).

### EPIDEMIOLOGY/PATHOGENESIS

The virus is transferred by nasopharyngeal secretions to the respiratory tract or conjunctiva of susceptible patients. The virus is highly contagious and is typically contracted in childhood. Congenital infections can occur. Prenatal transmission in the first trimester may cause abortion; infection later may result in premature birth or malformations such as cardiomyopathy, cataract, deafness, and pigmentary retinopathy.

### OCULAR MANIFESTATIONS

The ocular manifestations of congenital infection include cataract and pigmentary retinopathy.<sup>37</sup> The most common ocular manifestations of acquired infection are a self-limited keratitis or conjunctivitis. Retinopathy can occur with acquired measles infections. During the acute stages of retinal involvement, the fundus vessels may appear attenuated. There may be diffuse retinal edema associated with optic disc swelling, small hemorrhages, and stellate macular lesions. Irregular, flat, depigmented areas may also appear with some decline in vision. As the retinopathy resolves, a secondary pigment retinopathy with a salt-and-pepper appearance may occur. Retinal findings associated with SSPE include macular edema, pigment epithelial abnormalities, choroiditis, whitish retinal infiltrates, serous macular detachments, areas of retinal depigmentation, and optic neuritis.<sup>38–41</sup>

Macular retinitis may occur first and then the neurological finding of SSPE may result. Early recognition may allow earlier serological testing for SSPE and allow an earlier diagnosis of this disease.<sup>42</sup>

### DIAGNOSIS AND ANCILLARY TESTING

Fluorescein angiography may demonstrate a diffuse leakage associated with retinal edema or increased transmission of choroidal fluorescence related to the pigment epithelial disease. There may be vascular occlusions, retinal pigment epithelial disturbances, and cystic areas of hyperfluorescence. Serological tests for measles virus include complement fixation, enzyme immunoassay, immunofluorescence, and the hemagglutination

inhibition test.<sup>39</sup> In addition, PCR techniques may be used for detecting viral RNA.<sup>43</sup>

## PATHOLOGY

Histological specimens have been documented in patients who have suffered from SSPE. Histologically, there are areas of focal retinal necrosis with invasion of pigment-laden macrophages. The retinal pigment epithelium may show patchy areas of loss. Intranuclear inclusions can be seen in the nuclear layers of the retina.<sup>39</sup>

### TREATMENT

Measles retinopathy may result in the onset of acute blindness a few weeks following the measles rash and in general resolving over the following months. No therapy exists for measles-related retinopathy.

## RUBELLA VIRUS

The ophthalmic manifestations of rubella virus are similar to those of measles virus infections, and both can be seen in congenital and acquired forms. The congenital rubella retinitis may present as a salt-and-pepper fundus appearance. Ophthalmic manifestations include conjunctivitis, keratitis, and iritis. A retinitis may appear and can be associated with exudative detachments of the retina and retinal pigment epithelium.<sup>44,45</sup>

### SUMMARY

Multiple viruses can cause intraocular inflammation. Many of them can cause decreased vision and can have devastating long-term effects. Ocular manifestations of other viral infections are being discovered. New diagnostic techniques such as PCR may allow testing for the presence of a viral cause for some of the idiopathic intraocular inflammations.

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## Syphilitic and Other Spirochetal Uveitis

## 7.6

Julie H. Tsai

## SYPHILITIC UVEITIS

**Definition:** Intraocular inflammation as a result of infectious and/or immunologically mediated responses to *Treponema pallidum*.

## Key Features

- Intraocular inflammation typically associated with systemic manifestations.
- Latent disease associated with intraocular/systemic findings.

## Associated Features

- Conjunctival gummas and chancres.
- Episcleritis or scleritis.
- Cataracts (congenital or acquired).
- Secondary glaucoma.
- Interstitial keratitis.
- Light-near dissociation (Argyll–Robertson pupil).
- Retinitis, typically placoid.

## INTRODUCTION

Infection with the spirochete *Treponema pallidum* (*T. pallidum*) results in multiple systemic and ocular manifestations. This occurs primarily via sexual contact, with secondary routes of infection including contact with an infectious lesion, maternal–fetal transmission, and transfusions. Historically, syphilis carried significant social stigma and was associated with high morbidity and mortality. After penicillin became widely available, a steep decline in the incidence of infection was noted, but bacterial resistance, high-risk sexual behavior, infection with human immunodeficiency virus (HIV), and changing socioeconomic factors have all contributed to a recent resurgence of disease worldwide.<sup>1,2</sup>

Ocular manifestations, while uncommon, are typically associated with neurosyphilis, which can occur early or late in the course of infection.<sup>3</sup> Uveitis is the most common sign, ranging from 0.7% to 16.4% of patients with secondary or tertiary syphilis.<sup>4</sup> The clinical presentation is diverse, with various inflammatory presentations such as iritis, chorioretinitis, vitritis, and panuveitis.<sup>1,5</sup>

## EPIDEMIOLOGY AND PATHOGENESIS

The World Health Organization (WHO) reported an estimated incidence of 5.6 million new cases of venereal syphilis and a prevalence of 18 million cases worldwide in 2012.<sup>6</sup> Recent outbreaks in Europe and North America have been seen in areas where individuals often have multiple sexual partners and in populations of men who have sex with men (MSM). Specifically, between 2015 and 2016, new syphilis cases increased 176% in the United States (US) and 12% in the United Kingdom.<sup>2,7</sup> As of 2018, the total reported case counts in the US are the highest to date since 1994, and increased 176% between 2015 and 2016 alone, with 58.1% of cases attributed to the subpopulation of MSM.<sup>2</sup>

The pathogenesis of syphilitic disease is complex and is initiated as the bacteria enter the body through intact mucosa or areas of abraded skin. Local invasion of the tissues occurs with dissemination via blood and the lymphatic system. Microscopically, lymphocytic infiltration is seen, either diffuse or focal, surrounding the blood vessels of affected organs along

with chronic granulomatous inflammation including epithelioid histiocytes and multinucleated giant cells. Mononuclear cells, sensitized T lymphocytes, macrophages, and plasma cells can also be seen. It is likely that this inflammation and the resulting adaptive immune response cause the tissue destruction characteristic of syphilis, as the bacteria do not produce an intrinsic toxin.

Local antibodies are also produced against the lipid, protein, and lipoprotein components of *T. pallidum*. The majority of bacteria are eradicated by opsonization and engulfed by macrophages. Those organisms resistant to phagocytosis may persist locally at the site of inoculation. Dissemination can occur despite the development of the humoral and cellular response, and without treatment, the bacteria can persist in the human host for decades, resulting in continued transmission and end organ damage.

## OCULAR MANIFESTATIONS

Ocular findings play a critical diagnostic role in the evaluation and treatment of infection. Keratic precipitates, iritis, vitritis, focal retinitis, papillitis, periphlebitis, outer retinitis, and exudative retinal detachments have been described among HIV-positive and HIV-negative patients.<sup>8</sup> The most common forms of uveitis in syphilitic infection are nonspecific iritis and iridocyclitis, and these may manifest as granulomatous or nongranulomatous inflammation. Dilated iris capillaries (roseola) have been described as a distinctive feature and may result from obliterative endarteritis.

Chorioretinitis is also common and presents in various ways. Vitritis, vasculitis, macular edema, exudative retinal detachment, uveal effusion, central retinal vein occlusion, choroidal neovascularization, retinal necrosis, and neuroretinitis have all been described (Fig. 7.6.1).<sup>9–11</sup> In patients with HIV, placoid lesions ranging in color from yellow to gray have been described in juxtapapillary locations as well as adjacent to the macula. This condition is also termed acute syphilitic posterior placoid chorioretinitis.<sup>5,12</sup> These lesions are often atrophic in the center and flat. Fluorescein angiography reveals early hypofluorescence and late stain of the lesions, termed “leopard-spot” hypofluorescence (Fig. 7.6.2). This finding is also labeled acute syphilitic posterior placoid chorioretinitis. It is not pathognomonic of HIV-related syphilitic retinitis, however, and can be seen in infected

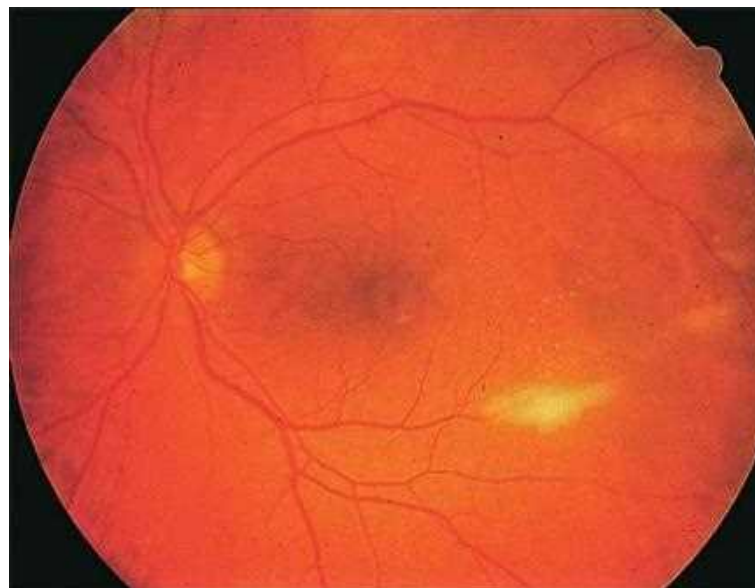
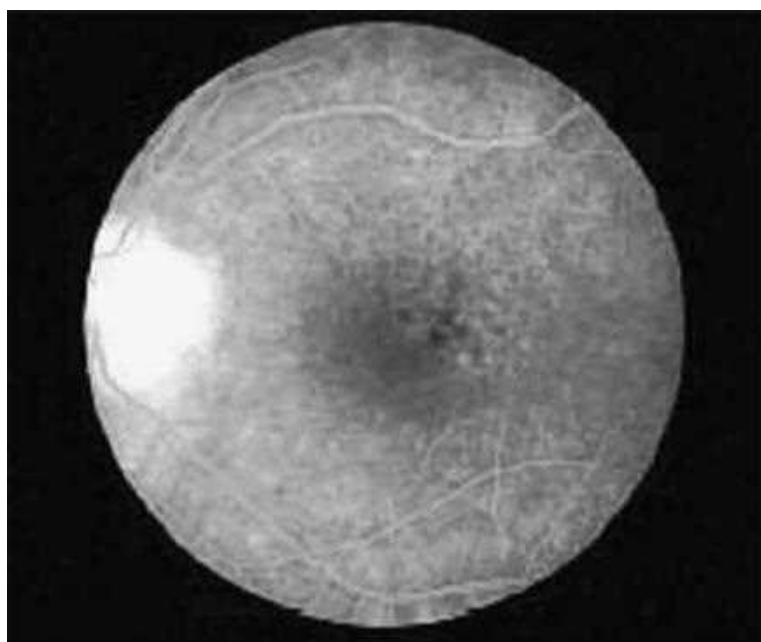


Fig. 7.6.1 Retinitis in a Patient With Positive Serology for Syphilis.





**Fig. 7.6.2** “Leopard Spot” Hypofluorescence in the Macula of a Patient With Neurosyphilis. (Courtesy Chao et al. Syphilis: reemergence of an old adversary. Ophthalmology 2006;113:2074–9.)

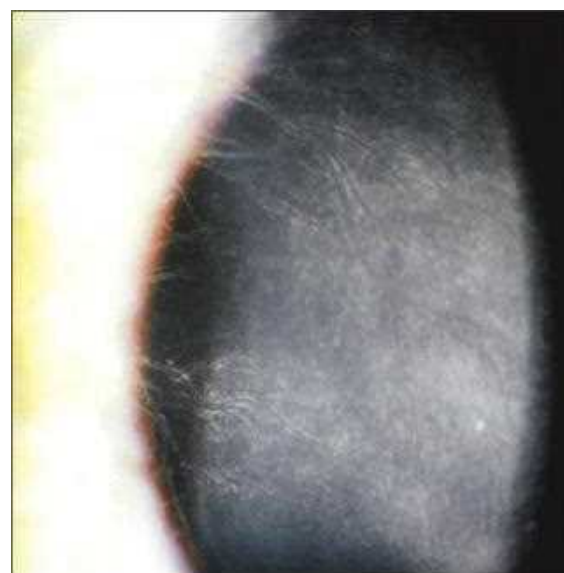


**Fig. 7.6.3** Descemet's Ridges and Bands Seen in Interstitial Keratitis Prior to Treatment With Corticosteroids. (Courtesy Krachmer JH, Palay DA. Cornea atlas. 2nd ed. Elsevier; 2006.)

individuals with normal immunity. Dense vitritis may also be the only presenting sign of infection in HIV-positive patients.<sup>13,14</sup>

Other ocular structures may also be affected, including the cornea, conjunctiva, sclera, and optic nerve. Syphilitic interstitial keratitis in the corneal stroma is probably the best known presentation and often results from congenital disease. In acquired infection, stromal inflammation is seen in the peripheral cornea, with marginal infiltrates observed in the anterior corneal stroma. Anterior uveitis may also be present. Deep stromal vascularization anterior to Descemet's membrane is the most distinctive feature of interstitial keratitis. Ridges or scrolls of Descemet's membrane may also be noted (Fig. 7.6.3). Once the infection is treated and the inflammation resolved, corneal scarring and thinning are often the end result, and the inactive neovascular vessels (i.e., “ghost” vessels) may be difficult to identify due to surrounding stromal scarring (Fig. 7.6.4).

Conjunctival involvement may occur in any stage. A chancre may develop, similar to lesions seen elsewhere on the body. The ulcerative



**Fig. 7.6.4** Ghost Vessels in Syphilitic Interstitial Keratitis. (Courtesy Krachmer JH, Palay DA. Cornea atlas. 2nd ed. Elsevier; 2006.)

lesion often has a rounded edge and is surrounded by conjunctival injection. Discharge is rare, and local irritation caused by the lesion is the most common complaint. A mild, nonspecific papillary reaction associated with secondary syphilis may be easily overlooked. Episcleral and scleral involvement is generally associated with conjunctival disease, with isolated cases uncommon at any stage of infection. Necrotizing conjunctivitis with marked pain and injection may be seen in tertiary disease.

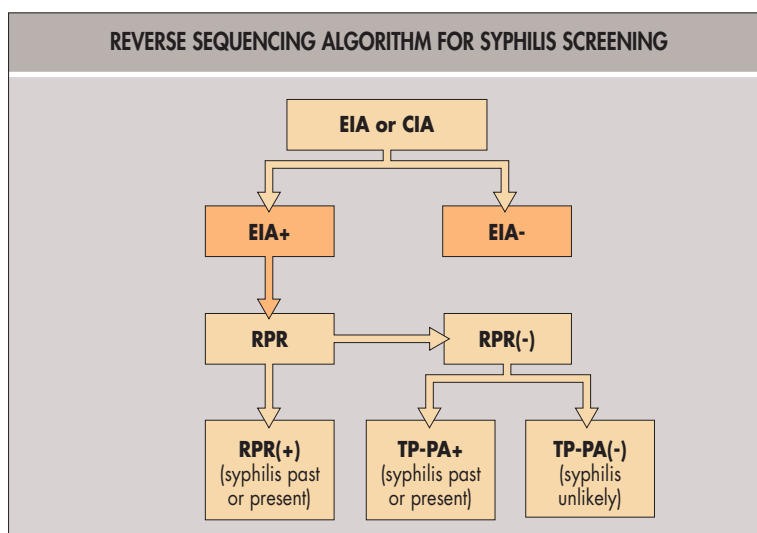
Other ocular manifestations include cataract, glaucoma, and pupillary abnormalities. Cataracts may be found in congenital or acquired disease, but the finding itself is not a distinctive feature. Glaucoma in syphilis is often secondary to uveitis and may also occur in either congenital or acquired infection. It is postulated that failure to develop a mature anterior segment and angle in infants with congenital or acquired disease may result in narrow-angle glaucoma in later life. The Argyll–Robertson pupillary abnormality, seen in neurosyphilis, is a classic finding. The patient exhibits anisocoria, often with irregularly shaped pupils, and clinical testing may reveal light-near dissociation. Horner's syndrome and internuclear ophthalmoplegia may also be observed. Late neurosyphilis may cause general paresis and tabes dorsalis.

## DIAGNOSIS

The clinical presentation of syphilitic uveitis is extremely variable and thus the disease has acquired the nickname “the great masquerader.” A high level of clinical suspicion is required, and appropriate laboratory studies are necessary to confirm the diagnosis and rule out other disease entities. The gold standard remains the use of dark field microscopy or immunofluorescent staining of mucocutaneous lesions to demonstrate the presence of live organisms. Diagnosis can be confirmed as early as 10–20 days post-contact, even before seroconversion. The tests are highly specific but not very sensitive for widespread use.

Two different types of antibody tests are utilized in serological testing: nontreponemal tests, which detect antibody to cardiolipin cholesterol antigen, and treponemal tests, which detect antibodies against treponemal antigens. In the past, two commonly used nontreponemal tests are the Venereal Disease Research Laboratory (VDRL) and rapid plasma reagin (RPR) tests. These were best suited for general screening in a population with a low prevalence of syphilis. The nontreponemal tests quantitatively measure antibody production and can determine cases of active infection. They can also be used to monitor treatment efficacy as the titers decrease with appropriate therapy.

Positive results from the nontreponemal tests were then verified using treponemal tests. These include the fluorescent treponemal antibody absorption tests (FTA-ABS) and microhemagglutinin assay for *T. pallidum* (MHA-TP). They may be used initially in individuals with a high probability of disease. The treponemal tests document cases of tertiary or latent syphilis and show evidence of previous exposure even if screening tests are negative. Once the treponemal test is positive, the patient generally remains positive for life. These tests are more specific than the nontreponemal tests and may be just as sensitive, but their expense and



**Fig. 7.6.5 Reverse Sequencing Algorithm for Syphilis Screening.** An immunoassay for treponemal antibodies is used to initiate the testing protocol. Negative results rule out syphilis, but a positive result is followed by a nontreponemal quantitative test. A positive nontreponemal test is considered diagnostic of syphilis infection, either past or present. Further confirmation can be performed with a sensitive and specific treponemal agglutination test. *CIA*, Chemiluminescence immunoassay; *EIA*, enzyme immunoassay; *RPR*, rapid plasma regain; *TP-PA*, treponemal pallidum particle agglutination. (Adapted from the Centers for Disease Control and Prevention. Reverse sequence syphilis screening webinar [Internet] [cited 6 Jan 2017]. Available from: <http://www.cdc.gov/std/syphilis/Syphilis-Webinar.htm>.)

proportionate increase in false positives reduce their utility as a screening test, especially in a low-risk population.

Currently, in cases of suspected syphilitic uveitis, newer treponemal tests, such as enzyme immunoassays (EIA) and chemiluminescence assays (CIA), utilizing specific treponemal antigens have been approved by the Food and Drug Administration (FDA) and are recommended by the Centers for Disease Control and Prevention (CDC) as initial screening tests for syphilis (<http://www.cdc.gov/std/syphilis/Syphilis-Webinar.htm>). These new tests have specific IgM and IgG antitreponemal antibodies for the detection of early and late syphilis, respectively, and remain positive for life. They have high sensitivity and low specificity for diagnosis, and false-positive test results may be associated with certain infections (e.g., Lyme disease, leptospirosis, malaria) and medical conditions (e.g., autoimmune disorders, intravenous drug use, pregnancy). Given these diagnostic limitations, a confirmatory treponema particle agglutination test would be submitted (Fig. 7.6.5). This new “reverse sequence” algorithm would capture those individuals with either very early disease or late findings (e.g., neurosyphilis with ocular complications) who would be positive by treponemal-specific testing but negative by RPR.

In individuals infected with HIV, false positives and persistent high titers may occur in nontreponemal testing due to polyclonal B cell activation, thus making it difficult to assess the efficacy of treatment. Treponemal testing is also suspect in the setting of abnormal serological response to infection.<sup>15</sup> False-negative tests may occur due to insufficient production of antibody to bacterial proteins or an overall lack of immunoreactivity. With such atypical presentations of syphilitic uveitis in these cases, a high level of suspicion for infection is required.

In cases of neurosyphilis, the CDC recommends the use of cerebrospinal fluid (CSF)-VDRL testing for establishing the diagnosis if nontreponemal and treponemal testing is negative. The use of CSF-FTA-ABS is still controversial, as the test is often too sensitive. CSF-VDRL has an advantage over CSF-FTA-ABS in cases requiring differentiation of current active infection from past infection, though none of the tests are absolute for diagnosis of neurosyphilis. Leukocytosis and elevated protein concentrations are often present for more than a year in those individuals with neurological symptoms. Treatment for presumed neurosyphilis is then warranted, even if test results are negative.

## DIFFERENTIAL DIAGNOSIS

The possible differential diagnoses for syphilitic uveitis are protean (Box 7.6.1). A high degree of clinical suspicion is necessary to make the diagnosis, and serological confirmation is required. The most critical diagnosis to

### BOX 7.6.1 Differential Diagnosis in Ocular Syphilis

Toxoplasmosis  
 Rubella  
 Cytomegalovirus (CMV)  
 Human immunodeficiency virus (HIV)  
 Herpes simplex virus (HSV)  
 Varicella zoster virus (VZV)  
 HLA-B27-related uveitis  
 Primary intraocular lymphoma  
 Sarcoidosis  
 Tuberculosis  
 Idiopathic uveitis

make may be acute syphilitic posterior chorioretinitis, and differentiating it from acute posterior multifocal placoid pigment epitheliopathy (APMPPE) and atypical serpiginous choroidopathy is of utmost importance, due to the possible use of systemic immunosuppressive therapy for treatment of these conditions.

## SYSTEMIC ASSOCIATIONS

The three clinical stages are accompanied by characteristic clinical findings. The chancre, an ulcerative lesion occurring at the site of inoculation, is pathognomonic for the primary stage of infection. It may be associated with a flu-like syndrome secondary to the initial bacteremia, though it is rare. The chancre spontaneously heals within 2 weeks, during the organism's incubation period, which ranges from 3 days to 3 months, with an average of 3 weeks.

Several weeks after contact, systemic manifestations of fever, malaise, lymphadenopathy, and mucocutaneous eruptions can be seen. This marks the second stage of infection and occurs in 60%–90% of patients. One third of these individuals may also have primary lesions. Up to 25% of patients with early syphilis, defined as primary, secondary, or early latent stages of disease of less than 1-year duration, develop neurological symptoms.

The tertiary stage is often associated with late complications. Focal inflammatory lesions (gummas) may affect any organ, and those in the central nervous system (CNS) may lead to visual field deficits. One third of untreated patients develop tertiary syphilis, and neurosyphilis develops in less than 1%. In HIV-positive patients, necrotizing encephalitis may occur and is usually more aggressive than the findings seen in tertiary syphilis (e.g., tabes dorsalis and general paresis).

## PATHOLOGY

Lymphocytic infiltration, diffuse or focal, surrounds the blood vessels of affected organs in syphilitic uveitis. The iris, ciliary body, and choroid all exhibit these findings along with signs of chronic granulomatous inflammation. Obliterative vasculitis with a predominance of mononuclear and plasma cells may also be seen.

## TREATMENT

Penicillin G is the mainstay of treatment for all stages of syphilis (Table 7.6.1). The treatment is determined by the stage and clinical findings. Sexual partners of the infected patient also need to be evaluated and treated accordingly.<sup>16</sup> For individuals with a penicillin allergy, alternative antibiotics may be used, though they are not as effective. Skin testing and desensitization may be recommended or required, particularly in cases where the patient is concurrently infected with HIV. For patients diagnosed with congenital syphilis, treatment with aqueous penicillin G or procaine penicillin G via intravenous administration is considered the standard of care. Other antibiotics (e.g., ceftriaxone and ampicillin) have been used, but there is currently no optimal therapy for congenital infection. Neurosyphilis requires treatment with penicillin, as there is no effective alternative.<sup>3</sup>

Failure of primary therapy with evidence of tertiary disease prompts further evaluation of the CSF. In HIV-positive individuals, the infection is more aggressive, and abnormalities in serological response and CSF findings make these situations more challenging. The dose and duration of therapy must be sufficient to cure neurosyphilis, regardless of CSF findings.<sup>16–18</sup>

Success with therapy at any stage may be evaluated by improvement in clinical findings and seroconversion or low titers on nontreponemal

TABLE 7.6.1 Recommended Treatment of Syphilis

Stage of Disease	Preferred Treatment	Alternative Treatment
Primary, secondary, or early latent	Benzathine penicillin G 2.4 million units IM, single dose	Doxycycline 100 mg po bid × 2 weeks or tetracycline 500 mg po qid × 2 weeks
Late latent, latent syphilis of unknown duration, tertiary stage, or those who fail primary therapy	Benzathine penicillin G 2.4 million units IM, administered weekly × 3 weeks	Doxycycline 100 mg po bid × 4 weeks or tetracycline 500 mg po qid × 4 weeks
Neurosyphilis	Aqueous penicillin G 3–4 million units IV every 4 hrs × 10–14 days	Procaine penicillin 2.4 million units IM daily × 10–14 days and probenecid 500 mg po qid × 10–14 days

Note: HIV-positive patients should be treated with penicillin at all stages of infection, and those allergic to penicillin should be desensitized and then treated with the full regimen. All patients with tertiary syphilis should have a cerebrospinal fluid analysis and be evaluated for neurosyphilis. Adapted from Workowski KA, Bolan GA, Centers for Disease Control and Prevention. Sexually transmitted diseases treatment guidelines, 2015. MMWR Recomm Rep 2015;64:1–137. Erratum in MMWR Recomm Rep 2015;6:924.

testing. Published criteria describe a four- to eightfold decrease in nontreponemal titers that should occur by 3 and 6 months, respectively. However, these criteria should not be used in monitoring treatment efficacy in the HIV-positive population, as serological testing is often inaccurate. This often justifies the aggressive treatment regimen in these patients.

Adjunct therapy with corticosteroids may be initiated once the infection has been appropriately treated. Residual ocular inflammation may be treated with topical applications, in the cases of anterior uveitis and interstitial keratitis. Systemic medications are often necessary in those individuals with residual scleritis, posterior uveitis, or optic neuritis. Antibiotic therapy should always be administered concurrently with corticosteroid regimens.

## COURSE AND OUTCOME

Early diagnosis and appropriate therapy with antimicrobial agents often determine the outcomes of syphilitic uveitis. With treatment, full visual recovery is common, with improvement in other systemic findings. If untreated, worsening of intraocular inflammation and the development of secondary glaucoma, retinal necrosis, chronic vitritis, and optic atrophy all limit visual potential. Treatment in HIV-positive individuals should be pursued aggressively and initiated early, regardless of CSF findings.

## LYME DISEASE

**Definition:** Multisystem manifestations resulting from tick-borne transmission of *Borrelia burgdorferi*, including ophthalmic, dermatological, neurological, rheumatic, and cardiac findings.

### Key Features

- Primary, or initial, phase with rash noted at the site of the inoculum (erythema chronicum migrans); associated flu-like symptoms can be noted.
- Secondary, or dissemination, phase with systemic signs and symptoms including dermatological, neurological, and cardiac manifestations.
- Tertiary, or late, phase with associated arthritis, meningoencephalitis, polyneuropathies involving both cranial and peripheral nerves, and carditis.

### Associated Features

- Stage 1: Conjunctivitis.
- Stage 2: Cranial nerve palsies, inflammation of optic nerve.
- Stage 3: Inflammation involving cornea, uvea, or retina.

## INTRODUCTION

Lyme disease is a multisystem disorder found in North America, Europe, and Asia. In the United States, the manifestations are caused by infection with *Borrelia burgdorferi* (*B. burgdorferi*), a spirochete transmitted by the Ixodes tick species. The disease can be broken down into stages:

- Stage 1 begins days to weeks after the tick bite and is denoted by the pathognomonic finding of erythema migrans in conjunction with fever, malaise, and arthralgias.



Fig. 7.6.6 Erythema Chronicum Migrans.

- Stage 2 is the phase of dissemination of the spirochete to multiple organs in the days, weeks, or months after infection.
- Stage 3 often occurs after a disease-free period lasting months to years.

Ocular findings can manifest at any stage of infection.

## EPIDEMIOLOGY AND PATHOGENESIS

The disease is named after the town of Lyme, Connecticut, where an outbreak of chronic arthritis in children occurred in 1975. This geographic cluster of cases of oligoarthritis with a seasonal onset was associated with erythema chronicum migrans, severe headaches, and neurological symptoms. Other endemic areas include the Northeast as far south as Virginia; Minnesota, Michigan, and Wisconsin in the Midwest; and Northern California in the West. The pathogenesis of the disease is similar to that induced by *T. pallidum*. The first stage, or early infection, is believed to be caused by spirochetemia. Incubation can occur between 3 and 32 days, and a proinflammatory response occurs in both the innate and adaptive immune systems.<sup>19</sup> This is clinically observed as erythema chronicum migrans, the classic skin rash at the site of the tick bite (Fig. 7.6.6).

The remaining two stages likely result from the immunological response of the host to parasitic invasion.<sup>20</sup> The specific IgM response provides for polyclonal B cell activation and increased levels of circulating immune complexes, while the specific IgG response develops over weeks in response to spirochetal polypeptides and nonprotein antigens. If left untreated, *B. burgdorferi* may survive for several years in the joints, skin, and nervous system.<sup>21</sup> Recent reports seem to support this observation, as in vitro studies indicate that these infectious strains are capable of forming cystic bodies and biofilm aggregates, and current antibiotics have varying effects on these different morphological forms.<sup>22,23</sup>

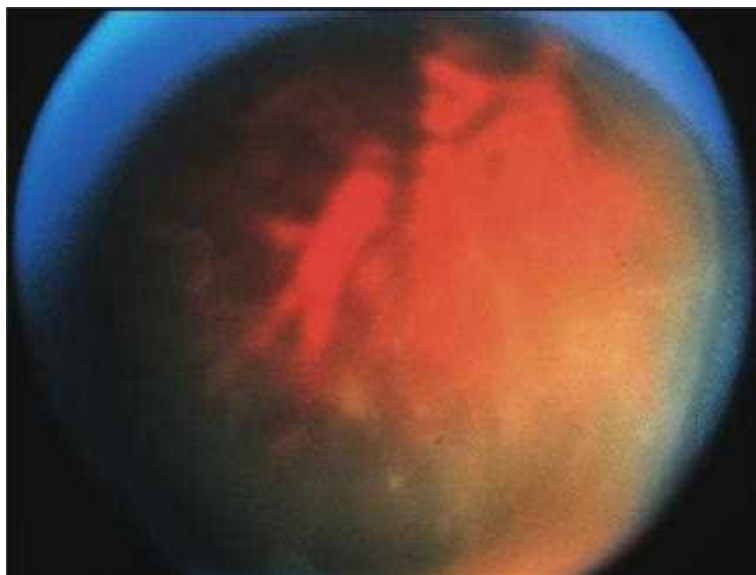
## SYSTEMIC ASSOCIATIONS

Systemic findings in stage 1 disease begin days to weeks after the tick bite and include erythema migrans, fever, malaise, and arthralgias. A history of tick bite may be absent in 50% of individuals.<sup>24</sup> The dissemination of the spirochete in the second phase occurs within days, weeks, or months after infection. The organism spreads to multiple organ systems, particularly the skin, heart, joints, and nervous system. Neurological manifestations seen





**Fig. 7.6.7 Dense Vitreous Debris in Lyme Disease.**



**Fig. 7.6.8 Moderate Vitritis in Lyme Disease Simulating Intermediate Uveitis.**

at this stage include cranial and peripheral neuropathies and meningoencephalitis.<sup>25</sup> Chronic arthritis and conduction defects may also develop.<sup>21</sup> The lymphocytoma, another skin lesion, may develop, especially on the earlobe or breast, and the initial erythema migrans fades and reappears.<sup>25</sup>

Recurrent manifestations are the hallmark of the third stage and include chronic relapsing arthritis, commonly affecting the knee; acrodermatitis chronica atrophicans, a rash that eventually resolves and leaves atrophy of the skin and underlying structures; and late neurological manifestations such as encephalopathy, demyelination, and dementia.<sup>21,25–27</sup> These findings can occur despite early treatment.

## OCULAR MANIFESTATIONS

Ocular findings in Lyme disease are less prominent compared to the systemic manifestations and can appear at any stage of disease. Conjunctivitis is present in 11% of patients with early stage infection and is considered the most common finding.<sup>28</sup> Nonspecific conjunctival and periorbital inflammations are mild in nature and self-limited. Neuro-ophthalmic complications are associated with stage 2 disease and commonly manifest as ocular motility problems due to cranial nerve palsies, optic neuritis, papilledema, and pseudotumor cerebri in the setting of meningoencephalitis.<sup>26,29,30</sup> Stromal keratitis, episcleritis, and symblepharon formation have been reported in stage 3 disease.<sup>31</sup> Intraocular inflammation often presents as chorioretinitis and vitreous inflammation (Figs. 7.6.7 and 7.6.8).

## DIAGNOSIS

The clinical diagnosis is dependent on the following: appearance of the pathognomonic skin rash (erythema migrans) in a patient with a history of tick bite and/or residence in an endemic region; or a skin lesion with

**TABLE 7.6.2 Differential Diagnosis for Lyme Disease**

Infectious Disorders	Noninfectious Disorders
Syphilis	Sarcoidosis
Tuberculosis	Collagen vascular diseases
Viral keratitis	Vasculitis
Infectious arthritis	Multiple sclerosis
Infectious mononucleosis	Vogt–Koyanagi–Harada disease
Viral encephalitis/meningitis	
Mumps	

### BOX 7.6.2 Criteria for Diagnosis of Lyme Disease

The presence of any one of the following criteria satisfies the diagnosis of Lyme disease.

1. Development of erythema migrans (EM) within 30 days of exposure in an endemic area; size of lesion should be at least 5 cm
2. In the absence of EM, history of exposure to endemic area, with signs involving one organ system and positive laboratory test
3. No history of exposure to endemic area, but with EM as well as involvement of two organ systems
4. No history of exposure to endemic area, but with EM and a positive serology

Adapted from: Case definitions for public health surveillance. MMWR Recomm Rep 1997;46(RR-10):1–55. Recommendations for public health surveillance. MMWR Morb Mortal Wkly Rep 1995;44:590–1.

involvement of two organ systems in those patients without a history of a tick bite or residence in a nonendemic region (Box 7.6.2). Serological testing becomes a useful adjunct, and current CDC recommendations include a two-step process involving an enzyme-linked immunosorbent assay (ELISA) to detect immunoglobulins G and M (IgG, IgM) specific to *B. burgdorferi*. Equivocal results are then tested using Western blot analysis. These results, along with a clinical history suggestive of infection, provide the basis for diagnosis.

## DIFFERENTIAL DIAGNOSIS

The clinician needs to rule out both infectious and noninfectious etiologies with similar clinical presentations, given the various manifestations of Lyme disease. The differential diagnosis is summarized in Table 7.6.2.<sup>32</sup>

## PATHOLOGY

Direct invasion of tissues by the *Borrelia* spirochete can be seen in stage 1. In the later stages, perivascular infiltration of plasma cells has been observed, leading to small-vessel obliteration and vasculitis.

## TREATMENT

Preventive measures in endemic areas include protective clothing, repellents, and acaricides. Tick checks and landscape modifications can reduce exposure. Vaccination is no longer available, and a single dose of doxycycline (200 mg) is no longer recommended for prophylaxis after a documented tick bite. Appropriate antibiotic therapy for a minimum of 10–20 days duration is preferred.<sup>33–35</sup>

The most effective treatment strategy for ocular disease is unclear. Generally, patients benefit from systemic treatment (Table 7.6.3). Topical corticosteroids have been beneficial in treating anterior segment manifestations such as keratitis and episcleritis. Systemic corticosteroids have been utilized in severe cases of ocular inflammation such as vision-threatening uveitis, scleritis, or optic neuritis, but the use may be controversial, as a higher incidence of relapses has been observed.<sup>26</sup> Clinical response may take as long as one year. Inadequate treatment in early stages may lead to relapses and development of late-stage manifestations.<sup>26</sup> Concomitant infections should also be treated if the clinical findings persist despite prolonged antibiotic therapy.

## COURSE AND OUTCOME

The majority of patients respond well to systemic therapy, though posterior uveitis, stromal keratitis, and neurotrophic keratitis are slow to respond to

TABLE 7.6.3 Treatment of Lyme Disease

Early Infection – Local or Disseminated	
Adults	Doxycycline 100 mg orally twice daily for 14–21 days
	Amoxicillin 500 mg orally three times a day for 14–21 days
In case of doxycycline/amoxicillin allergy:	
	Cefuroxime 500 mg orally twice daily for 14–21 days
	Erythromycin 250 mg orally four times daily for 14–21 days
Children	Amoxicillin 50 mg per kilogram of body weight per day in three divided doses for 14–21 days
In case of penicillin allergy:	
	Cefuroxime 30 mg per kg per day in two divided doses for 14–21 days
Neurological and/or Ocular Abnormalities (Early or Late)	
Adults	Ceftriaxone 2 g IV once a day for 14–28 days
	Cefotaxime 2 g IV every 8 hours for 14–28 days
In case of ceftriaxone or penicillin allergy:	
	Doxycycline 100 mg orally 3 times a day for 30 days
Children	Ceftriaxone 75–100 mg per kg per day (maximum 2 g) IV once a day for 14–28 days
	Cefotaxime 150 mg per kg per day in 3–4 divided doses (maximum 6 g) for 14–28 days
Avoid doxycycline in pregnant women.	
Adapted from Steere AC. Lyme disease. N Engl J Med 2001;345:115–25.	

treatment. Untreated disease can have a relapsing course for several years, with late neurological sequelae similar to those seen in syphilis.

## LEPTOSPIROSIS

**Definition:** A zoonotic infection caused by *Leptospira* species, with effects seen in worldwide distribution.

### Key Features

- Two key phases.
- Leptospiremic: associated with severe myalgia, fever and headache.
- Immune: associated with meningismus, high fever, and central and peripheral neurological manifestations.
- Ocular manifestations are found in the majority of patients and can include subconjunctival hemorrhages, conjunctivitis, and uveitis.

### Associated Feature

- Hemorrhages, renal failure, and jaundice (Weil's disease).

## INTRODUCTION

A severe condition characterized by acute fever, malaise, and uveitis was initially described by Adolf Weil in 1886. The spirochetes of the genus *Leptospira* were discovered as the etiological agents in 1915. This zoonotic infection has a worldwide distribution, with higher incidence in tropical and subtropical climates. Most human infection may be asymptomatic, and there is a wide spectrum of disease presentation that ranges from non-specific febrile illness to multiorgan involvement. Two strains of *Leptospira* exist: *L. biflexia*, a saprophytic strain, and *L. interrogans*, the pathological organism responsible for infection in humans.

## EPIDEMIOLOGY AND PATHOGENESIS

The natural reservoir for pathogenic *Leptospira* is wild animals, especially rodents, but domestic livestock and dogs can also be affected. It is excreted by animal hosts with chronic renal infection, which contaminates soil and water, and humans become accidental hosts on contact with infected urine, tissues, or water. Those at high risk of infection include farmers, veterinarians, abattoir workers, miners, and sewer workers who contract the disease via direct contact. Indirect contact is more common after exposure to wet soil or water through occupational exposure (e.g., rice or taro farming) or

TABLE 7.6.4 Systemic Manifestations of Leptospirosis

Stage	Leptospiremic	Immune
Onset	First week of disease, abrupt onset	Second week
Duration	4–9 days	Undetermined
Manifestations – common	Severe headaches, fever with spikes, chills, myalgia, abdominal pain, skin rash, arthralgias	High fever, meningismus, encephalitis, cranial nerve palsies of sixth, seventh, and eighth cranial nerves, peripheral neuropathy
Manifestations – rare	Jaundice, altered consciousness, cardiac	Spontaneous abortion during pregnancy

TABLE 7.6.5 Ocular Manifestations of Leptospirosis

Anterior	Posterior	Miscellaneous
Conjunctivitis	Intermediate uveitis	Periorbital pain
Subconjunctival hemorrhage	Vitritis	Facial palsy
Scleral icterus	Periphelebitis	Palpebral herpes
Keratitis	Retinal exudates	
iridocyclitis	Choroiditis	
	Papillitis	
	Optic neuritis	
	Macular edema	
	Retinal hemorrhage	
	Retinal arteritis	

recreational exposures (e.g., adventure tourism in endemic regions). Infection may also be seen in urban centers of developing regions secondary to a lack of sanitation in areas of rapid expansion and growth. Sporadic outbreaks have also been reported in developed countries.<sup>36,37</sup>

The pathogen enters the body through intact mucous membranes, abraded epidermis, or inhalation. The organisms quickly disseminate throughout the body, and a systemic vasculitis ensues that facilitates migration of the spirochetes into organs and tissues. Severe vascular injury can occur, and end organ damage can be seen in the lungs, liver, and kidneys.

## SYSTEMIC MANIFESTATIONS

This broad spectrum of illness may present as subclinical disease, self-limited systemic illness (anicteric, seen in 90% of affected individuals), or severe infection associated with multiorgan involvement (icteric). It is biphasic, with an initial septicemic phase followed by defervescence and the immune phase of illness (Table 7.6.4). The most severe presentation that may develop after the initial phase is Weil's disease, which is characterized by impaired function of the liver and kidneys. The symptoms may progress directly from the acute phase without any improvement prior to the development of more severe symptoms. Mortality rates in these patients range from 5% to 40%.

## OCULAR MANIFESTATIONS

Ocular complications can occur in both the acute and immune phases of illness and can lead to decreased vision and blindness. Conjunctival hyperemia, chemosis, and subconjunctival hemorrhage are most commonly seen in these cases. Changes in the retinal vasculature and the presence of retinal hemorrhages have been reported, along with disc hyperemia and retinal vasculitis.<sup>34</sup> Table 7.6.5 summarizes the ocular findings associated with leptospirosis.

## DIAGNOSIS

Clinical diagnosis of systemic leptospirosis is difficult, given the non-specific symptoms and variable presentations. The diagnostic dilemma extends to the ocular manifestations, where the differential diagnosis for leptospiral uveitis includes both infectious and noninfectious etiologies. Examination alone is unreliable; rather, a high index of suspicion in an endemic region, or in individuals who may have exposure due to socioeconomic or recreational factors, is required. Potential diagnoses of leptospirosis will require laboratory testing for confirmation.

Indirect methods such as the microscopic agglutinin test (MAT) are widely utilized and considered the reference standard assay for serological

**BOX 7.6.3 Differential Diagnosis of Leptospirosis**

HLA-B27 related uveitis	Sarcoidosis
Behçet's disease	Syphilis
Eales' disease	Toxoplasmosis
Endophthalmitis	Leprosy
Tuberculosis	

confirmation of infection.<sup>38,39</sup> However, the sensitivity of these tests is low, particularly on acute phase serum samples, and interpretation of test results is often complicated. Cross-reaction with circulating IgM can confound the results in acute phase samples. The results on acute and convalescent specimens are slightly more sensitive, and overall, these tests are useful adjuncts for confirmation of leptospirosis. Other diagnostic procedures, including a *Leptospira* dipstick test, ELISA, and microscopic slide agglutination tests, have replaced the MAT for more routine use. Polymerase chain reaction (PCR) for the detection of leptospiral DNA may be more sensitive for early identification of *Leptospira* outbreaks.<sup>40</sup>

**DIFFERENTIAL DIAGNOSIS**

The differential diagnosis for leptospirosis is summarized in Box 7.6.3. It is important to note that the manifestations are protean and often mimic influenza-like illnesses, and diagnosis can be difficult, with the exception of Weil's disease.

**TREATMENT**

Systemic disease is effectively treated with antibiotic therapy. Severe infection can be treated with intravenous penicillin (1.5 million units every 6 hours) or ampicillin (0.5–1.0 g every 6 hours) and mild disease with oral doxycycline (100 mg twice daily by mouth), ampicillin (500–750 mg orally every 6 hours), or amoxicillin (500 mg orally every 6 hours).<sup>41</sup> Doxycycline (200 mg given weekly by mouth) can also be used for prophylaxis. Once daily ceftriaxone (1 g intravenous injection) has been shown to be as effective as penicillin. Supportive care for individuals suffering from multiorgan involvement should also be initiated.

Treatment of ocular disease can be accomplished using amoxicillin plus clavulanic acid (1.5 g orally in divided doses each day) and pefloxacin (800 mg daily) for 3 weeks. Corticosteroids, both topical and systemic, may be required for control of intraocular inflammation.

**COURSE AND OUTCOME**

The prognosis for patients with ocular disease is generally good, with one large series reporting that more than 50% of patients regained 20/20 vision.<sup>42</sup> Specifically, anicteric leptospirosis is associated with a better outcome, but Weil's disease is associated with a fatal outcome in 5%–30% of untreated patients.<sup>36,43</sup>

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# Tuberculosis, Leprosy, and Brucellosis

Soumyava Basu, Narsing A. Rao

7.7

## Definitions:

- Tuberculosis is a chronic infection caused by *Mycobacterium tuberculosis*. It can involve any part of the eye, though uveitis appears to be most common.
- Leprosy is a chronic granulomatous inflammation of the skin and peripheral nerves, caused by *Mycobacterium leprae*, that affects ocular adnexa and the anterior segment of the eye.
- Brucellosis is a zoonotic disease caused by *Brucella spp.* with a wide range of ocular manifestations.

## Key Ocular Features

### Tuberculous Uveitis

- Mainly presents as posterior or pan uveitis either multifocal choroiditis or multifocal serpiginous-like choroiditis (multifocal, serpiginoid choroiditis), typically involving the posterior pole and midperiphery.
- Retinal vasculitis with or without healed/active chorioretinitis lesions.
- Choroidal tubercles, single or multiple, at the posterior pole.
- Anterior uveitis, mainly granulomatous.

### Leprosy Uveitis

- Chronic granulomatous anterior uveitis with diffuse iris atrophy and miotic pupil.
- Lagophthalmos, hypoesthesia of cornea, exposure keratitis.
- Complicated cataract.

### Brucellosis Uveitis

- Anterior uveitis (low grade), choroiditis.
- Optic neuritis, rarely endophthalmitis.

## Associated Systemic Features

**Tuberculosis** – Pulmonary or extrapulmonary tuberculosis, miliary tuberculosis, positive tuberculin skin test or QuantiFERON-TB Gold test.

**Leprosy** – Few, well-defined (tuberculoid) or widespread, poorly defined (lepromatous) skin macules; peripheral neuropathy, loss of cilia and or eyebrow hair.

**Brucellosis** – History of contact with domestic animals or consumption of unpasteurized milk products, constitutional symptoms, rising titers of *Brucella* antibodies.

## TUBERCULOSIS

### INTRODUCTION

Tuberculosis (TB) is a chronic infection caused by *Mycobacterium tuberculosis* (*Mtb*) characterized by the formation of necrotizing granulomas.<sup>1</sup> The bacteria primarily infect the alveolar macrophages in the lung, from where they are carried to regional lymph nodes and other parts of the body, including the eye. In the eye, TB most often presents as uveitis. The diagnosis of ocular tuberculosis remains largely presumptive and mostly depends on presence of suggestive clinical signs, evidence of past *Mtb* infection, and exclusion of non-TB entities.<sup>2</sup>

## EPIDEMIOLOGY AND PATHOGENESIS

The true prevalence of tuberculous uveitis is difficult to determine, primarily due to the challenges of making an accurate diagnosis of the disease. Most patients with uveitis do not have evidence of systemic TB (active or healed). Microbiological evidence of *Mtb* is rarely found in ocular samples, and the clinical signs of ocular TB are nonspecific and mimic several other infectious and noninfectious uveitis. Not surprisingly, published prevalence of tuberculous uveitis varies widely not only between TB-endemic and nonendemic countries but also between different centers in the same country.<sup>3-4</sup>

The role of *Mtb* in pathogenesis of ocular TB is not clearly understood.<sup>5</sup> Histopathological studies have shown that ocular TB is a paucibacillary infection.<sup>6</sup> A clinically relevant guinea pig animal model of intraocular TB was developed by aerosol delivery of *Mtb*. This model showed ocular lesions mimicking human infection, primarily granulomatous choroiditis.<sup>7</sup>

## OCULAR MANIFESTATIONS

Ocular TB manifests with variable clinical features. It can involve any part of the eye; however, uveitis appears to be a common presentation. The clinical presentation varies between endemic and nonendemic areas. In endemic areas, the disease is more severe and affects all age groups, whereas in nonendemic areas, it is mainly seen in individuals migrated from TB-endemic countries and it appears to be less severe. Moreover, in nonendemic countries it is seen in elderly and immunocompromised individuals.<sup>8</sup> In a patient presenting with granulomatous uveitis in general, the goal in non-TB-endemic regions is to rule out ocular TB, whereas in TB-endemic regions it is to rule out non-TB entities.

### Anterior Uveitis

TB anterior uveitis commonly manifests as granulomatous inflammation with mutton-fat keratic precipitates, posterior synechiae, Koeppe iris nodules at the pupillary margin and iris or angle granulomas.<sup>9</sup> Nongranulomatous anterior uveitis is rare.

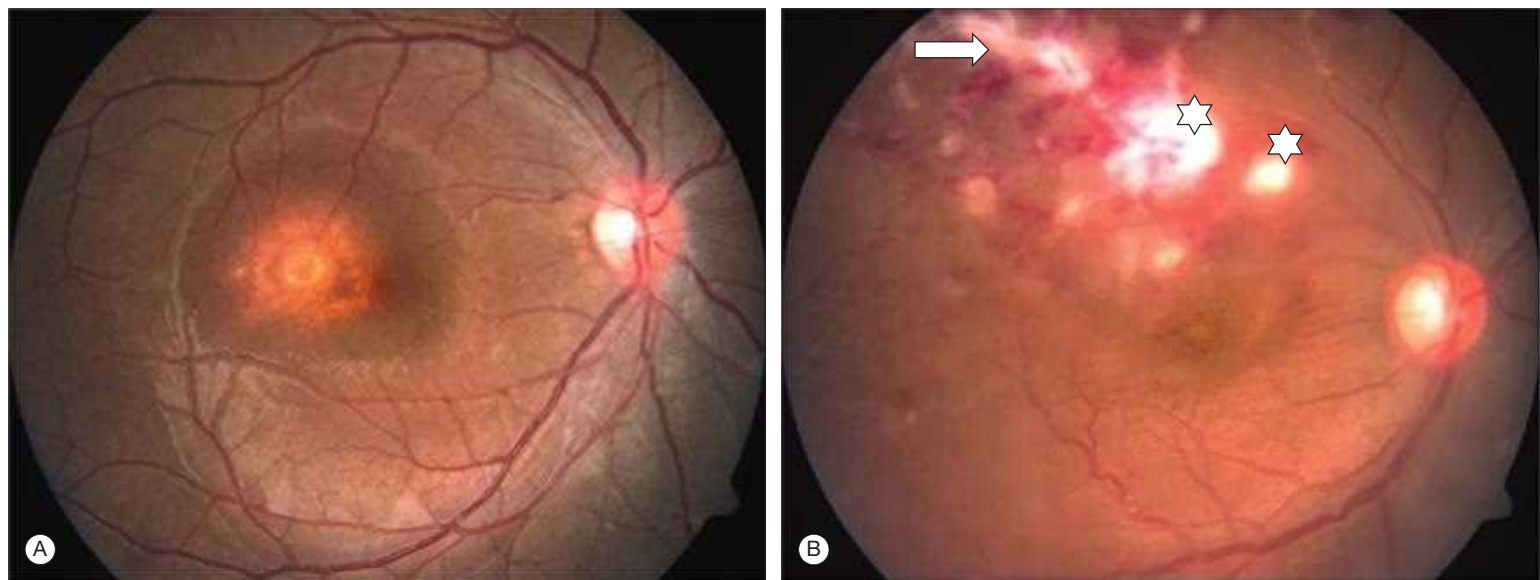
### Intermediate Uveitis

Intermediate uveitis commonly presents with chronic, low-grade vitritis with snowball opacities, peripheral vascular sheathing, healed or active peripheral chorioretinitis lesions, and cystoid macular edema.

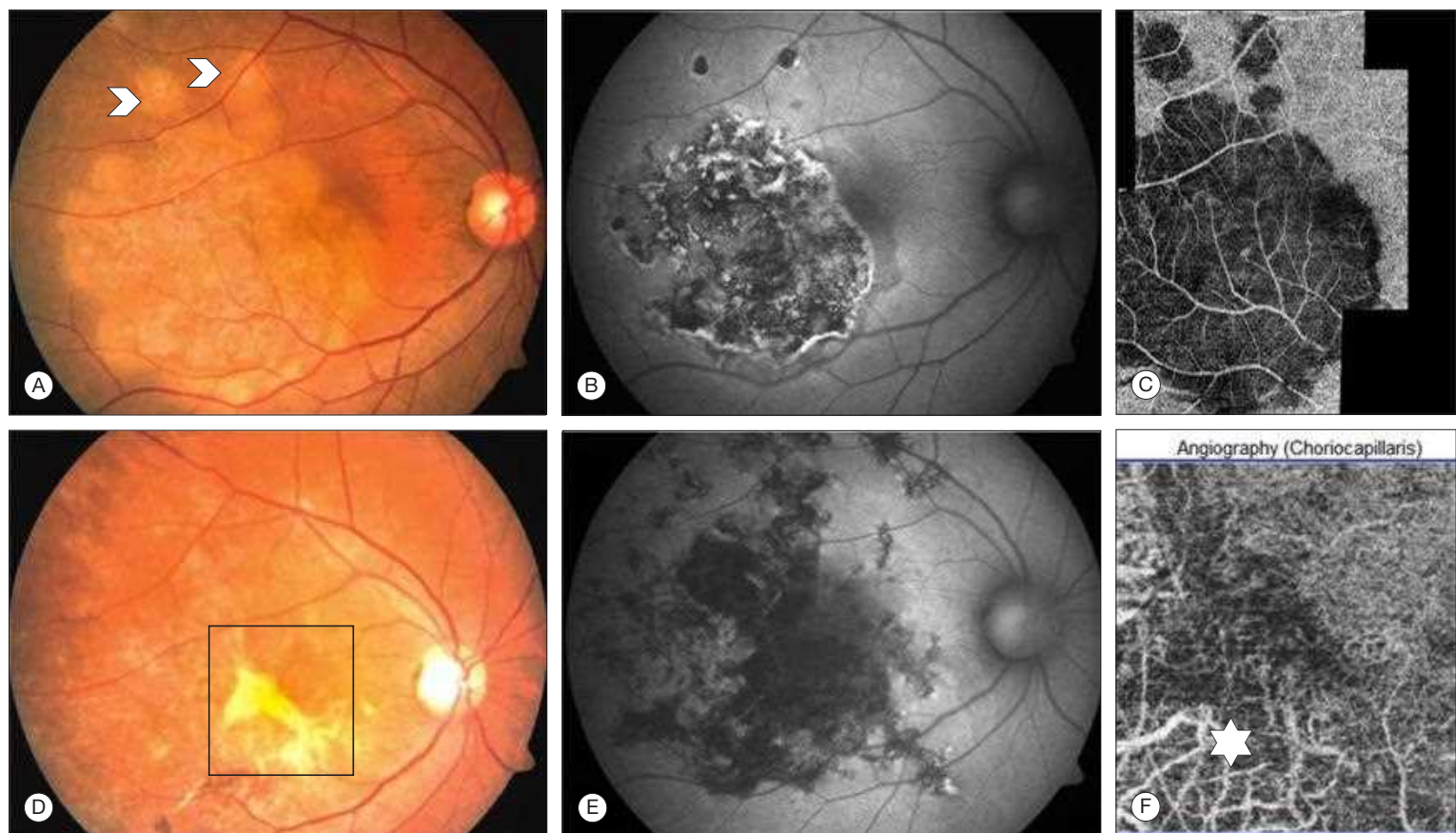
### Posterior and Pan-Uveitis

These include a wide range of manifestations, such as: retinal vasculitis, multifocal serpiginoid choroiditis in TB-endemic countries such as India, multifocal choroiditis, choroidal tubercles, choroidal or optic nerve head tuberculomas, and subretinal abscess.<sup>10-11</sup>

Choroidal tubercles are the most recognized manifestation of intraocular tuberculosis and result from hematogenous spread of the mycobacteria when a caseous pulmonary lesion erodes blood vessels/lymphatics. These tubercles are generally less than five in number, unilateral or bilateral, grayish white to yellow in color with indistinct borders, and located mostly in the posterior pole (Fig. 7.7.1A). On fluorescein angiography, they are hypofluorescent during the dye transit and hyperfluorescent in the late phase. On healing, the tubercles result in pigmented and atrophic scars. Choroidal tuberculoma generally presents as a solitary subretinal mass that begins as a small, round, whitish lesion gradually becoming yellowish, mimicking a choroidal tumor. Retinal vasculitis is a common manifestation of ocular TB, especially in TB-endemic countries.<sup>12</sup> It presents



**Fig. 7.7.1** (A) Right eye fundus photograph showing choroidal tuberculoma in a patient in treatment for pulmonary tuberculosis. (B) Fundus photograph of right eye showing retinal periphlebitis (*arrow*), associated with active chorioretinitis (*stars*) overlying blood vessels.



**Fig. 7.7.2 Multifocal Serpiginoid Choroiditis in the Right Eye Before and After Treatment.** (A–C) At presentation, clinical photograph showing central scarring and active edges and skip lesions (*arrowheads*). Active choroiditis is represented by hyperautofluorescence (B) and flow void areas in the choriocapillaris layer (C) on OCT angiography. (D–F) Healed lesions characterized by hypoa autofluorescence (E) and “tangled meshwork” of vessels (F, *star*) on OCT angiography (*inset in color photograph*).

as retinal periphlebitis or occlusive vasculitis, often associated with healed or active focal chorioretinal lesions (Fig. 7.7.1B).<sup>13</sup> The occlusive vasculitis can lead to retinal or disc neovascularization, vitreous hemorrhage, and tractional retinal detachment.

Multifocal serpiginoid choroiditis (MSC) is a recently recognized manifestation of TB-associated uveitis in TB-endemic countries.<sup>11,13–15</sup> The multifocal lesions typically show central healing, and active amoeboid margins; some appear healed and others show active choroiditis features (Fig. 7.7.2). Fundus autofluorescence (FAF) is a quick imaging tool for monitoring the clinical course of these lesions. It can vividly display active versus healed lesions (Fig. 7.7.2B and E).<sup>16</sup> More recently, multimodal imaging with simultaneous recording of topographic and tomographic images has helped in combining FAF with optical coherence tomography (OCT) and OCT-Angiography (OCT-A).<sup>17</sup> In active lesions, OCT shows hyperreflectivity

in the outer retina and RPE, whereas OCT-A reveals flow-void areas in the choriocapillaris layer that appear as a tangled meshwork after resolution (Fig. 7.7.2C and F). Rarely, intense inflammatory response in intraocular TB may result in destruction of ocular tissues with a resultant clinical picture of endophthalmitis or rarely panophthalmitis.

## DIAGNOSIS

Ocular TB usually is diagnosed as confirmed (or definitive) or presumed based on the level of evidence supporting tuberculous etiology.<sup>2</sup> Any patient presenting with granulomatous uveitis requires eliciting history of previous exposure to tuberculosis and ruling out other causes of granulomatous inflammation. Such patients require investigations to support clinical diagnosis of tuberculous uveitis. These include:



- Immunological tests; the tuberculin skin test (TST) or interferon-gamma release assay (IGRA).
- Chest radiography (preferably high-resolution computed tomography).
- Intraocular fluid examination to detect *Mtb* DNA by various polymerase chain reactions (PCR).

In general, patients with granulomatous uveitis and positive TST or IGR with the chest imaging findings suggestive of pulmonary TB (active or healed lesions) are diagnosed as presumed intraocular tuberculosis requiring anti-TB treatment. However, the chest imaging can be negative in presumed cases due to the extrapulmonary nature of intraocular tuberculosis. In rare cases, where microbiological (ocular fluid smear or culture) evidence or ocular tissue biopsy evidence of *Mtb* is available, such cases are called confirmed ocular TB. Several uveitis experts consider PCR-positive cases as confirmed, although occasionally the results can be false positive. However, all PCR-positive cases are treated with anti-TB agents in clinical practice when other causes of uveitis have been excluded.

## PATHOLOGY

The characteristic tubercular granulomas show central caseous necrosis surrounded by epithelioid cells, Langerhans giant cells, lymphocytes, and plasma cells.<sup>6,7,18</sup> The granuloma formation is unusual in immunocompromised individuals who mostly show a purulent infection that reveals necrotic and viable neutrophils mixed with macrophages. These lesions contain numerous bacteria.

## TREATMENT

The treatment of TB is complex, and inappropriate management can result in loss of vision and life-threatening consequences and development of drug-resistant organisms. It is advisable to consult a pulmonologist, infectious disease specialist, or internist experienced in the management of systemic tuberculosis. The most commonly employed anti-TB drug regimen consists of isoniazid, rifampicin, pyrazinamide, and ethambutol for the first 2 months, followed by isoniazid and rifampicin for 4–7 months.<sup>19–20</sup> Systemic corticosteroids together with multidrug anti-TB treatment may limit damage to ocular tissues. A unique challenge in management of ocular TB is the high incidence of paradoxical worsening after initiation of anti-TB therapy.<sup>21</sup> This usually occurs in the initial stages of treatment and needs to be distinguished from missed alternative diagnosis, drug-resistant TB, and reinfection. Once confirmed, paradoxical worsening is managed by escalating the corticosteroid dosage while continuing anti-TB therapy.

## LEPROSY

### INTRODUCTION

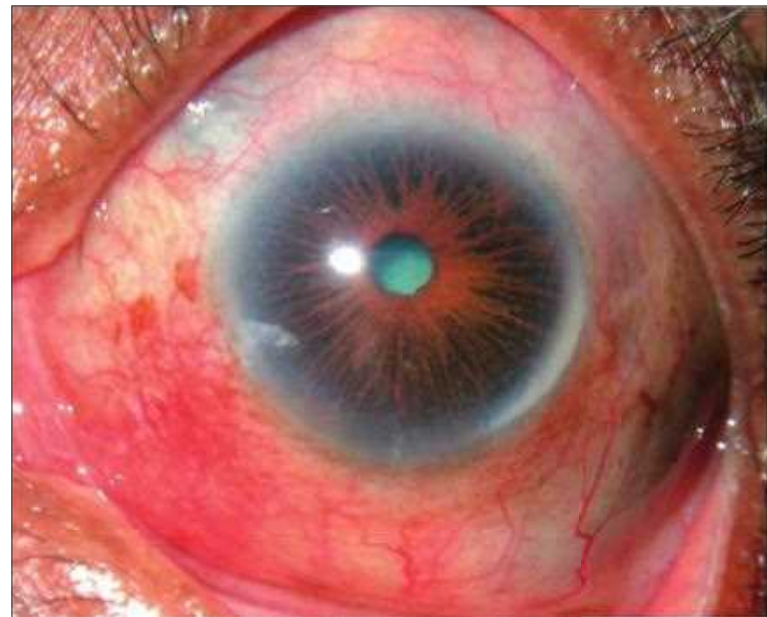
Leprosy has the highest incidence of ocular complications among all systemic bacterial infections.<sup>22</sup> The ocular complications of leprosy are also largely preventable with early-stage intervention. The disease is caused by *Mycobacterium leprae* and usually spreads by nasal secretions. The disease typically occurs in two stages: the first stage arising from the mycobacterial infection and affecting primarily the skin and upper respiratory tract and the second stage resulting from the cellular immune responses to the leprae organisms that lead to peripheral neuropathy and potentially long-term consequences.

### EPIDEMIOLOGY

As per the World Health Organization (WHO), leprosy has been eliminated from all the 122 countries where it was known to be endemic.<sup>23</sup> This is defined by a prevalence rate of less than 1 per 10,000 population. However, pockets of endemicity still persist in the developing world, especially in Africa and Asia. Current estimates suggest that ocular complications occur in 70%–75% patients with leprosy, with blindness in about 5% of such patients.<sup>24</sup>

### SYSTEMIC MANIFESTATIONS AND PATHOGENESIS OF OCULAR DISEASE

Leprosy has been classified (using the Ridley–Joplin classification) into tuberculoid (TT), lepromatous (LL), and borderline (BT, BB, and BL).



**Fig. 7.7.3 Lepromatous Leprosy Patient With Recurrent Sclerouveitis and Iris Atrophy Due to Autonomic Nerve Fiber Loss.** (Courtesy Sivakumar Rathinam, Aravind Eye Hospital, Madurai, India.)

Tuberculous disease is characterized by one or few skin lesions—well-defined macules or plaques that are scaly, dry, hairless, and anesthetic. Lepromatous disease presents with widespread but poorly defined and erythematous macules, papules, or nodules. Subsequently, peripheral neuropathy involving sensory, motor, and autonomic functions leads to beaded, palpable nerves (most commonly posterior tibial and ulnar) and several forms of disability and deformity.

## CLINICAL PRESENTATION

The most common setting for ocular manifestations is in patients with lepromatous leprosy with ongoing or completed multidrug therapy (MDT). Broadly, these can be subdivided into involvement of the adnexa, ocular surface, and intraocular structures. *Adnexal involvement* includes madarosis or loss of eyebrows and eyelashes due to direct infection of follicles, trichiasis, entropion, ectropion, decreased blinking rate (hypometropic blink), and paralytic lagophthalmos (due to facial nerve palsy in type 1 reaction). Ocular surface involvement manifests as corneal hypoesthesia, corneal nerve beading, dry eyes, exposure keratitis due to lagophthalmos, and secondary infectious keratitis and corneal scarring. Besides these, episcleritis (more common) and scleritis (in type 2 reaction) can also occur. The most common intraocular manifestation is chronic granulomatous iridocyclitis, associated with diffuse iris atrophy, iris pearls (military iris lepromata), miotic pupils, and complicated cataract (Fig. 7.7.3). Retinal and posterior choroidal involvement is extremely rare.

## DIAGNOSIS

The diagnosis of ocular leprosy is based on presence of characteristic systemic disease in high endemic populations and may be confirmed by histopathology of corneal, conjunctival, and subcutaneous skin scrapings.

## TREATMENT

Treatment of leprosy involves rifampicin, dapsone, and clofazimine for a period of 6–12 months. Uveitis requires intensive treatment with topical corticosteroids, while oral corticosteroids may be required in more severe cases in conjunction with antileprosy agents. Phenylephrine is preferred for management of miosis.

## BRUCELLOSIS

### INTRODUCTION

Brucellosis is a zoonotic disease that is mostly spread through ingestion of infected raw milk, dairy products, or raw meat. It is caused by *Brucella* species that are facultative intracellular Gram-negative bacteria. Although

the disease has been eradicated in most countries due to improvements in dairy processing, it remains endemic in parts of the Mediterranean, Middle East, Latin America, and Asia.<sup>25</sup>

## SYSTEMIC MANIFESTATIONS

Brucellosis is a multisystemic disease with both acute (<8 weeks) and chronic (≥8 weeks) manifestations. The incubation period is about 3 weeks. Common presenting symptoms are fever, chills, sweating, myalgia, anorexia, splenomegaly, and diffuse lymphadenopathy. Specific organ systems such as central nervous system, heart, and eye may be involved in 10%–15% cases.<sup>26</sup>

## OCULAR MANIFESTATIONS

As with systemic involvement, brucellosis can have wide range of ocular manifestations. It can be seen in up to a quarter of patients with systemic disease, mostly in the chronic phase of the disease. The most common ocular manifestations are conjunctivitis, anterior uveitis, choroiditis/posterior uveitis, dacryoadenitis, endophthalmitis, and optic neuritis.<sup>27</sup>

## DIAGNOSIS

The diagnosis is based on appropriate history, presence of systemic disease supported by positive serological test (*Brucella* serum agglutination test), and/or positive blood culture (in highly enriched media).

## TREATMENT

Treatment of acute brucellosis requires multidrug treatment with oral doxycycline 100 mg twice daily for 6 weeks along with oral rifampin for 6

weeks or intramuscular streptomycin for 2–3 weeks (preferable). Chronic brucellosis requires antimicrobial therapy with all the three drugs.

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# Bartonella-Related Infectious Uveitis (Cat Scratch Disease) and Whipple's Disease

7.8

Robert C. Wang

**Definition:** Cat scratch disease and Whipple's disease are clinical syndromes characterized by ocular inflammation due to systemic infection from bacillus organisms.

## Key Features

### Cat Scratch Disease

- Most commonly presents as a unilateral granulomatous conjunctivitis with regional lymphadenopathy.
- Typical intraocular presentation includes discrete white retinal or choroidal lesions and the more easily recognizable neuroretinitis with macular star formation.
- More sight-threatening presentation includes retinal vasculitis and vascular occlusions.
- Typically self-limited disease, but more severe presentation may require treatment.

### Whipple's Disease

- Clinical syndrome with gastrointestinal symptoms including diarrhea and weight loss.
- Rare ocular manifestations presenting as a retinal vasculitis and panuveitis, with or without systemic symptoms.
- Multifocal choroiditis and retinitis can be seen as well as retinal vascular occlusions.
- Typically requires antibiotic therapy for up to one year as relapses commonly occur.

## INTRODUCTION

Cat scratch disease has become an increasingly recognized cause of uveitis that has a clinical spectrum ranging from a mild self-limiting disease with neuroretinitis and macular star formation to severe vision loss from retinal vasculitis. Whipple's disease is a less frequent cause of ocular inflammation that is mainly associated with gastrointestinal symptoms including diarrhea. Typical ocular presentation includes panuveitis and vasculitis.

## CAT SCRATCH DISEASE: *BARTONELLA HENSELAE*-ASSOCIATED UVEITIS

## EPIDEMIOLOGY AND PATHOGENESIS

*Bartonella* species are a Gram-negative bacillus that has been associated with a clinical syndrome of a self-limited lymphadenopathy related to a cat scratch or bite or transmission through vectors such as fleas or flies. The causative organism of cat scratch disease (CSD) has been identified as *Bartonella henselae*. The disease has been reported to affect 22,000 patients in the United States but has a worldwide distribution, commonly affecting children and young adults.<sup>1</sup> There is a higher prevalence in the autumn and winter during the seasonal breeding of the domestic cat.

In humans, infection can be relatively asymptomatic or produce symptoms such as fever, malaise, fatigue, and lymphadenopathy. In 25%–60% of cases, an erythematous papule occurs at the site of inoculation with systemic symptoms occurring in the following days to weeks. Typically,

symptoms are self-limited. However, more serious complications can occur, such as splenomegaly, splenic abscess, encephalopathy, granulomatous hepatitis, pneumonia, bacillary angiomatous, and osteomyelitis.<sup>2</sup> Ocular manifestations typically occur following systemic symptoms.

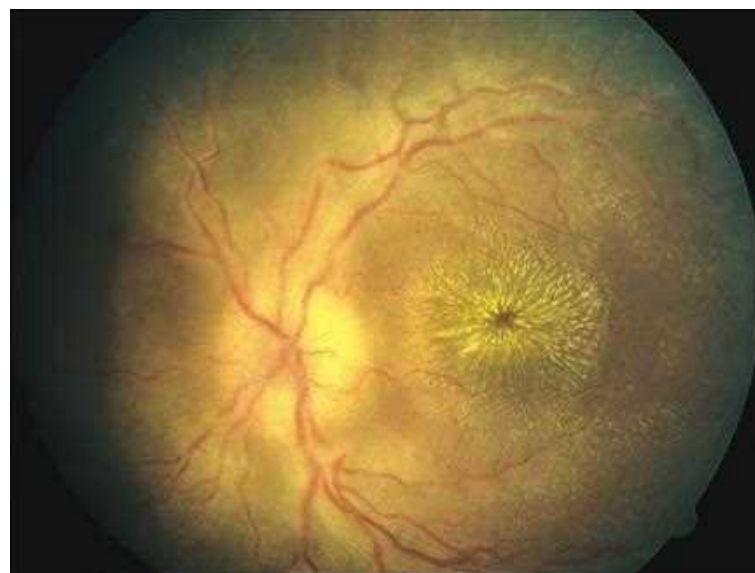
Cat fleas have been identified as a vector for CSD. Other vectors such ticks and biting flies have recently been identified as new potential sources of transmission. Although cats are the main reservoir for *Bartonella henselae*, dogs can be infected and can become accidental hosts. Human infections occur from direct inoculation of open wounds or mucous membranes through scratching or licking.

## OCULAR MANIFESTATIONS

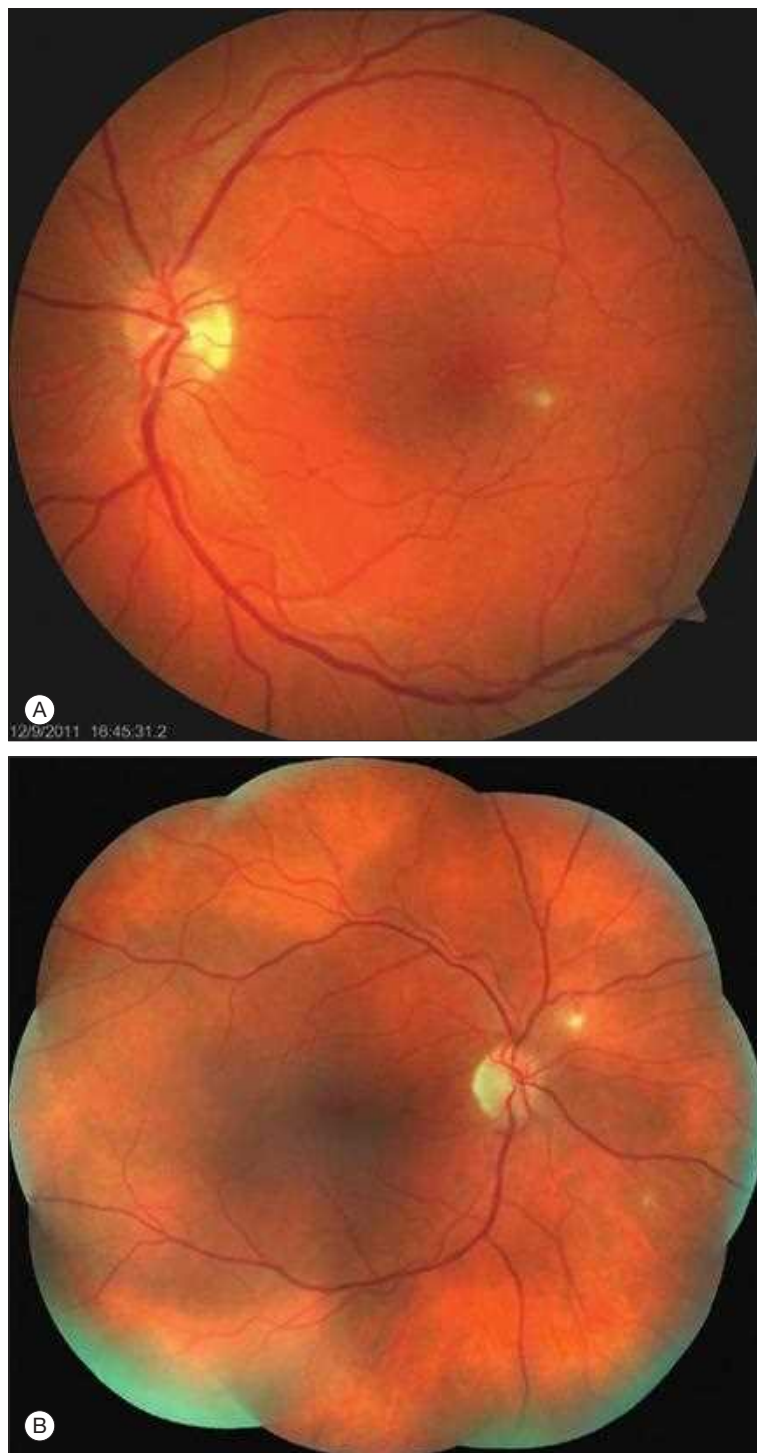
Parinaud's oculoglandular syndrome is the most common presentation of *Bartonella* infection.<sup>3</sup> Patients typically present with a unilateral granulomatous conjunctivitis and regional lymphadenopathy. Patients demonstrate symptoms of unilateral conjunctiva injection, foreign body sensation, and epiphora. Preauricular, submandibular, or cervical lymph nodes are typically affected. Conjunctival epithelium ulcerations and necrosis are commonly seen, producing a purulent discharge.<sup>4</sup>

More sight-threatening presentations of CSD include optic nerve swelling with a complete or partial macular star formation (Fig. 7.8.1). In 1984 Gass termed this appearance *neuroretinitis* to distinguish this entity from primary inflammation of the optic nerve head.<sup>4</sup> Vascular leakage from the optic nerve head results in macular star formation, which may persist for months despite resolution of the neuroretinitis. Additionally, an afferent pupillary defect is typically present in unilateral cases, and a cecentral scotoma is present on visual field testing.

Patients typically present with unilateral decline in vision (20/80) with systemic symptoms present in 67%.<sup>5</sup> Ocular exam typically demonstrates a mild vitritis, with a multifocal retinitis and choroiditis as one of the most common posterior segment findings (Fig. 7.8.2).<sup>3,5</sup> Neuroretinitis is the



**Fig. 7.8.1 Neuroretinitis With Complete Macular Star Formation.** (Courtesy Ehud Zamir MD, the Royal Victorian Eye and Ear Hospital, Melbourne, Australia.)



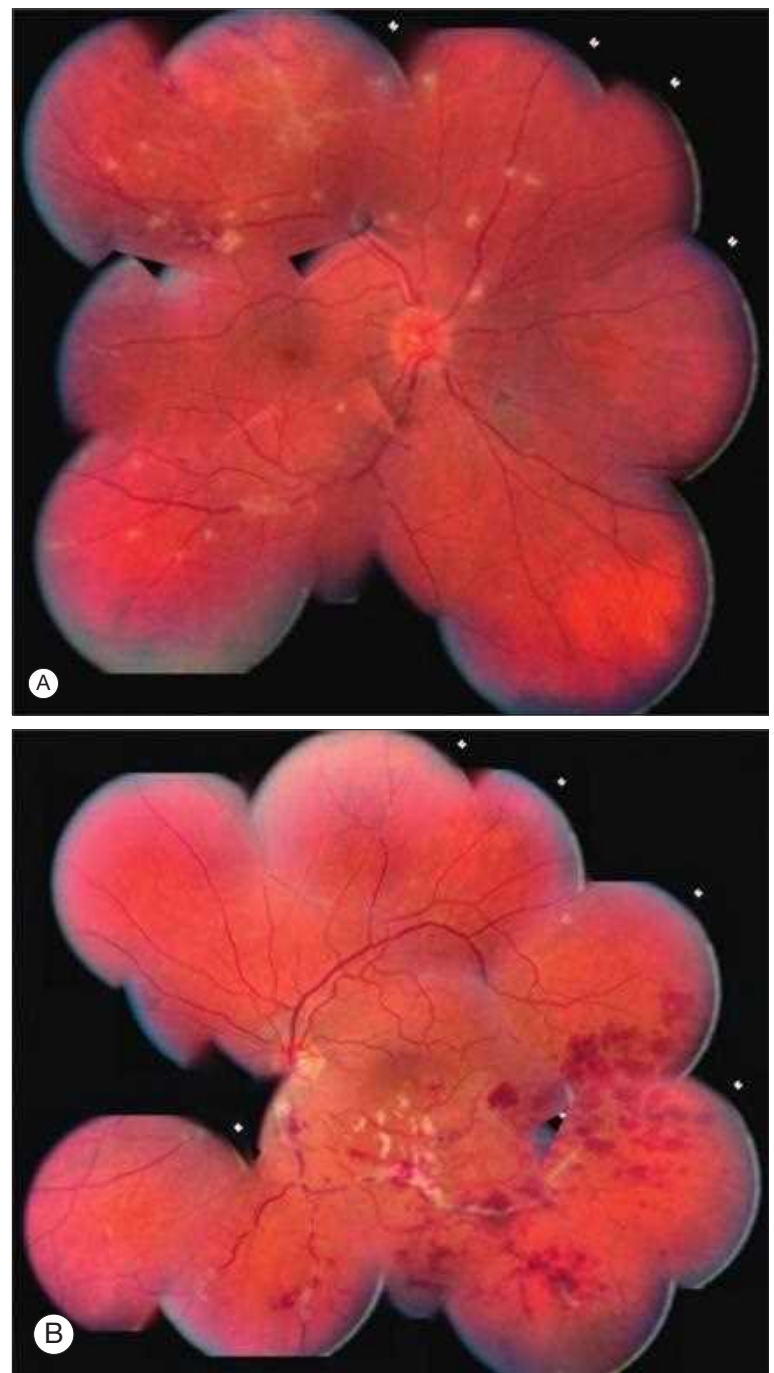
**Fig. 7.8.2 Discrete "White" Retinal Lesions in Cat Scratch Disease.** (Courtesy Chris Fuller MD, Sam Leiji, COA Berkeley Eye, Houston, Texas.)

most recognizable finding but presents less frequently than the retinal and choroidal lesions. It can present from the overt to a very mild blurring of the disc margins. Macular star formation is seen in approximately 43% of cases.<sup>5</sup> Though macular star formation can be seen at the time of diagnosis, formation can occur 2–4 weeks following the initial onset of neuroretinitis.

Less common posterior segment findings include branch retinal artery and vein occlusion and local serous retinal detachments that can mimic Vogt–Koyanagi–Hamada disease (Fig. 7.8.3).<sup>6</sup> In addition, focal lesions are occasionally associated with angiomas-like proliferation of capillaries.<sup>7</sup> HIV-positive patients can present with a subretinal mass associated with an abnormal vascular network.<sup>8</sup>

## DIAGNOSIS

Diagnosis of CSD is straightforward in the presence of easily recognizable neuroretinitis and macular star formation. Additionally, recognition of isolated discrete white retinal and chorioretinal lesions can lead to a rapid diagnosis in the absence of a macular star or neuroretinitis.



**Fig. 7.8.3 Less Commonly Seen Severe Retinal Vasculitis and Vascular Occlusion in Cat Scratch Disease.** Composite photo. (A) Right eye, (B) left eye.

Typical history of prodromal symptoms, lymphadenopathy, and cat exposure help strengthen the diagnosis, especially when presenting young adults or children.<sup>7</sup> Serological evaluation for anti-*Bartonella henselae* antibodies can aid in the diagnosis with sensitivity and specificity of 62% and 100%, respectively.<sup>9</sup> Occasionally, *Bartonella* bacilli can be isolated from lymph node biopsy in areas of lymphadenopathy.<sup>10</sup>

## IMAGING

Optical coherence tomography (OCT) images can demonstrate hyperreflective inner retina layers in the areas of white retinal lesions with shadowing of the posterior layers and choroid. Intraretinal and subretinal fluid can be seen along with exudates in the area of macular star formation. Fluorescein angiogram can demonstrate hyperfluorescence and leakage of the optic nerve and of any retinal lesions.<sup>11</sup>

## DIFFERENTIAL DIAGNOSIS

Etiologies that must be differentiated include other causes of optic nerve head swelling such as optic neuritis and sarcoid papillitis. Also, infectious



etiologies such as syphilitic perineuritis and (rarely) toxoplasmosis can produce similar clinical appearance. Pseudotumor cerebri can mimic the less frequent appearance of bilateral CSD. However, optic nerve vessels typically demonstrate obscuring of the vessels at the disc margin in pseudotumor and not in neuroretinitis. Finally, diabetic retinopathy with macular star formation can appear similar.

## **PATHOLOGY**

In animal models, *Bartonella* organisms typically invade and colonize mature erythrocytes. However, endothelial cells are also a target for *Bartonella* organisms and appear to be the target host cells in humans. Endothelial invasion leads to a proinflammatory response and formation of vasoproliferative tumors.<sup>12</sup>

In animal models, gamma-interferon activated macrophages have been documented to aid in clearing of *B. henselae* and may explain the self-limited nature of the infection.<sup>13</sup>

## **TREATMENT**

CSD tends to be a self-limiting disease. Usually no treatment is recommended, but antibiotic treatment has led to dramatic clinical responses in immunocompromised patients.<sup>3</sup> However, a course of antibiotics should be initiated in patients with severe ocular or systemic complications. Doxycycline (100 mg twice daily) tends to be the mainstay of therapy. It has good intraocular and central nervous system (CNS) penetration. In patients 8–12 years of age, erythromycin (30–50 mg/kg/day divided four times a day) is recommended due to the risk of tooth decoloration. Gentamycin, azithromycin, and rifampicin have also been used for systemic CSD.<sup>1</sup> Azithromycin has been observed to cause rapid resolution of lymphadenopathy.<sup>14</sup> However, the distribution of azithromycin into the eye appears higher for conjunctival tissue but lower in intraocular fluids.

## **WHIPPLE'S DISEASE: TROPHYRYMA WHIPPLEI-ASSOCIATED UVEITIS**

### **EPIDEMIOLOGY AND PATHOGENESIS**

Whipple's disease is a rare multisystemic disease caused by *Tropheryma whippelii*, a Gram-positive *Actinobacteria*. *Actinobacteria* are found in soil and water. Similar to fungi, they are important for decomposing organic material that are then taken up by plants and other living material. The classic clinical syndrome of a migratory arthritis, diarrhea, and weight loss can be seen, but symptoms vary widely. The disease most commonly affects white men in the fourth to sixth decades with an occupational exposure to soil or animals, although it has been reported to occur at any age.<sup>15</sup>

Arthritis is typically the first symptom experienced. The arthritis is migratory, occurring in 80% of patients. Gastrointestinal symptoms occur in approximately 75% of cases, producing abdominal pain with diarrhea, steatorrhea, and intestinal malabsorption. Weight loss is also common, with pitting edema due to protein-losing enteropathy. However, when gastrointestinal symptoms are not present, diagnosis can be difficult and can often be delayed for several years. Cardiac involvement can result in secondary heart failure or valvular regurgitation. Progression can lead to more serious CNS involvement producing dementia, coma, and seizures. Cranial nerves can also be involved, producing ophthalmoplegia and nystagmus.<sup>15</sup> Low-grade fever is present in 50% of cases. If left untreated, Whipple's disease can be ultimately fatal.

### **OCULAR MANIFESTATIONS**

Ocular involvement is estimated to occur in less than 5% of patients with Whipple's disease.<sup>16</sup> In most reported cases of Whipple's disease, ocular involvement typically is secondary to CNS involvement. These include nystagmus, oculomasticatory myorhythmia, and a progressive supranuclear-like palsy.

Inflammation can be bilateral with panuveitis and retinal vasculitis. Typically, both anterior uveitis and moderate vitritis are present. Rarely, unique white granular crystalline deposits can be seen at the pupillary margin and in the cornea.<sup>17</sup> Diffuse chorioretinal inflammation has also been observed. Diffuse vasculitis, typically in the perifoveal and midperipheral areas, are accompanied by hemorrhages and retinal vascular occlusions.<sup>18</sup> Optic nerve involvement can occur with prolonged involvement

leading to optic atrophy. A birdshot-like pattern of inflammation can also be seen.

## **DIAGNOSIS**

Diagnosis of Whipple's disease can be difficult in the absence of systemic signs. Duodenal biopsy remains the gold standard for diagnosis of Whipple's disease. The presence of strongly positive periodic acid-Schiff (PAS) bacillus within macrophages is virtually pathognomonic for the disease.<sup>16</sup> However, polymerase chain reaction (PCR) analysis of peripheral blood or vitreous samples has increasingly become an accurate and rapid form of identification.<sup>19</sup> Early diagnosis through PCR analysis of a vitreous biopsy may prevent the progression to more serious CNS involvement.

## **DIFFERENTIAL DIAGNOSIS**

Differential diagnosis includes entities that have multisystemic involvement and retinal vasculitis. These include systemic lupus erythematosus (SLE), polyarteritis nodosa (PAN), and Behçet's disease. Unlike Whipple's disease, SLE rarely produces intestinal malabsorption. Similarly, SLE and PAN tend to present with more vasculitic signs, with gastrointestinal hemorrhages or ischemia. Oral and genital ulcers seen in patients with Behçet's disease differentiate patients from Whipple's disease. Sarcoidosis can present with retinal vasculitis and ocular inflammation, but severe gastrointestinal findings are less frequently seen. In immunocompromised patients, mycobacterium avium intracellulare (MAI) can produce a similar systemic symptoms and histological picture (PAS positive). However, MAI tends to produce a multifocal choroiditis rather than a primary vasculitis.

## **PATHOLOGY**

*Tropheryma whippelii* has been difficult to culture, and no animal models of the infection currently exist. However, PAS-positive rod-shaped bacilli have been identified within macrophages and outside of cells in intestinal villi specimens.

## **TREATMENT**

Whipple's disease is a chronic recrudescence disease that can be fatal. Intestinal symptoms typically resolve within 1–3 months with treatment. However, relapses can occur in up to one-third of patients, requiring prolonged treatment for up to one year.<sup>20</sup> With ocular involvement, drugs that cross the blood-brain barrier are preferred. Double strength trimethoprim-sulfamethoxazole or doxycycline (100 mg twice daily) are the preferred first-line therapy. In sulfonamide-allergic patients, ceftriaxone or chloramphenicol can be tried. Retinal vasculitis typically responds to antibiotic treatment.<sup>18</sup> However, antibiotic treatment seldom resolves neurological signs, as they frequently become permanent. Doxycycline is typically combined with hydroxychloroquine (600 mg/day for 12 months) in patients with severe neurological symptoms, with doxycycline continued for life.

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Infectious Endophthalmitis

Damien C. Rodger, Yevgeniy (Eugene) Shildkrot, Dean Elliott

7.9

**Definition:** Endophthalmitis is caused by infiltration of intraocular structures by an infectious agent, with associated inflammatory reaction involving the anterior and/or posterior segments of the eye.

Key Features

- Decreased vision.
- Pain.
- Conjunctival hyperemia.
- Intraocular inflammation, usually with hypopyon.

Associated Features

- Recent surgery.
- Trauma.
- Immunosuppression.
- Diabetes.
- Systemic infection.
- Indwelling catheters.
- Intravenous drug use.

INTRODUCTION

Infectious endophthalmitis is a potentially devastating condition involving the internal structures of the eye. It is one of the most feared complications of cataract extraction and other intraocular surgeries. Rarely, it can occur endogenously from a systemic nidus of infection.

EPIDEMIOLOGY AND RISK FACTORS

The pathogenic agents involved in endophthalmitis as well as the sources of infection are myriad. The following section and Table 79.1 summarize the common etiological associations and mimicking conditions.

TABLE 79.1 Categories of Endophthalmitis With Corresponding Mimicking Conditions

Type of Endophthamitis	Association	Mimicking Conditions
• Exogenous	• Penetrating surgery (cataract extraction, penetrating keratoplasty, glaucoma filtration surgery, vitreoretinal procedures)	• Toxic anterior segment syndrome
		• Postoperative inflammation
		• Retained lens material
• Endogenous	• Intravitreal injections	• Transient inflammation
	• Ocular trauma	• Chalcosis (occult intraocular foreign body)
	• Bacteremia (intravenous drug use, septicemia, endocarditis, liver abscess, indwelling catheters)	• Intraocular lymphoma
	• Fungemia	• Diffuse retinoblastoma (children)
	• Parasites	• Uveitis (panuveitis, intermediate, or posterior uveitis)
		• Medication-induced inflammation (e.g., rifabutin)

Endophthalmitis is classified on the basis of the source of the infection, as *exogenous*, which is the most common subtype, or *endogenous*. The avascular densely packed collagenous matrix of the cornea and sclera serves as a potent barrier against infectious infiltration in normal eyes. Violation of these structures, typically by surgery or trauma, makes the eye susceptible to the entry of pathogenic organisms and may lead to exogenous endophthalmitis. Bacteria are often the causative agents in these cases. There are typically no associated systemic findings, such as fever and minimal, if any, peripheral leukocytosis.<sup>1</sup>

Endogenous endophthalmitis occurs in otherwise stable eyes in association with transient or persistent bacteremia or fungemia. It is observed most frequently in immunosuppressed patients and intravenous drug users and less commonly in patients with cardiac valvular disease and persistent sites of infection elsewhere in the body and in those undergoing dental work. Fungal infections are most common, but a third of patients will present with bacterial endophthalmitis, often caused by Gram-negative species.<sup>2,3</sup>

Diabetes is the most frequent comorbidity in patients presenting with endophthalmitis of various causes and may be associated with an increased incidence of Gram-negative<sup>4</sup> and Gram-positive coagulase negative organisms.<sup>5</sup> Diabetes appears to increase the risk and possibly even the severity of endophthalmitis in patients undergoing glaucoma filtration procedures, vitrectomy, and cataract surgery and in patients with systemic *Klebsiella* infection.<sup>4,6–8</sup>

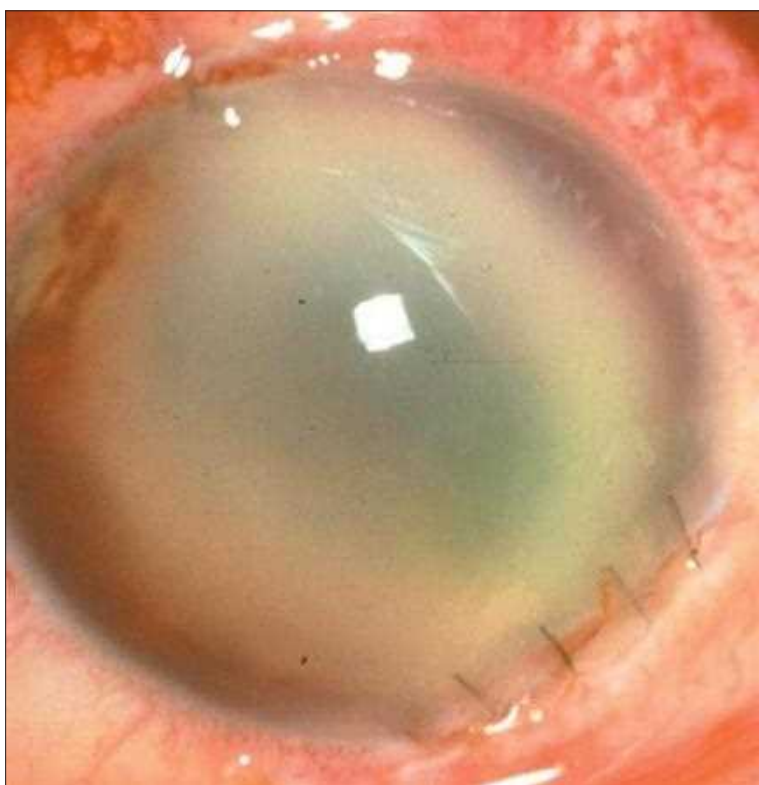
Exogenous Endophthalmitis

Trauma

The risk of endophthalmitis after open globe injuries (defined as a full-thickness defect of the cornea and/or sclera) in the Western world ranges from 4.2% to 7%.<sup>9–12</sup> In contrast, endophthalmitis is exceedingly rare after closed-globe injuries. Staphylococcal species are the most common causative agents in trauma-related endophthalmitis, and some species, such as *Bacillus cereus*, are seen almost exclusively in the context of trauma.<sup>13</sup> The source of the infection is typically the penetrating material, although the infection may rarely extend from contiguous sinuses in cases with orbital wall fracture. The rate of infection rises dramatically to 10%–15% when an intraocular foreign body is present and if the repair is delayed beyond 24 hours of the injury.<sup>9,11,12,14,15</sup> Even without overt infection, prophylactic intravitreal antibiotics should be considered at the time of the foreign body removal because in nearly a quarter of patients, cultures of the intraocular material will be positive for bacteria, and the risk of intravitreal antibiotics is generally low. In rural settings, where organic material contamination is common, endophthalmitis following penetrating ocular trauma reaches rates as high as 30%, with *Bacillus* species isolated in 46% of cases (Fig. 79.1) and polymicrobial isolates in 42%.<sup>16</sup> Of note, however, among patients within military combat zones, one study reported no cases of endophthalmitis after high-velocity projectile injury with intraocular foreign body despite delayed foreign body removal,<sup>17</sup> possibly a result of autosterilization from thermal heating<sup>18</sup>

Cataract Surgery

Postcataract endophthalmitis is categorized on the basis of the time to onset after surgery, as acute (within 6 weeks) or delayed. The incidence of endophthalmitis after cataract extraction is reported to be 0.04%–0.15%.<sup>19–23</sup> Some authors suggest an increase in the incidence of endophthalmitis beginning in the late 1990s/2000, in parallel with the increased use of clear corneal cataract wound placement.<sup>23,24</sup> Analysis of the large Medicare cataract databases, however, does not show a significant increase in the rate of endophthalmitis during 1994–2001 (0.2%) and 2003–2004 (0.1%).<sup>19,24</sup>



**Fig. 7.9.1** Endophthalmitis with corneal ring abscess caused by *Bacillus cereus* after penetrating trauma with a metal object.

Postcataract endophthalmitis is typically associated with defects in the surgical wound and violation of the posterior lens capsule, which can provide a route of entry for the infectious agents.<sup>25</sup> The patient's own periocular flora is the source of infection in the majority of cases of endophthalmitis. In 68%–82% of postcataract endophthalmitis cases, an identical genetic or molecular signature was present in the vitreous isolates and the commensal bacteria occupying the patient's conjunctiva, eyelids, or nose.<sup>26,27</sup> The Endophthalmitis Vitrectomy Study (EVS) was a major prospective randomized clinical trial analyzing the treatment of acute postoperative endophthalmitis, and it identified coagulase negative *Staphylococcus* in 70% of cases<sup>28</sup>; less common were *Staphylococcus aureus* in nearly 10%, *Streptococcus* species in 9%, *Enterococcus* in 2%, and Gram-negative organisms in 6%.<sup>28</sup>

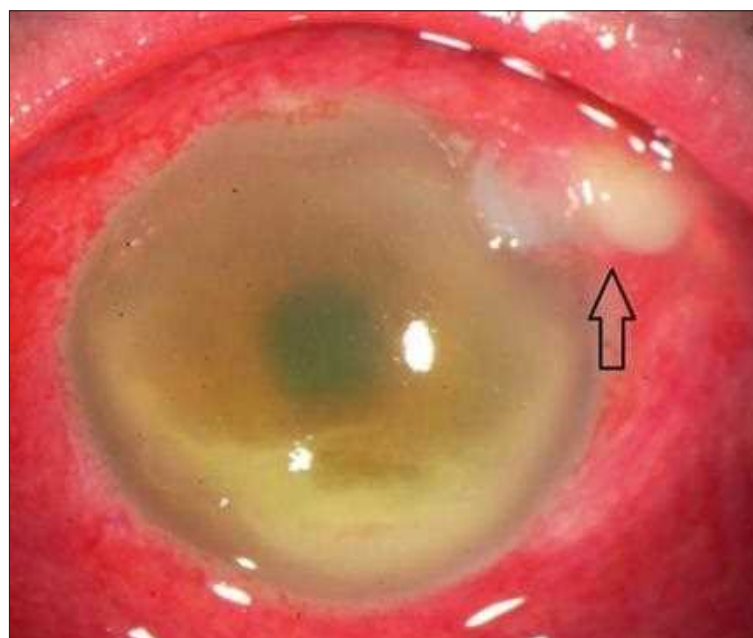
In delayed-onset endophthalmitis, *Propionibacterium acnes* is the most commonly implicated pathogen, accounting for nearly 40% of isolates.<sup>29,30</sup> It has a subtle presentation and indolent course.

In pediatric patients undergoing intraocular surgery, the risk of endophthalmitis is estimated to be 0.07%–0.16%, with 82% of cases presenting by postoperative day 3.<sup>31,32</sup> Pediatric endophthalmitis is typically caused by Gram-positive bacteria; 47% of cases are associated with nasolacrimal duct obstruction or upper airway infection.<sup>31</sup>

Among the various antiseptics studied, 5% povidone iodine solution was the only perioperative intervention that was able to reduce the incidence of endophthalmitis.<sup>33</sup> A major randomized prospective trial conducted by the European Society of Cataract and Refractive Surgeons (ESCRS) suggested a benefit of using intracameral cefuroxime for reducing postcataract surgery endophthalmitis.<sup>34</sup> However, the results are controversial because the observed endophthalmitis incidence of 0.35% is significantly higher than previously described.<sup>34</sup> In addition, many surgeons routinely use intracameral vancomycin at the end of cataract surgery; however, this has been recently associated with hemorrhagic occlusive retinal vasculitis, a rare but devastating disease.<sup>35</sup> Short-term use of preoperative antibiotics may be beneficial, especially in patients with significant blepharitis and ocular surface disease.

### Penetrating Corneal Surgery

Corneal transplantation with penetrating keratoplasty appears to have a relatively high risk of infection compared with most other intraocular procedures. This probably results from the large circumferential incision and the use of donor tissue. Endophthalmitis occurs in 0.2%–0.4% of cases with a decline in incidence over the past decade.<sup>36</sup> The incidence of endophthalmitis following the implantation of a permanent keratoprosthesis



**Fig. 7.9.2** Endophthalmitis After Glaucoma Filtration Surgery. Note the white bleb filled with purulent material (arrow), conjunctival injection, corneal edema, and a hypopyon.

is higher, ranging from 5.4% to 7%, unless long-term postoperative topical vancomycin drops are used.<sup>37,38</sup> The causative agents following both the penetrating keratoplasty and keratoprosthesis surgeries are predominantly Gram-positive cocci, including *Streptococcus* and *Staphylococcus*, but Gram-negative organisms account for nearly 20% of cases.<sup>38,39</sup>

The overall frequency of endophthalmitis in corneal surgery is expected to decrease significantly with expanding indications for partial corneal transplantation utilizing smaller incisions, including Descemet's membrane stripping endothelial keratoplasty.

### Glaucoma Filtration Procedures

Glaucoma filtration surgery is associated with endophthalmitis in 2.1%–2.6% of cases.<sup>40,41</sup> Endophthalmitis following these procedures, unlike postcataract infections, tends to be delayed and is often associated with prior episodes of blebitis (Fig. 7.9.2).<sup>7</sup> Diabetes; use of antimetabolites, such as 5-fluorouracil and mitomycin; and inferior bleb location all increase the risk and hasten the onset of endophthalmitis.<sup>7,40–42</sup> The risk of endophthalmitis appears lower with fornix-based flaps. Delayed onset bleb-related endophthalmitis is associated most commonly with *Streptococcus* species (25%) and Gram-negative organisms, particularly *Haemophilus influenzae* (18%).<sup>41,43</sup>

### Vitrectomy

With the increasing shift to small-gauge sutureless surgery, there has been a concern regarding the increased incidence of postvitrectomy endophthalmitis. Although initial reports demonstrated an increased risk in patients undergoing 25-gauge surgery,<sup>44,45</sup> subsequent studies failed to confirm these findings, probably because of the increased use of conjunctival displacement, biplanar shelved incisions for cannula placement, and judicious use of sutures, when necessary. Recent studies estimate the incidence of endophthalmitis as 0.02%–0.04% in 20-gauge, 0.03% in 23-gauge, and 0.01%–0.02% in 25-gauge vitrectomies.<sup>44,46,47</sup> In addition, the use of tamponade agents, such as gas or oil, may further lower the risk.<sup>48</sup> *Staphylococcus* species account for more than 50% of cases.<sup>49</sup>

### Intravitreal Injections

Intravitreal injections of triamcinolone for various causes, although they can cause a sterile inflammatory response easily confused for infectious endophthalmitis, also have a 0.87% incidence of infectious endophthalmitis,<sup>50</sup> possibly as a result of inhibition of immune function against inadvertently introduced pathogenic agents.<sup>51</sup> Accordingly, the intravitreal injections of anti-vascular endothelial growth factor medications, including ranibizumab, are associated with significantly lower endophthalmitis rates of 0.02%–0.08%.<sup>52–54</sup> Patients with diabetes may, however, be at higher risk. Most of the cases are caused by *Streptococcus* or *Staphylococcus* species representing the commensal flora of ocular adnexa and oropharynx.<sup>53,54</sup>





**Fig. 7.9.3 Gross Specimen of Coagulation Necrosis With Extensive Tissue Destruction.** Note the optic (translucent arrow) and the haptic (black arrow) of an intraocular lens.

The risk of infection may be lessened by decreasing the oropharyngeal droplet transmission at the time of the injection.<sup>55</sup>

Parceling single medications, such as bevacizumab, into multiple intravitreal injections by compounding pharmacies can theoretically increase the incidence of infection and has been associated with local outbreaks of endophthalmitis.<sup>56</sup> Recent data have shown, however, that endophthalmitis rates with bevacizumab, ranibizumab, and aflibercept intravitreal injections are statistically no different.<sup>57</sup> The use of postinjection antibiotics does not appear to decrease the frequency of subsequent endophthalmitis but, in fact, may lead to selection of drug-resistant bacteria in the nasopharynx and on the ocular surface.<sup>58</sup>

### Endogenous Endophthalmitis

Hematogenous spread of a bacterial infection is often seen in patients with transient or persistent bacteremia from various causes. Endogenous endophthalmitis is caused more commonly by Gram-positive organisms in the Western world, while Gram-negative organisms account for as many as 70% of isolates from eyes with endogenous endophthalmitis in Asian countries.<sup>59,60</sup> A common Gram-negative pathogen is the K1 subtype of *Klebsiella pneumoniae*, which is associated with concurrent hepatobiliary infections in 48%–77% of cases.<sup>8,59,61,62</sup> Fungal dissemination of *Candida albicans*, *Aspergillus* species, and other fungi may also lead to endogenous endophthalmitis, usually in patients with concomitant fungemia, underlining the importance of dilated funduscopic examinations in patients with positive fungal blood culture results.

## PATHOLOGY AND PATHOGENESIS

The clinical course of endophthalmitis is associated with intravitreal elaboration of inflammatory cytokines, including tumor necrosis factor- $\alpha$ , interleukin-1 $\beta$ , and interferon- $\gamma$ .<sup>63</sup> This results in neutrophil aggregation leading to suppurative or nonsuppurative inflammation and a variable degree of tissue necrosis (Fig. 7.9.3). Fas ligand, which functions in retinal apoptotic pathways, appears critical in preventing *S. aureus* endophthalmitis following experimental inoculation, and the complement pathway does not appear to have an important role.<sup>64</sup>

## CLINICAL PRESENTATION AND EVALUATION

Acute endophthalmitis is an ophthalmological emergency requiring a high degree of suspicion leading to prompt recognition, diagnosis, and therapy. A thorough history should be obtained, with particular emphasis on identifying possible causes of immunosuppression, a history of trauma, and medication allergy status. An indolent course and impaired immune function can lead to severe infections that can be easily misdiagnosed as uveitis. The examination of the anterior segment should include a Seidel test for occult leakage of a wound (Fig. 7.9.4A–C), evaluation for the presence of a vitreous wick to the wound (Fig. 7.9.5) or the presence of a white plaque on the intraocular lens or capsule. The view of the posterior segment is often limited, and ultrasonographic evaluation may be necessary to document the baseline presence of tractional membranes or retinal detachment. The morphological features of any infectious nidus or abscess can also aid in diagnosis, as fungal lesions often project from the retina into the vitreous

cavity in a mushroom-like configuration (Fig. 7.9.6A, B), whereas bacterial abscesses, such as those caused by *Klebsiella*, may appear subretinally (see Fig. 7.9.6C). Unless a clear etiology is present, a systemic evaluation for sources of infection may be prudent, including blood cultures, chest radiography, liver ultrasonography, and cardiac ultrasonography, to look for valvular vegetations or a patent foramen ovale.

The presenting symptoms and signs of endophthalmitis are variable. In the EVS, 98% of patients with acute endophthalmitis presented with  $\geq 1$  of the four classic symptoms, including decreased vision (93%), conjunctival injection (81%), pain (75%), and lid swelling (33%) (Fig. 7.9.7A).<sup>65</sup> These findings are not universal, however, as pain and hypopyon were found to be absent in one quarter of patients with acute endophthalmitis.<sup>65</sup> Hypopyon can sometimes be very small (see Fig. 7.9.7B). In patients with delayed endophthalmitis, the presenting features are even more variable and often subtle. *Propionibacterium acnes* endophthalmitis can present with mild iritis, pigmented keratic precipitates in the absence of severe pain, or visual decline.<sup>66</sup> Hypopyon is seen in fewer than half of cases of delayed endophthalmitis.<sup>30</sup> The symptoms may be precipitated or exacerbated by laser capsulotomy. On examination, the most common findings are vitritis, a white plaque on the posterior capsule or the intraocular lens (Fig. 7.9.8), beaded fibrin strands, hypopyon, granulomatous-appearing keratic precipitates, and cystoid macular edema.<sup>30,66</sup>

## MICROBIOLOGICAL TESTING

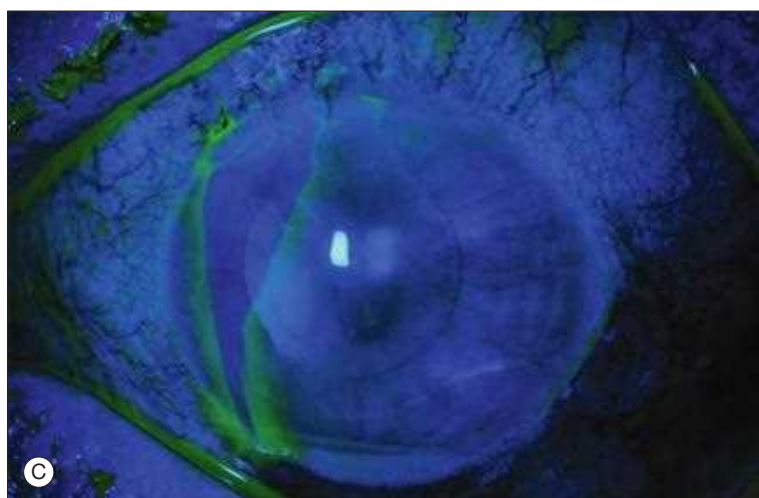
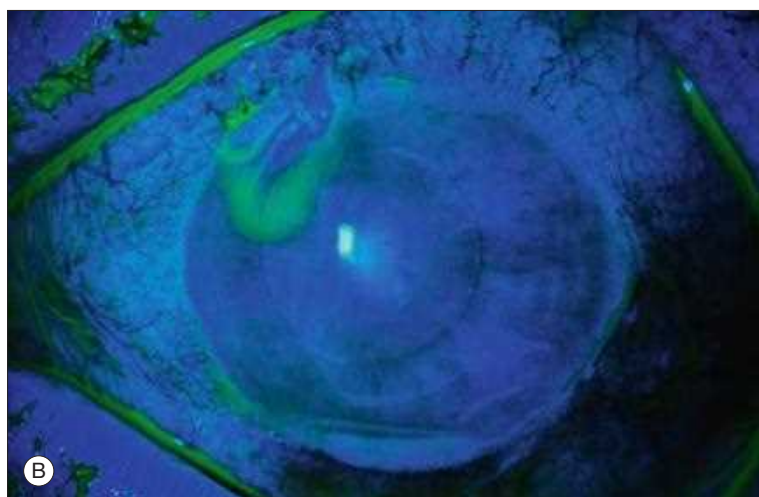
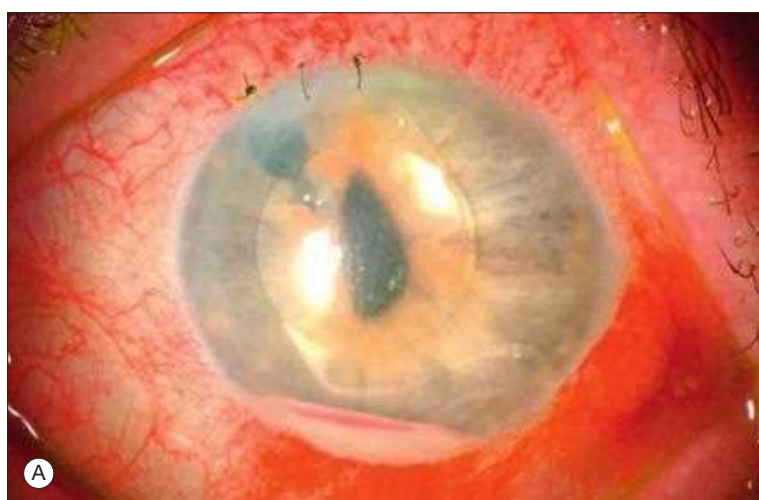
Gram stain and culture are central to determining the ultimate diagnosis and are a critical step in the management; however, they rarely influence the choice of antibiotics and should be obtained typically concomitantly with initial presumptive treatment. The cultures should include aerobic, anaerobic, and fungal media. The diagnostic material is usually obtained in the office by aqueous paracentesis and vitreous aspirate or in the operating room via pars plana vitrectomy. Portable vitrectomy machines enable in-office emergent vitrectomy, although this is rarely performed. The EVS did not demonstrate any difference in the microbiological yield between needle vitreous aspiration and mechanized vitreous biopsy, with successful identification of the causative organism in 41%–42% on initial Gram stain and 66%–69% on culture.<sup>67,68</sup> Culture of both the undiluted vitreous biopsy specimen and the vitreous cassette can further increase the yield after vitrectomy.<sup>68,69</sup>

When *P. acnes* is suspected as the causative agent, the microbiology laboratory should be instructed to incubate the culture for at least 14 days because of the slow growth rate.<sup>66</sup>

Newer techniques, such as DNA microanalysis and polymerase chain reaction (PCR) testing, can increase the diagnostic yield by 20% and provide rapid results, often within 24 hours, with only small amounts of vitreous being required.<sup>70,71</sup> This is of particular benefit in suspected fungal infections, where it often takes many days for fungal cultures to result positively.

## DIFFERENTIAL DIAGNOSIS

See Table 79.1 for the mimicking conditions that should be considered in the workup of endophthalmitis in various clinical scenarios.



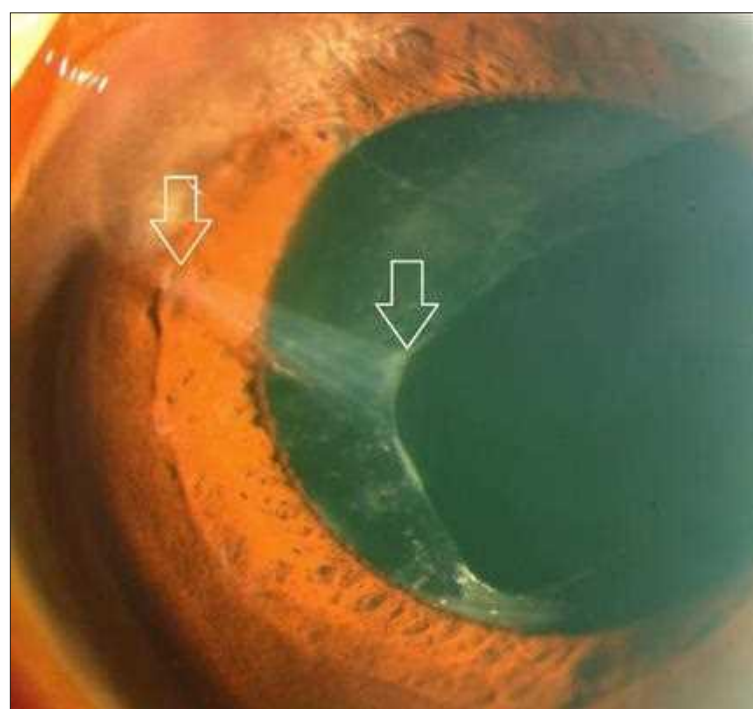
**Fig. 7.9.4** Endophthalmitis following cataract surgery with incomplete wound closure (A) and wound leakage on Seidel testing (B–C).

## TREATMENT

The treatment of endophthalmitis is dependent on the etiology of the inciting agent. The treatment may include intravitreal antibiotics, surgery, and/or systemic therapy. The algorithm for the management of acute postcataract endophthalmitis is dictated to some extent by the findings of the EVS (see below).

### Medications

Various agents may be considered for intravitreal injection (Box 7.9.1). The most commonly used medications in suspected bacterial endophthalmitis include vancomycin and ceftazidime. Intravitreal vancomycin provides broad coverage for over 99% of Gram-positive organisms, and ceftazidime is effective against 100% of Gram-negative bacteria observed in



**Fig. 7.9.5** Vitreous wick (arrow) extending to the corneal paracentesis.

postoperative endophthalmitis.<sup>72</sup> Second-line agents can be considered in patients with documented medication allergies, although their efficacy and potential for complications should be balanced against the severity of the stated allergy to a first-line medication. Intravitreal gentamycin should be avoided because of the well-known association with macular infarction. Other aminoglycosides, including amikacin and tobramycin, also have a well-documented potential for macular toxicity.<sup>73</sup> Furthermore, in recent years, there has been increasing frequency of resistance to the medications used for the prophylaxis of endophthalmitis, leading to reduced efficacy for the treatment of the infection. Resistance to ciprofloxacin and ceftazolin was observed in nearly 40% of the bacterial isolates from eyes with postcataract endophthalmitis.<sup>72</sup> Gram-negative bacteria, particularly *Pseudomonas*, although fortunately rare as a cause of endophthalmitis, can demonstrate multidrug resistance in up to 78.6% of the isolates in some series.<sup>74</sup> Periocular and subconjunctival antibiotics do not appear to have sufficient vitreous penetration nor significant clinical benefit to warrant routine use.<sup>75,76</sup>

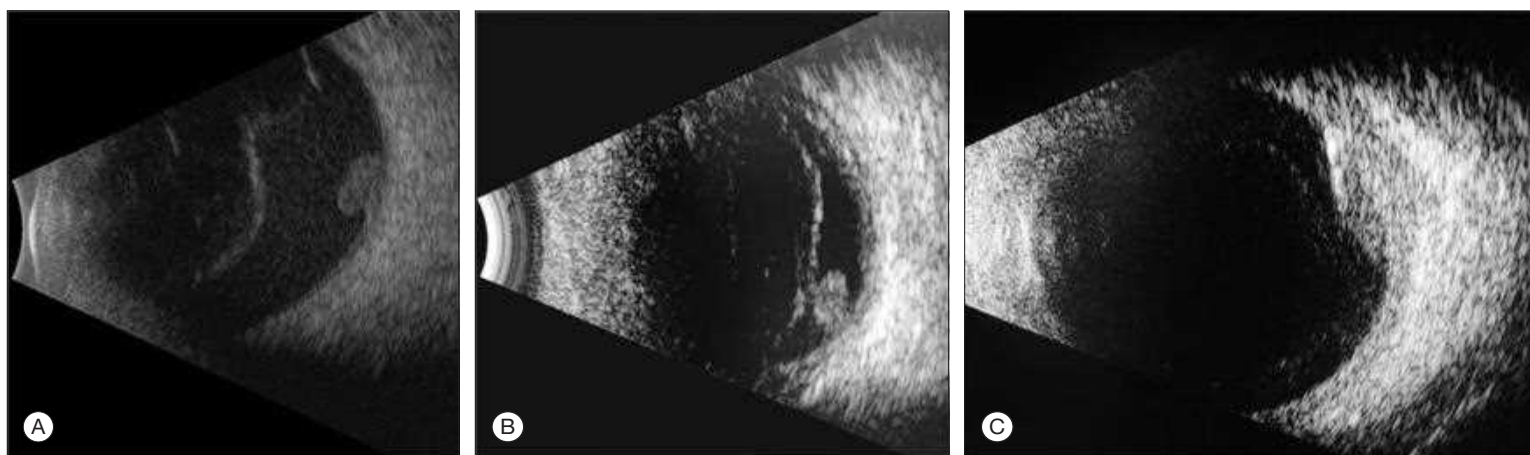
Intravitreal corticosteroids, coadministered with antibiotics, may ameliorate the immune-driven destruction of ocular tissues and improve outcomes in eyes with endophthalmitis caused by *S. aureus*, *S. epidermidis*, and *B. cereus*.<sup>77–79</sup> Intravitreal dexamethasone may also be beneficial in cases of delayed bleb-associated endophthalmitis.<sup>80</sup> However, treatment of endophthalmitis with corticosteroids remains controversial.

The EVS did not demonstrate a benefit of adjunctive systemically administered medications optimized for Gram-negative coverage.<sup>81</sup> However, because Gram-positive organisms are implicated in the majority of postoperative endophthalmitis cases, systemic treatment with appropriate medications may be warranted, particularly in severe cases. Fluoroquinolones, including levofloxacin and gatifloxacin, even when administered orally, are able to achieve therapeutic intravitreal levels for the most important pathogenic agents, albeit not for *Pseudomonas aeruginosa* or *Enterococcus*.<sup>82,83</sup> Mycotic endophthalmitis is usually treated with systemic antifungal agents with good vitreous penetration, such as fluconazole, voriconazole, ketoconazole, or amphotericin B, and intravitreal voriconazole or amphotericin B.<sup>84</sup>

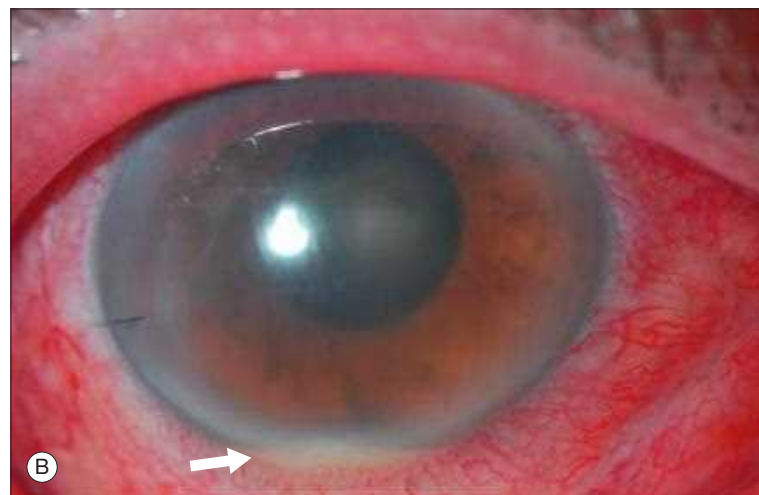
### Surgical Intervention

The results of the EVS are still applicable to postcataract endophthalmitis cases today, with some modifications. In patients presenting after cataract surgery with intraocular inflammation and visual acuity at the level of light perception, compared with intravitreal antibiotics alone, pars plana vitrectomy with injection of intravitreal antibiotics appeared to improve the visual outcomes. For patients with visual acuity of hand motion or better, vitrectomy with intravitreal antibiotics appeared to provide no additional visual benefit when compared with intravitreal antibiotics alone. Subanalysis, however, suggested that among patients with diabetes and better

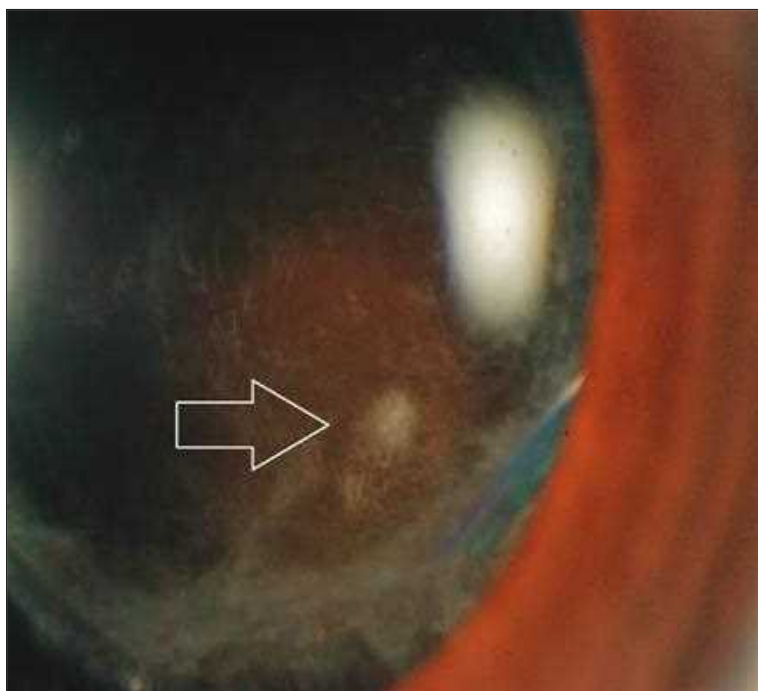




**Fig. 7.9.6** B-scan ultrasonography images depicting the mushroom-like configuration of *Candida* (A) and *Aspergillus* (B) endogenous lesions compared with the subretinal abscess of *Klebsiella* (C).



**Fig. 7.9.7** Acute postcataract endophthalmitis can vary in presentation depending on the causative agent from a fulminant picture with corneal edema and a large hypopyon (A) to a more moderate form with a subtle hypopyon (arrow) (B).



**Fig. 7.9.8** Acute focal posterior capsular plaque (arrow) seen in a patient with *Propionibacterium acnes* endophthalmitis.

#### BOX 7.9.1 Intravitreal Agents Used in the Treatment of Endophthalmitis

First-line therapy	Vancomycin Ceftazidime Voriconazole Dexamethasone
Alternatives	Amikacin Cefazolin Cefuroxime Clindamycin Amphotericin B

presenting vision, more will achieve 20/40 or better ultimate vision if vitrectomy is performed.<sup>6</sup>

The main goals of pars plana vitrectomy in endophthalmitis are to obtain sufficient tissue for diagnosis and to debulk the proinflammatory debris. In practice, a culture result of the removed material alters clinical management in <5% of cases. Although the EVS included limited vitrectomy, more extensive debridement may provide better outcomes. In addition, early surgical intervention may be of particular benefit in fungal endophthalmitis, where retinal detachment rates for *Candida* infections were found to be far lower when vitrectomy was performed within 1 week of presentation compared with delayed vitrectomy. Removal of the intraocular lens implant is typically not required, except in cases of chronic low-grade endophthalmitis associated with *P. acnes* resistant to medical therapy.<sup>30,85</sup>



## OUTCOMES

In general, the outcomes for endophthalmitis are poor despite aggressive therapy and the frequent need for subsequent surgical procedures. The virulence of the infectious agent dictates the course and outcome of the infection. Less aggressive organisms elicit milder intraocular inflammation and are associated with longer delay from inoculation to clinical manifestations. Consequently, media opacity mild enough to allow visualization of retinal vessels at the time of the diagnosis purports better outcomes.<sup>5,59</sup> Visual outcomes are worse with endophthalmitis developing within 2 days of surgery, presenting vision of light perception or worse, the presence of an afferent pupillary defect, and in patients with diabetes.<sup>4-8</sup> Outcomes in children with exogenous endophthalmitis are particularly poor, with >60% having worse than 20/400 vision, even with aggressive therapy involving vitrectomy and intravitreal antibiotics.<sup>31,86</sup>

Best visual outcomes are observed in patients with *P. acnes* species, where 91% of patients achieve at least 20/100 vision.<sup>30</sup> In the EVS, this level of vision was achieved in 84% of eyes with Gram-positive coagulase-negative infections, but in only 50% of *S. aureus* infections and 56% of Gram-negative infections.<sup>87</sup> *Pseudomonas*, *Klebsiella*, *S. pneumoniae*, and *Bacillus* species are associated with a particularly aggressive course and severe vision loss. *P. aeruginosa* endophthalmitis is associated with nearly universal vision loss beyond 20/400 and the ultimate need for enucleation in 64%.<sup>88</sup> *Klebsiella* endophthalmitis leads to no light perception vision in 58%–89% and enucleation in 21%–41%.<sup>8,89</sup> *S. pneumoniae* endophthalmitis has a slightly better, although still poor, outcome, with 30% of patients achieving vision of 20/100 or better, and 37% with no light perception.<sup>86,90</sup> Endophthalmitis involving *Bacillus* species is associated with 20/400 or better vision in 36%, with nearly half of those eyes achieving vision of 20/60 or better, whereas enucleation is necessary in only 5%.<sup>13</sup> Endogenous mycotic infections have a generally poor prognosis, and of these, *Aspergillus* species infections have significantly worse outcomes than those of *Candida* species.<sup>91</sup>

Endophthalmitis following penetrating globe injuries is associated with very poor visual outcomes, including no light perception vision or enucleation in 82.3%.<sup>9</sup>

Additional surgical intervention may be required in more than a third of patients with postoperative endophthalmitis, often with poor ultimate outcome.<sup>92</sup> In the EVS, retinal detachment was observed in 8.3% of patients after either vitreous tap/inject or vitrectomy.<sup>93</sup>

## CONCLUSIONS

The devastation caused by infectious bacterial endophthalmitis can be vision and eye threatening. Patients with a history of diabetes, trauma, or

surgery are at a particularly high risk for developing endophthalmitis. The typical signs, including pain and hypopyon, are not universally present, so a high index of suspicion is warranted to prevent delay in diagnosis.

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# Histoplasmosis

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# 7.10

**Definition:** Ocular histoplasmosis is an intraocular inflammation induced by *Histoplasma capsulatum*, a diphasic fungus.

## Key Features

Three characteristic presentations:

- Endophthalmitis.
- Solitary granuloma.
- Syndrome characterized by peripheral “punched-out” chorioretinal scars, absence of inflammatory cells in the anterior chamber or vitreous, and positive histoplasmin skin test results (most common).

## Associated Features

- Peripapillary chorioretinal atrophy.
- Choroidal neovascularization.
- Peripheral punched-out lesions.
- Linear chorioretinal scars (“linear streaks”).
- Endemic in the Ohio River and Mississippi River valleys in the United States.

## INTRODUCTION

*Histoplasma capsulatum* is a diphasic, soil-borne fungus. Humans and other mammals inhale wind-blown soils and aerosolized bird droppings that contain these organisms and so become infected. These organisms infect the lungs and can be disseminated through the systemic circulation to other organs such as the liver, kidney, spleen, and the eye. *H. capsulatum* is responsible for three different forms of ocular involvement in humans:

- Endophthalmitis with diffuse uveal and retinal involvement from disseminated histoplasmosis.
- Solitary chorioretinal granuloma.
- Ocular histoplasmosis syndrome (OHS).

The *Histoplasma* organisms have been identified in ocular tissues in all three of these forms.<sup>1</sup>

Histoplasmic endophthalmitis occurs mainly in immunocompromised patients, particularly those who have acquired immune deficiency syndrome (AIDS). Symptoms can include floaters, decreased vision, and pain in the affected eye. Ophthalmic examination reveals conjunctival injection, anterior chamber flare and cells, yellow iris infiltrates, posterior synechiae, vitreous cells, and multiple white, creamy foci of retinochoroiditis.<sup>1,2</sup> Diagnosis is based on the presence of active pulmonary or disseminated histoplasmosis and positive cultures from sputum, bronchial washings, and biopsy specimens from the anterior chamber or vitreous cavity. Complement fixation titers are elevated (>1:32) in disseminated disease. Histopathological evaluation of eyes with histoplasmic endophthalmitis demonstrates diffuse granulomatous inflammation that involves the entire uveal tract, focal retinal inflammation, and intracellular and extracellular *H. capsulatum* that are detected with periodic acid-Schiff and Gomori’s methenamine-silver (GMS) stains.<sup>1,2</sup> Prompt treatment with systemic amphotericin B or itraconazole is recommended in affected patients.

Solitary histoplasmic granuloma is an extremely rare condition found in immunocompromised patients,<sup>1</sup> often in the absence of an identifiable primary source infection, characterized by a unilateral, ill-defined choroidal lesion.<sup>1</sup> Vitritis is variable. Histopathological evaluation shows a dense, granulomatous mass containing lymphocytes, epithelioid and giant cells,

and few *Histoplasma* organisms.<sup>1</sup> Treatment with systemic amphotericin B should be considered if a granuloma appears to be growing or is associated with severe vitritis.

OHS is by far the most common form of ocular disease caused by *H. capsulatum*. It continues to be an important cause of central visual loss during the productive years of human life. The syndrome consists of:

- Peripapillary chorioretinal atrophy and scarring.
- Peripheral punched-out chorioretinal scars.
- Hemorrhagic macular lesions secondary to choroidal neovascularization (CNV).
- Absence of anterior segment and vitreous inflammation.
- A positive histoplasmin skin test result.<sup>3</sup>

## EPIDEMIOLOGY AND PATHOGENESIS

OHS is endemic in the Ohio and Mississippi River valleys of the eastern half of the United States. Up to 80 million people are at risk of developing OHS in this part of the country.<sup>4</sup> *H. capsulatum* may cause a subclinical systemic infection in patients in the endemic areas prior to the development of the typical ocular manifestations of OHS. This may be a self-limited upper respiratory tract illness. Subsequent routine radiological studies of patients in endemic areas may disclose asymptomatic pulmonary, hepatic, splenic, and renal granulomas. In endemic areas, 60% or more of the population may have positive histoplasmin skin tests, and 5% of these people have peripheral atrophic scars and peripapillary atrophy. Additionally, 95% or more of patients who have typical signs of OHS have positive histoplasmin skin test results.<sup>5</sup> Although *H. capsulatum* has not been cultured from chorioretinal or disciform scars, organisms have been demonstrated histopathologically in both,<sup>6</sup> and fragments of the DNA of *H. capsulatum* have been detected by polymerase chain reaction (PCR) in atrophic scars.<sup>7</sup> These observations suggest that *H. capsulatum* causes OHS.

Genetic factors may be important in the pathogenesis of OHS, because patients with macular or peripapillary hemorrhagic lesions have a significantly higher prevalence of human lymphocyte antigen B-7 (HLA-B7) than the general population or those who have only peripheral atrophic spots associated with OHS.<sup>8</sup> Smoking increases threefold the risk of the development of CNV in patients with OHS.<sup>9</sup> Conversely, there is evidence that many of the genes that confer increased risk of CNV for AMD do not increase risk of CNV in OHS.<sup>10</sup>

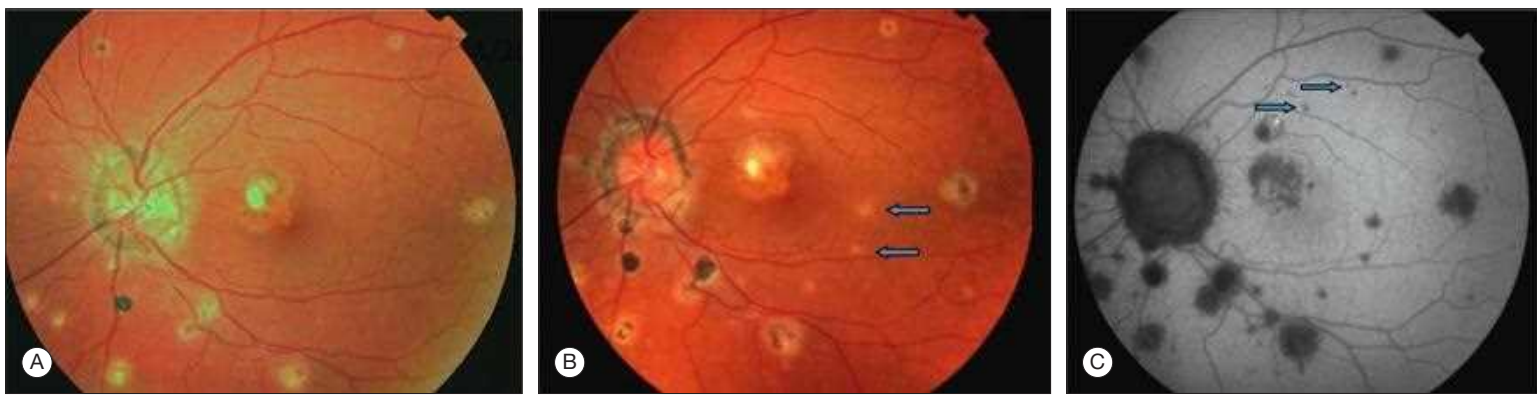
## OCULAR MANIFESTATIONS

Ocular manifestations of histoplasmosis classically are confined to chorioretinal pathology. However, there have been case reports of scleritis and ocular adnexal involvement.<sup>11,12</sup>

With intraocular disease, anterior segment and vitreous inflammation are notably absent. The characteristic fundus findings of OHS include:

- Small oval to round, punched-out, chorioretinal scars in the midperiphery or posterior pole (Fig. 7.10.1A).
- A macular lesion that varies from atrophic scar to active choroidal neovascularization (see Fig. 7.10.1A) to disciform scar.
- Peripapillary atrophy or scarring (see Fig. 7.10.1A).

The peripheral chorioretinal lesions are discrete, punched-out, atrophic scars that are 0.2–0.6 disc diameters in size. They often have pigmented borders and may be located in the midperiphery or in the posterior pole. The macular lesions may begin as atrophic scars. A CNV can arise from the scar and can be associated with a pigment ring, overlying subretinal fluid, and/or hemorrhage. If untreated, these lesions may evolve into disciform scars. The disciform lesion may appear yellowish to whitish, fibrotic,



**Fig. 7.10.1** (A) Peripheral punched-out scars, macular lesion, and peripapillary atrophy with pigmented ring in the left eye of a patient with ocular histoplasmosis syndrome. (B) New lesions demonstrating a subclinical inflammatory component. Same patient as in Fig. 7.10.1A 10 years later with new lesions on clinical examination. (C) Fundus autofluorescence showing more lesions than clinically evident. Arrows show foci of retinal pigment epithelial disruption and scarring that cannot be seen on biomicroscopy.



**Fig. 7.10.2 Choroidal Neovascularization in OHS.** (A) Autofluorescence image of the right eye of a patient with new metamorphopsia shows a hyperautofluorescent juxtafoveal choroidal neovascular membrane (CNVM). (B) Fluorescein angiogram shows lacy hyperfluorescence consistent with classic CNVM. (C) Spectral domain optical coherence tomography shows the neovascular lesion and adjacent subretinal fluid.

and associated with variable amounts of pigmentation. The size of the disciform macular scar can vary depending upon the amount of serum and blood in the subretinal space prior to its development.<sup>7</sup> Peripapillary scarring is associated with a thin area of chorioretinal atrophy adjacent to the optic nerve and a peripheral zone of hyperpigmentation at the edge farthest from the optic nerve (see Fig. 7.10.1A). Choroidal neovascularization also may develop in the peripapillary area and result in peripapillary subretinal hemorrhage and serous retinal detachment, which may occasionally involve the macula. In addition to the three characteristic retinochoroidal lesions, linear streak lesions at the equator have been found in some patients with OHS. Equatorial linear streak lesions, however, also may be seen in idiopathic multifocal choroiditis.<sup>13</sup> Patients may also develop new lesions over time that are demonstrative of a subclinical, ongoing inflammatory component to the disease (see Fig. 7.10.1B).

Patients who have OHS generally are asymptomatic unless choroidal neovascularization causes metamorphopsia.<sup>14</sup> This usually is followed by visual loss and the development of a small scotoma in the central or para-central visual field. Patients who have OHS usually seek treatment for these symptoms between their third and sixth decades.<sup>14</sup>

## DIAGNOSIS

The diagnosis of OHS is made by funduscopic examination alone. Skin testing with *H. capsulatum* antigen is not recommended because of the high prevalence of positive results in endemic areas and controversy as to whether the skin test may actually cause activation of otherwise quiet, atrophic chorioretinal scars.<sup>15</sup>

Patients with known asymptomatic OHS should be instructed to perform frequent Amsler chart self-monitoring for early detection of choroidal neovascularization.<sup>14</sup> Fundus autofluorescence may also demonstrate small, clinically unapparent macular scars that may suggest the need for closer Amsler grid monitoring<sup>16</sup> (see Fig. 7.10.1C). Patients who have OHS who have symptoms of metamorphopsia or scotoma should have

### BOX 7.10.1 Differential Diagnosis of Ocular Histoplasmosis Syndrome

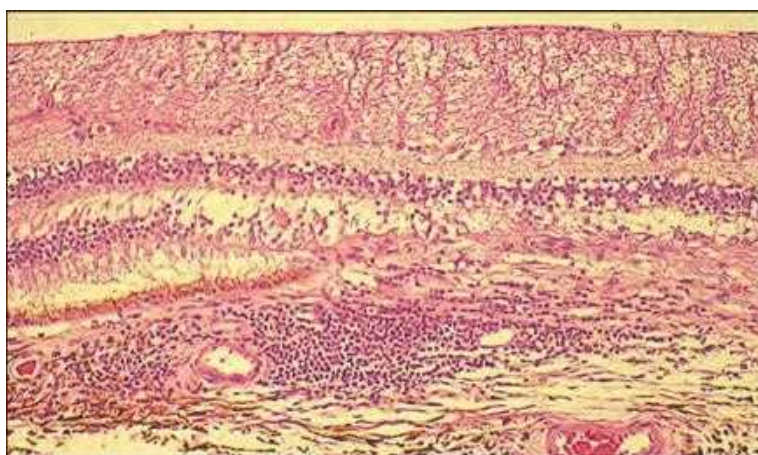
- Punctate inner choroiditis
- Sarcoid panuveitis
- Vogt–Koyanagi–Harada syndrome
- Sympathetic ophthalmia
- Idiopathic multifocal choroiditis
- Myopic degeneration

fluorescein angiography performed (see Fig. 7.10.2A). In asymptomatic patients, fluorescein angiographic findings consist of late staining of the peripapillary scar, midperipheral atrophic spots, and atrophic macular scars. If clinical examination suggests the presence of subretinal fluid or a subretinal hemorrhage, fluorescein angiography demonstrates early hyperfluorescence and late leakage from a complex of lacy, small blood vessels in the subretinal space or subretinal pigment epithelial space (Fig. 7.10.2B). This is consistent with the diagnosis of choroidal neovascularization. Similar findings are seen on indocyanine green angiography, which may be helpful in delineating the CNV when it is obscured by subretinal hemorrhage. Spectral domain optical coherence tomography (SD-OCT) can also be used to visualize and quantify subretinal fluid due to CNV and the response to treatment (see Fig. 7.10.2C). SD-OCT of “histo spots” and peripapillary atrophy demonstrates outer retinal loss and retinal pigment epithelial (RPE) atrophy, and the infrared image of peripapillary atrophy (PPA) shows a hyperreflective halo.<sup>16</sup>

## DIFFERENTIAL DIAGNOSIS

All of the syndromes listed in Box 7.10.1, except myopic degeneration and punctate inner choroiditis, have anterior segment and vitreous





**Fig. 7.10.3 Histopathology of an “Active” Atrophic Chorioretinal Scar in Ocular Histoplasmosis Syndrome.** Note the lymphocytic infiltrate of the choroid, disruption of Bruch’s membrane and retinal pigment epithelium, and extension of inflammation from choriocapillaris into the subretinal space. Typical Histoplasma organisms are not demonstrated here but have been isolated from other lesions. (Courtesy Yanoff M, Fine BS. Ocular pathology: a text and atlas. 4th ed. St Louis: Mosby; 1994. p. 395.)

inflammation in association with the chorioretinal findings. Peripheral, punched-out scars, atrophic and disciform macular scarring, and peripapillary atrophy, scarring, and choroidal neovascularization also may occur in all of these syndromes. Differentiating punctate inner choroiditis (PIC) and idiopathic multifocal choroiditis (MFC) from OHS is of particular importance in endemic areas because the management of the chronic, inflammatory component of PIC and MFC may be required, and the incidence of new CNV is much higher in PIC compared to OHS (see Chapter 7.22).

## PATHOLOGY

Histopathology of peripheral lesions demonstrates the infiltration of lymphocytes.<sup>17</sup> Caseating granulomatous foci with fibrohyaline scarring may be present.<sup>17</sup> The granulomas may contain *H. capsulatum*.<sup>6,7</sup>

The macular lesions of OHS show disruption of Bruch’s membrane with ingrowth of a neovascular complex into the subretinal space (Fig. 7.10.3).<sup>18</sup> There may be an overlying serous retinal detachment and subretinal hemorrhage. A variable amount of lymphocytic infiltration may be present. The CNV may appear only loosely adherent to the overlying photoreceptors and underlying native RPE.<sup>18</sup> If left untreated, the subretinal hemorrhage and serum in the subretinal space may lead to proliferation and metaplasia of RPE into fibrovascular tissue that organizes into an inactive disciform plaque.<sup>17</sup> Lymphocytes can sometimes become a prominent feature of the choroid adjacent to the subretinal scar.<sup>17</sup> The peripapillary scar also demonstrates RPE proliferation and replacement of much of the choroid by fibrovascular tissue.<sup>17</sup> Disruption of Bruch’s membrane and extensive destruction of the overlying photoreceptors also may occur in this area.<sup>19</sup>

Surgically excised CNVs demonstrate the expression of various growth factors—basic fibroblast growth factor, transforming growth factor  $\beta$ -1, and procollagen.<sup>20</sup> These growth factors play a role in the development of choroidal neovascularization.

## TREATMENT

Most patients who have OHS are asymptomatic unless they develop choroidal neovascularization in the peripapillary or macular regions. Macular choroidal neovascularization was traditionally subdivided into the following<sup>20</sup>:

- Extrafoveal lesions, when the foveal edge is more than 200  $\mu$ m from the center of the fovea.
- Juxtafoveal lesions, when the foveal edge is 1–199  $\mu$ m from the center of the fovea.
- Subfoveal lesions, when any part of the membrane has clearly grown underneath the center of the fovea.

This location classification system was important when laser photocoagulation with argon green<sup>21</sup> or krypton red<sup>22</sup> laser was the treatment of choice. Untreated eyes with CNV and ocular histoplasmosis have a

3–6 times greater risk of losing six or more lines of visual acuity than do treated eyes. Laser treatment, however, leaves a scotoma in the treated area and has recurrence rates of 26%.<sup>21,22</sup> Hence laser is rarely used today since the advent of anti-vascular endothelial growth factor (VEGF) therapy. Continued Amsler chart monitoring for new metamorphopsia is important.

Today laser treatment is rarely, if ever, used for juxtafoveal and subfoveal CNVs. Inhibition of VEGF, an important vasoproliferative cytokine, using monoclonal antibodies (bevacizumab, ranibizumab, and aflibercept) directed against VEGF and its receptor has shown to be a highly effective method of controlling many forms of ocular neovascularization. Intravitreal bevacizumab (IVB) is now the preferred treatment for juxtafoveal and subfoveal choroidal neovascular membranes in OHS.

Unlike thermal laser treatment for CNV, IVB therapy does not produce a scotoma.<sup>23</sup> The largest retrospective study to date, of 117 eyes with OHS and CNV,<sup>23</sup> demonstrated that 30% of patients gained three or more lines of vision, 80% maintained stable or better after 3 years of follow-up and after receiving an average of three IVB injections per year. In addition, after 3 years of follow-up, less than 10%<sup>23</sup> of eyes had visual acuity less than or equal to 20/200, compared with 75% by natural history.<sup>24</sup> Ocular complications such as endophthalmitis, vitreous hemorrhage, or retinal detachment need to be discussed with the patient before initiation of IVB therapy. Despite its widespread ocular use worldwide for 12 years, bevacizumab is not yet approved by the US Food and Drug Administration (FDA) for use in the eye. There are reports of the use of ranibizumab and aflibercept in OHS, but these medications may remain cost prohibitive in the absence of an FDA indication for CNV secondary to OHS.<sup>25,26</sup>

Ocular photodynamic therapy using verteporfin may also be utilized for subfoveal<sup>27</sup> and juxtafoveal<sup>28</sup> CNVs. The Verteporfin in Ocular Histoplasmosis (VOH) study, a multicenter, uncontrolled, prospective clinical trial for subfoveal CNV,<sup>27</sup> concluded that after 24 months and an average of 2.9 treatments, 45% (14/22 eyes) had improved seven or more Early Treatment of Diabetic Retinopathy Study (ETDRS) letters of visual acuity from baseline. There were no systemic or ocular adverse events reported.<sup>27</sup>

Subfoveal surgery to remove CNVs in ocular histoplasmosis requires pars plana vitrectomy, disinsertion, and removal of the posterior hyaloid, a small retinotomy, and careful delamination, dissection, and removal of the CNV from the subretinal space.<sup>29–31</sup> The Submacular Surgery Trials (SST) were multicenter, randomized, clinical trials designed to determine whether there was significant clinical and quality of life benefit in surgical removal of subfoveal choroidal neovascularization in various disorders, including OHS compared to observation alone. The 24-month data from 225 patients enrolled in this trial showed no treatment benefit for idiopathic or OHS-associated subfoveal choroidal neovascularization.<sup>32</sup> Risks of surgery including retinal detachment, cataract, and recurrence of subfoveal choroidal neovascularization (in more than 50% within 1 year)<sup>31</sup> preclude the need for subfoveal surgery since the advent of highly effective anti-VEGF therapy.

## COURSE AND OUTCOME

Patients with OHS but without macular complications of the disease enjoy excellent visual acuity and visual prognosis. Treatment of extrafoveal choroidal neovascularization with argon or krypton laser photocoagulation reduces the risk of serious visual loss by at least 50%.<sup>21</sup> Extrafoveal choroidal neovascularization has an excellent visual prognosis after treatment.<sup>21</sup> The visual prognosis for juxtafoveal and subfoveal choroidal neovascularization has improved substantially with PDT<sup>27</sup> and IVB.<sup>23</sup> In earlier studies, more than 75% of patients who have subfoveal choroidal neovascularization had visual acuity of 20/100 (6/30) or worse after 3 years.<sup>24</sup> Today, only about 10% of patients developed severe visual loss ( $\leq$ 20/200) after 3 years of IVB therapy.<sup>23</sup> However, natural history data demonstrates that up to 14% of eyes with subfoveal choroidal neovascularization may retain visual acuity of 20/40 (6/12) or better if the patient is less than 30 years of age, has small CNVs involving less than 50% of the foveal avascular zone, and has no visual loss secondary to OHS in the fellow eye.<sup>33</sup> Spontaneous visual acuity recovery has also been reported in younger patients with smaller central disciform scars and shorter intervals of sequential visual loss, particularly when visual acuity drops to 20/80 (6/24) or worse in the fellow eye.<sup>33</sup> Such visual acuity recovery also may occur from spontaneous involution of subfoveal choroidal neovascularization in some rare instances.

Patients with a disciform scar or choroidal neovascularization in one eye and evidence of macular atrophic scars in the high-risk region (defined vertically between the temporal arcades, nasally by the temporal disc margin, and temporally by disc to fovea distance from the foveal center) in the fellow eye have approximately a 20% risk over a 2- to 3-year period of



developing choroidal neovascularization in the macula of the fellow eye.<sup>24</sup> Patients who do not have macular lesions are at significantly lower risk of developing choroidal neovascularization. However, de novo choroidal neovascularization has been reported in patients with OHS who did not appear to have macular scars.

Reactivation of inflammatory lesions may also occur in patients with OHS.<sup>34</sup> This phenomenon dispels the notion of OHS being a static disease and may explain the development of new lesions and enlargement of old chorioretinal scars in patients with OHS. Patients with reactivation may complain of decreased vision and metamorphopsia. Reactivation usually is not accompanied by vitritis. Clinical examination may demonstrate mild graying of the choroid and/or RPE and thickening of the retina. Fluorescein angiography of reactivated lesions demonstrates progressive leakage with irregular borders without evidence of underlying CNV.<sup>34</sup> Patients may be treated with systemic itraconazole combined with oral corticosteroids, which also may be used alone.<sup>34</sup> Most lesions improve within 4–12 weeks. Choroidal neovascularization only rarely occurs after several months at the site of these reactivated lesions.<sup>34</sup>

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# Fungal Endophthalmitis

Dimitra Skondra, Dean Elliott

# 7.11

**Definition:** Fungal endophthalmitis is an intraocular inflammation leading to various degrees of inflammation, either acute or chronic, induced by fungi such as *Candida albicans*, *Fusarium* species, *Coccidioides immitis*, and *Aspergillus* spp.

## Key Features

- Candidal intraocular infection typically manifests as a fluffy white choroidal or retinal lesion with white snowball-like vitreous opacities.
- *Aspergillus* causes necrotizing chorioretinitis or endophthalmitis via hematogenous spread, usually from the lung.
- Coccidioidal intraocular inflammation may appear as chronic iridocyclitis, iris granuloma, choroiditis, or chorioretinitis.

## Associated Features

### Candidal Intraocular Infection

- Usually seen in immunocompromised or diabetic individuals, those with indwelling catheters, intravenous drug users, presence of candidemia.

### *Aspergillus* Endogenous Endophthalmitis

- Usually seen in immunocompromised individuals but rarely in healthy patients.

### Coccidioidal Intraocular Inflammation

- Systemic coccidioidal infection, endemic in American Southwest, including the San Joaquin Valley in California, northern Mexico, and Argentina.

Fungal endophthalmitis is a vision-threatening condition that presents diagnostic and management challenges. Fungi can reach the eye hematogenously or exogenously, as a complication of trauma or surgery or from extension from periocular and orbital sites.

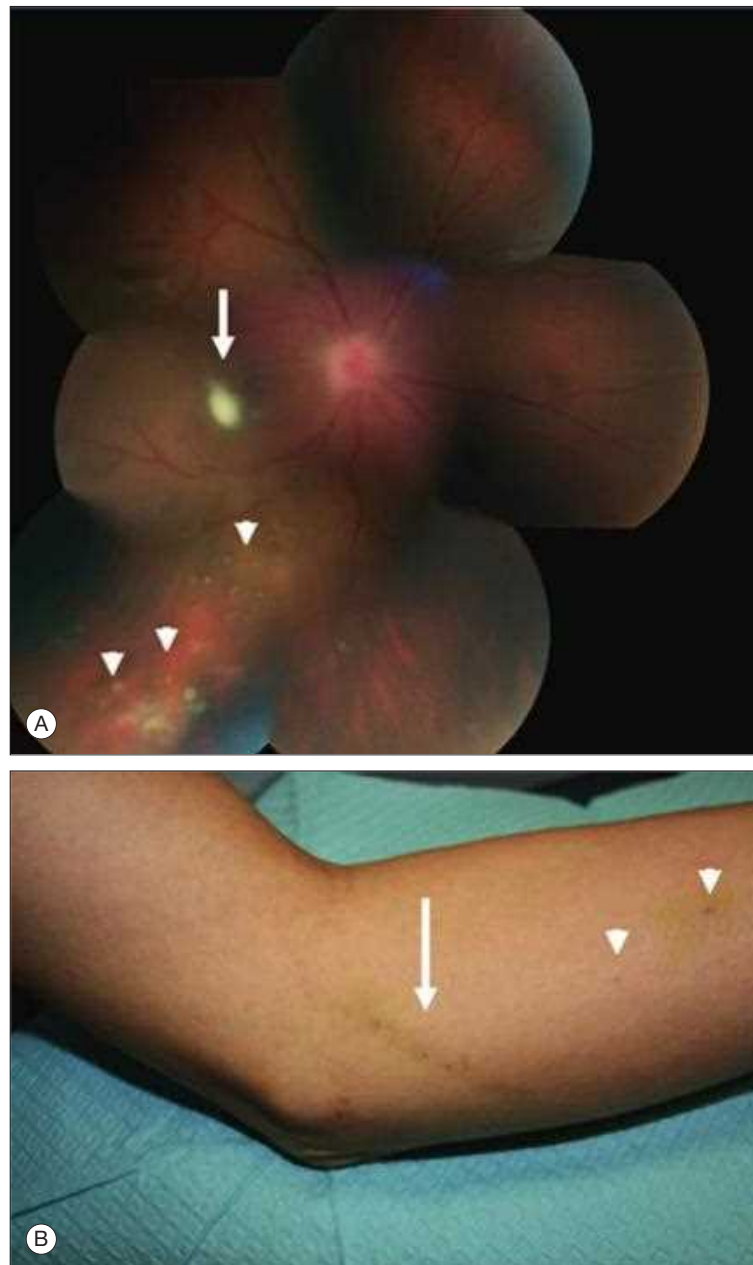
## CANDIDA

### INTRODUCTION

Candidemia is the most common cause of endogenous fungal endophthalmitis. *Candida albicans*, an important nosocomial pathogen, is the most common *Candida* species.<sup>1</sup>

### EPIDEMIOLOGY AND PATHOGENESIS

*Candida* yeasts reach the eye most commonly by hematogenous spread to the choroid or rarely from direct inoculation following ocular trauma or surgery.<sup>1,2</sup> With candidemia, the organisms typically cause one or more foci of chorioretinitis, which may progress to involve the vitreous, where it is then termed endophthalmitis. Predisposing conditions include diabetes, intravenous drug use, prolonged hospitalization, history of major surgery, bacterial sepsis requiring broad-spectrum systemic antibiotics, hyperalimentation, chronic indwelling catheters, and immunosuppression secondary to organ transplantation, chemotherapy or acquired immunodeficiency syndrome (AIDS).<sup>1,3</sup>



**Fig. 7.11.1 25-Year-Old Woman With a History of Intravenous Drug Abuse With Endogenous *Candida* Endophthalmitis.** (A) Montage fundus color photo. Note vitreous haze from vitritis, vitreous white fluffy lesion overlying fovea (arrow), multiple round white lesions inferiorly at the level of posterior hyaloid (arrowheads), hyperemic and edematous disc. (B) External color photo. Note needle tracks along veins (arrow) and injection sites (arrowheads) at the forearm.

### OCULAR MANIFESTATIONS

The typical clinical features are white fluffy chorioretinal lesions with overlying vitritis. There may be focal vitreous involvement, which appear as small, white, snowball-like opacities, or there may be diffuse involvement manifesting as dense vitreous haze (Fig. 7.11.1). At least half the patients have multiple lesions, and two-thirds have bilateral involvement. There



may be satellite lesions and retinal vascular sheathing. Iridocyclitis of variable severity is a frequent finding, and hypopyon may be present.<sup>1</sup>

## HISTOPATHOLOGY

Eyes with *Candida* endophthalmitis have acute, progressive inflammation in the vitreous cavity (Fig. 7.11.2). Involvement of the retina and uvea usually is mild, though foci of retinal damage from invasion of the organisms can be seen. Regarding the distribution of fungi, yeasts are mainly localized to the vitreous abscess with the presence of few organisms in the retina. Retinal vessel wall invasion is not seen in *Candida* endophthalmitis.<sup>4</sup>

## ASPERGILLUS

### EPIDEMIOLOGY AND PATHOGENESIS

*Aspergillus* endophthalmitis is a devastating ocular infection. *Aspergillus fumigatus* is the most common pathogen. *Aspergillus* species are saprophytic molds that grow in soil and decaying vegetation with airborne spores. Exposure is relatively common, but infection is rare. Risk factors are chronic pulmonary disease, intravenous drug use, and severe immunocompromise, especially after liver transplantation, but it has even been reported in immunocompetent patients without predisposing conditions.<sup>5</sup>



**Fig. 7.11.2** Vitreous Biopsy Specimen From a Patient With *Candida* Endophthalmitis. Note *Candida* yeasts and hyphae in wet mount (KOH) preparation.

*Aspergillus* fungi reach the eye via hematogenous spread to the choroid, and *Aspergillus* is the most common fungal species isolated in postoperative fungal endophthalmitis cases.<sup>2,5</sup>

## OCULAR MANIFESTATIONS

Patients usually present with rapid-onset severe pain and decreased visual acuity. Often the central macula is involved. A confluent, yellowish macular infiltrate begins in the choroid and subretinal space (Fig. 7.11.3A). A layering of inflammatory exudate may occur in the subhyaloid space.<sup>5</sup>

The degree of retinal involvement is variable from subretinal or subhyaloid infiltrate to vascular occlusion and full-thickness retinal necrosis with intraretinal hemorrhages. Vitreous involvement is seen later in the disease process, and eventually the anterior segment can be involved.

## HISTOPATHOLOGY

Eyes with *Aspergillus* infection have acute inflammatory cells in the retina, subretinal space, and choroid. Although fungi can be seen in the vitreous (Fig. 7.11.3B), involvement of the retina and choroid is common, and the hyphae are often present in the subretinal space, under the retinal pigment epithelium, and in other locations (Fig. 7.11.4). Retinal and choroidal vessel wall invasion by fungal elements is also noted, and hemorrhage is present in all retinal layers and occasionally even in the choroid.<sup>4</sup>

## FUSARIUM

### EPIDEMIOLOGY AND PATHOGENESIS

*Fusarium* species are ubiquitous filamentous molds commonly found in soil and on plants. *Fusarium* is the most common fungal pathogen in endophthalmitis resulting from keratitis with contiguous spread, and the most common cause of keratomycosis in the southeastern United States. Rare cases of *Fusarium* endophthalmitis have been reported after cataract surgery. Endogenous *Fusarium* endophthalmitis is rare and almost all cases involve disseminated infection in immunocompromised patients, either secondary to leukemia or other severe systemic conditions.

## OCULAR MANIFESTATIONS

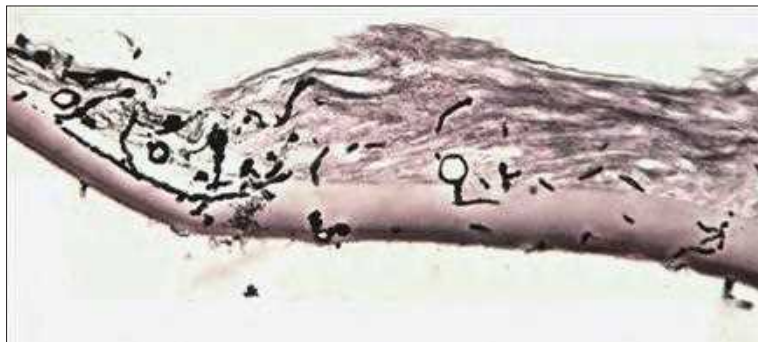
Exogenous *Fusarium* endophthalmitis tends to be more localized, with the inflammation and fungal mass confined to the anterior chamber, pupillary space, and anterior vitreous, but it can extend to diffuse vitritis and posterior segment involvement (Fig. 7.11.5). Endogenous *Fusarium* endophthalmitis is characterized by a fibrinous reaction in the anterior chamber, vitritis, and a variable degree of retinal ischemia and necrosis.<sup>6</sup>



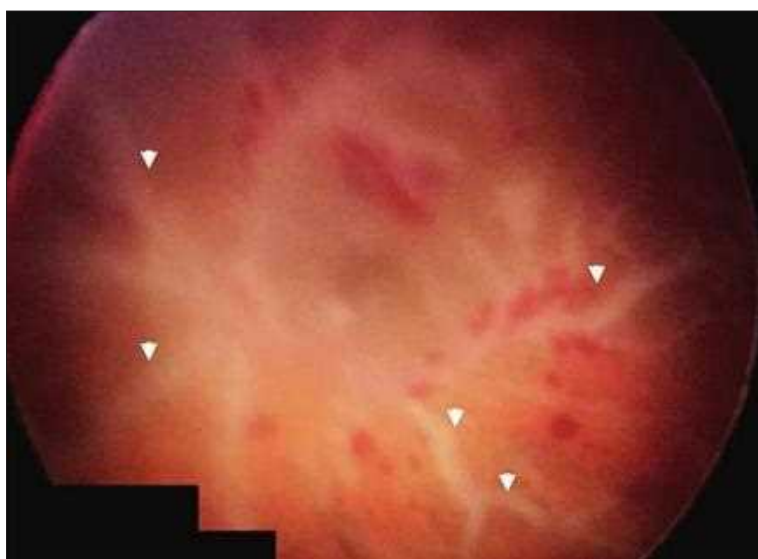
**Fig. 7.11.3** Young Man With a History of Intravenous Drug Abuse With Endogenous *Aspergillus* Endophthalmitis. (A) Color fundus photo. Note vitreous haze from vitritis and macular lesion with retinal hemorrhages. (B) Vitreous biopsy specimen. Note multiple *Aspergillus* filaments in undiluted vitreous specimen staining with alcian blue.

## COCCIDIODES IMMITIS—OCULAR COCCIDIOIDOMYCOSIS

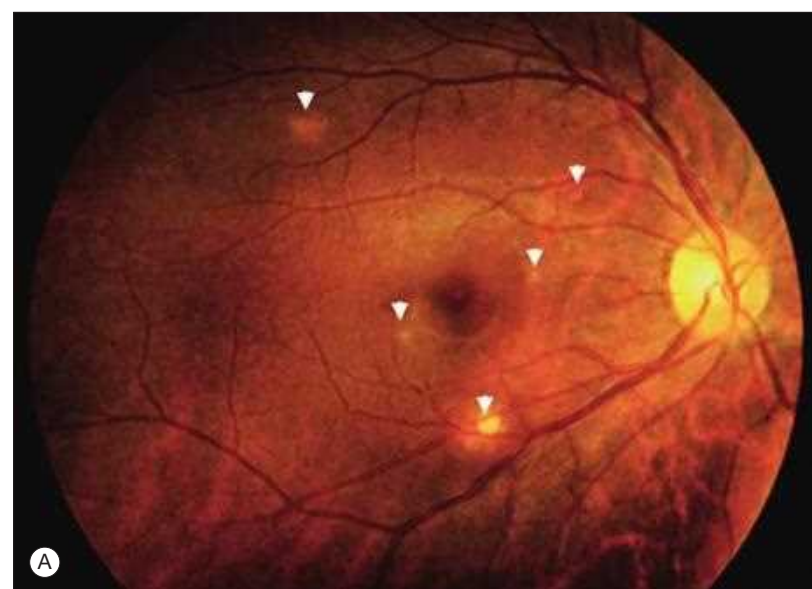
*Coccidioides immitis* is a dimorphic fungus found in soil and is endemic to the San Joaquin Valley of central California, Arizona, and parts of Central and South America. The incidence of coccidioidomycosis is increasing in



**Fig. 7.11.4** Lens Capsule Specimen From a Patient With Chronic *Aspergillus* Endophthalmitis. Note multiple *Aspergillus* filaments, which stain with Gomori's methenamine silver. (Courtesy Narsing A. Rao, MD, and Daniel V. Vasconcelos-Santos, MD.)



**Fig. 7.11.5** 70-Year-Old Woman With *Fusarium* Endophthalmitis. Note vitreous haze from vitritis and severe vasculitis (arrowheads). (Courtesy Lucia Sobrin, MD.)



the United States. Infection follows inhalation of the highly infectious, dust-borne spores and usually results in pulmonary disease, but *Coccidioides* endophthalmitis may present with no concomitant systemic involvement.

The typical posterior infection is a multifocal choroiditis with numerous scattered, discrete, yellow–white lesions less than one disc diameter in size (Figs. 7.11.6 and 7.11.7). Vascular sheathing, retinal hemorrhage, serous retinal detachment, and vitreous haze may occur in the acute phase of infection.<sup>7</sup>

## CRYPTOCOCCAL ENDOPHTHALMITIS

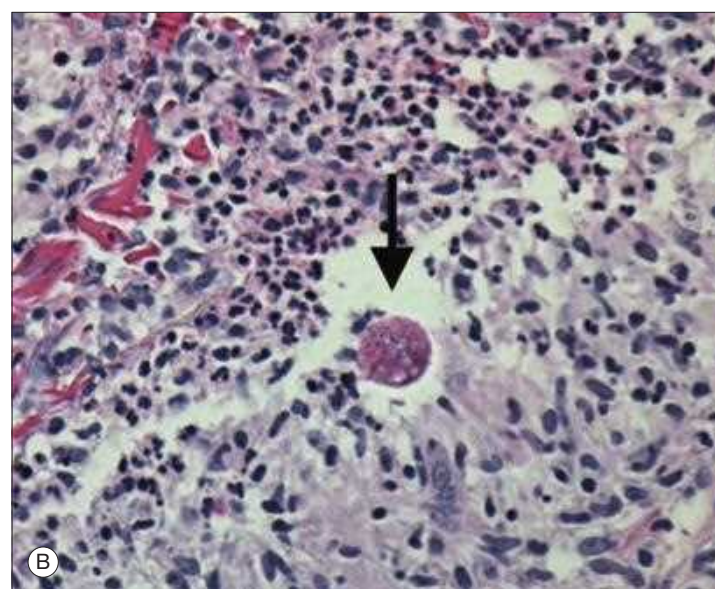
*Cryptococcus neoformans* is a yeast with worldwide distribution frequently found in pigeon feces. Infection is acquired through the respiratory tract. It usually causes an opportunistic infection, especially of the central nervous system in AIDS or debilitated patients. The most frequent presentation of ocular cryptococcosis is a multifocal choroiditis with discrete, yellow–white lesions of variable size. Other findings may include optic nerve involvement, vascular sheathing, and exudative retinal detachment. Cryptococcal infection may rarely progress to endophthalmitis (Fig. 7.11.8).<sup>8</sup>

## HISTOPLASMA ENDOPHTHALMITIS

*Histoplasma capsulatum* is a dimorphic fungus endemic to the southeastern and central United States. In the immunocompetent individual, the acute infection is usually self-limited with a localized granulomatous reaction. Disseminated histoplasmosis in the immunocompromised individual may lead to generalized systemic disease with involvement of multiple organs. Rare cases of *Histoplasma* endophthalmitis have been reported in immunocompromised patients, especially in those with AIDS, but it has also been described in immunocompetent patients. Ocular manifestations include granulomatous chorioretinitis with variable degrees of anterior chamber and vitreous involvement. Patients may develop diffuse intraretinal and subretinal exudation and hemorrhage with focal subretinal granulomas as well as tractional and rhegmatogenous retinal detachment.<sup>9</sup>

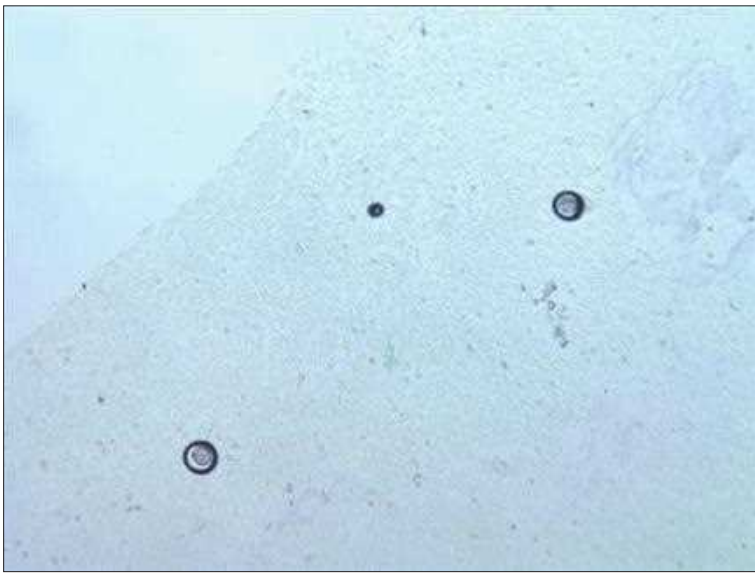
## DIAGNOSIS OF FUNGAL ENDOPHTHALMITIS

A high index of suspicion is critical because the clinical diagnosis of fungal endophthalmitis is usually based on the ophthalmological appearance in combination with the presence of fungemia or predisposing factors. In the absence of known fungemia, cultures of blood, catheter tips, wounds, and/or body fluids should be obtained. Cardiac imaging studies may be necessary to rule out the presence of septic emboli. A diagnostic vitreous aspirate with special stains and culture (see Figs. 7.11.2, 7.11.3B, 7.11.4, 7.11.7, and 7.11.8) is the gold standard for diagnosis, but the sensitivity is only approximately 44%.<sup>10</sup>

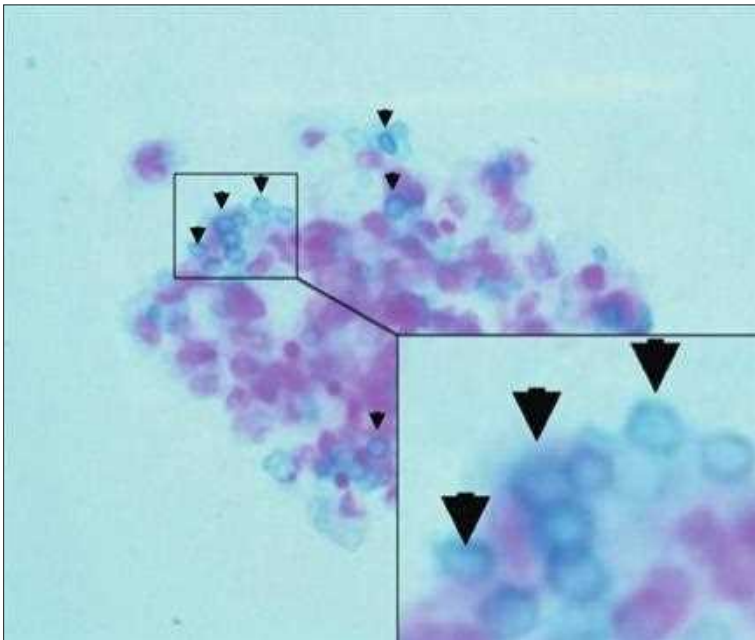


**Fig. 7.11.6** 36-Year-Old Man With *Coccidioides* Choroiditis and Pneumonitis. (A) Fundus color photo. Note multiple yellow choroidal lesions (arrowheads). (B) Bronchoalveolar lavage, histopathology specimen. Note *Coccidioides* spherule (arrow). (Courtesy J. Michael Jumper, MD.)





**Fig. 7.11.7 Undiluted Vitreous Specimen From 64-Year-Old Man With *Coccidioides* Endophthalmitis.** Note mature spherules of *Coccidioides* that stain with Gomori's methenamine silver. (Courtesy Narsing A. Rao, MD, and Daniel V. Vasconcelos-Santos, MD.)



**Fig. 7.11.8 Vitreous Specimen From 69-Year-Old Man With Endogenous *Cryptococcal* Endophthalmitis.** Note cryptococcal staining with alcian blue (arrowheads).

More recently, polymerase chain reaction (PCR) detection of fungal species in vitreous specimens has shown high sensitivity and specificity, enabling the rapid diagnosis of fungal endophthalmitis.<sup>11</sup> Vitrectomy is more likely to yield positive culture results as the primary diagnostic method rather than anterior chamber or vitreous tap, especially in cases of *Aspergillus* endophthalmitis.<sup>10</sup> In cases of endophthalmitis that result from keratitis, corneal biopsy with calcofluor white stain and cultures are useful in establishing the diagnosis. Histopathological examination of the vitreous and any associated epiretinal membranes with periodic acid–Schiff (PAS) and Gomori methenamine silver staining is helpful in the diagnosis of intraocular coccidioidomycosis because serological testing and cultures are frequently negative. A high index of suspicion is important, especially in endemic areas.<sup>7</sup> In cryptococcal cases, India ink and mucicarmine staining of vitreous samples, epiretinal membranes, and retinal biopsy samples are essential to reveal the characteristic broad capsule.<sup>8</sup>

### BOX 7.11.1 Differential Diagnosis of Fungal Endophthalmitis

Endogenous bacterial endophthalmitis  
Toxoplasma retinochoroiditis  
Primary intraocular lymphoma  
Cytomegalovirus retinitis  
Posterior uveitis

## DIFFERENTIAL DIAGNOSIS

The differential diagnosis of fungal endophthalmitis is given in Box 7.11.1.

## TREATMENT OF FUNGAL ENDOPHTHALMITIS

Systemic antifungal therapy should be administered to all individuals with endogenous fungal infections of the eye. Corticosteroid therapy should be avoided. The treatment with amphotericin B has been limited because of significant nephrotoxicity and relatively poor intraocular penetration. Newer antifungal drugs such as fluconazole and voriconazole have broad-spectrum antifungal activity, more than 90% oral bioavailability, and good ocular penetration.<sup>12</sup> Voriconazole is a newer azole compound that has shown the most promise, as therapeutic concentrations for most *Candida* and *Aspergillus* species are achieved in the vitreous, and it can be used in infections that are resistant to fluconazole and other agents.<sup>13</sup> Systemic treatment with either fluconazole (12 mg/kg loading dose, then 6–12 mg/kg daily) or voriconazole (6 mg/kg for 2 doses, then 4 mg/kg twice daily) is usually used for at least 4–6 weeks, with the final duration dependent on the response observed using repeated ophthalmological examinations.<sup>12</sup> Despite its considerable systemic toxicity, amphotericin B can be used for the most severe infections when treatments with other agents have failed.

Although a standard treatment protocol does not exist, in cases of macula-threatening involvement and in cases of *Aspergillus* endophthalmitis, intravitreal injection of an antifungal drug should be performed in addition to initiation of systemic therapy. Voriconazole (100 µg/0.1 mL) or amphotericin B (5 µg/0.1 mL) is given by intravitreal injection. Voriconazole is considered safer than amphotericin B, but there is more experience with amphotericin B, which also has the advantage of having a longer half-life after intravitreal injection. The need for repeated injections is dependent on the response to therapy.<sup>5,12,13</sup>

Early surgical intervention with pars plana vitrectomy is recommended for cases of fungal endophthalmitis with significant vitreous involvement, in cases of suspected aspergillosis, or if there is no significant improvement with intravitreal treatment.<sup>10,14</sup> Sampling the vitreous at the time of vitrectomy can provide important culture and PCR data to identify the pathogen and guide treatment.<sup>10</sup> Vitrectomy is combined with administration of intravitreal agents. Outcomes of early vitrectomy in addition to systemic antifungals have been favorable for cases of *Candida* and *Aspergillus* endophthalmitis.<sup>14</sup> The half-life of antifungal agents administered directly into the vitreous at the time of vitrectomy is shortened, and repeated administration may be necessary if there is evidence of persistent infection.

A team approach involving both a retina specialist and an infectious disease specialist is essential to ensure the most efficacious and safe treatment, as close monitoring for systemic manifestations and side effects is essential.

## COURSE AND OUTCOME

Early diagnosis and initiation of systemic and intravitreal treatment is important for reduction of both mortality and ocular morbidity.

Close follow-up is needed with examinations at least twice weekly initially to evaluate response to treatment. *Candida* endophthalmitis is associated with severe visual loss (20/200 or less) in 33%–60% of patients and final visual acuity of 20/50 or better in 42%.<sup>10</sup> The visual prognosis of *Aspergillus* endophthalmitis is worse, despite aggressive treatment, because of early macular involvement, with visual acuity 20/200 or worse in the majority of the eyes and 20/50 or better in only 7%.<sup>5</sup>

Factors associated with severe visual loss are poor visual acuity at presentation, lesions located in posterior pole, and the development of retinal detachment, which has been reported to occur in as many as 29% of patients. Early vitrectomy within 1 week of presentation has been associated with a lower incidence of retinal detachment and better visual outcomes.<sup>10,14,15</sup>



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# Ocular Toxoplasmosis

Daniel Vitor Vasconcelos-Santos

# 7.12

**Definition:** Ocular toxoplasmosis is a recurrent retinochoroiditis caused by *Toxoplasma gondii* and represents the most common cause of infectious posterior uveitis worldwide.

## Key Features

- Unilateral focal retinochoroiditis.
- May manifest either early after primary systemic infection or later, after reactivation of intraretinal *Toxoplasma gondii* cysts.
- Diagnosis made primarily on a clinical basis and supported by laboratory investigations.

## Associated Features

- Most commonly a unilateral focal retinochoroiditis.
- Multiple and even bilateral active lesions may occur in immunocompromised individuals and in the setting of recently acquired infection.
- Significant inflammatory involvement of the vitreous.
- Retinal vasculitis.
- Optic disc edema.
- Anterior uveitis.
- Treatment – combination therapy with antiparasitic drugs and corticosteroids.

## INTRODUCTION

Toxoplasmosis is caused by *Toxoplasma gondii*, an apicomplexan parasite infecting one-third of the human population.<sup>1,2</sup> Toxoplasmosis represents the main cause of infectious posterior uveitis worldwide and may lead to vision-threatening complications, including severe retinochoroidal scarring, vitreous opacities, cataract, glaucoma, and choroidal neovascularization.<sup>3-5</sup>

## ORGANISM AND LIFE CYCLE

*Toxoplasma gondii* is one of the most successful obligate intracellular parasites, capable of infecting virtually any warm-blooded animal and establishing lifelong chronic infection.<sup>2,6</sup> Sexual reproduction of the parasite only occurs in the intestine of members of the Felidae family, among which the domestic cat represents the archetypical definite host for *T. gondii*.<sup>1,7</sup>

The organism has several evolutive forms. The tachyzoite is the active proliferating form, present in intermediate and definite hosts during acute infection. It is able to penetrate any nucleated cell and circulate all over the body, leading to cell lysis, direct tissue damage, and subsequently to a strong, potentially destructive immune response. Under the pressure of the immune system, tachyzoites differentiate into bradyzoites, forming tissue cysts.<sup>8,9</sup> These are latent forms and may persist indefinitely in host tissues (such as striated muscle and central nervous system—particularly the neurosensory retina), without eliciting significant inflammatory response. These tissue cysts are also refractory to currently available antiparasitic drugs, which is the reason that chronic *T. gondii* infection cannot be cured. Tissue cysts can rupture later and release bradyzoites that convert to tachyzoites, leading to disease reactivation, especially in the retina.<sup>2,8</sup>

The definite host becomes infected by either ingesting meat containing tissue cysts/tachyzoites from intermediated hosts or by ingesting sporulated oocysts present in the soil and shed in the feces of feline hosts.<sup>7</sup> Once in the intestine, the parasite invades enterocytes and reproduces asexually

and sexually.<sup>9</sup> Sexual reproduction allows prolific genetic recombination, potentially facilitating emergence of more virulent strains of the parasite.<sup>10</sup> Felines shed oocysts 3–18 days after oral infection, and each of these animals contaminates the environment with millions of oocysts per day. These mature in the soil into sporulated oocysts, becoming infective after 1–21 days and persisting in the environment for up to 18 months.<sup>7,9</sup>

As for definite hosts, *T. gondii* also infects intermediate hosts (including humans) by means of oocysts contaminating the soil, water, or vegetables or by bradyzoite-containing cysts present in the tissues of other hosts. Transplacental transmission in recently infected hosts, and more rarely laboratory accidents and organ transplantation, are other possible modes of infection.<sup>2,7</sup>

## EPIDEMIOLOGY

*T. gondii* is a ubiquitous parasite and is present in all continents, with higher rates of human infection in humid and tropical areas and in those with larger populations of domestic cats.<sup>1,7</sup> In the United States, antibodies to *T. gondii* are found in nearly 20% of the human population. In France and in South America this rate reaches up to 80%.<sup>1-3</sup> Seroconversion increases with age and is particularly problematic in pregnant women because of risk of vertical transmission in the setting of recently acquired acute toxoplasmosis. In the first trimester of pregnancy, rates of transplacental infection are around 10%–25% and progressively increase to reach 60%–80% in the third trimester.<sup>11</sup> Conversely, the potential severity of fetal sequelae typically decreases during pregnancy.<sup>12</sup>

Human infection is classically associated with ingestion/handling of raw or undercooked meat containing tissue cysts of *T. gondii*.<sup>7</sup> Recent evidence, however, supports the importance of water contaminated with oocysts as an emerging source of infection.<sup>1,13-15</sup> Vegetables and fruits may also be contaminated by oocysts and lead to human infection.<sup>7</sup>

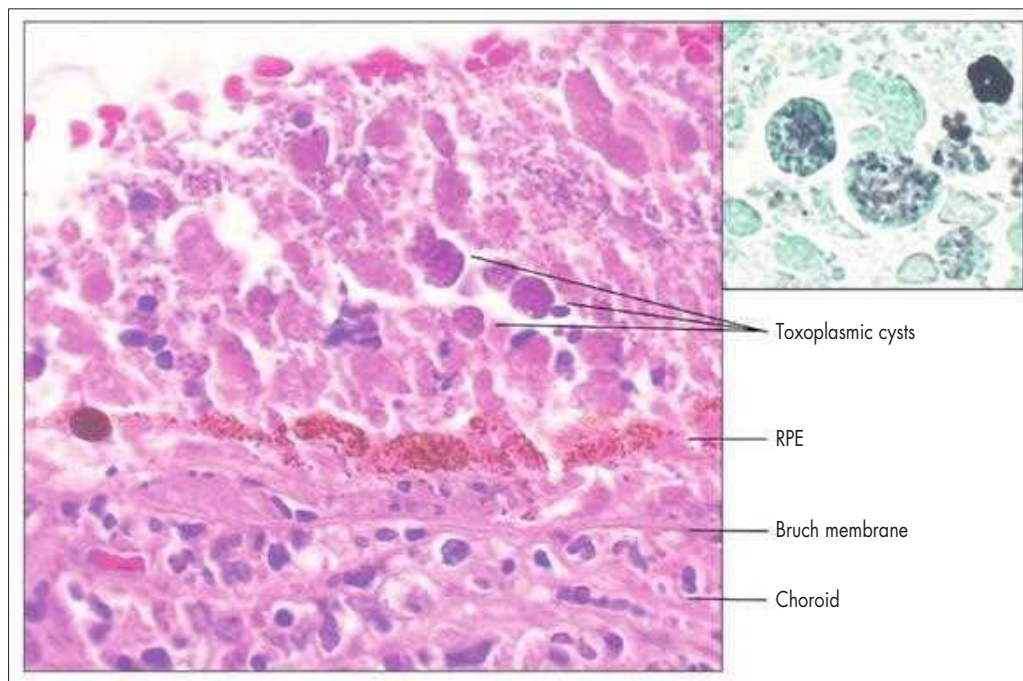
Congenital toxoplasmosis used to be blamed for most cases of ocular toxoplasmosis.<sup>1,16,17</sup> This is in line with the large proportion (approaching 80%) of infected infants displaying retinochoroidal lesions.<sup>18-20</sup> However, more reliable data on the relatively low incidence of congenital toxoplasmosis, in addition to increased documentation of postnatally acquired disease (often asymptomatic), support the hypothesis that the latter may be far more important than previously suspected.<sup>13,21-23</sup> Still, the rates of ocular involvement following postnatally acquired toxoplasmosis fall between 2% and 3%<sup>17,24,25</sup> but may be as high as 20% in some areas.<sup>1,22</sup>

## PATHOLOGY AND PATHOGENESIS

Histopathologically, active ocular toxoplasmosis manifests as a focal retinochoroiditis, with necrotizing granulomatous inflammation of the retina associated with reactive granulomatous involvement of the choroid, vitreous, and even the anterior uveal tract. Parasites may be seen as free tachyzoites or tissue cysts within the necrotic focus (Fig. 7.12.1) but also in the adjacent retina.<sup>26,27</sup> Mononuclear inflammatory infiltrates surrounding retinal blood vessels are also frequently seen. Disruption/migration of the retinal pigment epithelium (RPE) is commonly observed.<sup>26,28</sup> The inflammatory process can extend to underlying sclera. A retinochoroidal scar is left (chorioretinal adhesion) after resolution of inflammation, with variable proliferation of RPE. Intact *T. gondii* cysts without reactive inflammation may be found in histologically normal retina.<sup>29,30</sup>

Pathogenesis depends on a delicate balance between host immunity and parasite virulence.<sup>2,30</sup> Immunoimmaturity associated with congenital toxoplasmosis is clearly associated with more extensive systemic/ocular lesions, some of which are related to disruption of embryogenesis and fetogenesis.<sup>12</sup> Immunosuppressed adults are also more susceptible to severe systemic and ocular disease.<sup>2,4</sup>





**Fig. 7.12.1 Histopathology of Toxoplasmic Retinochoroiditis, Showing Extensive Necrosis of the Neurosensory Retina and Retinal Pigment Epithelium (RPE).** The choroid displays reactive diffuse granulomatous inflammation (hematoxylin-eosin stain, original magnification 400×). Toxoplasmic cysts are seen within the necrotic retina, staining with Gomori's methenamine silver (GMS, inset). (Courtesy N. Rao, University of Southern California.)

In immunocompetent individuals with postnatal infection, however, parasite proliferation can be contained earlier by the immune system, limiting the extent of tissue damage. A small number of these individuals develop ocular disease soon after seroconversion, but a higher proportion of them have local recurrences later in life, associated with cysts that were previously seeded even in normal-looking retina.<sup>1,30</sup> Rupture of such cysts releases bradyzoites that convert to tachyzoites, establishing active parasite proliferation locally, with subsequent cell lysis and release of cytotoxic mediators and eliciting a vigorous necrotizing granulomatous response that may also lead to further tissue damage.<sup>30,31</sup> Hypersensitivity to retinal antigens may also play a role in maintaining intraocular inflammation during recurrences.<sup>32</sup>

The first line of immune defense to *T. gondii* after oral infection is in the gastrointestinal tract. In addition to the barrier effect of enterocytes, the local innate immune response driven by a variety of cells including polymorphonuclear leukocytes, macrophages, B/T lymphocytes, and natural killer (NK) cells may at least partially contain parasite proliferation both directly and indirectly.<sup>33</sup> These cells, in addition to others such as dendritic cells, also help to trigger the adaptive immune response, the main responsible for successful control of *T. gondii* infection.<sup>6,34,35</sup>

The adaptive immune response is coordinated by CD4+ T lymphocytes and macrophages. This Th1 (T-helper-1) reaction leads to the synthesis of various proinflammatory cytokines, particularly interleukin-12, interferon- $\gamma$ , and tumor-necrosis-factor- $\alpha$ , which act synergistically to contain parasite replication. CD8+ T lymphocytes are also cytotoxic to infected cells. A Th2 response counterbalances the proinflammatory Th1 pathway, down-regulating the protective immunity to *T. gondii*.<sup>6,34,35</sup>

Parasite virulence is also an important determinant of pathogenesis.<sup>2</sup> In this regard, *T. gondii* has three main genetic lineages with different virulence/geographic distribution.<sup>36,37</sup> Type I parasites are highly virulent, eliciting a strong proinflammatory response that is potentially associated with severe tissue damage. Type II parasites are the least virulent and under immune pressure promptly encyst in tissues and establish chronic infection in susceptible hosts. Type III parasites are also less virulent.<sup>38</sup> In addition to these three canonical genotypes, atypical recombinant genotypes emerging from sexual recombination in the definite host have been increasingly observed in highly endemic areas such as South America and in association with outbreaks of severe systemic/ocular disease worldwide.<sup>39–42</sup>

## CLINICAL MANIFESTATIONS

### Systemic Disease

Immunocompetent individuals with postnatally acquired toxoplasmosis are frequently asymptomatic. Some develop a mononucleosis-like syndrome, manifested with fever, malaise, and variable lymphadenopathy. Only a small number evolve to severe systemic disease, including pneumonitis,

hepatitis, myocarditis, and even encephalitis. Immunocompromised individuals, especially those with acquired immune deficiency syndrome (AIDS), are susceptible to life-threatening disease either at primary infection or during reactivation, particularly in the form of neurotoxoplasmosis (toxoplasmic encephalitis).<sup>2,4</sup>

Congenital toxoplasmosis is associated with a large spectrum of systemic manifestations ranging from intrauterine death or severe malformations to a neonatal infectious syndrome including anemia, thrombocytopenia, cutaneous rash, hepatitis, pneumonitis, myocarditis, and even encephalitis.<sup>2,12</sup> Hydrocephalus or microcephaly, intracranial calcifications, mental retardation, and retinochoroiditis represent the Sabin's tetrad, occurring in less than 10% of newborns with congenital toxoplasmosis.<sup>12,19</sup> The leading clinical manifestation, however, is retinochoroiditis, present in up to 80% of newborns at birth.<sup>5,18,19</sup>

### Ocular Disease

Postnatally acquired toxoplasmosis is rarely associated with ocular disease in immunocompetent individuals early after seroconversion,<sup>1,16</sup> but reactivation of intraretinal cysts may lead to retinochoroiditis any time later in life. The active retinochoroidal lesion presents clinically as a whitish or yellowish exudate involving the inner retina with adjacent retinal edema. Typically the lesion arises at the margins (or close to) a pre-existent retinochoroidal scar (satellite lesion, Figs. 7.12.2 and 7.12.3) but may also present as an isolated focal lesion (Fig. 7.12.4).<sup>3,43,44</sup> The lesion progresses to involve full thickness of the retina with reactive inflammatory thickening of the underlying choroid (see Fig. 7.12.3).

Inflammatory cellular infiltration of overlying vitreous is invariably present and may lead to granulomatous precipitates on the posterior hyaloid and even to denser vitreous opacities or bands. Active lesions associated with more severe vitreous haze can typically display a "headlight-in-the-fog" aspect on fundus examination. Perivascular sheathing, particularly of venules, is also commonly seen, even distant to the primary inflammatory focus. Adjacent periarterial lipidic exudates (*Kyrieleis arteriolitis*) can also be found (see Fig. 7.12.4). Perivascular exudative lesions may complicate with vascular (especially venular) occlusions, leading to further retinal edema or hemorrhages. Larger active lesions are often associated with macular or optic nerve head edema. Reactive involvement of the anterior uveal tract may also be seen, as a granulomatous or nongranulomatous iridocyclitis. Intraocular pressure is elevated in 10%–30% of these cases. Toxoplasmic retinochoroidal scars are clinically polymorphic but frequently have some degree of pigmentation, indicating RPE hyperplasia or hypertrophy. Some can be so atrophic as to show the underlying sclera.<sup>3,22</sup>

Congenital toxoplasmosis is associated with retinochoroidal lesions in up to 80% of infected newborns, mostly in the macular area and even bilaterally. The typical wagon-wheel scar in the macula (Fig. 7.12.5) strongly suggests congenital toxoplasmosis, but other variably pigmented lesions can be present elsewhere. Active satellite or isolated focal lesions may also be

seen, either early after birth or any time later in life, with features virtually indistinguishable from those of reactivations associated with postnatally acquired disease. Large necrotizing lesions can also rarely develop.<sup>5,18,19</sup>

In addition to satellite and isolated focal lesions, ocular toxoplasmosis may have atypical forms of presentation.<sup>44</sup> Outer retinal toxoplasmosis is characterized by minimal vitreal involvement and punctate infiltrates primarily in the outer retina, often leading to serous retinal detachment. Toxoplasmic neuroretinitis occurs in the setting of juxtaglial exudative lesions, culminating in edema of the optic nerve head and even in a macular star.<sup>43,44</sup> Extensive, multifocal, and even bilateral active lesions may present similarly to a picture of viral retinitis (Fig. 7.12.6) and are more frequent in immunosuppressed and elderly individuals and in those with recently acquired infection, either congenital or postnatal.<sup>3,4,23,43,45</sup> Toxoplasmic intraocular inflammation without concomitant necrotizing

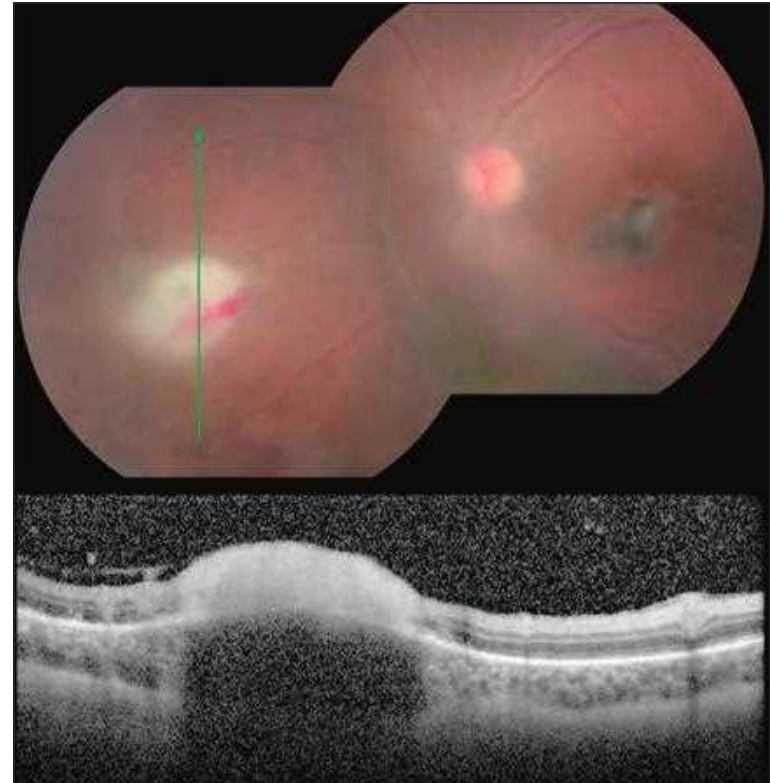
retinochoroiditis is relatively rare and may manifest as isolated anterior uveitis, retinal vasculitis, and optic neuritis. These atypical forms of presentation have been increasingly reported in the presence of recent postnatally acquired disease.<sup>4,46</sup>

## DIAGNOSIS

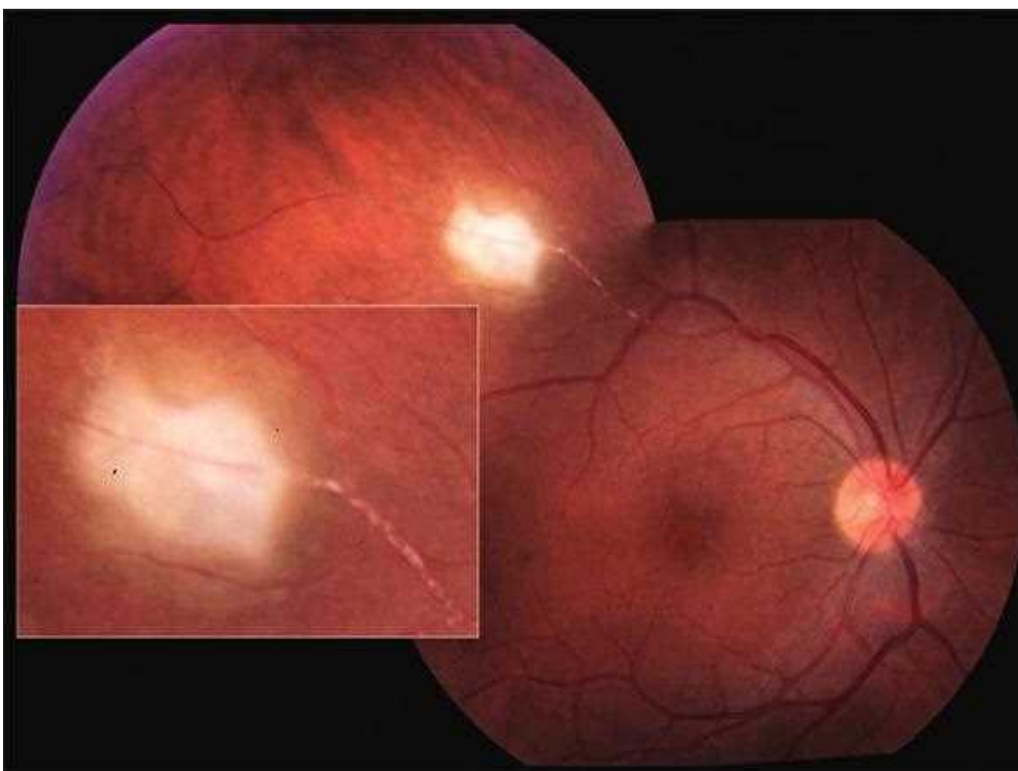
The diagnosis of ocular toxoplasmosis is essentially clinical, based on the presence of a focal necrotizing retinochoroiditis (see Figs. 7.12.2, 7.12.3, and



**Fig. 7.12.2 Fundus Appearance of Toxoplasmic Retinochoroiditis With a Typical Active Satellite Lesion Adjacent to Pigmented Retinochoroidal Scars.**

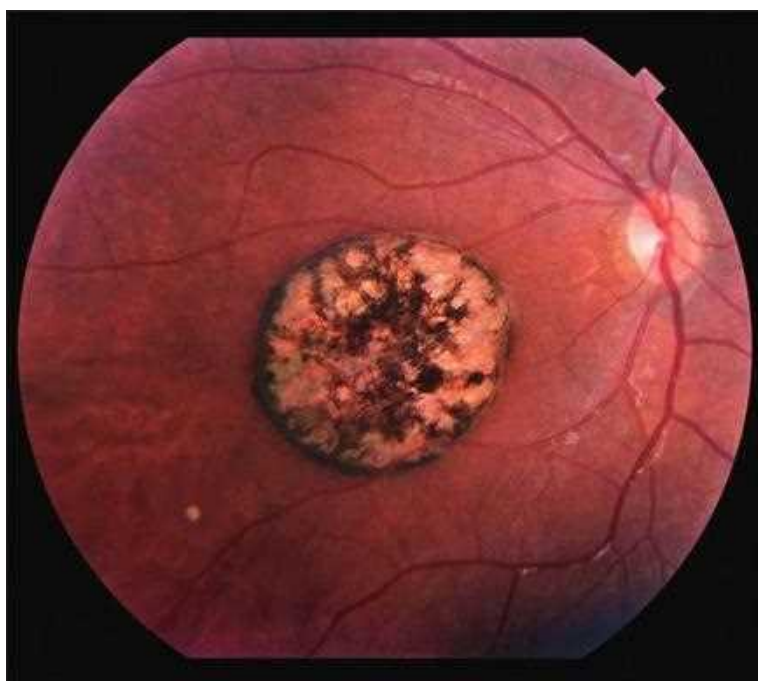


**Fig. 7.12.3 Fundus and Tomographic Appearance of Toxoplasmic Retinochoroiditis.** An exudative toxoplasmic lesion is seen nasally to the optic disc in association to vitreous haze and perivenular sheathing (top). Vertical optical coherence tomography section of the lesion (green line) discloses nodular hyperreflective retinal focus with posterior shadowing. Fusiform thickening of underlying choroid can also be appreciated (bottom).

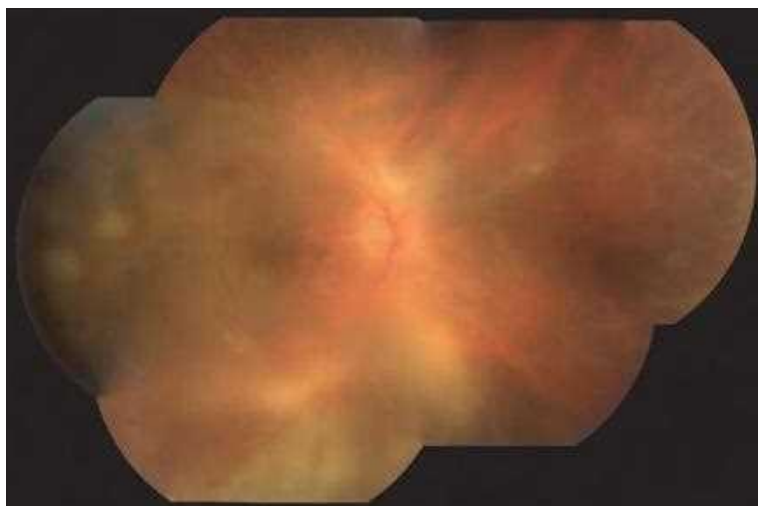


**Fig. 7.12.4 Fundus Appearance of Toxoplasmic Retinochoroiditis, With an Active Exudative Lesion in the Absence of Retinochoroidal Scars (Isolated Focal Lesion).** Inset shows surrounding retinal edema and periarteriolar exudates (Kyrleis arteriolitis).





**Fig. 7.12.5 Fundus Appearance of Congenital Toxoplasmosis.** A typical “wagon-wheel” scar is seen in the right macula.



**Fig. 7.12.6 Fundus Aspects of Atypical Toxoplasmic Retinochoroiditis.** Multiple and extensive exudative toxoplasmic lesions simulating herpetic retinitis are seen in a patient with AIDS.

7.12.4), often associated with an adjacent or distant retinochoroidal scar. Variable inflammation of vitreous, retinal blood vessels, optic nerve, and anterior segment is also frequently present.<sup>3,43,44</sup>

Serological tests are supportive, revealing in most cases only the presence of IgG antibodies to *T. gondii* and denoting chronic infection. Absence of specific IgG and IgM virtually excludes the possibility of toxoplasmosis, whereas their presence, particularly in significant titers, indicates recently acquired disease, which may also be suggested by low avidity of specific anti-*T. gondii* IgG antibodies. For congenital toxoplasmosis, the diagnosis is sealed by IgM and/or IgA and/or persistently high levels of IgG antibodies to *T. gondii* after 12 months of life.<sup>2,3,12,43</sup>

In cases of less typical presentation, invasive investigations may be employed, including assessment of intraocular antibody synthesis and polymerase chain reaction (PCR) of ocular fluids.<sup>43,47–49</sup> The former is possible through calculation of the Goldmann–Witmer or Witmer–Desmonts coefficient based on the correlation between titers of specific antibodies to *T. gondii* in aqueous humor or serum versus the globulin titers in the same fluids.<sup>49</sup> A high coefficient indicates intraocular synthesis of anti-*T. gondii* antibodies, and a low coefficient has an opposite interpretation, although this may also occur in the setting of severe disruption of the blood–ocular barrier.

In yet uncertain cases, PCR of aqueous humor or vitreous can be an invaluable tool to definite diagnosis of toxoplasmosis and other infectious etiological factors. Particularly for toxoplasmosis, positivity of vitreous

**TABLE 7.12.1 Differential Diagnosis of Primary or Recurrent Toxoplasmic Retinochoroiditis**

#### Infectious

##### Bacterial

Syphilis  
Tuberculosis  
Bartonellosis (neuroretinitis, focal retinitis, and angiomatous lesions)  
Lyme disease  
Endogenous endophthalmitis  
Others

##### Viral

Acute retinal necrosis/necrotizing herpetic retinopathy  
CMV retinitis  
Progressive outer retinal necrosis  
Others

##### Fungal

Candidiasis (particularly endogenous endophthalmitis)  
Aspergillosis  
Others

##### Parasitic

DUSN  
Toxocariasis  
Others

#### Noninfectious

##### Associated with systemic disease

Behçet’s disease  
Sarcoidosis  
Others

##### Primarily not associated with systemic disease

Serpiginous/ampiginous choroiditis and others  
Multifocal choroiditis and panuveitis  
Punctate inner choroidopathy  
Multiple evanescent white dots syndrome  
Unilateral acute idiopathic maculopathy  
Others

#### Neoplastic

Primary vitreoretinal lymphoma  
Others

CMV, Cytomegalovirus; DUSN, diffuse unilateral subacute neuroretinitis.

samples often exceeds that of aqueous humor samples but is lower than for herpes family viruses.<sup>47–49</sup>

Imaging modalities including echography, fluorescein or indocyanine green angiography, and optical coherence tomography are seldom decisive to the diagnosis but may otherwise help to better delineate the vitreal and retinochoroidal changes (see Fig. 7.12.3) and to document or assess local complications such as vascular occlusions, macular edema, and choroidal neovascularization.<sup>3,43,50</sup>

## DIFFERENTIAL DIAGNOSIS

Infectious, noninfectious, and even neoplastic entities are considered in the differential diagnosis of ocular toxoplasmosis (Table 7.12.1).<sup>43</sup>

In newborns with suspicion of congenital disease, exclusion of infections by agents of the TORCHS acronym (*T*Oxoplasmosis, *R*ubella, *C*ytomegalovirus, *H*erpes, *S*yphilis) is mandatory. Other less common congenital infections simulating toxoplasmosis include West Nile virus fever, acute lymphocytic choriomeningitis, and more recently Zika virus, the latter particularly in the setting of microcephaly.<sup>51</sup> Tumors such as retinoblastoma and retinocytoma and noninflammatory entities such as retinochoroidal colobomata and persistent hyperplastic vitreous are also to be considered in the differential diagnosis of these young children.<sup>3,43</sup>

Primary or recurrent toxoplasmic retinochoroiditis in older children or adults may be either congenital or postnatally acquired and should be equally differentiated from infectious (bacterial, viral, fungal, parasitic), noninfectious (associated or not with a systemic disease), and neoplastic entities (see Table 7.12.1).<sup>3,43</sup>

## THERAPY

Toxoplasmic retinochoroiditis may be self-limited in some patients. The decision to treat should thus be based on several factors, including individual immune status and location, size, and local repercussion of the active lesion (Box 7.12.1).<sup>3,4,52</sup>

In immunocompetent patients, small, peripherally located, active lesions and those with no significant exudation may be observed



### BOX 7.12.1 Main Factors Influencing Treatment Decision on Active Toxoplasmic Retinochoroiditis

- Immune status of the individual
- Location and size of the active lesion
- Presence of macular and/or optic disc edema
- Degree of vitritis and of decreased vision
- Clinical course
- Special situations (newborns, pregnant women, drug allergy)
- Adverse effects of antiparasitic drugs and corticosteroids

initially. Worsening of intraocular inflammation and the development of sight-threatening complications indicates the necessity to treat.<sup>3,4,52</sup>

Treatment is a combination of antiparasitic drugs/systemic corticosteroids. Topical corticosteroids, mydriatic, and hypotensive agents are also employed as needed. The most widely used regimen (and still considered the standard, so-called classic therapy) is the association of sulfadiazine and pyrimethamine.<sup>2,52,53</sup> All patients on pyrimethamine should be monitored with periodic complete blood counts and should also receive supplementation with folic acid (not *folic acid*) to prevent bone marrow suppression.<sup>2,53</sup> In the setting of allergy or intolerance to sulfonamides, clindamycin or azithromycin may be utilized. Relevant details on main antiparasitic drugs for the treatment of toxoplasmosis are summarized in Table 7.12.2.

Oral corticosteroid (0.5–1 mg/kg/day of prednisone or equivalent) is also typically used in a tapering regimen, with favorable effect on inflammation of the vitreous, retina, and optic nerve.<sup>3,4,52</sup> It should be initiated at least 24 hours after starting antiparasitic drugs and tapered off before stopping them. Caution should be taken to avoid corticosteroids without concomitant antiparasitic coverage because of risk of progressive/devastating intraocular inflammation. The use of pericocular or intravitreal depot corticosteroids is relatively contraindicated for the same reasons. Treatment duration is often 5–6 weeks but may be longer for larger active lesions and persistent intraocular inflammation.<sup>4</sup> Resolution of the active lesion is typically centripetal, with progressive flattening of the margins and decreased exudation.<sup>3</sup> Lesion pigmentation may be delayed, and is a variable and unreliable feature.

Alternative antiparasitic drugs in different regimens have also been proposed (Table 7.12.2).<sup>3,52</sup> Intravitreal therapy with clindamycin has also been reported, with single or repeated injections through the pars plana of 1 mg of clindamycin and 0.4 mg of dexamethasone.<sup>54</sup> Some of these alternative regimens are regarded as comparable to the classic antiparasitic therapy in small randomized clinical trials.<sup>55,56</sup> However, experimental in vivo and in vitro studies and those enrolling immunosuppressed patients and neonates with congenital toxoplasmosis are still largely supportive of the classic therapy as opposed to alternative antiparasitic regimens.<sup>2,53</sup> These regimens may be particularly useful in the setting of drug allergy (sulfadiazine is the main culprit) and other adverse effects and in some specific situations in the presence of smaller and less exudative lesions.

Immunosuppressed individuals with active toxoplasmic retinochoroiditis should always be treated, because of its progressive nature with a high risk of complications and even loss of the eye in this population. Neonates with congenital toxoplasmosis are also invariably treated during the first year of life, receiving antiparasitic drugs regardless of the presence of retinochoroidal lesions. Pregnant women with documented recent seroconversion also need treatment with spiramycin (even in the absence of retinochoroiditis) to decrease the risk of vertical transmission. Because spiramycin does not cross the placenta, when fetal infection is confirmed by either PCR of amniotic fluid or ultrasound, other antiparasitic drugs are to be employed.<sup>2,53</sup> Reactivations during gestation may be initially followed if the posterior pole is not threatened, due to the very low risk of fetal infection.

Laser photocoagulation and even cryotherapy have been suggested for extramacular chronically exudative lesions in individuals nonresponsive to or not tolerating systemic therapy.<sup>3,52</sup> Their efficacy is unclear, however, and recurrences may still occur out of treated area. Other surgical modalities, such as pars plana vitrectomy and phacoemulsification (phaco), are employed mostly for management of complications, including persistent vitreous opacities, epiretinal membranes, retinal detachment, and cataract.<sup>3,52</sup>

Secondary prophylaxis with sulfamethoxazole/trimethoprim (800/160 mg 3×/week or every other day) has been shown to decrease risk of recurrences in immunocompetent adults.<sup>57</sup> This may be useful in

TABLE 7.12.2 Main Antiparasitic Drugs for the Treatment of Toxoplasmosis

Drug and Dosage	Precautions and Observations
Sulfadiazine 1 g qid in adults 50–100 mg/kg/day in children	Caution and dose correction for hepatic renal failure Contraindicated in G6PDH deficiency Hydration and alkalinization of urine may prevent crystalluria Avoid at the end of gestation (risk of kernicterus) Hypersensitivity and allergies demand suspension Stevens–Johnson syndrome possible but rare Bone marrow suppression in <0.1%
Pyrimethamine Loading dose of 100 mg, followed by 25–50 mg/day 1 mg/kg/day in children	Caution in hepatic or renal failure Contraindicated in first trimester (teratogenic) Common gastrointestinal disturbances Risk of bone marrow depression demands concomitant use of folic acid (5–7.5 mg/day or 15 mg 3×/week) and periodic CBC monitoring
Clindamycin 300 mg qid 10–25 mg/kg/day in children	Caution in hepatic or renal failure Common gastrointestinal disturbances Risk of pseudomembranous colitis (suspend if bloody diarrhea)
Azithromycin 250–500 mg/day 5 mg/kg/day in children	Food decreases oral absorption Gastrointestinal disturbances in less than 10% May be used in pregnancy
Sulfamethoxazole/trimethoprim 800 mg/160 mg bid 40–50 mg/8–10 mg/kg/day in children	Better tolerated than classic therapy but probably less effective Caution and dose correction in case of hepatic/renal failure Contraindicated in G6PDH deficiency Avoid during gestation (risk of teratogeny and kernicterus) Risk of sulfa hypersensitivity Bone marrow suppression uncommon
Spiramycin 1.5 million IU (500 mg) qid	High levels in placenta Safest antiparasitic drug in pregnancy Limited intraocular penetration Gastrointestinal disturbances and hypersensitivity
Atovaquone 750 mg qid 30 mg/kg/day in children	Caution with liver failure Food increases drug absorption Maculopapular rash in up to 20% No safety studies concerning gestation/lactation

CBC, Complete blood count; G6PDH, glucose-6-phosphate dehydrogenase; IU, international units.

Adapted from Orefice F, Vasconcelos-Santos DV, Cordeiro CA, et al. Toxoplasmosis. In: Foster CS, Vitale AT, editors. Diagnosis and treatment of uveitis. 2nd ed. New Delhi: Jaypee-Highlights; 2013. p. 671–7; Kim SJ, Scott IU, Brown GC, et al. Interventions for toxoplasma retinochoroiditis: a report by the American Academy of Ophthalmology. Ophthalmology 2013;120:371–8.

individuals with multiple recurrences threatening the central macula and in the immunosuppressed. Even though the ideal duration is not definitely established, recent evidence suggests that prophylaxis for 12 months may prevent recurrences for up to 2 years thereafter.<sup>57</sup>

Primary prophylactic measures are essential in seronegative women right before and during pregnancy and in immunosuppressed patients. These measures include:

- Avoiding ingestion of raw/undercooked meat (freezing at –20°C/–4°F overnight also destroys tissue cysts).
- Drinking only well-filtered or boiled water.
- Carefully washing vegetables/fruits before consumption.
- Using gloves and washing hands/kitchen utensils after manipulating meat/soil.
- Avoiding contact with felines and their feces (even in soil or litter boxes).<sup>2,3,7</sup>

Monthly serological screening of susceptible women during pregnancy is also highly recommended.<sup>2,53,58</sup>

## COURSE AND PROGNOSIS

Toxoplasmic retinochoroiditis is a recurrent disease, with up to two-thirds of patients developing reactivations later in life.<sup>1,3,59</sup> These are more common in congenital than in postnatally acquired toxoplasmosis and occur especially in the first year after the previous episode. Some patients, however, sustain long-lasting disease remission.<sup>59</sup>

Prognosis depends on the immune status and age of the patient and on the size and location of the lesion(s). Local complications such as

persistent vitreous opacities, macular edema, epiretinal membranes, extensive retinochoroidal scarring, choroidal neovascularization, optic atrophy, and even retinal detachment may be associated with significantly decreased vision.<sup>3,4,23,45</sup>

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# Posterior Parasitic Uveitis

Dipankar Das, Jyotirmay Biswas

# 7.13

**Definition:** Posterior parasitic uveitides encompass a number of parasitic infestations caused by different parasites. Various vectors spread the diseases, and areas of endemicity vary from region to region in the world. Clinical manifestations include characteristic ocular lesions, dermatological involvement and other extraocular sites affection. Parasitic diseases other than toxoplasmosis are described here.

## Key Features

- Ophthalmic and systemic examination is essential for the diagnosis of posterior parasitic diseases.
- Early diagnosis of these conditions is necessary to prevent ocular morbidity.
- Food hygiene and vector control is important in preventing the spread of the diseases.
- Parasitic diseases like toxocariasis is found in children.

## INTRODUCTION

Parasitic infections can produce severe damage to various ocular tissues, especially the uvea, thereby causing significant visual morbidity. It is important for ophthalmologists to be aware of the clinical presentation of the parasitic infestations for prompt diagnosis and management. Proper diagnoses of ophthalmic parasites can help to save vision and sometimes lives. Therefore, it is important to have appropriate coordination between clinicians, pathologists, and parasitologists for effective management of ocular parasites.

## OCULAR CYSTICERCOSIS

Ocular cysticercosis is the most common tapeworm infection caused by *Cysticercus cellulosae*, which is a larval form of the pork tapeworm *Taenia solium*.<sup>1-3</sup> Sometimes it may be caused by beef tapeworm. Consumption of undercooked pork and use of contaminated vegetables or water by humans can cause this infection.<sup>1,2</sup> Cysticercosis primarily affects the central nervous system (CNS), subcutaneous tissue, external eye structures, muscles, and intraocular structures like vitreous and retina.<sup>1,2</sup> Cysticercosis is found in worldwide distribution with about 50 million people being affected by this parasitic disease.<sup>1-3</sup> It is prevalent in South and Central America, Eastern Europe, Mexico, the Indian subcontinent, Russia, and the Philippines. It is rare in Great Britain and United States.<sup>1-3</sup>

## CLINICAL PRESENTATION

Intraocular cysticercosis may be asymptomatic in the early stages when the parasite is small. Ophthalmic cysticercosis can cause features such as loss of vision, periorbital pain, scotoma, and photopsia. Cysticercosis may present as neurocysticercosis or subcutaneous or muscular cysticercosis. The cyst may be localized to the subconjunctival space or orbit or may invade the globe and present in anterior or posterior segment.<sup>3</sup>

Intravitreal cysticercosis appears as a translucent white cyst with a dense spot formed by the invaginated scolex. The shape and undulating movements are typical. The cyst may remain asymptomatic when it is small and alive. Subretinal cysticercosis may present as acute central retinitis with retinal edema and subretinal exudates. The subretinal organism eventually develops into a cyst (Fig. 7.13.1). The macular area is the common site where the subretinal cysticercus lodges because of the vascularity of the area. B-scan ultrasound with identification of an intralesional scolex is

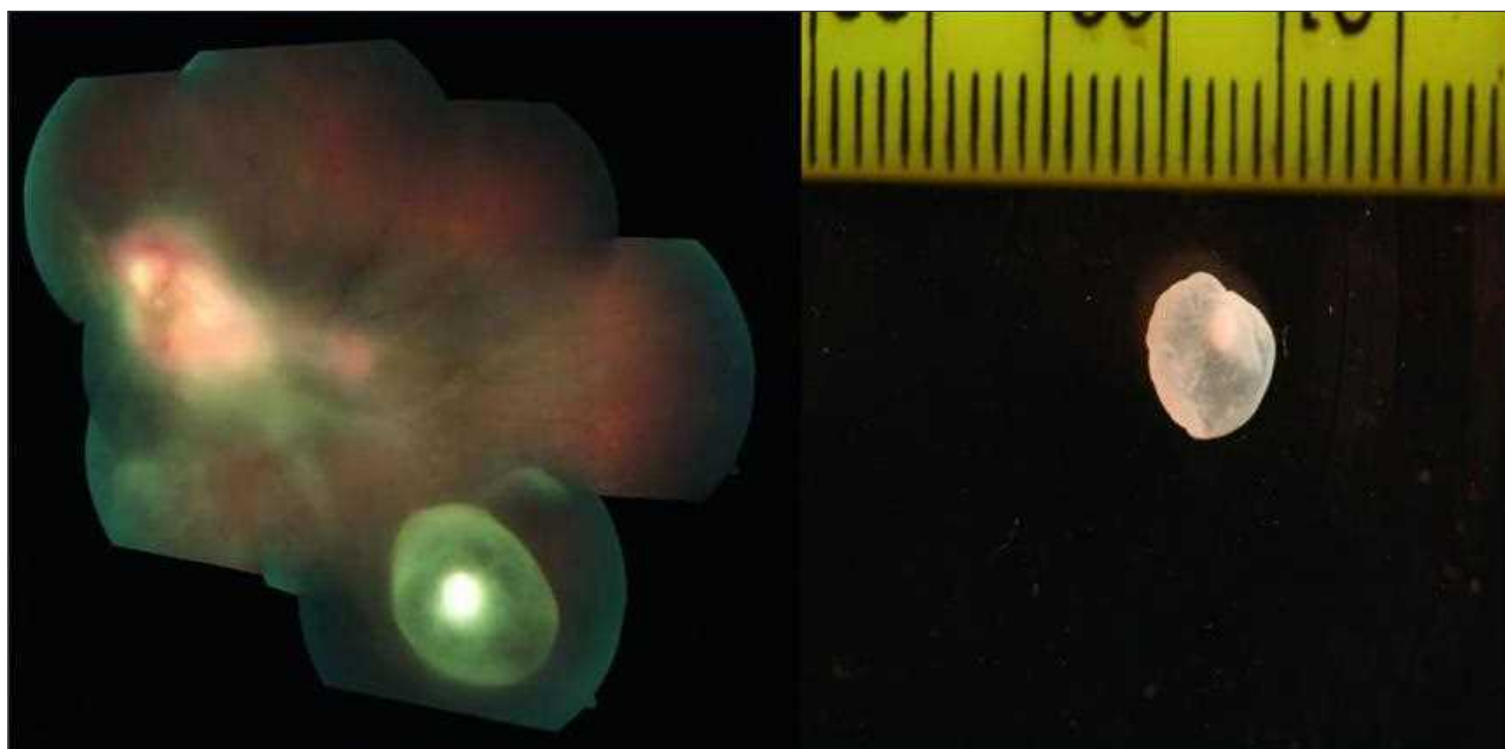
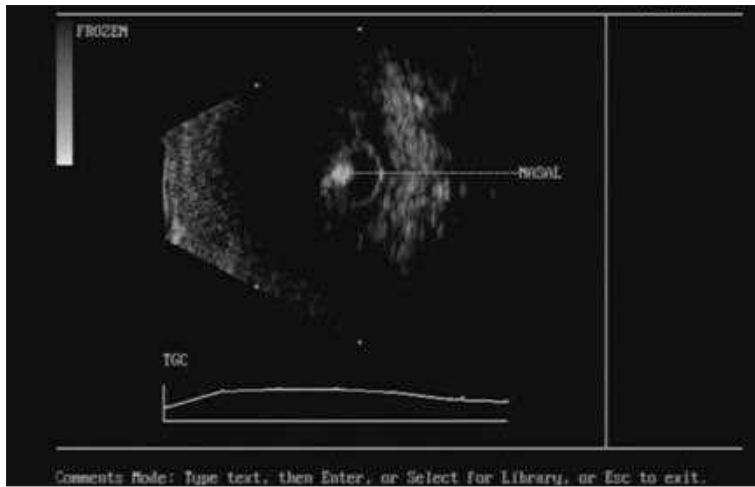


Fig. 7.13.1 Intravitreal Cysticercus With Cyst Isolated in Pathology.



**Fig. 7.13.2 B-Scan Ultrasound Showing a Scolex in a Case of Intraocular Cysticercosis.**

diagnostic in cases of intraocular cysticercosis (Fig. 7.13.2). The movements of the cysticercus are easily seen through the thin macular tissues. The cyst often migrates into the vitreous, leaving behind a chorioretinal scar in this area. One mode of presentation is that of fibrinous anterior uveitis with secondary glaucoma; the uveitis resolves with removal of the cyst. The posterior segment manifestation of ocular Cysticercosis can be variable, ranging from mild to intense vitritis with evidence of cystic larvae. Retinal break, rhegmatogenous retinal detachment, exudative retinal detachment, chorioretinal scar, or atrophy with epimacular membrane can be seen. Optic atrophy, optic disc edema, and sometimes atypical optic neuritis may be the remote presentation. Because of CNS involvement, the patient may have epileptiform seizures and mild fever.<sup>3,4</sup>

Diagnosis becomes difficult when the parasite dies, because it produces marked inflammatory response presenting as pan uveitis with dense opacification of the vitreous. In severe cases the patient may present with a painful blind eye. In these cases, a B-scan ultrasound is useful in confirming the diagnosis. B-scan usually demonstrates the complete cyst with an eccentric high reflective opacity (scolex). Other diagnostic modalities include neuroimaging such computed tomography (CT) imaging or magnetic resonance imaging (MRI) of brain and orbit. Coin-shaped lesion(s) with perilesional edema can be picked up in an MRI scan of the brain.<sup>1-4</sup> Serologically, cysticercosis can be diagnosed by precipitin reaction, complement fixation, or indirect hemagglutination assay.<sup>5</sup> Anticysticercus antibodies can be detected by enzyme-linked immunosorbent assay (ELISA) in approximately 80% cases of neurocysticercosis, 57% of ocular cysticercosis, and 50% with myocysticercosis.<sup>5</sup>

## TREATMENT

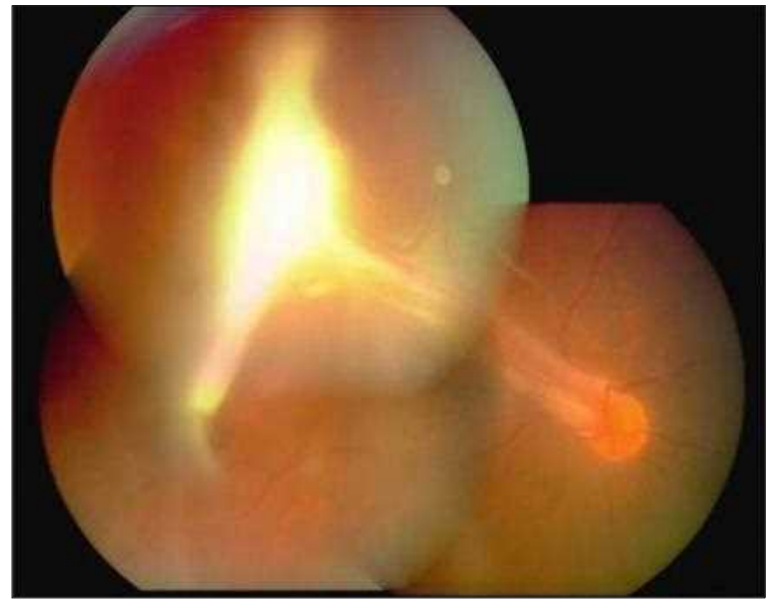
Surgical removal of the cyst is recommended. Intraocular cysticerci are removed either by external sclerotomy with choroidal incision or via pars plana vitrectomy.<sup>4,5</sup> Transscleral approach is used for subretinal cysts positioned anterior to the equator. The pars plana vitrectomy or transvitreal approach is used for intravitreal and subretinal cysts located posterior to the equator.<sup>4</sup> If there are both intraocular and CNS cysticercus cysts, then the complete intraocular cyst must be removed surgically, first followed by antiparasitic medication and corticosteroid.<sup>4,5</sup> Only use of antihelminthic medication in intraocular cysticercosis in the first attempt without surgical removal can kill the intraocular live parasite and thereby can induce severe intraocular reaction causing eventual blindness.<sup>4</sup> Albendazole and praziquantel are principal antiparasitic drugs that are used in treating neurocysticercosis and primary external ocular disease.<sup>4-10</sup>

## OCULAR TOXOCARIASIS

Ocular toxocariasis is caused by the dog roundworm *Toxocara canis*. It usually affects young patients. The various clinical presentations of the disease are:

### Chronic Endophthalmitis

This can present as a vitreous abscess or a dense white inflammatory mass usually associated with a retinal detachment. It may be associated with



**Fig. 7.13.3 Peripheral Toxocara Lesion.**

a granulomatous response in the anterior chamber and a hypopyon. The acute inflammatory phase is followed by a cicatricial stage.

## Posterior Pole Granuloma

Initially presents with a hazy vitreous and signs of acute inflammation with the posterior pole granuloma seen as an ill-defined hazy mass with surrounding vitreous inflammation. The media clears as the inflammation subsides. The spherical granulomatous mass is white or gray, and traction bands are seen running from the mass to the surrounding retina.

## Peripheral Granuloma

It is seen as a dense white localized inflammatory mass in the retinal periphery. Localized traction on the retina results in a fold or tractional detachment extending from the mass to the posterior pole. This can cause dragging of the macula toward the granuloma (Fig. 7.13.3).

## Atypical Presentations

These include optic nerve head inflammation, motile subretinal nematode, and diffuse chorioretinitis.

## DIFFERENTIAL DIAGNOSIS

- Retinoblastoma.
- Retinopathy of prematurity.
- Familial exudative vitreoretinopathy.
- Coats' disease.
- Persistent hyperplastic primary vitreous.
- Endogenous endophthalmitis.

## ANCILLARY TESTING

A serum ELISA titer of 1:8 is sufficient to support a diagnosis of ocular toxocariasis if the patient also has compatible clinical features.

## TREATMENT

Antihelminthics such as thiabendazole and diethylcarbamazine have a limited role. In cases with severe inflammation, topical corticosteroids, cycloplegics, and systemic corticosteroids may be necessary. Vitrectomy is indicated in cases of tractional retinal detachment.

## ONCHOCERCIASIS

This infection is caused by the filarial worm *Onchocerca volvulus* or *Onchocerca caecutiens*. The disease is widely endemic in tropical Africa and

tropical parts of the Americas. The disease is spread by the black (biting) fly (*Simulium*), which freely breeds in the rivers. The blindness caused by onchocerciasis is known as river blindness. About half a million people in the world are blind or partially blind due to onchocerciasis. Systemic manifestations consist of skin nodules (lymphadenopathy). Ocular manifestations are very common and include swelling of eyelids, proptosis, thickening of the conjunctiva, and nummular keratitis. It is not rare to see microfilaria wandering in the anterior chamber and vitreous cavity.

Uveoretinal inflammation is the most important pathology of onchocerciasis so far as visual loss is concerned. The toxins liberated from the dead worms induce the uveal pathology. Plastic iritis associated with edema of iris stroma produces the spongy pumice stone appearance of the iris. Light brown exudative deposits in the lower part of the anterior chamber produce an inverted pear-shaped appearance of the pupil that is considered a characteristic ocular sign of the disease. Chorioretinal inflammation leading to atrophy of the neural tissue with consecutive optic atrophy is the ultimate cause of blindness. Ophthalmoscopic examination of the fundus shows clumping of retinal pigment, atrophy of choriocapillaris, and subretinal fibrosis. Glaucoma and cataract may be complications of uveoretinal inflammation. The effective treatment of onchocerciasis is with ivermectin, diethylcarbamazine (Hetrazan) and suramin (Antrypol).

### GNATHOSTOMIASIS

This is due to a parasite known as *Gnathostome*, ingested by people by eating semicooked fish, usually found in dirty shallow drains. Cases of gnathostomiasis had been reported from the eastern region of undivided India including present-day Bangladesh.<sup>2</sup> Clinical features of the disease may be cutaneous and visceral, including ocular involvement. Ocular manifestations of the disease occur due to migration of the larvae as well as host response to the toxins. The most common presenting feature is anterior uveitis.<sup>3,5,9-13</sup> Other features include lid swelling, iritis, iris atrophy, iris holes (Fig. 7.13.4), and rarely glaucoma. Intravitreal gnathostomiasis is a very rare entity. Macular scarring or retinal tear with choroidal hemorrhage near the optic disc points to the posterior retina as a possible route of entry to the eye. The worm roams in the eye, causing retinal hemorrhage and subsequent chorioretinitis (Fig. 7.13.5). Surgical removal of the live worm may be done while it is visible in the anterior chamber.

### DIFFUSE UNILATERAL SUBACUTE NEURORETINITIS

Diffuse unilateral subacute neuroretinitis (DUSN) is also called unilateral wipe-out syndrome. It can be caused by a number of motile, nematode roundworms including *Toxocara canis*, *Gnathostoma*, *Brugia malayi*, *Ancylostoma caninum*, and the trematode *Altaria*.<sup>1-3,11,14-16</sup> Males are more frequently affected than females. Nematodes in DUSN may invade the skin

and migrate hematogenously to retinochoroidal complex.<sup>2,3</sup> These small worms are thought to induce toxic, inflammatory, and autoimmune reaction to the choroid and overlying retina. DUSN can present with either early or late stage manifestations.<sup>4,5,17</sup> Patients may present with central and paracentral scotomas, floaters, and visual field defect without any significant ocular pain. In the early stage, optic disc edema, mild to moderate vitritis, subretinal, multifocal yellow gray-white lesions are seen in the fundus with papillitis.

Late stages include optic nerve atrophy, retinal arteriolar narrowing, increased internal limiting membrane reflections (Oréface's sign), and subretinal tunnels (Garcia's sign) with retinal pigment epithelium (RPE) degeneration.<sup>1,17</sup> A relative afferent pupillary defect (RAPD) may be present on the affected eye. DUSN is now believed to be caused also by small number of different nematode larvae.<sup>15</sup> The first pathological change secondary to nematode larva infestation presents as granulomas in the whole globe.<sup>1</sup>

There have been variable sizes of worms detected and reported, with longer worms leaving a tract of coarse clumping of pigment epithelium.<sup>1,16</sup> The shorter worms predispose to leave focal, chorioretinal atrophic scars. The focal chorioretinal white spots are an immune response to a secretion or excretion from the worm. Worms, regardless of species, have been observed in the eye for up to 3 years. The diagnosis is mostly clinical. The live worm may not be visible on many occasions. Fluorescein angiography (FA) may show an increase in background choroidal fluorescence, diffuse changes in RPE, and capillary dye leakage near the optic nerve.

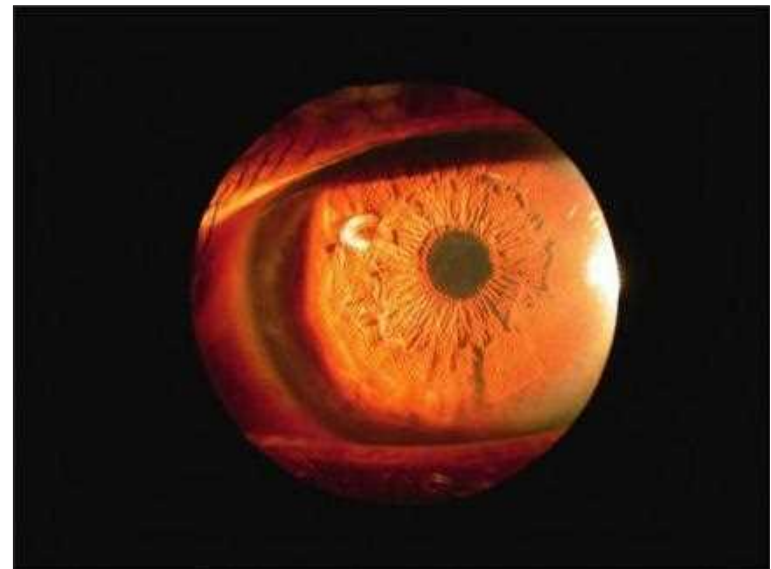


Fig. 7.13.4 *Gnathostoma* Worm Migrating Through Iris Creating Iris Hole.

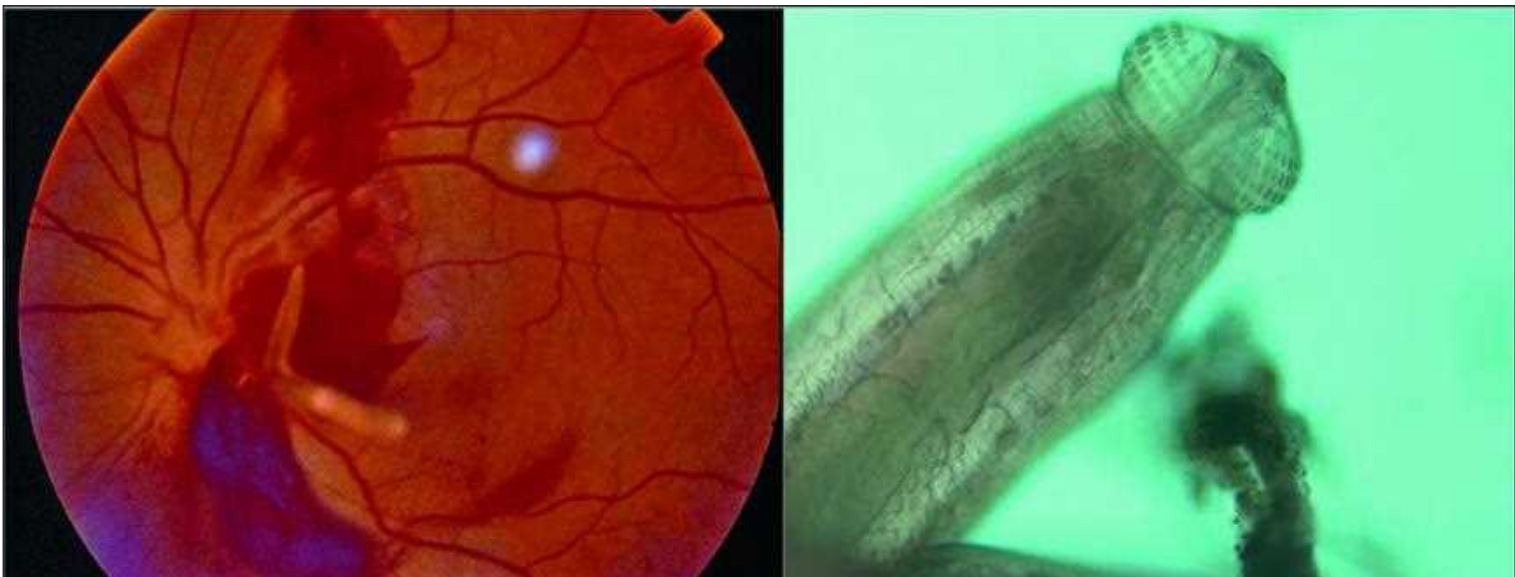


Fig. 7.13.5 Retinal and Vitreal *Gnathostoma* With Wet Mount Preparation of the Parasite.



Indocyanine green angiography (ICGA) is sometimes useful to locate the lesions as hypofluorescent spots and corresponding choroidal infiltration and inflammation. Electrophysiological tests such as electroretinogram (ERG) and electro-oculogram (EOG) are helpful for ancillary support for the diagnosis. In ERG, A:B ratio can be normal in early stages of the disease, but B wave can be defective when significant retinal involvement is seen. The inner retina is more involved than the outer retina.<sup>4,17</sup> EOG may show reduced response in moderate to late involvement.

Optical coherence tomography (OCT) is an important tool to demonstrate degeneration of retinal nerve fiber layer (RFNL) and thinning of the macula. Here also, inner retinal volume is more affected than the outer retinal volume. In some cases there may be loss of foveal depression. Laboratory diagnosis should include eosinophils count for the nematode infections.

Other diseases that should be ruled out include syphilis, sarcoidosis, and toxoplasmosis. Optic neuritis, pars planitis, and some of the white dot syndromes need to be excluded for making the diagnosis. A macular cyst has also been an associated finding in DUSN.<sup>1,3,16</sup> Management of DUSN depends on whether the worm is visible. Visible live nematodes are treated with retinal photocoagulation. Systemic treatment involves 400 mg albendazole daily for one month with oral corticosteroid 1 mg/kg/day in tapering dose for one month. The course of the disease depends on the disease stage. Early detection stops the vision loss effectively.<sup>1-3,6-9,16,18,19</sup>

## AMEBIASIS

Infection by *Entamoeba histolytica* is quite frequent in tropical countries. It is estimated that about 20% of rural populations are the victims of this parasitic intestinal disease, which causes dysentery, hepatitis, and liver abscess.

Ocular involvement of amebiasis involves:

- Anterior and posterior uveitis.
- Recurrent vitreous hemorrhage.
- Retinal periphlebitis.

In none of the affected cases, however, could *Entamoeba histolytica* be isolated from the eye. The presumptive diagnosis was based on coexistent disease process and definite improvement of the eye condition after antiamebic treatment.

## GIARDIASIS

Intestinal infection by *Giardia lamblia* is common in the Indian subcontinent. Keratitis, uveitis, extensive chorioretinitis, and retinal hemorrhages in patients with giardiasis have been reported. Some of the common presentations of giardia are anterior uveitis, choroiditis, and retinal pigment changes. All the reported cases responded well to the treatment of giardiasis.

## MALARIA

There are about 300 million cases of malaria worldwide annually, and 30 million persons from nonendemic countries visit malaria-endemic countries. Thus there is a significant possibility of traveler's malaria. The parasite responsible for malaria in humans belongs to Plasmodium family *P. vivax* (tertian malaria), *P. malariae* (quartan malaria), *P. falciparum* (subtertian malaria), and *P. ovale*. Ocular complications are more common in *P. falciparum* infection. Almost all the structures of the eye may be involved in malaria.

Conjunctival hyperemia, subconjunctival hemorrhage, conjunctival pigmentation, dendritic ulcer, interstitial keratitis, uveitis, vitreous hemorrhage, retinal hemorrhage, retinal detachment, optic neuritis, paralysis of extraocular muscles, and orbital cellulitis have been reported.<sup>4,5,10,17</sup> Retinal hemorrhage is considered to be due to rheological complications—the parasitized erythrocytes tend to clump along the vessel wall leading to occlusion.<sup>7</sup> Other ocular lesions include retinal hemorrhages, transient ocular nerve palsies, orbital edema, choroiditis, retinal embolism, papilledema, paralysis of the pupillary light reflex, and accommodation. The presence of ocular lesions in malaria indicates poor prognosis, especially in patients

with cerebral malaria.<sup>7,11</sup> Therefore, a patient with unexplained large retinal hemorrhages should always be investigated thoroughly for malaria, especially in an endemic country such as India.

## LEISHMANIASIS

Leishmaniasis is widespread in central and eastern Asia, Africa, and a few countries in Europe. The disease is caused by the protozoan *Leishmania*, which is transmitted to humans by sand fly (*Phlebotomus*). Three distinct types have been recognized:

- Visceral leishmaniasis is caused by *Leishmania donovani* and is responsible for kala-azar.
- Cutaneous leishmaniasis is caused by *Leishmania tropica* and is manifested as granulomatous sores in the exposed parts of the body, known as oriental sore.
- Nasopharyngeal leishmaniasis (espundia) is caused by *Leishmania braziliensis* and is mostly prevalent in South America.

Characteristic features of kala-azar are persistent irregular fever for a long period, enormous enlargement of the spleen, moderate enlargement of liver, and marked degree of anemia. The diagnosis is made by identifying *L. donovani* in smears from spleen and bone marrow puncture.

## OCULAR MANIFESTATION

Retinal hemorrhages occur perhaps due to severe anemia.<sup>6</sup> Thrombosis of the central retinal vein also may occur. Ocular involvements of post kala-azar dermal leishmaniasis include episcleral nodules that may lead to deep corneal vascularization. Post kala-azar uveitis also has been reported.<sup>7,8,12,13,20</sup> In oriental sore, tiny ulcerating papules may be found in the eyelids at the site of the bite by the sand fly. It may be associated with conjunctivitis. In espundia, the ulcer is limited to the face and mucous membrane of the anterior third of the nasal septum. In severe cases, the ulcer may destroy the nose and the eyelids.

## PEDIATRIC PRESUMED TREMATODE INFECTION

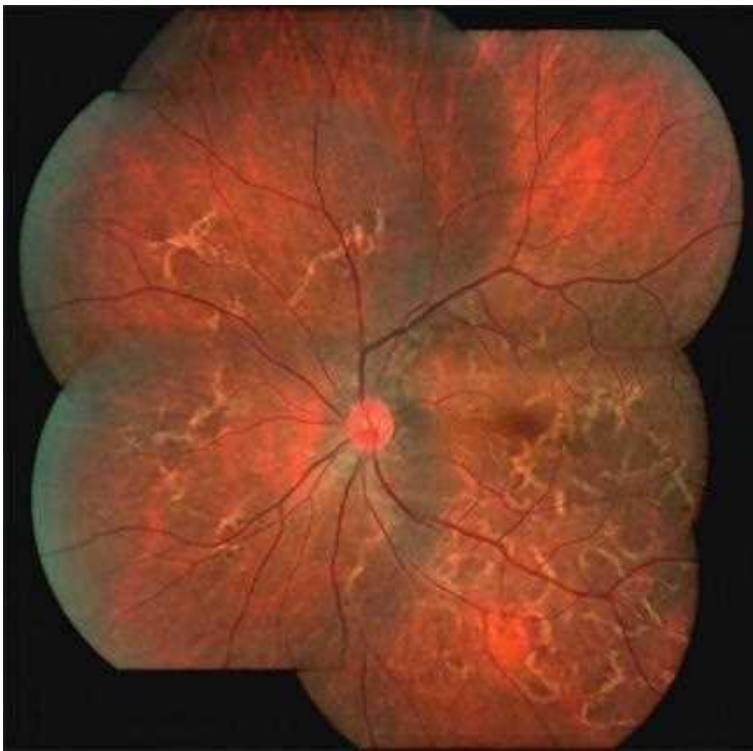
This has been reported in patients from South India who were exposed to pond water. The causative parasite was identified as *Philophthalmus*. The external body surface, referred to as a tegument, is made up of an external plasma membrane and an internal trilaminar plasma membrane.<sup>9,14</sup> Dermatitis may be an associated extraocular feature. The ocular manifestations are subconjunctival nodules, anterior chamber nodules, and granulomatous uveitis (but rarely panuveitis or posterior uveitis). Histologically, the nodules have eosinophilic infiltration along with chronic inflammatory cells and a specific inflammatory reaction known as Splendore Hoeppli phenomenon. This phenomenon is characterized by a central deposit of granular, acellular eosinophilic material surrounded by eosinophilic leukocytes, epithelioid cells, histiocytes, and lymphocytes. Occasionally, teguments of parasite may also be seen.

## OPHTHALMOMYIASIS

This is a condition where the eye or adnexa are invaded by maggots (larvae). Cattle, sheep, horse, deer, and humans are the known hosts. Eggs are deposited by the flies in the lid margins or on the conjunctiva, producing local inflammatory changes (ophthalmomyiasis externa). In ophthalmomyiasis interna, larvae pass through their second stage and can penetrate the eye and orbit causing tissue damage (Fig. 7.13.6). Small conjunctival hemorrhages may occur because of tissue damage from oral hooks. Subretinal tracts are representative of mechanical injury to retinal pigment epithelium.<sup>5</sup> The death of the larva can cause uveitis.

## ACKNOWLEDGEMENT

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**Fig. 7.13.6** Montage Fundus Picture of Suspected Ophthalmomyiasis Interna (Retinal Tract)

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# Uveitis Related to HLA-B27 and Juvenile Idiopathic Arthritis–Associated Uveitis

7.14

Carlos E. Pavesio

## UVEITIS RELATED TO HLA-B27

**Definition:** Ocular inflammation associated with the HLA-B27 antigen.

### Key Features

- Acute and recurrent unilateral nongranulomatous anterior uveitis.
- Ocular pain and photophobia.
- Ciliary injection.
- Often severe anterior uveitis with fibrin deposition or hypopyon.
- Frequent posterior synechiae.

### Associated Features

- Often ankylosing spondylitis.
- Sometimes reactive arthritis.

## JUVENILE IDIOPATHIC ARTHRITIS-ASSOCIATED UVEITIS

**Definition:** Uveitis associated with chronic arthritis of at least 6 weeks duration in a child younger than 16 years of age when other causes have been excluded.

### Key Features

- Asymptomatic, bilateral, nongranulomatous anterior uveitis.
- Symptomatic in some acute forms and in the presence of complications.
- Posterior synechiae, cataract, glaucoma, and less frequently cystoid macular edema (CME) are complications.
- Screening very important for early detection and treatment.

### Associated Features

- Oligoarthritis.
- Antinuclear antibodies.

## UVEITIS RELATED TO HLA-B27

### INTRODUCTION

The most common form of uveitis worldwide is acute, unilateral, and nongranulomatous, involving only the anterior segment (acute anterior uveitis [AAU] or iridocyclitis). Most affected patients are systemically well, but studies suggest that between 40% and 50%—and perhaps up to 80%<sup>1</sup>—are positive for HLA-B27. Those who manifest associated systemic inflammation usually have ankylosing spondylitis (AS); a smaller number have inflammatory bowel disease, reactive arthritis, or psoriatic arthropathy.

The locus for human leukocyte antigens (HLA) is on chromosome 6p. HLA types are autosomally inherited, partly explaining the increased familial risk of AAU and AS in those carrying HLA-B27. The antigen is polymorphic with more than 31 subtypes.<sup>2</sup> In Northern Europeans, 90% of those who are HLA-B27–positive express HLA-B\*2705 (which may be the primary ancestral HLA-B27 subtype)<sup>3</sup>; this subtype is more common in men. All common subtypes are associated with both AAU and AS, exceptions being B\*2706 or B\*2709.<sup>4</sup>

The prevalence of HLA-B27 differs markedly between populations (more common in white races), and this fact is reflected in a wide disparity in the incidence of related inflammatory disease.<sup>5</sup> In Bantus in Zaire, the prevalence of HLA-B27 is very low at 0.7%<sup>6</sup>; in the United Kingdom and United States the figure is 6%–8%, rising to 14% in Finland,<sup>7</sup> and maximally, 50% in the Haida Indians of Canada, where one in 10 men has AS.<sup>8</sup>

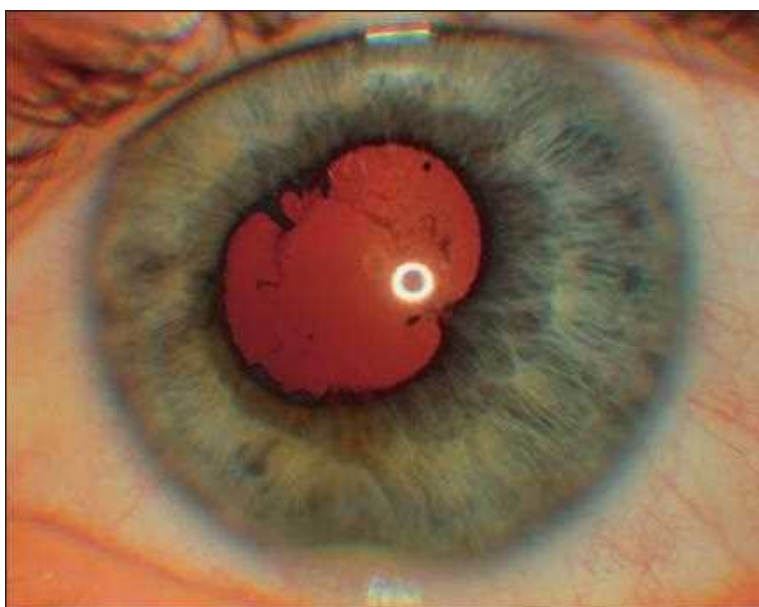
### PATHOGENETIC MECHANISMS

The presence of HLA-B27 predisposes to AAU, AS, and reactive arthritis, but the lifetime risk of AAU for those who are HLA-B27–positive is only 1%.<sup>9</sup> Therefore it is clear that further provocation is necessary to trigger AAU in this susceptible population. There are well-known associations between infection with some Gram-negative bacteria and *Chlamydia* and AAU. The original theories of molecular mimicry by homologous regions on HLA-B27 and bacterial receptors<sup>10</sup> have not been fully elucidated. It is becoming increasingly clear that AAU is a polygenic disease; it is known that some polymorphisms of the tumor necrosis factor alpha promoter region are protective against AAU in HLA-B27–positive patients, whereas others are proinflammatory<sup>11</sup> and knowledge of other cytokine polymorphisms important to the induction of attacks of inflammation is advancing.<sup>3</sup>

Evidence from numerous studies suggests a strong genetic component in the pathogenesis of acute anterior uveitis,<sup>3,12,13</sup> with increasing evidence that genes other than HLA-B27 influence the risk of developing AAU. Recent genome-wide studies of large cohorts of patients detected three non-major histocompatibility complex (MHC) loci: IL23R, the intergenic region 2p15, and ERAP1, which were associated with AAU and AS ( $p < 5 \times 10^{-8}$ ).<sup>3,14</sup> In addition, five loci harboring the immune-related genes IL10-IL19, IL18R1-IL1R1, IL6R, the chromosome 1q32 locus harboring KIF21B, and EYS were also associated at a “suggestive level of significance.”

### CLINICAL FEATURES AND LABORATORY INVESTIGATIONS

The paradigm for HLA-B27–associated AAU is a young man with acute-onset unilateral ocular pain and photophobia with redness and visual blur. Visual acuity in the affected eye is usually somewhat (but not markedly) reduced. Ocular examination is characteristically difficult because of photophobia. There is marked ciliary injection and severe AAU with small keratic precipitates inferiorly, anterior chamber (AC) cells 2–4+, often with fibrinous coagulum inferiorly, and sometimes with an hypopyon. Fibrin may form a web within the AC, the aqueous humor may be plasmoid (full of leaked plasma proteins so that normal thermal flow is sluggish), and incipient posterior synechiae are common (Fig. 7.14.1). The intraocular pressure is reduced, usually less than 10 mm Hg. Cells in the anterior



**Fig. 7.14.1 Acute Anterior Uveitis After Partial Mydriasis.** There are residual synechiae, a pupillary pigment imprint on the anterior lens capsule, and an inferior fibrinous coagulum.

vitreous are common. Macular edema is not uncommon, and optic nerve head swelling is occasionally seen.

HLA-B27 is positive in many patients with AAU. Notably, in those under 40 with acute unilateral recurrent AAU without mutton-fat keratic precipitates, the concordance with HLA-B27 is so high<sup>15</sup> that laboratory confirmation of positivity may be unnecessary. A recent report described a small series of patients over the age of 70 who had a very aggressive picture of acute anterior uveitis at presentation.<sup>16</sup>

Recurrent AAU is common, usually in the same eye. Frequently, patients have several recurrences of ipsilateral AAU followed by several in the other eye. Some patients develop bilateral uveitis, and a minority go on to develop chronic unremitting inflammation. Poorly controlled inflammation and chronicity are associated with poorer outcomes.<sup>17</sup> Pupillary block will require laser iridectomy or (because these tend to block), surgical iridectomy. Glaucoma induced by peripheral anterior synechiae (PAS) requires medical or surgical treatment. Raised intraocular pressure, although identified in about one-quarter of all presentations,<sup>18</sup> is more common in chronic-phase disease. HLA-B27–associated AAU carries a worse prognosis than HLA-B27–negative uveitis.<sup>19</sup> However, despite multiple recurrences and/or chronic disease, bilateral visual loss is fortunately very uncommon.<sup>20</sup>

Posterior segment involvement in HLA-B27–associated uveitis is very uncommon but can be so severe as to mimic infective endophthalmitis.<sup>21</sup> In rare cases severe uveitis with a serous retinal detachment might develop in HLA B27–positive patients and may be complicated by protracted hypotony, macular edema, and poor visual outcome.<sup>22</sup> Retinal vasculitis, papillitis, cystoid macular edema, and epiretinal membrane formation are all seen occasionally.<sup>23</sup> Associated systemic disease is more common in this group.<sup>24</sup>

## ASSOCIATED SYSTEMIC DISEASE

Associated systemic inflammation can be identified in up to 78% of patients.<sup>25</sup> The AAU often precedes diagnosis of an arthropathy, and the ophthalmologist must identify the relevant disease and refer if necessary. Some patients presenting with AAU have had AS diagnosed already; others should be specifically asked about chronic lower back pain with morning stiffness and referred for investigation and treatment (Fig. 7.14.2).

Reactive arthritis (Reiter's syndrome) may unusually present with conjunctivitis. The classic clinical scenario is a man with nonaxial lower limb arthropathy and/or enthesitis with circinate balanitis and a vesiculopustular rash, sometimes keratinized, on the palms and soles, known as keratoderma blennorrhagicum. There may also be mouth ulcers.

Psoriasis is extremely common and therefore will be randomly associated with uveitis in some patients. However, the minority who have associated arthropathy have a specific risk of acute or chronic anterior uveitis. Characteristically the distal small-joint polyarthritis is destructive (Fig. 7.14.3), sometimes leading to very severe finger damage with characteristic



**Fig. 7.14.2 Fusion of the Sacroiliac Joint Space With Sclerotic Change in Ankylosing Spondylitis.**



**Fig. 7.14.3 Characteristic Dactylitis in Psoriatic Arthropathy.**

swan-neck deformities. A genuine association between nonarthritic psoriasis and uveitis is unproven, but in the absence of arthropathy, any uveitis tends to be more chronic, and posterior segment involvement with or without retinal vasculitis may be seen. This contrasts with psoriatics who are HLA-B27–positive<sup>26</sup> or those with spondyloarthropathy,<sup>27</sup> where more characteristic AAU is seen.

Inflammatory bowel disease (IBD), most commonly Crohn's disease, is associated with uveitis, but as for psoriasis, in those who are HLA-B27–negative this is commonly bilateral and chronic and may involve the posterior segment.<sup>28</sup> Crohn's disease can be associated with AS in the absence of HLA-B27,<sup>29</sup> but nongranulomatous anterior uveitis does not appear to be. Interestingly, patients with both psoriatic and IBD-related arthropathy are more likely to have axial than peripheral arthropathy if HLA-B27–positive.<sup>27</sup> HLA-B27 appears capable of modifying the disease pattern in those with a pre-existing underlying arthropathy, and it is tempting to suggest the same for associated uveitis.

## TREATMENT AND PREVENTION

Untreated AAU tends to be self-limiting within a few weeks, leaving substantial posterior synechiae and often PAS. Subsequent attacks frequently result in seclusio pupillae, pupil block glaucoma, and painful blindness. In contrast, early and effective treatment eliminates pain, more rapidly resolves inflammation, and minimizes complications.

Immediate and diligent mydriasis and cycloplegia is imperative; rapid analgesia results and incipient synechiae are usually broken. Subconjunctival procaine, atropine, and epinephrine can break recalcitrant synechiae, especially with warm compresses. Frequent, strong, topical corticosteroid is highly effective. Although the level of evidence for topical corticosteroid potency is poor,<sup>30</sup> the clinical impression is that intensive prednisolone acetate 1%, which has a very high anterior chamber penetration,<sup>31</sup> is most useful; its introduction has markedly reduced the need for subconjunctival corticosteroid injection. Topical nonsteroidal anti-inflammatory

drugs (NSAIDs) are inadequate to treat any substantial uveitis. However, oral NSAIDs have been found useful in some instances.<sup>32</sup> In severe cases, both daily subconjunctival and single-dose periocular depot corticosteroid can be helpful, and rarely, high-dose oral corticosteroid achieves control. If fibrin deposition is extreme and pupil block likely, intracameral tissue plasminogen activator has been used successfully<sup>33</sup> but not widely, as there is a substantial risk of hyphema. Topical corticosteroid treatment is tapered according to response, but overly aggressive dose reduction can lead to a flare-up of inflammation. Most attacks require 6–10 weeks of topical corticosteroid. Associated macular edema usually subsides with topical corticosteroid alone.

Some go on to develop chronic inflammation, either anterior or panuveitis. Inadequate topical corticosteroid will inevitably lead to destructive complications. In some, oral immunosuppression is needed. Early treatment has been recommended.<sup>34</sup> Some patients are frustrated by multiple recurrences and ask about prophylaxis. The evidence base is poor, but in small groups, both sulphasalazine<sup>35</sup> and methotrexate<sup>36</sup> have been considered useful. Further, much larger studies are necessary.

A large retrospective study suggested that infliximab and adalimumab reduced the rate of uveitis, while the frequency of uveitis in patients with spondyloarthritis treated with etanercept remained unchanged.<sup>37</sup> A large meta-analysis, involving the data from four placebo-controlled studies with anti-tumor necrosis factor (TNF) agents in AS (two with etanercept and two with infliximab) and three open-label studies, showed that infliximab and etanercept seem to reduce the incidence of uveitis versus placebo, and further, infliximab appeared to be more effective than etanercept, even though the difference between them did not reach statistical significance.<sup>38</sup>

Adalimumab was also evaluated from data of 1250 patients with active AS in a prospective open-label study. Adalimumab achieved an approximately 50% reduction in uveitis flares.<sup>39</sup>

Although, there are no prospective head-to-head randomized studies comparing efficacy of anti-TNF $\alpha$  agents in HLA-B27 uveitis management, infliximab and adalimumab are generally accepted to be more effective than etanercept.<sup>40</sup>

Reports of the efficacy of golimumab have recently appeared, but conclusive data is not yet available.<sup>41</sup>

## JUVENILE IDIOPATHIC ARTHRITIS

### INTRODUCTION

Juvenile idiopathic arthritis (JIA) is defined as a chronic arthritis of at least 6 weeks' duration in a child younger than 16 years of age when other causes of arthritis have been excluded.<sup>42</sup> It is the most common cause of uveitis of childhood in Europe and North America.<sup>43,44</sup> It has an estimated prevalence of 113 per 100 000 children in the United States,<sup>45</sup> and the annual incidence is 10–20 per 100 000,<sup>46</sup> similar to that seen in the United Kingdom. The highest rates occur in Scandinavia, but rates are lower in southern Europe.

The criteria published by the International League of Associations of Rheumatology (ILAR) covers all childhood arthritides under the name JIA.<sup>42</sup> Apart from unifying the name, it has established that the disease duration for the diagnosis should be 6 weeks and includes juvenile ankylosing spondylitis (JAS), juvenile psoriatic arthritis (JPsA), and arthropathy associated with IBD under this broad definition.

The new classification of JIA has divided it into seven subtypes, defined after the first 6 months of disease.

Oligoarthritis is the most common subtype (50%–70%), followed by polyarthritis (30%), with the great majority being rheumatoid factor (RF) negative. Systemic onset and enthesitis-related arthritis each occur in about 5% of patients. These figures are valid for populations of European ancestry, and ethnic differences have been reported, with the polyarticular form being more common in nonwhite populations.<sup>47</sup>

### PATHOGENETIC MECHANISMS

The pathogenesis of JIS is not well understood, and the evidence indicates that JIA is a multifactorial and polygenetic disease, but it does seem that the genetic contribution is modest, which is evidenced by the modest increase in risk to family members of JIA cases and multiple genetic associations involving mainly the MHC locus.<sup>48</sup>

The chronic and remitting course has led to assumption that problems with control of the regulatory processes over effector cells may lead to loss of immune homeostasis, and the role of the regulatory T cells has also been considered as a potential determinant of the course of the disease.<sup>48,49</sup>

## CLINICAL PICTURE

*Oligoarthritis* occurs predominantly in young girls and affects four or fewer (usually large) joints, with the knee being the most commonly involved, during the first 6 months of disease.<sup>50</sup>

*Rheumatoid factor-negative polyarthritis* has a chronic course, affecting both small and large joints, with more than four joints involved in the first 6 months of disease. It is more common in girls, with a higher age at onset.

*Psoriatic arthritis* may have characteristics of both oligo- and polyarticular disease, but the occurrence of psoriasis and arthritis helps establish the diagnosis.<sup>42</sup> These patients do not show an increased frequency of HLA-B27 and rarely will manifest sacroiliitis or lumbosacral spinal arthritis.<sup>50</sup>

*Enthesitis-related arthritis* is a chronic inflammation of entheses and particularly involves the foot, knee, and pelvis. It is common in boys, with the uveitis being symptomatic and occurring in older adolescents and adults. Most of these patients will have HLA-B27 and will eventually develop sacroiliitis and lumbosacral spinal disease.

## UVEITIS IN JIA

As much as 80% of anterior uveitis in the pediatric population is associated with JIA.<sup>51</sup> A recent meta-analysis revealed that the cumulative incidence of JIA-associated uveitis is 8.3%; in the oligoarticular group is 12.4%, in the polyarticular group is 4.3%, and in patients with systemic onset, 1.8%.<sup>52</sup>

## RISK FACTORS

Risk factors for the development of uveitis include oligoarticular arthritis type, early age at onset of arthritis, positive antinuclear antibodies (ANAs), negative RF, and female sex.<sup>53,54</sup> A meta-analysis showed that oligoarticular onset tripled the risk when compared to polyarticular onset, a positive ANA nearly tripled the risk of oligoarticular onset patients, and unexpectedly, female sex alone was a weak risk factor.<sup>52</sup> Even though ANAs are a risk factor for developing uveitis, their levels are not predictive of uveitis recurrences.<sup>55</sup>

Factors associated with long-term complications include severe disease at presentation,<sup>55</sup> short interval between onset of arthritis and the diagnosis of uveitis,<sup>56</sup> male sex,<sup>57</sup> presence of complications at initial presentation,<sup>58</sup> and early age at onset of uveitis.<sup>53</sup> Male sex and shorter interval between onset of arthritis symptoms and the diagnosis of uveitis were found to be the only significant risk factors for severe uveitis at diagnosis,<sup>59</sup> whereas poor outcome is strongly linked to severity of disease at presentation<sup>55</sup> and also male sex.<sup>57</sup>

## CLINICAL PICTURE

In 80% of patients, the uveitis is insidious, asymptomatic, and may result in blindness if left untreated.<sup>56</sup> During exacerbations, patients may manifest discomfort and redness. This picture is most frequently bilateral, with either simultaneous presentation or with second eye involvement generally occurring after a few months and rarely after 1 year.<sup>60</sup>

The typical presentation is bilateral, nongranulomatous iridocyclitis with small keratic precipitates in the inferior half of the cornea and mild-to-severe anterior chamber flare and cells and anterior vitreous cells. Granulomatous presentation has been reported, but it is important here to exclude other diseases, especially sarcoidosis.<sup>61</sup>

An acute anterior uveitis may be seen in enthesitis-related arthritis and tends to occur in older HLA-B27-positive boys, with pain, redness, and photophobia. These patients may develop spondyloarthropathy in adult life, with recurrent acute anterior uveitis.<sup>46</sup>

Most cases of uveitis are diagnosed within 4 years of the onset of arthritis<sup>60,62</sup> but may occur sooner, especially in those with extended oligoarthritis, who tend to fall ill quite early on.<sup>63</sup> Some individuals may develop uveitis after the age of 16, and this could be either asymptomatic or symptomatic. One study found that many patients with uveitis continue to show disease activity in adult life and that this was usually associated with activity of the joint disease.<sup>63</sup> The same study found that patients with acute symptomatic uveitis had their first attack of uveitis later in life and that they were all HLA-B27-positive and ANA-negative.

A study of 358 children with oligoarthritis and rheumatoid factor-negative polyarthritis showed that an elevated ESR appeared to be a predictor for the occurrence of uveitis in patients with JIA, and the authors propose its use as a biomarker in daily practice.<sup>64</sup>



## COMPLICATIONS AND PROGNOSIS

The chronic nature of the disease, with periods of exacerbation, will determine the complications associated with this condition. Most of the damage involves the anterior segment of the eye, but permanent alterations may also affect the posterior segment.<sup>65</sup> The most common complications include: band keratopathy, posterior synechiae, cataract, glaucoma, cystoid macular edema, and cyclitic membrane with hypotony.<sup>46</sup>

Another factor associated with complications is a high flare, with a reading of less than 20 photon units per second (pms) at the time of initial assessment being associated with significantly lower prevalence of complications.<sup>66</sup>

Cataract, usually posterior subcapsular, is common, with a cumulative incidence of 20.5%,<sup>52</sup> and results from chronic inflammation and chronic use of corticosteroid therapy. Anterior subcapsular opacities will also appear in places where posterior synechiae develop. The reported prevalence is variable but approaches 50%.<sup>67,68</sup>

Secondary glaucoma can be sight threatening. In the majority of affected eyes the intraocular pressure increases shortly after control of inflammation is achieved, suggesting recovery of ciliary body function and chronic damage to trabecular meshwork from chronic inflammation, peripheral anterior synechiae, and corticosteroids.<sup>69</sup> The cumulative incidence of glaucoma has been found to be 18.9%,<sup>52</sup> with a reported range of 14%–42%.<sup>67,70,71</sup>

Band keratopathy occurs in long-standing inflammation and tends to affect the interpalpebral area, with a cumulative incidence of 15.7%.<sup>52</sup> Other less frequent complications are vitritis, cystoid macular edema, disc edema, and disc neovascularization.<sup>72</sup> In severe cases, retinal detachment, hypotony, and phthisis bulbi may occur, indicating poor prognosis.<sup>46</sup>

Hypotony is uncommon and usually reflects severe and mostly poorly controlled uveitis, and this can be reduced by more aggressive immunosuppression and better control of the inflammation.<sup>73</sup>

A higher frequency of complications is associated with severe disease, uveitis onset before arthritis at a young age, and delayed referral to a specialist with consequent delay in therapy.

Recent work on assessment of quality of life in adult patients with JIA has shown that having a history of uveitis has a negative effect on the vision-related quality-of-life scores in adulthood even in the presence of good visual acuity. The same work showed that the general quality of life scores was not different in relation to presence of absence of uveitis but was affected by the use of systemic immunomodulatory treatment.<sup>74</sup>

## MANAGEMENT

Early identification with prompt and aggressive therapy is the cornerstone of prevention of complications and visual loss. The benefit of early aggressive intervention can be demonstrated by a reduction of the anterior chamber flare readings associated with risk of complications in patients with active uveitis and uveitis duration of less than 1 year.<sup>66</sup> The management should be carried out by an experienced ophthalmologist, often with the help of a pediatric rheumatologist. Even with aggressive, early therapy, long-term visual loss can result.

Local therapy involves the use of high-potency corticosteroid eyedrops, initially at a high frequency, associated with short-acting mydriatic drops, such as tropicamide or cyclopentolate, with the main objective of preventing the formation of posterior synechiae. Long-acting mydriatics such as atropine should be avoided because their use may result in synechiae in a dilated position and because of cycloplegia may induce amblyopia.<sup>75</sup> Other forms of local therapy include topical NSAIDs<sup>75,76</sup> and periocular injections of corticosteroids, mainly in refractory cases. It is important to remember that systemic absorption from both frequent strong topical corticosteroid and periocular corticosteroid injection can be substantial; systemic adverse reactions including Cushing's syndrome may be seen in children.<sup>77,78</sup>

A study on 16 eyes with recalcitrant JIA-related uveitis showed that the use of sustained-release dexamethasone device can result in better control of anterior inflammation and resolution of macular edema. Development of cataract and increase in intraocular pressure remain the most common complications of this approach.<sup>79</sup>

Some patients will require systemic therapy. Long-term oral corticosteroids are a poor option, and the early introduction of immunosuppressive agents will result in better disease control and will be corticosteroid-sparing. Methotrexate (MTX) can be administered either orally or subcutaneously—especially if patients develop gastric side effects during oral therapy—at a dose of 10–15 mg/m<sup>2</sup> per week (typical dose: 7.5–25 mg/week) and seems

to be quite effective in 70%–80% of patients.<sup>80</sup> Relapses may occur soon after withdrawal of MTX, and a period of inactivity longer than 2 years is necessary to reduce the risk of such events.<sup>81</sup>

Azathioprine has been used with success,<sup>82</sup> and others, including cyclosporine (not very effective as monotherapy) and alkylating agents for the most severe cases, have been used.<sup>82,83</sup>

Mycophenolate mofetil has also demonstrated effectiveness in childhood uveitis, with corticosteroid-sparing success in 88%–92% of patients.<sup>80</sup>

Biological agents offer a new modality of treatment for autoimmune diseases. A recent retrospective study of high-dose infliximab in 17 children with chronic uveitis (10 with JIA uveitis) has shown it to be effective and well tolerated in refractory cases.<sup>84</sup> Adalimumab is currently preferred following a study demonstrating it to be effective in severe JIA/polyarthritis.<sup>85</sup> It is considered the most efficacious TNF- $\alpha$  blocker for childhood uveitis and the preferred biological drug for the treatment of uveitis associated with JIA (23 of 13). Another prospective open-label, noncomparative, multicenter study assessed the safety and efficacy of adalimumab in 39 patients with JIA-associated refractory uveitis. They found a significant difference in the mean immunosuppression load baseline and end of follow-up and a decrease in mean dose of corticosteroids during the same period.<sup>86</sup>

A systematic review of 128 articles published on use of anti-TNF agents in children with autoimmune chronic uveitis showed that despite the fact that no randomized controlled trials are available, there is some evidence that switching to a second anti-TNF agent results in improvement of ocular activity for 75% of the treated children.<sup>87</sup> Tocilizumab (TCZ), an anti-interleukin 6 receptor antibody, appears to represent an option for severe cases that have been refractory to MTX and TNF- $\alpha$  inhibition.<sup>88</sup>

Rituximab has been suggested for use in severe cases that fail to respond to all other options.<sup>89,90</sup> This response is compatible with histopathological findings reporting a heavy infiltration of CD20+ cells.<sup>91</sup> Other alternatives include abatacept, which showed benefit in cases refractory to anti-TNF therapy,<sup>92</sup> and daclizumab, which also showed good response when higher doses were used.<sup>93</sup>

## MANAGEMENT OF COMPLICATIONS

The management of cataract poses a special challenge, especially in younger children. Control of the inflammatory process is essential for a favorable outcome, but young patients need intervention quickly to prevent the development of amblyopia. With good control of inflammation and use of immunosuppressive therapy, favorable outcomes can be achieved with the use of intraocular lenses (IOLs).<sup>94</sup> No difference in complication rate was found between aphakic and pseudophakic children who had maximum control of inflammation for 3 months prior to surgery, but there was significant superiority of visual acuity in the pseudophakic group.<sup>95,96</sup> However, there is some evidence that an intact posterior capsule and anterior vitreous are associated with a higher incidence of cyclitic membrane formation and progression to hypotony and phthisis.<sup>97</sup> For this reason, many authors suggest total removal of the lens either by vitreo-lensectomy or by phacoemulsification (phaco) combined with vitrectomy and without IOL implantation. This approach has shown good outcomes, with visual acuity of 20/40 or better in 75% of the eyes.<sup>98</sup>

Secondary glaucoma is often refractory to medical therapy, with a poor response to topical beta-blockers, sympathomimetics, and carbonic anhydrase inhibitors. Prostaglandin analogues may be used when these options fail. Conventional filtering surgery may be used but will require antimetabolites. Glaucoma implant devices, such as the Molteno implant, seem to be well tolerated and produce good control of intraocular pressure.<sup>99</sup>

Cystoid macular edema initially can be treated with a topical combination of corticosteroid and nonsteroidal drugs, with the option of periocular corticosteroids in case of failure. Systemic therapy including immunosuppression can be used in resistant cases, especially if sight is threatened.<sup>75</sup> Vitrectomy may be helpful in some cases. Symptomatic band keratopathy may be treated by chelating agents or excimer laser.

Intervention in cases of retinal detachment and hypotony is often unsuccessful.

## OUTCOMES

Older studies found that one-third of affected eyes develop visual impairment and one-tenth become blind.<sup>100</sup> Even now, poor visual acuity is found in as many as 20% of the children, and as many as 10% of eyes are blind.<sup>101</sup> In a recent meta-analysis, the adverse visual outcome cumulative incidence was found to be 9.2%, which is lower than some reports.<sup>52</sup> Poor visual outcome is more common in those who have developed uveitis prior to or

TABLE 7.14.1 Frequency of Ophthalmological Visits for Children With Juvenile Idiopathic Arthritis and Without Known Iridocyclitis

Juvenile Idiopathic Arthritis Subtype at Onset	Age at Onset of Arthritis	
	<7 Years <sup>†</sup>	>7 Years <sup>‡</sup>
Pauciarticular (ANA positive)	H <sup>§</sup>	M
Pauciarticular (ANA negative)	M	M
Polyarticular (ANA positive)	H <sup>§</sup>	M
Polyarticular (ANA negative)	M	M
Systemic	L	L

\*High-risk (H) patients should have ophthalmological examinations every 3–4 months. Medium-risk (M) patients should have ophthalmological examinations every 6 months. Low-risk (L) patients should have ophthalmological examinations every 12 months. ANA indicates the antinuclear antibody test.

<sup>†</sup>All patients are considered at low risk 7 years after the onset of their arthritis and should have yearly ophthalmological examinations indefinitely.

<sup>‡</sup>All patients are considered at low risk 4 years after the onset of their arthritis and should have yearly ophthalmological examinations indefinitely.

<sup>§</sup>All high-risk patients are considered at medium risk between 4 and 7 years after the onset of their arthritis.

Adapted from American Academy of Pediatrics Section on Rheumatology and Section on Ophthalmology. Guidelines for ophthalmologic examinations in children with juvenile rheumatoid arthritis. Pediatrics 1993;92:295–6.

at the same time as arthritis.<sup>44</sup> Poor prognosis has not been associated with the presence of a positive ANA.<sup>101</sup>

Eyes with ocular hypertension or secondary glaucoma have close to threefold higher incidence of legal blindness, and this risk can be reduced by early introduction of immunosuppressive therapy.<sup>102</sup>

The Systemic Immunosuppressive Therapy for Eye Diseases (SITE) study assessed the incidence of—and risk factors for—visual acuity loss and ocular complications in patients with JIA-associated uveitis. The study included 327 patients from five tertiary uveitis clinics in the United States. It found that 60% of the patients had at least one ocular complication. Increasing uveitis activity was associated with increased risk of vision loss, and the risk was reduced by the use of immunosuppressive drugs.<sup>103</sup>

### SCREENING

The purpose of screening programs is to identify and closely monitor patients who are considered to be at high risk of developing uveitis and its complications following the diagnosis of arthritis. Several strategies have been used and are usually based on the subtype of arthritis, gender, age at onset of arthritis, and ANA status (Table 7.14.1).<sup>104,105</sup> A recent analysis of risk factors used severity of disease at diagnosis as a surrogate measure of the effectiveness of current screening programs. Because of a lack of improvement in this marker in the recent past, it was suggested that

current screening strategies should be improved, and it was proposed that female patients with JIA should have an eye examination every 2 months for the first 6 months after developing arthritis and that males should have the same frequency of examinations but for a period of 12 months.<sup>59</sup>

Another report suggests that routine eye examinations should continue during early adult life, since some patients first developed asymptomatic uveitis at this age.<sup>63</sup>

An assessment of the outcome of ophthalmological screening for uveitis in a cohort of Swedish children with JIA concluded that almost all children developed uveitis within 4 years following arthritis onset, which reinforced the need for frequent follow-ups during this period. In this study the most important predictor for the development of uveitis was ANA positivity.<sup>106</sup>

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# Sarcoidosis

Claude L. Cowan, Jr.

# 7.15

**Definition:** A multisystem inflammatory disorder characterized histologically by the presence of noncaseating granulomas in involved tissues.

## Key Features

- Anterior and posterior uveitis.
- Bilateral hilar lymphadenopathy and/or pulmonary parenchymal disease.

## Associated Features

- Cutaneous lesions.
- Neurological abnormalities, including optic neuropathy.
- Cardiomyopathy.
- Orbital and conjunctival infiltration.
- Arthropathy.

## INTRODUCTION

Sarcoidosis is a chronic multisystem disorder characterized histologically by the accumulation of noncaseating epithelioid granulomas in affected tissues. The wide variability in clinical features and prevalence are felt to reflect the effects of genetic and environmental influences that shape the characteristics of the disease. Its course shows a similar variability, ranging from an asymptomatic self-limiting process to a chronic progressive disorder resulting in severe functional impairment or death. Ocular involvement is common and may precede the clinical manifestations of systemic sarcoid. Corticosteroids remain the mainstay of treatment for both ocular and systemic sarcoidosis, but adjunctive therapy with other immunomodulatory agents may be required in the face of intolerable corticosteroid side effects or progressive disease.

## EPIDEMIOLOGY AND PATHOGENESIS

Sarcoidosis is worldwide in distribution, but its prevalence and clinical manifestations vary widely from one region to another. This variability may reflect differences in study design, case definition, population demographics, the limited use of population-based screening, and seasonal variations in activity. In addition, the asymptomatic and nonspecific nature of many findings may lead to missed opportunities for diagnosis. Nevertheless, true regional and ethnic differences appear to exist.<sup>1-6</sup> The incidence has been highly correlated with race in the United States, where the age-adjusted incidence is more than three times higher among African Americans than among European Americans, with the highest incidence being reported among African-American women.<sup>3,6</sup> A similar predilection for people of African descent has not been confirmed throughout Africa but has been noted in South Africa.<sup>7</sup> Sarcoidosis tends to be a disorder of young and middle-aged adults, but it is also well described in children and in the elderly.

The etiology of sarcoidosis remains elusive, but evidence suggests that it is a genetically determined immune response to some environmental trigger. Bacteria and bacterial DNA fragments have been found in sarcoid granulomas and bronchoalveolar lavage (BAL) fluid, and localized and regional granulomatous responses have been produced following inoculation of sarcoid material into laboratory animals.<sup>8-11</sup> However, experimental exposures have not been followed by the development of a systemic disease

comparable to that seen in humans. Nevertheless, reports of “transmission” of sarcoidosis through organ transplantation and clustering of the disease in families and coworkers suggests that transmissible agents may be contributing factors.<sup>12-14</sup>

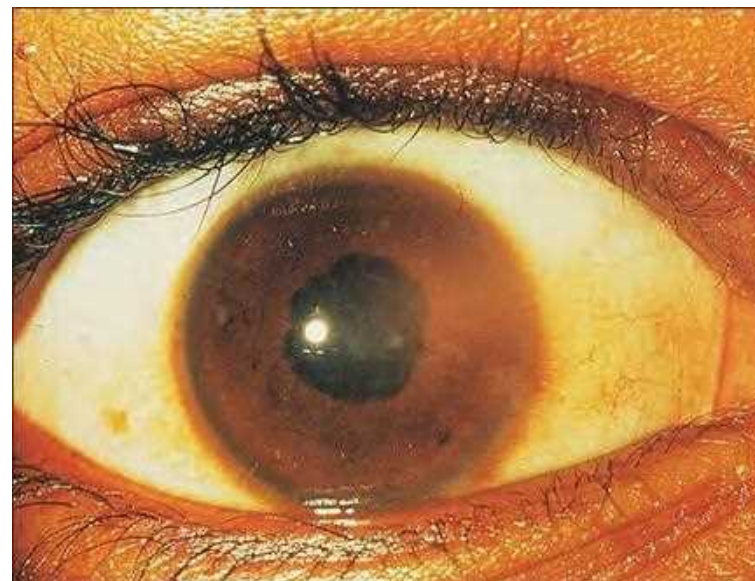
The similarity between sarcoidosis and chronic beryllium disease, along with other environmental associations, has stimulated an interest in the relationship between occupational exposures and sarcoid.<sup>15-19</sup> However, recall bias, the inability to establish exposure thresholds, and association with disparate occupational categories make linkage of specific exposures to disease difficult.

The role of genetic factors is supported by the association of several human leukocyte antigen (HLA) haplotypes and ethnicity with disease risk and clinical course.<sup>20-24</sup> In addition, although familial clustering is consistent with an environmental agent, the greater prevalence among certain parent-offspring and sibling pairs suggests that genetic influences are at least as important as environmental ones.<sup>25</sup> It is likely that multiple genotypes exist that, in the presence of one or more environmental triggers, predispose to an immunological response that is recognized phenotypically as sarcoidosis.

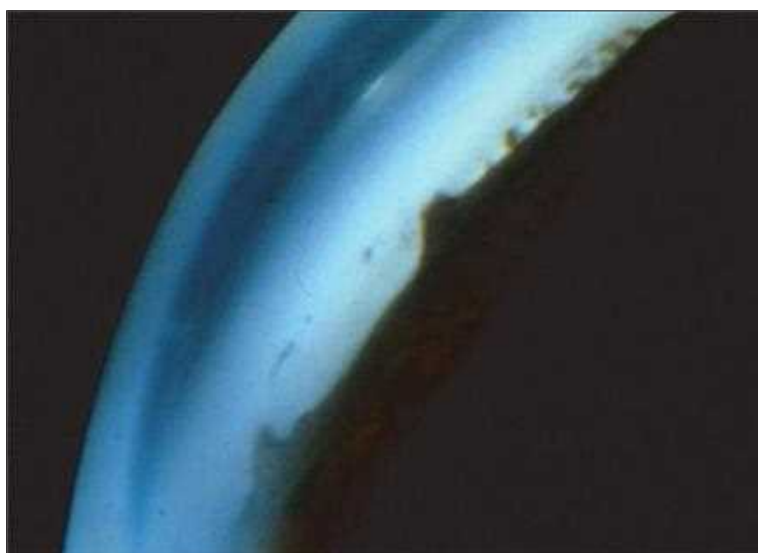
## OCULAR MANIFESTATIONS

Ocular involvement is common, having been reported in up to 83% of patients. It may be second only to pulmonary disease as the presenting manifestation of sarcoid.<sup>26-31</sup>

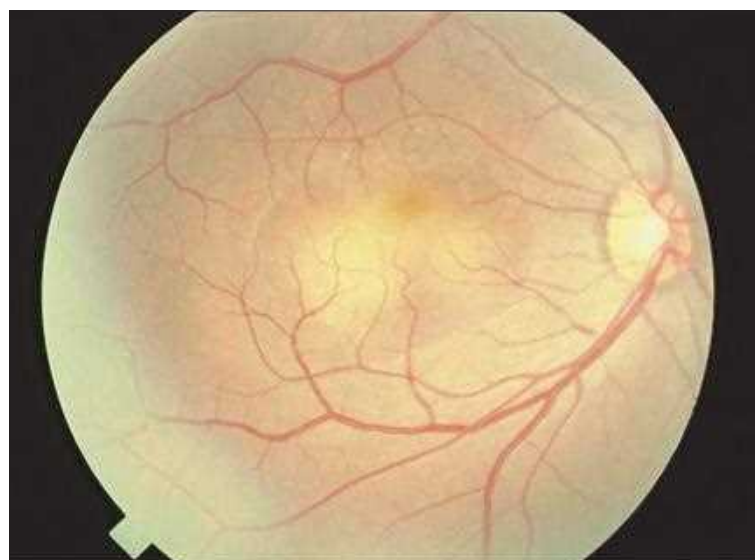
Anterior uveitis is an important cause of sarcoid-related ocular morbidity. It frequently presents early in the disease course and may present a year or more before the diagnosis of systemic sarcoid. It is usually granulomatous in character (Fig. 7.15.1) and may be accompanied by iris and trabecular nodules (Fig. 7.15.2), the latter being frequently associated with ocular hypertension. Although unilateral disease occurs, bilaterality is typical. An insidious onset is not uncommon, and patients may have anterior or posterior synechiae at the time of initial presentation. Acute anterior uveitis is not characteristic, but it is a feature of acute sarcoidosis or Lofgren's syndrome, which features hilar adenopathy, polyarthritides, fever, and erythema nodosum. The course of anterior uveitis can be monophasic,



**Fig. 7.15.1 Chronic Sarcoid Uveitis.** Multiple iris nodules and posterior synechiae.



**Fig. 7.15.2 Chronic Sarcoid Uveitis.** Tent-shaped peripheral anterior synechiae. (Courtesy Manabu Mochizuki, MD, Tokyo, Japan.)



**Fig. 7.15.4 Choroidal Infiltrate.** Note overlying serous detachment of the retina. Lesion was responsive to corticosteroids.



**Fig. 7.15.3 Waxy-Appearing Periphlebitic Exudates.** Patient with resolving periphlebitis; lesions becoming more discrete in appearance.



**Fig. 7.15.5 Optic Disc Granuloma.** Infiltration of optic nerve in sarcoidosis. (Courtesy Hiroshi Takase, MD, PhD, Tokyo, Japan.)

relapsing, or chronic and may not parallel the severity or activity of the systemic disease.

Other anterior segment and external manifestations include conjunctival granulomas, scleral nodules, a nonspecific conjunctivitis, episcleritis, interstitial keratitis, and band keratopathy. Conjunctival granulomas are often located in the inferior fornix and are generally asymptomatic. When extensive, they can resolve with symblepharon formation. Anterior and posterior scleral nodules can be seen and are variably responsive to corticosteroids but are not typically associated with severe pain or necrosis. Diffuse or multifocal gray infiltrates are seen with sarcoid keratitis and may leave faint superficial opacities with resolution.

Periphlebitis and vitritis are the most common manifestations of posterior-segment sarcoid and often occur together. Periphlebitis frequently involves the midperipheral or peripheral retina, but any venous segment can be involved. When severe, the involved venous segments may demonstrate extensive perivascular exudation that has been likened to candle wax drippings. These periphlebitic foci can take on a hard, smooth texture as they resolve (Fig. 7.15.3). Periphlebitis can be complicated by venous occlusion leading to neovascularization that may simulate the sea fans of sickle retinopathy in the peripheral retina. Retinal arteritis is less commonly reported and has been associated with multifocal arterial ectasias.<sup>32,33</sup>

Vitritis may be generalized with a diffuse loss of media clarity or characterized by discrete gray-white opacities that can be scattered throughout the vitreous or primarily involve the inferior vitreous. These “snowball”

opacities can occur singly, in clusters, or in a linear array or strand, like a “string of pearls.” Veil-like condensations often cause bothersome symptoms, but in the absence of severe media opacification or macular edema, the vision usually remains good. Sarcoid retinitis is relatively uncommon and can be difficult to distinguish from other causes of retinal inflammation such as viral retinitis or toxoplasmosis.

Choroidal lesions vary considerably in their appearance, ranging from isolated tumefactions to multifocal granulomas simulating multifocal choroiditis (Fig. 7.15.4). Dalen–Fuchs’-like nodules may slowly increase in number over time and evolve into focal atrophic spots. On fluorescein angiography, the lesions may be nonfluorescent, hypofluorescent, show early blocking with late staining, or hyperfluorescent throughout. If the eye is otherwise uninvolved, patients may be entirely asymptomatic. Vision loss can be associated with serous detachment of the macula, pigment epithelial dropout, or subretinal neovascularization.

Sarcoid involves the optic nerve infrequently but can be the presenting feature of the disease.<sup>34</sup> Clinical manifestations include nodular infiltration, swelling associated with adjacent retinitis, papillitis, juxtapapillary granulomas, or papilledema associated with increased intracranial pressure (Fig. 7.15.5). Retrobulbar or chiasmal lesions can present with progressive vision loss in the face of a normal-appearing nerve until advanced disease leads to optic atrophy. The combination of optic neuropathy and intermediate uveitis can cause confusion with multiple sclerosis.

Dacryoadenopathy is part of the spectrum of orbital sarcoid and is its most common expression.<sup>35</sup> Patients often present with asymptomatic



swelling that is most pronounced over the lateral aspect of the upper lid or with a palpable mass in the anterior orbit. One or both eyes may be involved, and adenopathy can occur in the absence of other evidence of sarcoid. Severe infiltration can lead to proptosis and may be associated with keratoconjunctivitis sicca. Other orbital manifestations include isolated orbital granulomas, extraocular muscle lesions, and optic nerve sheath infiltration.

Although any ocular structure may be involved, the individual signs of ocular sarcoid are nonspecific, and evidence of sarcoid in other organs and/or biopsy are frequently required to establish the diagnosis. However, in 1976, Iwata and colleagues identified six clinical findings that were felt to be most suggestive of sarcoidosis.<sup>27</sup> These included:

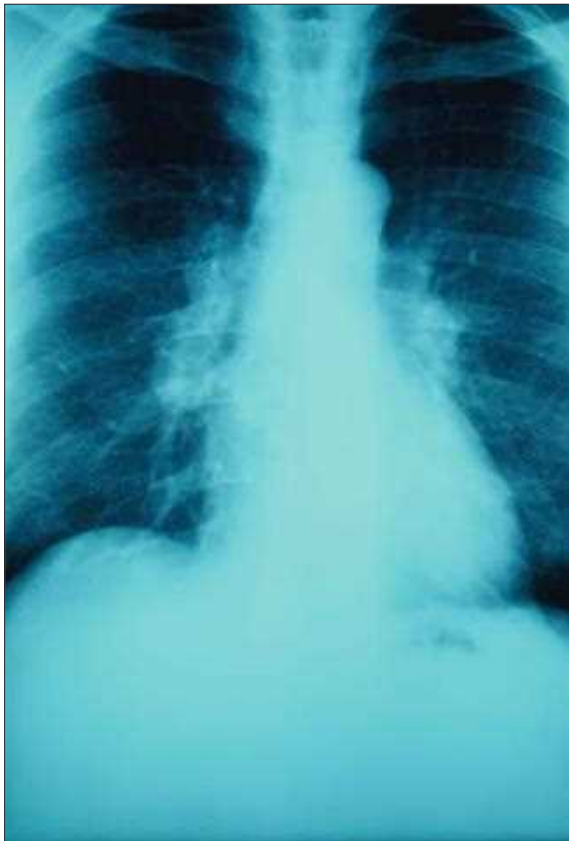
- Nodular infiltration of the angle.
- Nodular iridocyclitis and large mutton-fat keratic precipitates.
- Chorioretinal granulomas and placoid lesions.
- Vitreous string of pearls and snowball opacities.
- Retinal perivasculitis.
- Candlewax drippings and yellow “waxy” spots.

Their predictive value increased when multiple lesions were present and ranged from 75%–100% when three or more signs were present. Nodular trabeculitis was the single most suggestive finding. Subsequent reports have identified similar suggestive signs, and Herbot et al. added tent-like peripheral anterior synechiae, optic disc granulomas, retinal macroaneurysms, and bilaterality as signs compatible with a diagnosis of sarcoidosis.<sup>36–40</sup>

Conversely, findings such as hyphema, angle neovascularization, epithelial keratitis, hypopyon, peripheral ulcerative keratitis, acute orbital inflammation, and iris atrophy are unusual in sarcoid and should suggest other diagnoses.

## DIAGNOSIS

There is no specific diagnostic test for sarcoid. Diagnosis is based on the presence of a compatible clinical picture, supportive laboratory and radiological findings, a confirmatory biopsy, and the exclusion of other likely causes of granulomatous inflammation. Bilateral hilar adenopathy (Fig. 7.15.6) with or without parenchymal infiltrates is the radiological hallmark of sarcoid; in the absence of symptoms, abnormal findings on physical exam, or anemia, other diagnoses are unlikely.<sup>41</sup> The greater sensitivity of



**Fig. 7.15.6 Bilateral Hilar Adenopathy in a Patient Without Pulmonary Symptoms.** Note the symmetry of the hilar node enlargement.

chest computed tomography (CT) allows detection of parenchymal abnormalities that are invisible on chest X-ray and permits visualization of disease along the bronchovascular bundles as well as subpleural disease, locations that are suggestive of sarcoid.<sup>42</sup> Although pleural effusion has been variably described, it and asymmetric or unilateral adenopathy should prompt consideration of other disorders. One or more skin lesions occur in approximately 25% of patients, but they frequently mimic other dermatological lesions.<sup>26,43</sup> However, when associated with bilateral hilar adenopathy, lupus pernio and erythema nodosum are sufficiently characteristic that a presumptive diagnosis of sarcoid should be considered. Typical skin lesions are neither painful nor pruritic, and genital lesions should prompt other considerations. Other nonocular extrapulmonary manifestations are less reliable predictors of sarcoid, but in the appropriate clinical setting, nontender peripheral lymph adenopathy, Bell's palsy, and early childhood arthritis should raise the index of suspicion for sarcoid.

Serum angiotensin-converting enzyme (ACE) is elevated in approximately 60% of patients and correlates with the degree of active pulmonary disease.<sup>44</sup> However, diabetes, alcoholic liver disease, hyperthyroidism, leprosy, chronic renal disease, and tuberculosis can also elevate serum ACE, and levels are normally higher in children.<sup>45</sup> Conversely, a normal ACE does not rule out sarcoid as levels may be lower in patients on ACE inhibitors.<sup>46</sup> In addition, genetic polymorphism can modify ACE expression, thus affecting the interpretation of enzyme levels.<sup>47</sup> Although elevated ACE levels have moderate sensitivity and good specificity, in isolation they are neither specific nor sensitive for the diagnosis of sarcoidosis.<sup>48</sup> Interleukin-2 receptor has been shown to be a marker for pulmonary and ocular sarcoid and may be more sensitive than ACE.<sup>49,50</sup> However, it is not specific for sarcoid and may be elevated in other disorders.<sup>51</sup> Serum lysozyme may also be elevated in sarcoidosis and other inflammatory conditions and can be particularly useful in young patients where ACE levels are normally elevated. Other tests such as serum and urine calcium, immunoglobulin electrophoresis, and liver function tests are less useful as isolated investigations, but when used selectively can support the diagnosis. Nevertheless, with 90% or more of patients having thoracic disease, chest imaging may be the single most useful investigation.

Impaired recruitment of helper cells in the skin leads to relative anergy to recall antigens in sarcoidosis, and anergy panels can provide useful information when patients are known to have been previously positive to the test antigen. The association of anergy with sarcoidosis is sufficiently strong that a negative tuberculin skin test in an individual previously exposed to or living in areas endemic for tuberculosis suggests sarcoidosis associated anergy. Conversely, a positive tuberculin skin test in a patient suspected of having sarcoid should prompt further workup for tuberculosis.<sup>52</sup>

Gallium-67 scanning is used relatively infrequently to diagnose sarcoid, but in combination with serum ACE assays it can provide good sensitivity and specificity.<sup>53</sup> Bilateral hilar and right para tracheal uptake (lambda sign) combined with increased uptake in the parotids and orbits (panda sign) is highly suggestive of sarcoid even in the absence of a confirmatory biopsy.<sup>54,55</sup>

Tissue or fluid sampling is usually sought to provide histological confirmation of sarcoid. Bronchoscopy provides ready access to pulmonary tissue and samples can be obtained by endo- or transbronchial biopsy (TBB). TBB is most likely to be positive in patients with active pulmonary disease visible on chest X-ray, and the yield is increased when combined with endobronchial sampling, especially if done using ultrasound-guided endobronchial needle aspiration.<sup>56</sup> Analysis of bronchoalveolar lavage fluid can provide supporting evidence of disease as a lymphocytosis associated with an increased T lymphocyte CD4/CD8 ratio is consistent with the alveolitis of sarcoidosis.<sup>57</sup> Open lung biopsy and mediastinoscopy are higher risk alternatives when bronchoscopy fails to yield suitable samples. Conjunctiva, lacrimal gland, peripheral lymph nodes, skin, nasal mucosa, and minor salivary glands are attractive alternate biopsy sites, as they are easily accessible. Conjunctival biopsies are most likely to be positive when granulomas are visible and multiple samples are taken from both eyes. Intraocular fluid sampling can also demonstrate cytological features consistent with sarcoid in patients with intraocular disease.<sup>58,59</sup>

## DIFFERENTIAL DIAGNOSIS

The varied clinical presentations of ocular sarcoid and the features it shares with other diseases offer many opportunities for misdiagnosis.

Iris nodules are features of granulomatous uveitis and can be seen with tuberculosis, syphilis, leprosy, herpetic uveitis, toxoplasmosis, and Vogt–Kayanagi–Harada syndrome. Isolated or multifocal nodular iris lesions are

also seen with primary iris neoplasms, metastatic carcinoma, leukemic infiltrates, and seeding from retinoblastoma. Intermediate uveitis can be associated with Lyme disease, inflammatory bowel disease, tuberculosis, and multiple sclerosis, or it may occur on an idiopathic basis known as pars planitis. Choroiditis and choroidal infiltrates are manifestations of multiple disorders that may share some feature with sarcoid. These include infectious diseases such as histoplasmosis, tuberculosis, syphilis, toxoplasmosis, and pneumocystis choroidopathy and a variety of noninfectious disorders, including acute posterior multifocal placoid pigment epitheliopathy, birdshot choroidopathy, multifocal choroiditis with pan uveitis, Vogt-Koyanagi-Harada disease, sympathetic ophthalmia, and lymphoma. In addition, solitary lesions may suggest central serous choroidopathy, amelanotic melanoma, or a choroidal metastasis. Differentiating these from sarcoid may be difficult based on the fundus picture alone; the history and clinical course or associated systemic signs may provide crucial clues to the correct diagnosis.

Sarcoid-associated dacryoadenopathy and parotitis can mimic tuberculosis, Hodgkin's disease, lymphoma, and brucellosis. In addition, isolated lacrimal gland enlargement may be a feature of thyroid disease, orbital pseudotumor, primary lacrimal gland tumors, and Sjögren's syndrome. Peripheral retinal neovascularization occurs relatively infrequently in sarcoid, and more common causes such as diabetic retinopathy and venous occlusive disease should be ruled out. Proliferative sickle retinopathy must also be considered in patients genetically predisposed to sickling disorders.

Infiltrative disease of the optic nerve, other inflammatory optic neuropathies, ischemic optic neuropathy, optic nerve sheath meningioma, and disc edema from any cause all have features that can be mimicked by sarcoidosis. Avoidance of misdiagnosis can be difficult when other signs of sarcoid are absent, and delays in diagnosis are not uncommon.

## SYSTEMIC ASSOCIATIONS

Sarcoidosis is a multisystem disorder that can involve virtually any organ. It is accompanied by abnormalities in cell-mediated and humoral immunity that lead to impaired responsiveness to recall antigens, depressed circulating T cell levels, elevated globulin levels, and nonspecific elevation of antibody titers.

It involves the lungs and/or thoracic nodes in 90% of patients and is staged based on the radiographic findings (Scadding scale).<sup>60</sup> These stages do not represent the natural history of the disease but may be useful in predicting prognosis with pulmonary disease.

- Stage 0: No abnormalities on chest X-ray; parenchymal abnormalities may be detected on CT.
- Stage I: Bilateral hilar and mediastinal adenopathy; the most common stage at presentation.
- Stage II: Hilar adenopathy plus parenchymal involvement (nodular and reticular opacities).
- Stage III: Parenchymal disease alone.
- Stage IV: Advanced disease with fibrosis.

Sarcoid is often insidious in onset, and many patients are initially asymptomatic. Dyspnea, cough, and chest pain are common presenting complaints and may progress slowly. Airway obstruction is the most common functional abnormality consistent with the high prevalence of endobronchial disease found on bronchoscopy, and it may be associated with intractable coughing or wheezing.<sup>61</sup> Restrictive lung disease, impaired diffusing capacity, and pulmonary arterial hypertension are variably present, and pleural thickening can be demonstrated with CT.

Otorhinolaryngological involvement occurs in 10%–15% of patients and can be overlooked as the symptoms may suggest a nonspecific rhinitis.<sup>62</sup> Nasal mucosal disease is associated with mucosal friability causing crusting and bleeding as well as submucosal nodules. Xerostomia from salivary gland involvement, vestibular symptoms, and hearing loss may also occur. Rarely will lacrimal outflow obstruction lead to epiphora. Complaints of nasal stuffiness or congestion, postnasal drip, or recurrent sinusitis should prompt an examination of the nasal mucosa for lesions on the inferior turbinates or septum.

Cutaneous manifestations are common and include nodules, plaques, psoriasiform lesions, papules, ulcerations, and erythema nodosum.<sup>26,43</sup> Sarcoid may have a predilection for sites of recurrent trauma or old scars, but lesions can occur anywhere. Subcutaneous nodules are uncommon but are notable for their association with coexisting autoimmune disorders. Lupus pernio, plaque-like lesions that involve the face, can be disfiguring and may be of prognostic value because of their association with



**Fig. 7.15.7 Multiple Cutaneous Lesions Involving the Lids.** Papules, a few umbilicated lesions, and small plaques are evident in this patient.

chronic disease. Eyelid lesions mirror those seen elsewhere and should be considered part of the cutaneous disease (Fig. 7.15.7).

Peripheral lymphadenopathy occurs in up to 30% of patients and most often involves the cervical, axillary, epitrochlear, and inguinal nodes.<sup>26</sup> It is a nonspecific finding, but the nodes provide useful biopsy sites. Tender adenopathy is atypical for sarcoid and should suggest an alternative diagnosis.

Cardiac involvement is clinically apparent in approximately 5% of patients, but it has been reported in as high as 76% in autopsy series.<sup>63</sup> Conduction defects as well as ventricular and supraventricular arrhythmias may occur, but there are no specific clinical or electrocardiographic findings. The association of heart block with myocardial sarcoid requires caution when using beta-blockers in patients who have glaucoma, and a history of palpitations or other cardiac symptoms should prompt referral to a cardiologist.

Neurosarcoid is clinically evident in 5%–10% of patients and may precede other manifestations of the disease.<sup>64,65</sup> Any part of the nervous system can be involved and when isolated, the nonspecificity of symptoms may delay diagnosis. It has a predilection for the basal leptomeninges, and cranial nerve involvement is a common feature, especially the second, seventh, and eighth nerves. Hypothalamic and pituitary involvement can cause significant endocrine abnormalities and diffuse hemispheric disease may lead to seizures. Localized central nervous system (CNS) infiltration can simulate intracranial tumors and may cause hemianopic or quadrantanopic field defects. Spinal tract lesions are unusual but can cause paralysis. Peripheral neuropathy and myopathy occur less frequently than CNS disease and can lead to muscle weakness, paresthesias, and abnormal deep tendon reflexes. Psychiatric symptoms are rare and when present in patients taking systemic corticosteroids, an adverse medication effect should be considered. Notably, ocular sarcoid is reported to occur more frequently with neurosarcoid than other systemic manifestations.<sup>66</sup>

Hepatic and splenic involvement cause symptomatic disease in a minority of patients, but abnormal liver function tests are not uncommon, and hypodense lesions can be seen on CT and magnetic resonance imaging (MRI). Hypercalcemia and/or hypercalcuria occur secondary to increased production of 1,25 dihydroxyvitamin D by activated macrophages and increase the risk for nephrocalcinosis and nephrolithiasis. Arthralgias have been reported in 25%–38% of patients, some of whom demonstrate phalangeal bone cysts on imaging.

Pediatric sarcoid has two distinct clinical presentations.<sup>67</sup> Early onset sarcoid occurs in children less than 4 years of age and is characterized by the triad of granulomatous dermatitis, polyarthritis, and uveitis. It is believed to be the sporadic form of the disorder known as Blau syndrome.<sup>68</sup> Older children and adolescents typically present with features similar to those in adults and often have pulmonary involvement and lymphadenopathy. Anterior uveitis, when present, is more likely to be nongranulomatous.<sup>69</sup>

## PATHOLOGY

Sarcoid lesions demonstrate granulomas with central nodules of epithelioid cells surrounded by a mantle of lymphocytes and other mononuclear cells. Although mild central necrosis may be seen, caseation is not

a feature of sarcoidosis. Fibrosis may be associated with maturation of sarcoid granulomas.

## TREATMENT

No known cure exists for sarcoidosis, and recurrences are not unusual even after prolonged periods of quiescence. Treatment is primarily intended to reduce symptoms, lessen disability during periods of activity, and minimize the sequelae of inflammation. Corticosteroids remain the mainstay of treatment for ocular and extraocular sarcoid.

Chronic or recurrent anterior uveitis may require more aggressive therapy than would be suggested by the level of clinical inflammation, and progressive anterior and posterior synechiae can occur in patients with frequent episodes of “silent” reactivation. The latter group of patients may be best served by long-term low-dose maintenance therapy, even in the absence of clinically active disease. Conjunctival follicles often resolve spontaneously, but treatment may be indicated for extensive follicle formation as they can resolve with symblepharon formation. Dacryoadenopathy that is associated with dry eye or is cosmetically bothersome may respond well to systemic corticosteroids.

Posterior uveitis is managed primarily with periocular or systemic corticosteroids. Intravitreal administration is a useful alternative for patients with intolerance to systemic treatment, recalcitrant inflammation, or cystoid macular edema. In the absence of complications, small foci of peripheral periphlebitis or mild vitritis may not require treatment as they can wax and wane without progression. Treatment is variably effective in clearing choroidal infiltrates, but it can be very effective for accompanying serous retinal detachments. The association of subretinal neovascularization with choroidal inflammation suggests that a trial of empiric therapy should be considered for macular lesions even in the absence of symptoms or serous elevation of the retina. Optic nerve involvement can be resistant to even high doses of oral corticosteroids, and “pulsed” intravenous methylprednisolone may be required to achieve a response. Occasionally, retrobulbar injection is useful for patients with optic nerve disease who are intolerant of systemic corticosteroids. Cytotoxic and other immunomodulatory agents are useful adjuncts to corticosteroid therapy for refractory anterior or posterior segment disease and as part of a corticosteroid-sparing strategy.

Indications for the treatment of systemic sarcoid include intolerable symptoms, organ dysfunction, and biochemical or radiological deterioration. Treatment of asymptomatic patients is not usually indicated as it may offer little long-term benefit and can expose the patient to unnecessary side effects. In spite of the paucity of controlled clinical trials on their use, oral corticosteroids are the first line of therapy for most patients due to their relatively rapid onset of action and effectiveness, at least over the short term.<sup>70-72</sup> Inhaled corticosteroids have a limited role in the management of pulmonary sarcoid, and current evidence suggests that they provide no consistent benefit to lung function although they may provide symptomatic relief for patients with persistent cough or wheezing. Other immunomodulatory agents, including methotrexate, azathioprine, mycophenolate mofetil, pentoxifylline, cyclophosphamide, and chlorambucil have been used for refractory disease or to prevent unacceptable corticosteroid-related complications.<sup>73,74</sup> In addition, chloroquine and hydroxychloroquine has been used successfully for cutaneous sarcoid and hypercalcemia, and thalidomide may improve symptoms in early onset childhood sarcoidosis.<sup>75,76</sup>

Infliximab and etanercept have been used with varying success with ocular and systemic disease, but etanercept appears to be less consistently effective and is not recommended for ocular disease.<sup>77-79</sup> Adalimumab may be a useful alternative to infliximab for patients intolerant of the latter drug.<sup>80</sup>

## COURSE AND OUTCOME

The overall prognosis for systemic and ocular sarcoid is good, and most patients recover without significant functional impairment.<sup>81-83</sup> Chronicity increases the risk of complications as does delay in receiving appropriate therapy. Systemic features associated with chronicity or poorer outcomes include diffuse central nervous system disease, lupus pernio, nephrocalcinosis, late stage pulmonary disease, bone abnormalities, hepatosplenomegaly, and cardiac involvement. Clinical depression may occur in more than 50% of patients and even stable patients can have significant reductions in measures of health-related quality of life.<sup>84</sup> Black patients have been reported to be more likely to have symptomatic disease and ocular involvement as well as higher rates of severe complications. However, a systematic review of the literature failed to demonstrate a relationship between ethnicity and sarcoid mortality.<sup>85</sup> Posterior uveitis, cystoid macular edema, secondary glaucoma, and optic nerve involvement are associated with poorer visual outcomes and represent difficult therapeutic challenges.<sup>86-88</sup>

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# Behçet's Disease

Annabelle A. Okada

# 7.16

**Definition:** A multisystem vasculitis of unknown cause primarily involving the eyes, the mucosal surfaces, and the skin.

## Key Features

- Recurrent anterior and posterior uveitis.
- Recurrent oral ulcers (aphthae).
- Genital ulcers.
- Skin lesions such as erythema nodosum.

## Associated Features

- Arthritis of large joints.
- Epididymitis.
- Intestinal ulcers.
- Vascular lesions such as thrombophlebitis, arterial occlusions, and aneurysms.
- Central nervous system or cranial nerve involvement.

## INTRODUCTION

Behçet's disease is named after the Turkish dermatologist Hulusi Behçet, who described in 1937 the constellation of recurrent oral ulcers, genital ulcers, and uveitis in three patients.<sup>1</sup> Similar cases had been reported earlier by Shigeta in 1924, Adamantiades in 1931, and Whitwell in 1934.<sup>2</sup> Inflammatory manifestations may also occur in other organ systems, including the skin, the joints, the gastrointestinal tract, and the central nervous system.

## EPIDEMIOLOGY AND PATHOGENESIS

Although Behçet's disease occurs worldwide, it is a particularly common cause of uveitis in countries that line the ancient Silk Road, including Italy, Turkey, Greece, Israel, Saudi Arabia, Iran, China, Korea, and Japan. The age of onset of uveitis is usually in the third to fourth decades of life, with men being more commonly affected than women.<sup>3,4</sup> The uveitis of Behçet's disease is believed to be most severe in young men between 15 and 25 years of age.<sup>3</sup>

The pathogenesis of Behçet's disease remains obscure. The disease has long been associated with the HLA-B51 allele; in Japan, 55% of patients with Behçet's disease are positive for HLA-B51 as opposed to only 10%–15% of the general population.<sup>5</sup> It has been suggested that exposure to various microbial antigens may trigger cross-reactive autoimmune responses in genetically susceptible individuals, leading to the onset of Behçet's disease.

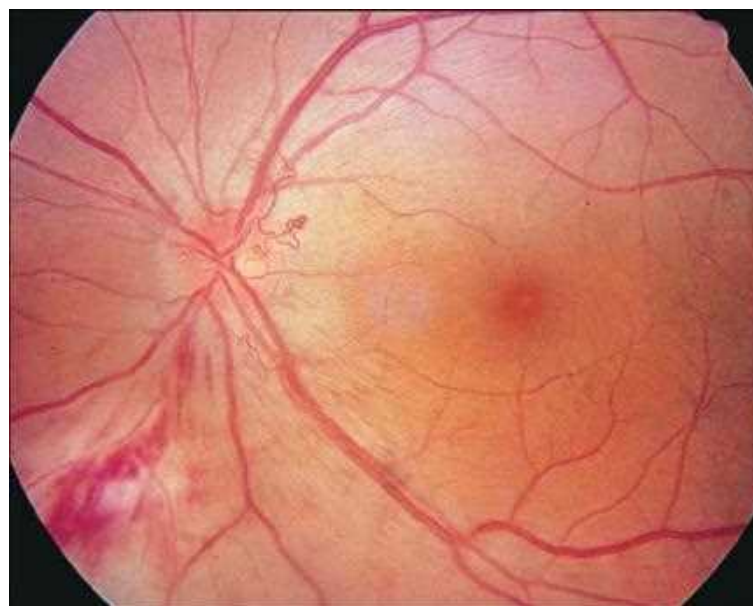
## OCULAR MANIFESTATIONS

Ocular involvement is seen in about 70% of patients with Behçet's disease.<sup>6</sup> In most cases, the onset of uveitis follows the onset of recurrent oral ulcers after 3–4 years, although ocular disease is the initial manifestation in about 20% of cases. Initial ocular involvement may be unilateral but progresses to bilateral disease in at least two-thirds of cases.

Patients with Behçet's disease often present to the ophthalmologist with decreased vision due to anterior chamber inflammation with or without hypopyon (Fig. 7.16.1). Pain, redness, and/or photophobia may be present. The hypopyon typically shifts with change in head position, and a very small hypopyon may be discovered only on gonioscopic examination. There is usually little iris synechia formation initially, although this can



**Fig. 7.16.1 Conjunctival Injection, Hypopyon, and Posterior Synechia.** The patient, who has Behçet's disease, is having an acute inflammatory attack.

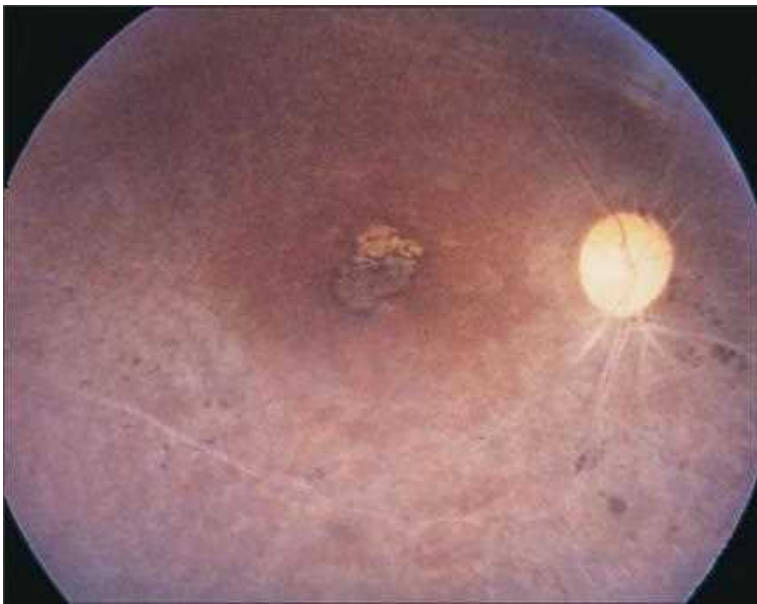


**Fig. 7.16.2 Acute Retinal Vasculitis With Retinal Hemorrhages and Cotton-Wool Spots.** Neovascularization at the optic disc is also present.

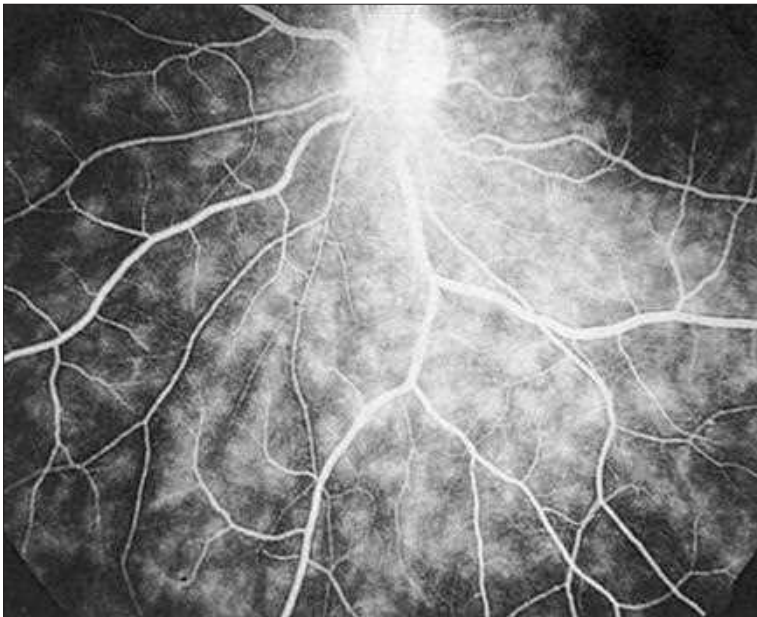
subsequently develop after repeated bouts of anterior segment inflammation. The intraocular pressure is often normal or low. Mild vitreous cells or mild-to-moderate vitreous opacification commonly occurs. Fundus examination may reveal scattered yellow–white retinal infiltrates, retinal hemorrhages, vascular engorgement, and/or disc hyperemia. However, the fundus may also appear entirely normal during an episode of anterior segment inflammation. Bouts of posterior segment inflammation can also occur in the absence of any anterior chamber cells.

Typically, the clinical course is one of acute exacerbations (“attacks”) and remissions over a background of chronic inflammation. Long-term complications in the anterior segment include iris neovascularization, glaucoma, and cataract. In the posterior segment, retinal vascular sheathing or occlusion, retinal or disc neovascularization (Fig. 7.16.2), vitreous





**Fig. 7.16.3 The Fundus of a Patient Who Has End-Stage Ocular Behçet's Disease.** Note the severe retinal atrophy, vascular attenuation with sheathing, and optic atrophy.



**Fig. 7.16.4 Fluorescein Angiogram of a Patient With Behçet's Disease.** Typical findings include widespread ("fern-like") leakage from the capillary tree and secondary vessels.

hemorrhage, progressive vitreous opacification, and optic atrophy (Fig. 7.16.3) may ensue.

## DIAGNOSIS

The diagnosis of Behçet's disease is based on the constellation of systemic and ocular clinical findings rather than on specific laboratory results. However, some tests are useful adjuncts in the evaluation of patients. Fundus fluorescein angiography may show marked focal or diffuse retinal vascular leakage, occlusion of retinal vessels, and/or optic disc hyperfluorescence. During presumably quiescent periods, in the absence of obvious inflammation in the fundus, dilatation of retinal capillaries with dye leakage is commonly observed (Fig. 7.16.4). Fluorescein angiography may also confirm cystoid macular edema and/or macular ischemia.

During episodes of acute inflammation, patients may have a high erythrocyte sedimentation rate, elevated C-reactive protein, or increased peripheral leukocytes. HLA typing may be helpful depending on the patient population.

There are two widely used diagnostic criteria for Behçet's disease. The first was initially proposed in 1972 by the Behçet's Disease Research

**TABLE 7.16.1 International Study Group Criteria for the Diagnosis of Behçet's Disease**

Finding	Definition
Recurrent oral ulceration	Minor aphthous, major aphthous, or herpetiform ulcers observed by the physician or patient that have recurred at least three times over a 12-month period
<i>Plus at least two of the following criteria:</i>	
Recurrent genital ulceration	Aphthous ulceration or scarring observed by physician or patient
Eye lesions	Anterior uveitis, posterior uveitis, or cells in vitreous on slit-lamp examination or retinal vasculitis detected by an ophthalmologist
Skin lesions	Erythema nodosum observed by physician or patient, pseudofolliculitis, or papulopustular lesions or acneiform nodules observed by physician in postadolescent patients not on corticosteroid treatment
Positive pathergy test	Interpreted by the physician at 24–48 hours
<sup>a</sup> Findings applicable only in absence of other clinical explanations.	

Committee of the Japanese Ministry of Health and Welfare,<sup>7</sup> and a second diagnostic criteria was created in 1990 by the International Study Group for Behçet's Disease (Table 7.16.1).<sup>8</sup> Using the international criteria, the diagnosis of Behçet's disease requires the presence of recurrent oral ulceration plus at least two other findings among recurrent genital ulceration, uveitis, skin lesions, and positive pathergy test (skin prick) result.

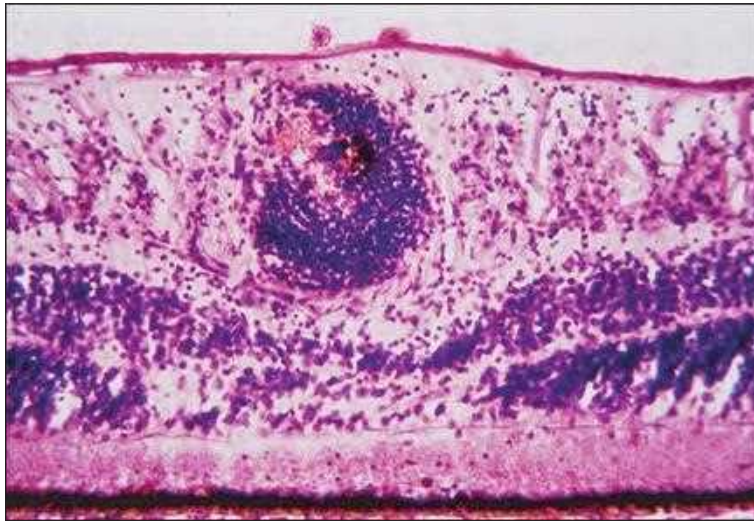
## DIFFERENTIAL DIAGNOSIS

The most common diseases mistaken for Behçet's disease with hypopyon formation are HLA-B27-associated acute anterior uveitis and infectious endophthalmitis. Diseases often mistaken for Behçet's disease with posterior segment inflammation include sarcoidosis, tuberculosis, toxoplasmosis, and syphilis. Behçet's disease with panuveitis may look like acute retinal necrosis in the early stages. Numerous other noninfectious and infectious disorders can mimic the ocular findings of Behçet's disease. Thus careful questioning of the patient for systemic signs or symptoms is crucial to making a diagnosis.

## SYSTEMIC ASSOCIATIONS

The major systemic associations are as outlined (see Table 7.16.1). Recurrent ulcers of the oral mucosa are the most common finding, occurring in up to 97.7% of patients,<sup>6</sup> and are usually the initial symptom in Behçet's disease. These lesions may appear anywhere in the mouth, including the lips, buccal mucosa, gingiva, tongue, hard palate, uvula, and oral pharynx. They tend to be painful but heal within 10 days, usually without scarring unless the lesion is particularly large. Skin and genital manifestations have been reported to occur in 90.4% and 79.8% of patients, respectively.<sup>6</sup> Skin manifestations include erythema nodosum, subcutaneous thrombophlebitis, acneiform lesions, and follicular rash. Of these, erythema nodosum occurs the most frequently and is characterized by a slightly raised red nodule with subcutaneous induration and tenderness. These lesions are usually found on the anterior surfaces of the legs, but they may also occur on the face, arms, and buttocks. They tend to involute in 10–14 days without scarring, although some hyperpigmentation may remain.<sup>2</sup> A history of pustular inflammation after accidental skin injury is usually included as skin involvement in Behçet's disease, and such cutaneous hypersensitivity forms the basis of the pathergy test. Genital ulcers may have deeper tissue involvement in comparison to oral ulcers, are generally painful, and often leave scars after healing. The lesions usually occur on the scrotum or vulva but may also be found on the penis and the perianal and vaginal mucosa.

Other manifestations include arthritis, intestinal ulcers, central nervous system disease, and epididymitis. Although rare, myocarditis, various cardiac vascular lesions, pulmonary hypertension, and renal involvement have also been reported in association with Behçet's disease. The most debilitating manifestation by far is central nervous system involvement, which can include both motor and sensory systems and may affect up to 10% of patients.<sup>2</sup> Signs and symptoms include headache, meningismus, nystagmus, tremor, ataxia, speech disturbances, memory impairment, behavioral changes, and dementia.



**Fig. 7.16.5 Behçet's Disease.** Heavy inflammatory cell infiltration around a retinal vessel (hematoxylin-eosin).

## PATHOLOGY

A characteristic feature is a necrotizing, leukocytoclastic, obliterative vasculitis affecting arteries and veins of all sizes. The vasculitic changes seen in the eyes are similar to those observed in other organs.

During acute inflammation, the iris, ciliary body, and choroid show diffuse infiltration with neutrophils. In the retina, there is severe vasculitis with marked infiltration of leukocytes in and around blood vessels (Fig. 7.16.5). During the chronic phase, a lymphocytic and plasma cell infiltration occurs. Retinal vessels develop thickened basement membranes with swollen endothelial cells that can lead to thrombus formation and vascular obliteration. In late stages, there is neovascularization of the iris and retina, formation of cyclitic membranes, and sometimes hypotony and phthisis bulbi. The phthisical globe may reveal a disrupted lens capsule with histological features of phacocanaphylaxis.<sup>9</sup>

## TREATMENT

The short-term goal of therapy for ocular involvement in Behçet's disease is to suppress active inflammation. The long-term goals are to reduce the frequency and severity of recurrences, minimize involvement of the retina and the optic nerve, and avoid complications such as cataract, synechia formation, and glaucoma. Treatment must be started early to be effective. Drug selection should be determined on the basis of the clinical history, location of intraocular inflammation, and the severity of inflammation. As this disease involves other organ systems, a multidisciplinary approach is necessary.<sup>10</sup>

### Corticosteroids

Corticosteroids are effective in the treatment of acute inflammation in Behçet's disease via their potent suppressive effects on the immune system, including neutrophil and macrophage migration and lymphocyte activity. However, they may have limited efficacy in decreasing the frequency of recurrences and preserving visual function.<sup>10–12</sup> Topical corticosteroids are used for anterior segment inflammation, whereas periocular injections (e.g., 20–40 mg triamcinolone acetonide) and/or systemic corticosteroids (e.g., starting dose of 30–80 mg/day prednisolone) are used for posterior segment inflammation. With systemic administration, the corticosteroid dose needs to be tapered slowly, often over years and in combination with a second corticosteroid-sparing agent such as cyclosporine, in order to avoid a rebound effect. The major side effects are hypertension, diabetes mellitus, electrolyte abnormalities, osteoporosis, and reduced resistance to infections. Because of the frequency and severity of side effects of systemic corticosteroid treatment, it is unlikely that patients can remain on this therapy for a prolonged period. Other agents, whether given in combination with low-dose corticosteroids or not, should be considered for long-term treatment in severe cases of uveitis.

## Immunophilin Ligands

Cyclosporine and tacrolimus (FK506) bind to cytoplasmic receptors termed immunophilins in T cells, thereby selectively inhibiting T-cell activity. A Japanese study showed that cyclosporine at a dose of 5 mg/kg/day was effective in decreasing the frequency of ocular inflammatory attacks in 70% of Behçet's patients who had refractory disease.<sup>13</sup> Starting doses of 3–5 mg/kg/day for cyclosporine and 0.05–0.20 mg/kg/day for tacrolimus are commonly used, depending on the severity of disease and whether other agents are being used in combination.<sup>10</sup> Major side effects of the immunophilin ligands are renal dysfunction, neurological abnormalities, gastrointestinal upset, and hirsutism for cyclosporine.

## Cytotoxic Agents

Both antimetabolites (e.g., azathioprine, methotrexate) and alkylating agents (e.g., cyclophosphamide, chlorambucil) have been used in refractory cases of ocular Behçet's disease, particularly before the widespread use of cyclosporine. One masked trial showed that azathioprine, with or without concomitant corticosteroids, was better than placebo in controlling disease.<sup>14</sup> Triple-drug therapy using corticosteroids, cyclosporine, and azathioprine has also been reported to successfully induce remission in some patients.<sup>15</sup> The side effects of cytotoxic drugs may be serious and include bone marrow suppression, hepatotoxicity, secondary malignancies, and decreased fertility.

## Biological Agents

Interferon- $\alpha$  (IFN- $\alpha$ ), infliximab, and adalimumab have shown efficacy for ocular Behçet's disease.<sup>16–25</sup> IFN- $\alpha$  achieved drug-free remission in roughly one-half of patients after discontinuation of the IFN- $\alpha$ , although the adverse effect of flu-like symptoms occurred in 100% of patients during the first weeks of therapy.<sup>17</sup> Other adverse effects of IFN- $\alpha$ , although much rarer, include depression/suicide risk, neutropenia, alopecia, and liver dysfunction.<sup>17,18</sup> Infliximab, the chimeric monoclonal antibody to tumor necrosis factor (TNF)- $\alpha$ , was reported in one multicenter study to stop inflammatory attacks in 44% and decrease the overall severity of uveoretinitis in 92% of 48 patients over one year of treatment,<sup>22</sup> but data on drug-free remission is still lacking. Adalimumab, a humanized anti-TNF- $\alpha$  monoclonal antibody, was also reported to be effective in selected patients.<sup>25</sup> Adverse effects of TNF-blocking agents include increased risk of opportunistic infections, onset or worsening of autoimmune disorders, central nervous system dysfunction, and thromboembolic events.<sup>16–26</sup>

An expert panel has recommended that infliximab (good-quality evidence) or adalimumab (moderate-quality evidence) may be considered as first-line corticosteroid-sparing therapy in ocular Behçet's disease.<sup>27</sup> There are case reports of the successful use of infliximab administered as an intravitreal injection in ocular Behçet's disease,<sup>28,29</sup> and the systemic use of other biological agents has also been reported in small numbers of patients.<sup>30</sup>

## COURSE AND OUTCOME

The natural history of uveitis in Behçet's disease is one of attacks and remissions over a background of low-grade inflammation. A poor visual outcome can be avoided mainly if the frequency of attacks is limited and irreversible complications are prevented. Decades ago, the visual outcome of Behçet's disease was uniformly dismal, but advances in therapeutics since then have greatly improved visual outcomes, leading to improvements in health and vision-related quality of life.<sup>31</sup>

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## Vogt–Koyanagi–Harada Disease

Narsing A. Rao

7.17

**Definition:** Bilateral uveitis featuring exudative retinal detachment, usually associated with meningismus with or without other extraocular manifestations.

**Key Features**

- Bilateral granulomatous posterior or panuveitis.
- Exudative retinal detachment.
- Cerebrospinal fluid pleocytosis.
- Depigmentation of the uvea (sunset glow fundus) in the chronic and recurrent phases.
- Multiple peripheral focal atrophic retinochoroidal lesions in the chronic phase.

**Associated Features**

- Meningitic manifestations: headache, nuchal rigidity.
- Auditory features: tinnitus and sensorineural hearing loss.
- Cutaneous changes: vitiligo, alopecia, and poliosis.

**INTRODUCTION**

Vogt–Koyanagi–Harada disease (VKH) is a bilateral uveitis that is often associated with meningismus and dysacusia during acute phase and alopecia, poliosis, and vitiligo during chronic phase. A recent study revealed the most common presentation of VKH during the acute phase is bilateral posterior or panuveitis associated with serious retinal detachment, whereas during the chronic phase it presents with “sunset glow” fundus changes.<sup>1</sup>

**EPIDEMIOLOGY AND PATHOGENESIS**

VKH disease occurs more frequently in those with darker complexions, such as people of Asian, Hispanic, or Native American descent.<sup>2</sup> The disease appears to affect women more frequently than men and occurs most often in the second to fifth decades of life.

Evidence of increased risk among those with certain HLA genotypes (DRB1 \*0405) indicates that there is a genetically determined susceptibility for VKH disease.<sup>3</sup>

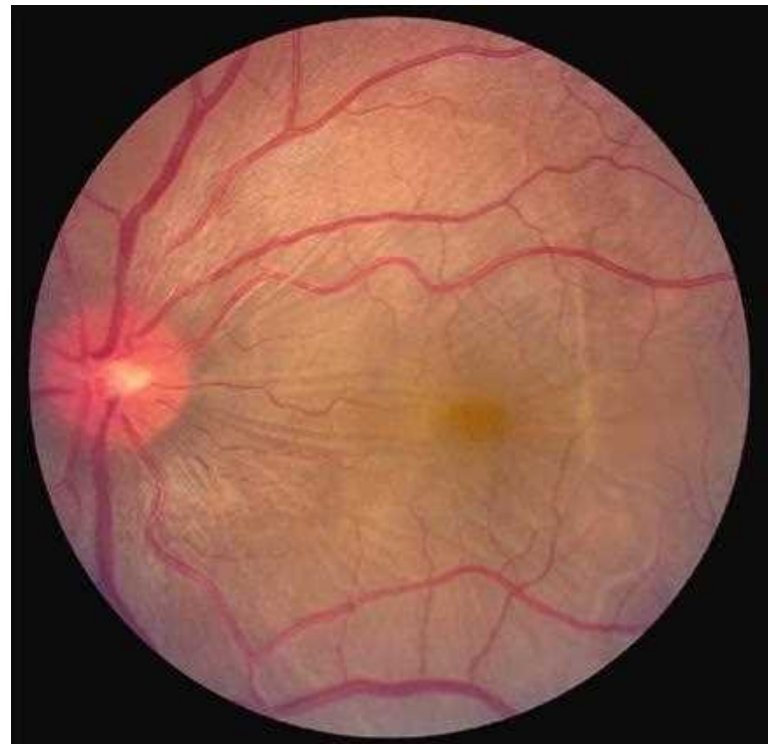
An autoimmune reaction to melanocytes or to their tyrosinase-related peptides has been suggested to play an important role in the pathogenesis.<sup>4</sup>

**OCULAR MANIFESTATIONS**

The diagnostic criteria for VKH disease were suggested by the International Committee on Nomenclature of the disease.<sup>5</sup> The distinguishing features of this disease are bilateral intraocular inflammation associated with retinal detachment or sunset glow fundus changes.<sup>1</sup> Clinically, the disease is categorized into four phases: prodromal, uveitic, chronic, and recurrent.<sup>6</sup>

**Prodromal Phase**

Patients with VKH disease may first visit their internists because of influenza-like symptoms, including fever, headache, and sometimes nausea. Within 1–2 days of the onset of the prodromal phase, the patient typically begins to complain of blurred vision, photophobia, redness of conjunctiva, and ocular pain. The patient also complains of sensitivity of the scalp hair to touch during the prodromal phase.



**Fig. 7.17.1 Fundus in the Uveitic Phase of Vogt–Koyanagi–Harada Disease.** Note the exudative retinal detachment, choroidal folds, and hyperemic optic disc.

**Uveitic Phase**

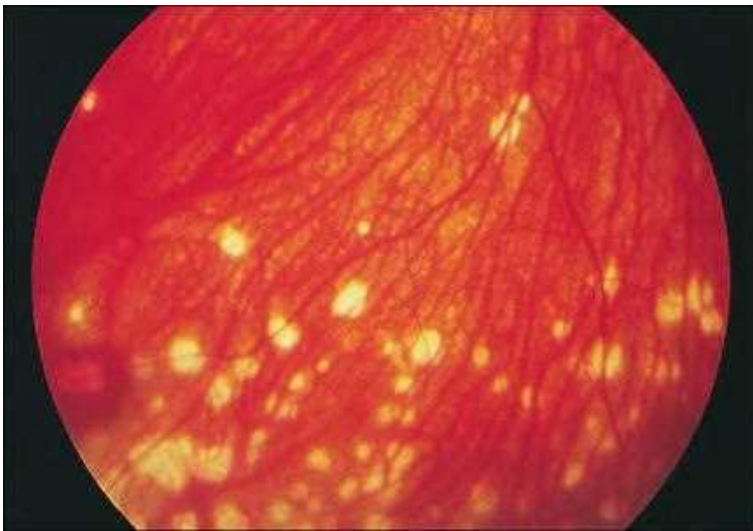
In the early uveitic phase, cells are present in the anterior chamber and/or the vitreous. In typical cases, the presence of bilateral exudative retinal detachments results in blurring of vision (Fig. 7.17.1). The retinal detachment shows discrete and shallow elevation of the neural retina, with small folds that radiate from the macula. A cloverleaf pattern of detachment is often seen in the posterior fundus. In severe cases, the detachment may become bullous. The optic disc becomes hyperemic and edematous.

**Chronic and Recurrent Phases**

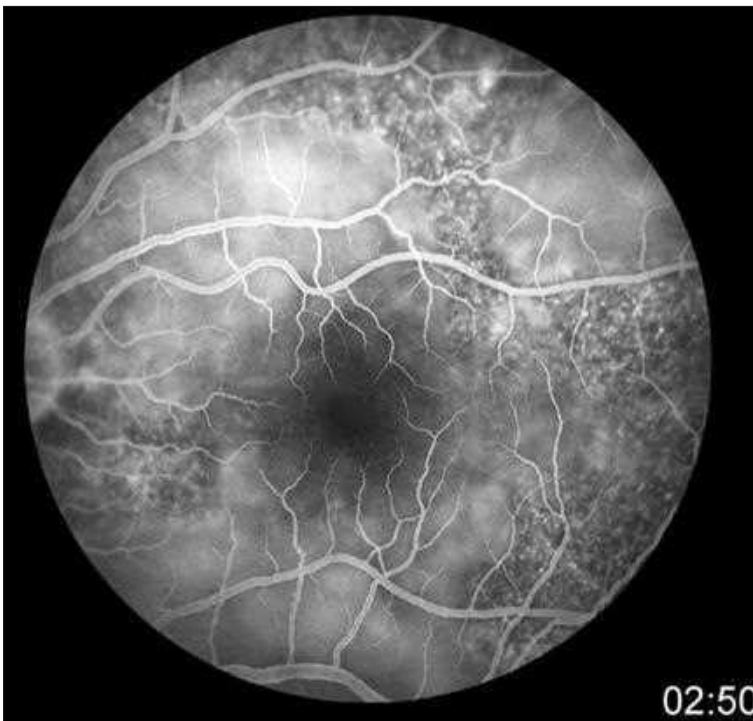
After treatment with systemic corticosteroids, elevation of the neural retina gradually disappears as the subretinal fluid is absorbed. Cells in the anterior chamber and vitreous decrease or disappear. As the uveal inflammation subsides, depigmentation occurs in the fundus, giving it a sunset glow appearance. Small, discrete, and scattered depigmented lesions are seen within the sunset glow fundus (Fig. 7.17.2). Most of these lesions represent degenerated or lost retinal pigment epithelium (RPE).<sup>7</sup> Depigmentation in the corneal limbus is sometimes noted about one month after the onset. This limbal depigmentation is known as Sugiura's sign.<sup>6</sup> The uveitis of chronic VKH may recur. In recurrent cases, anterior uveitis is more predominant than posterior uveitis. Choroidal neovascularization (CNV) may occur in the peripapillary region and the macula. Retinal pigment epithelial proliferation may result in subretinal fibrosis.

**DIAGNOSIS AND ANCILLARY TESTING**

In the early phase of VKH, fluorescein fundus angiography reveals numerous hyperfluorescent dots at the level of the RPE.<sup>8</sup> These dots have a



**Fig. 7.17.2 Sunset Glow Fundus in the Chronic Phase of Vogt–Koyanagi–Harada Disease.** The fundus has a slightly reddish appearance, mainly due to the disappearance of melanocytes in the choroid. Note the numerous small, depigmented lesions of degenerated retinal pigment epithelium.



**Fig. 7.17.3 Fluorescein Fundus Angiography in the Uveitic Phase of Vogt–Koyanagi–Harada Disease.** Note multiple pinpoint and large plaqueoid hyperfluorescent changes.

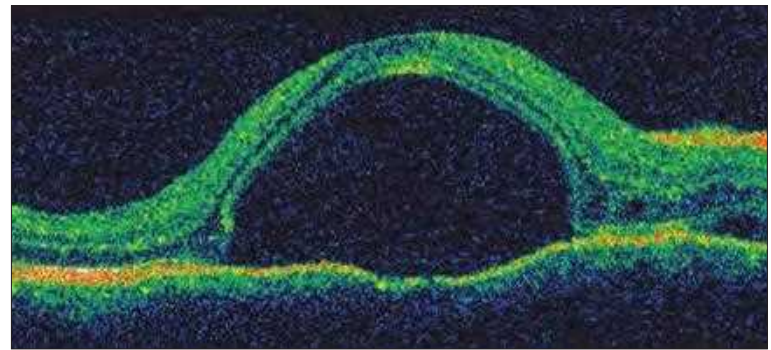
tendency to gradually enlarge. The dye leaks through the RPE and accumulates in the subretinal space (Fig. 7.17.3). Indocyanine green angiography shows choroidal vascular changes with hypofluorescence dark dots. In the chronic phase, fundus autofluorescence reveals hypo- and hyperautofluorescence changes from RPE damage.

The echographic manifestations include diffuse thickening of the posterior choroid, serous detachment of the retina, vitreous opacities, and posterior thickening of the sclera or episclera. The optical coherence tomography (OCT) often shows foci of retinal detachments (Fig. 7.17.4). OCT in the acute phase will reveal significant choroidal thickening along with the subretinal fluid. Fibrin in the subretinal fluid is not uncommon.

Pleocytosis is seen in the cerebrospinal fluid in approximately 80% of patients within one week and in 97% of patients within three weeks of the onset of the disease.<sup>4</sup> Most of the cells found in the cerebrospinal fluid are small lymphocytes and few melanin-containing macrophages.<sup>9</sup>

## DIFFERENTIAL DIAGNOSIS

Sympathetic uveitis should be differentiated from VKH disease. The only difference between sympathetic uveitis and VKH disease is a history of



**Fig. 7.17.4 Acute Vogt–Koyanagi–Harada Disease.** Optical coherence tomography shows retinal detachment.

penetrating ocular injury or intraocular surgery in patients with sympathetic uveitis and the absence of such a history in patients with VKH disease.

Central serous chorioretinopathy must be differentiated from the uveitic phase of VKH disease. Posterior scleritis often shows exudative retinal detachment. Computed tomography scans and ultrasonography help make the correct diagnosis because they reveal thickening of the posterior sclera.

Acute posterior multifocal placoid pigment epitheliopathy may be confused with VKH disease because of the presence of multiple white–yellow, flat to placoid lesions at the level of the RPE.<sup>10</sup> However, in acute posterior multifocal placoid pigment epitheliopathy there are usually no cells in the anterior chamber or vitreous.

## SYSTEMIC ASSOCIATIONS

### Auditory Signs

Auditory disturbance in VKH disease consists of a hearing loss caused by inner ear dysfunction. Some patients complain of tinnitus and vertigo at the onset. Hearing usually returns to normal within several weeks.

### Neurological Signs

Meningitic manifestations at the onset of the disease may include headache, nausea, and vomiting, but in many cases none of these signs occur. It should be noted that VKH can occur without cerebrospinal fluid pleocytosis.

### Dermal Signs

About 2–3 months after the onset of VKH, vitiligo occurs on the face, hands, shoulders, and back.

### Other Signs

Poliosis (whitened hair of eyelashes) and scalp alopecia (loss of hair) may occur.

## PATHOLOGY

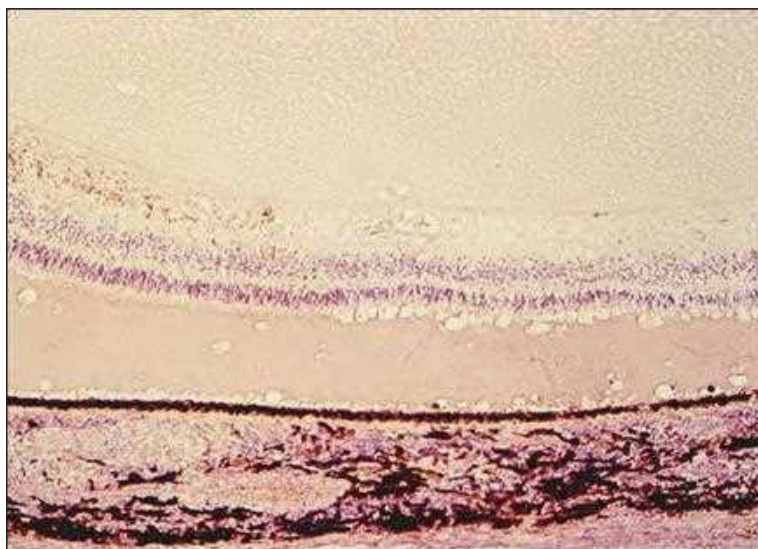
### Uveitic Phase

The pathology of VKH disease is basically the same as that for sympathetic uveitis, with granulomatous inflammation being seen throughout the uveal tissue. The uveal tissues are thickened by diffuse infiltration of lymphocytes, macrophages, and epithelioid cells, and the exudative retinal detachment (Fig. 7.17.5). The epithelioid and giant cells contain pigment granules. Immunohistochemical techniques reveal that the choroidal infiltrate in VKH disease is composed predominantly of T lymphocytes. Class II major histocompatibility complex antigens are expressed on choroidal melanocytes and on the endothelium of the choriocapillaris.<sup>11</sup> Dalen–Fuchs nodules, representing focal granulomas between the RPE and Bruch's membranes, can be observed.

### Chronic and Recurrent Phases

Uvea shows decreased melanocytes resulting in the sunset glow appearance of the fundus. Small, depigmented atrophic lesions, which are seen





**Fig. 7.17.5 The Uveitic Phase of Vogt-Koyanagi-Harada Disease.** The choroid is thickened with inflammatory cell infiltration. Note fluid accumulation in the subretinal space. (Courtesy Professor Hajime Inomata.)

predominantly in the peripheral fundi of the chronic phase, show degeneration or disappearance of the RPE cell, involvement of the choriocapillaris, and formation of chorioretinal scars.<sup>7</sup>

## TREATMENT

VKH disease is treated effectively by the systemic administration of corticosteroids, and, in most cases when the diagnosis is made early in the disease course, the prognosis for visual recovery is favorable. Inadequate treatment, however, can result in recurrent, long-standing uveitis, which may ultimately become intractable. In the early phase, high doses of corticosteroids should be given intravenously or orally. Prednisone 1.5–2 mg/kg is given orally for several weeks, with gradual tapering of the dose once an angiogram reveals the disappearance of dye leakage through the RPE. Topical corticosteroids and cycloplegics are administered until the cells in the anterior chamber disappear.

When the intraocular inflammation cannot be controlled with systemic corticosteroids within 2–3 weeks, or when a patient cannot tolerate the side effects of corticosteroids, immunomodulatory agents may be used; the latter include azathioprine, mycophenolate mofetil, cyclophosphamide, and ciclosporin.<sup>2</sup> The patients who present with chronic phase or chronic recurrent disease often require the concurrent use of immunomodulatory and corticosteroids to suppress the inflammation.<sup>8,12</sup>

## COURSE AND OUTCOME

Uveitis due to VKH disease usually is treated effectively by the systemic administration of corticosteroids. However, posterior subcapsular cataract, secondary angle-closure glaucoma, subretinal neovascularization, and subretinal fibrosis may develop.

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# Phacogenic Uveitis

Julie Gueudry, Bahram Bodaghi

# 7.18

**Definition:** Acute or chronic anterior segment and/or vitreous inflammation directed against released or residual lens protein.

## Key Feature

- Anterior uveitis occurring days to weeks after lens capsular surgical or traumatic disruption or spontaneously because of a hypermature cataract.

## Associated Features

- Hypopyon.
- Severe uveitis resembling infectious endophthalmitis.
- Elevated intraocular pressure.

## INTRODUCTION

Phacoanaphylactic, phacotoxic, and phacolytic uveitis represent varying manifestations of inflammatory processes induced by lens material and are referred to as “lens-induced uveitis” or “phacogenic uveitis.” Phacotoxic uveitis and phacoanaphylactic uveitis are the result of an immunological response from retained lens material after cataract extraction or of surgical or traumatic rupture of the lens capsule with subsequent release of lens proteins. The term “phacolytic” refers to nongranulomatous inflammation resulting from lens proteins leaking through an intact lens capsule in an eye with hypermature cataract. Phacolytic glaucoma is considered in this presentation as a lens-induced uveitis, although this remains controversial. A high degree of clinical suspicion is important to recognize these entities to start correct treatment. Moreover, lens-induced uveitis may be difficult to distinguish clinically from infectious postoperative endophthalmitis.

## EPIDEMIOLOGY AND PATHOGENESIS

Lens-induced uveitis is a relatively rare disorder, accounting for <1% of the cases in most uveitis series.<sup>1-3</sup> It was exceedingly rare when intracapsular cataract extraction was performed, and it is now more common as a result of extracapsular cataract extraction technique. Therefore, the peak age of incidence of phacogenic uveitis is in the fifth to seventh decades,<sup>4,5</sup> even though lens-induced uveitis can occur at any age essentially after ocular trauma. The pathogenesis of lens-induced uveitis is still not precisely understood. In fact, the term “phacoanaphylactic” or “phacotoxic” uveitis, previously used, seems misleading. Thus, this reaction does not appear to be a type 1 hypersensitivity reaction or anaphylactoid reaction. Moreover, there is no evidence that lens proteins may be “toxic” to ocular tissues. It was thought by some investigators that lens-induced uveitis is caused by immune rejection of previously “sequestered” lens proteins in an “intact” lens capsule. However, studies have suggested that this entity may be explained, in part, by loss of immunological tolerance to the lens.<sup>5-7</sup>

## OCULAR MANIFESTATIONS

Mostly, phacogenic uveitis occurs as a result of extracapsular cataract extraction or phacoemulsification or after spontaneous, traumatic, or surgical disruption of the lens capsule (Fig. 7.18.1). Typically, its onset is in the days following surgery or trauma, presenting as unilateral pain, redness, photophobia, and visual loss. Acute cases may occur within 24 hours of cataract surgery. A history of retained lens fragments may be obtained. In these cases, the ocular inflammation is severe, with large numbers of

cells in the anterior chamber and vitreous cavity. “Mutton fat” keratic precipitates are generally present, and extensive posterior synechia formation often occurs. Hypopyon can be present. Fragments of lens cortex may be observed in the anterior chamber or in the vitreous cavity (Fig. 7.18.2). The posterior segment is often not visible because of severe vitritis. Intraocular pressure (IOP) may be elevated as a result of trabeculitis, lens debris in angle, or synechiae. Clinical findings associated with severe phacogenic uveitis may be difficult to differentiate reliably from infectious endophthalmitis. However, visual acuity is usually diminished, but there is generally less pain than with acute infectious endophthalmitis.

Subacute or chronic cases are usually less severe, typically developing within 2–3 weeks after surgery or trauma. Clinical signs include cell and flare in the anterior chamber, keratic precipitates, and synechiae. IOP can increase. Epiretinal membrane and macular edema may develop.

Classically, phacolytic glaucoma is seen in patients who have a hypermature lens and an intact lens capsule and have no evidence of traumatic or surgical disruption of the lens capsule. Large, translucent cells with marked flare are seen in the anterior chamber, but keratic precipitates and posterior synechiae are usually absent (Fig. 7.18.3). It may also occur after complicated cataract surgery with loss of lens fragments in the vitreous cavity. IOP is markedly elevated and may often result in corneal edema.<sup>8</sup>

## DIAGNOSIS

Diagnosis of phacogenic uveitis is made on a clinical basis and is based on patient history and clinical examination. However, a complementary examination may be useful to rule out other entities (Table 7.18.1) and secondary complications.

Vitreous or aqueous tap associated with instillation of intravitreal antibiotics injections should be performed when there is any suspicion of infectious endophthalmitis. Gonioscopy may help identify lens material retained in the angle as well as an eventual malposition of an intraocular lens (IOL). Similarly, high-resolution B-scan ultrasonography and/or optical coherence tomography of the anterior segment can detect the position of the lens haptics if IOL-related uveitis is suspected. Posterior segment B-scan ultrasonography can detect posterior segment complications, such as vitritis, retinal detachment and choroidal detachment, retained lens material or intraocular foreign body after ocular trauma. Computed tomography can also help detect intraocular foreign bodies. Laboratory testing should be ordered if inflammation associated with previous uveitis is suspected.

## DIFFERENTIAL DIAGNOSIS

Bacterial/fungal endophthalmitis, low-grade endophthalmitis (e.g., *Propionibacterium acnes*), toxic anterior segment syndrome (TASS) and IOL-related uveitis, intraocular foreign body, flare-up of pre-existing uveitis, and sympathetic ophthalmia should be differentiated from lens-induced uveitis. As mentioned above, in this chapter, phacolytic glaucoma is considered a lens-induced uveitis.

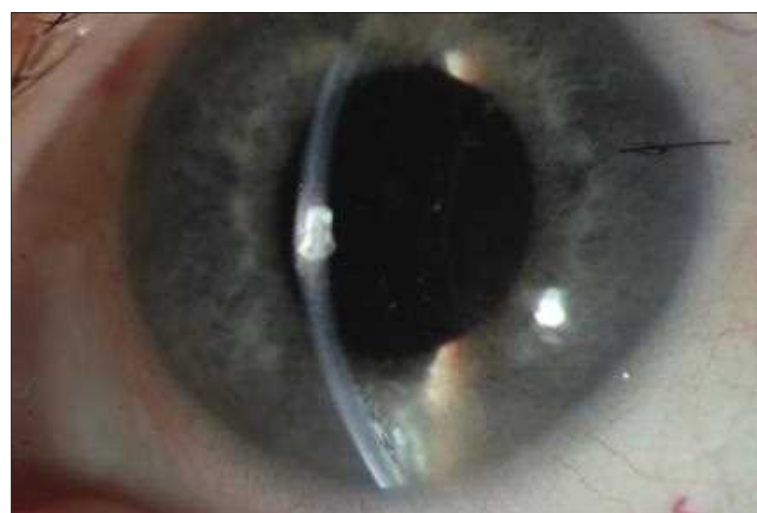
Acute infectious endophthalmitis after penetrating trauma or ocular surgery often presents with signs of severe intraocular inflammation and hypopyon. However, unlike lens-induced uveitis, it is unusual to observe large keratic precipitates. Bacterial or fungal endophthalmitis may be extremely difficult to differentiate from phacogenic uveitis. In such cases, a definitive diagnosis can be established by cytological examination and/or by aqueous and vitreous cultures. TASS is a sterile postoperative response to noninfectious agents, such as impurities in irrigating solutions used during intraocular surgery, anesthetics, and antibiotics, entering the anterior chamber or to improper cleaning or sterilization of instruments.<sup>9</sup> This syndrome usually occurs earlier after surgery (within 1 or 2 days) and may be associated with little or no pain as well as little or no posterior segment





**Fig. 7.18.1 Phacogenic Uveitis Post Trauma.** (A) History of perforating corneal injury with rupture of the lens capsule associated with traumatic cataract. (B) Slit-lamp photograph showing severe anterior inflammation and lens debris in anterior chamber. (C) Note corneal edema caused by increased intraocular pressure.

inflammation. It is also characterized by marked corneal edema. TASS usually responds to intensive topical corticosteroid therapy. IOL-related uveitis is caused by iris or ciliary body chafing from a malpositioned lens implant or from a single-piece IOL in the ciliary sulcus. It is characterized by iris transillumination defects caused by iris chafing. IOL-related uveitis should be treated by reposition or explantation of the intraocular lens (Fig. 7.18.4). Finally, sympathetic ophthalmia always occurs bilaterally, with characteristic yellow-white infiltrates (choroidal granulomas). However, phacogenic uveitis has been seen in association with sympathetic ophthalmia.<sup>10</sup>



**Fig. 7.18.2 Phacogenic Uveitis Post Cataract Surgery.** Fragments of lens cortex may be observed in the anterior chamber and in the angle after complicated cataract surgery.



**Fig. 7.18.3 Phacolytic Glaucoma.** (A) Slit-lamp photograph showing cataract with a dense nucleus setting inferiorly in the liquefied white cortex. (B) History of hypermature cataract associated with elevated intraocular pressure. Note the large cells in the anterior chamber.

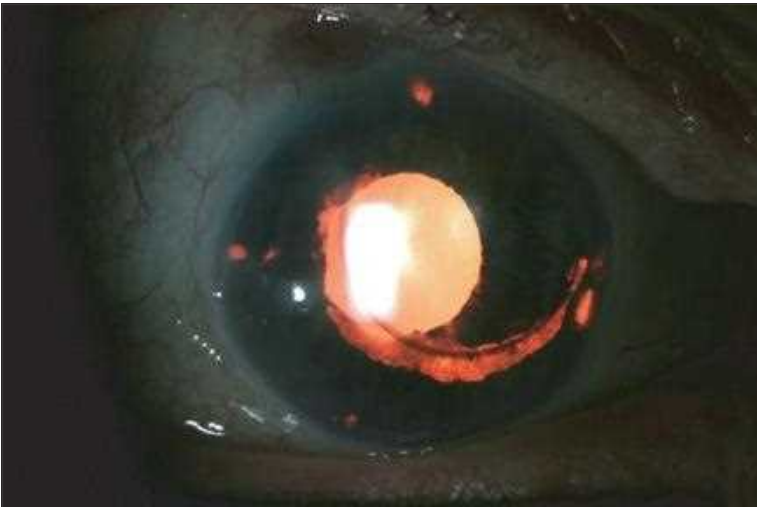
## PATHOLOGY

In phacogenic uveitis, aqueous humor cytopathological examination may reveal a zonal granulomatous inflammatory reaction, with polymorphonuclear leukocytes surrounding a nidus of damaged or retained material lens.<sup>11</sup> This is encircled by successive zones of granulomatous inflammation containing multinucleated giant cells and finally a nonspecific layer of mononuclear cells often eosinophils, plasma cells, and histiocytes. In

TABLE 7.18.1 Differential Diagnosis of Phacogenic Uveitis

Acute (days after surgery or trauma)	
Condition	Differentiating Features
Acute infectious endophthalmitis	Rapidly progressive Positive gram stain and culture
TASS	Within the first day after surgery Marked corneal edema Little or no posterior segment inflammation
Flare-up of pre-existing uveitis	Prior history of uveitis systemic or ocular signs of uveitis
Subacute or Chronic (several weeks following surgery or trauma)	
Condition	Differentiating Features
Low-grade endophthalmitis	Positive culture
Fungal endophthalmitis	White intracapsular plaques ( <i>Propionibacterium acnes</i> )
IOL-related uveitis	IOL poorly placed in uveal tissue Iris transillumination defects
Retained intraocular foreign body	Clinical visualization High-resolution and posterior-segment B-scan Ultrasonography CT
Sympathetic ophthalmia	Bilateral disease Prior surgery or trauma in fellow eye

CT, Computed tomography; IOL, intraocular lens; TASS, toxic anterior segment syndrome.



**Fig. 7.18.4 Intraocular Lens (IOL)-Related Uveitis.** Uveitis caused by iris chafing from a sutured iris IOL. One of the haptic is visible through the iris transillumination defect.

phacolytic glaucoma, diagnosis can be established by paracentesis of anterior chamber fluid and examination of the material for macrophages laden with lens material.

TREATMENT

Definitive treatment involves removal of the inciting agent (i.e., the lens or residual lens matter). However, in cases of mild inflammation caused by small retained cortical lens material, intensive topical, periocular, or oral corticosteroids can help manage the intraocular inflammation. In cases of more significant retained lens material, persistent inflammation despite corticosteroid treatment and/or increased IOP, removal of lens material is required, adjunctive to vitrectomy, if necessary. In cases of traumatic disruption of the capsular lens or in cases of phacolytic glaucoma, cataract extraction is indicated. Vitreous tap and injection of intravitreal antibiotics should be performed if there is any suspicion of infectious endophthalmitis. Chronic low-grade endophthalmitis may require surgical capsulectomy with irrigation of the capsular bag, or IOL explantation or even lens-bag complex removal. Treatment of glaucoma that persists even after complete control of inflammation includes either long-term medical treatment or surgical management as trabeculectomy or valve implantation.<sup>12</sup>

COURSE AND OUTCOME

There is often a good outcome with prompt and aggressive management. If the lens is not promptly removed, or in cases of prolonged inflammation and/or increased IOP, corneal endothelial cell loss, glaucoma, hypotony, macular edema, macular scarring, or retinal detachment can lead to visually significant morbidity.

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# Sympathetic Uveitis

Sivakumar Rathinam, Narsing A. Rao

# 7.19

**Definition:** Bilateral T cell–mediated autoimmune uveitis after penetrating injury to one eye.

## Key Features

- Bilateral granulomatous posterior uveitis or panuveitis.
- Penetrating ocular injury to the exciting eye.

## Associated Features

- Granulomatous keratic precipitates.
- Papillitis.
- Exudative retinal detachment.
- Dalen–Fuchs nodules.
- Diffuse choroiditis.

## INTRODUCTION

Sympathetic uveitis (sympathetic ophthalmia [SO]) was first described clinically by MacKenzie in 1833, although Hippocrates suggested its existence much earlier (460–370 BC). Fuchs established the pathological definition of SO in 1905, and this resulted in a decrease in its incidence through refinement of surgical technique and prompt disease recognition.<sup>1,2</sup> SO is a sight-threatening disease with a high visual morbidity. Accidental trauma is considered an important risk factor; however, surgical trauma can also result in SO. It is believed to be a cell-mediated autoimmune response to uveal antigens.<sup>3</sup> Aim of the treatment is to promptly and completely suppress this inflammation. Corticosteroids are the mainstay of treatment for initial suppression, which is maintained with addition of immunosuppressive agents.

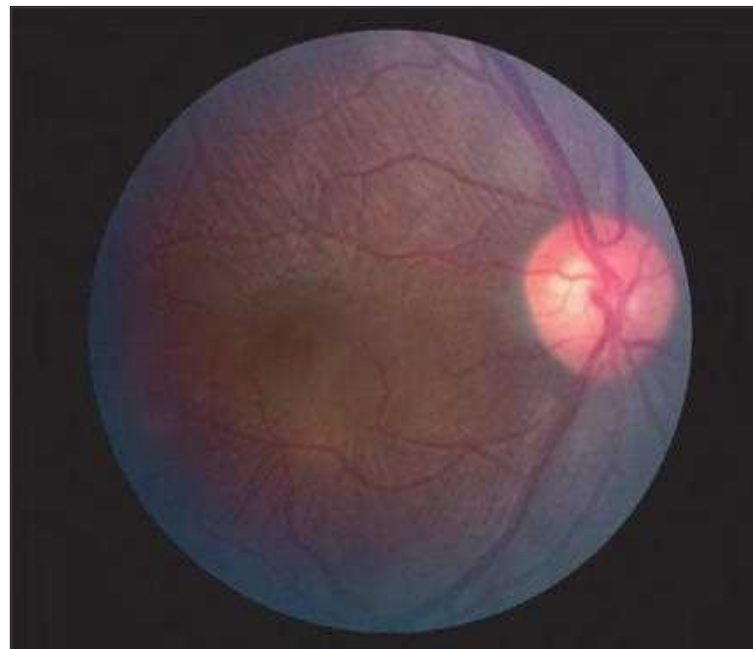
## EPIDEMIOLOGY AND PATHOGENESIS

SO is a relatively rare disease with a minimum estimated incidence of 0.03 per 100 000.<sup>4</sup> Previous studies report an incidence of 0.2–0.5% after trauma and 0.01% after intraocular surgery.<sup>5,6</sup> However, recently, more cases have been reported after intraocular surgery, including small-gauge sutureless vitrectomy.<sup>7,8</sup> A high index of suspicion is needed to diagnose SO in the early stage.

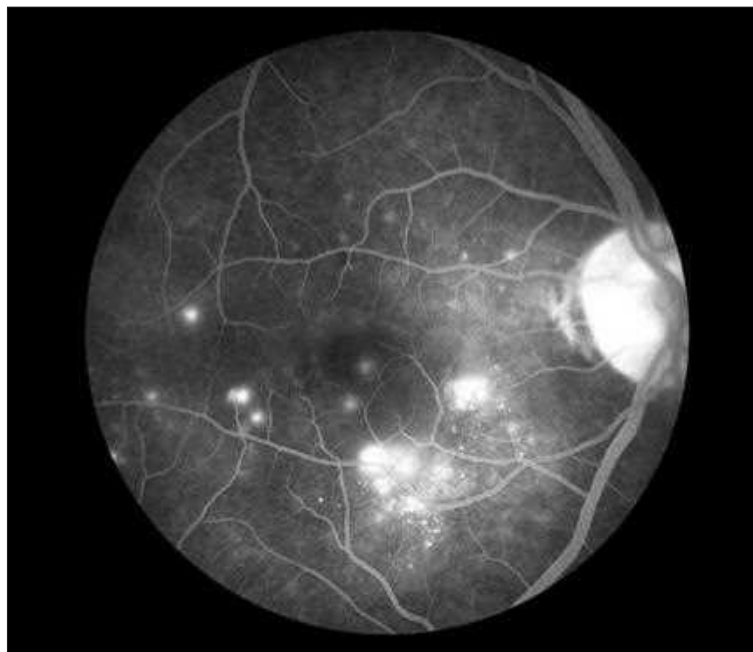
The exact cause of SO is unknown; however, the common denominator in an overwhelming majority of cases is the presence of a penetrating injury in which wound healing is complicated by incarceration of uveal tissue.<sup>3</sup> There is experimental evidence for a delayed hypersensitivity reaction to tyrosinase peptide antigen or melanocytes, resulting in bilateral nonnecrotizing granulomatous inflammation.<sup>3</sup> The retina seems to be spared in SO; however, mitochondrial oxidative stress could result in apoptosis of photoreceptors.<sup>9</sup> In the past, it was believed that a purulent eye infection would destroy the uveal tissue to such an extent that such eyes do not incite SO.<sup>10</sup> However, there are several reports on occurrence of SO even after purulent endophthalmitis.<sup>11</sup>

## OCULAR MANIFESTATIONS

Clinically, the presentation of SO is quite variable and can manifest either as bilateral posterior uveitis or panuveitis. Acutely, SO classically presents with optic nerve swelling and bilateral exudative retinal detachment, whereas granulomatous “mutton fat” keratic precipitates are usually seen in severe and/or chronic recurrent cases (Figs. 7.19.1 and 7.19.2). The focal,



**Fig. 7.19.1** Fundus photo of a patient with sympathetic ophthalmia with striae and subretinal fluid.



**Fig. 7.19.2** Fluorescein angiography in sympathetic ophthalmia with multiple hyperfluorescent foci of leakage.

elevated infiltrates at the level of the retinal pigment epithelium (RPE) correlate with Dalen–Fuchs nodules seen on histopathological analysis. Inflammation of the optic nerve (papillitis) provides a useful means for monitoring disease progress. Chorioretinal scarring may develop once the inflammation abates, and macular scarring may lead to considerable visual loss.<sup>12</sup>

## DIAGNOSIS

Diagnosing SO requires a high index of clinical suspicion, especially at a time when significant attention is being paid to the injured or surgically managed exciting eye. Roughly 80% occur within the first 3 months after injury; however, this period may range from 5 days to 66 years.<sup>13</sup> The characteristic fluorescein findings consist of multiple foci of leakage at the level of the RPE (Fig. 7.19.3). Hypofluorescent foci (which stain later) are occasionally seen early on angiography. Ultrasonography may demonstrate choroidal thickening and is particularly helpful in the differentiation of bilateral phacoanaphylactic endophthalmitis that presents as a bilateral anterior uveitis. Spectral-domain optical coherence tomography (SD-OCT) (Fig. 7.19.4A, B), can reveal neurosensory detachment with accumulation of fluid in the subretinal space, photoreceptor elongation, loss of the inner segment/outer segment hyperreflective band, and Dalen–Fuch nodules.<sup>14,15</sup>

## DIFFERENTIAL DIAGNOSIS

The differential diagnosis includes Vogt–Koyanagi–Harada (VKH) disease, bilateral phacoanaphylactic endophthalmitis, and bilateral posterior

scleritis with exudative retinal detachment. If a patient with ocular trauma is treated with corticosteroids for control of inflammation and develops loss of vision in the contralateral eye, it is important to rule out central serous chorioretinopathy because continuing corticosteroids could worsen vision in both eyes. Additionally, any pre-existing uveitis reactivated after trauma should also be considered.

## SYSTEMIC ASSOCIATIONS

The accompanying systemic findings are rare in SO; however, when they are present, they are similar to those seen in VKH disease. These include meningeal signs, headache, dysacusis, tinnitus, alopecia, poliosis, and vitiligo. The only known, reliably differentiating feature of SO from VKH disease is a history of penetrating ocular injury.<sup>12,13</sup>

## PATHOLOGY

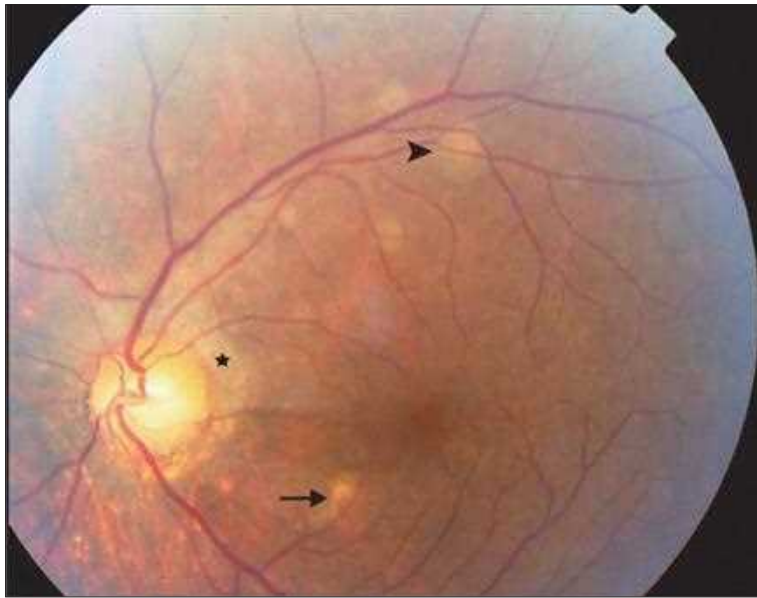
The exciting eye and the sympathizing eye demonstrate similar pathology, suggesting involvement of an autoimmune response. The typical histological picture is a bilateral, diffuse nonnecrotizing granulomatous infiltration of the choroid with mononuclear and pigment-containing epithelioid cells, lymphocytes, and giant cells. Dalen–Fuchs nodules project from the RPE/Bruch's membrane complex and correspond to the yellow-white spots observed on ophthalmoscopy. Other pathological changes include inflammatory infiltrates around the melanocytes of the sclera and optic nerve meningeal sheaths.<sup>12</sup> Atypical features, such as nongranulomatous choroiditis or chorioretinal adhesions with the inflammation of choriocapillaris, are occasionally seen, as in chronic VKH disease.<sup>16</sup> In addition to SO, phacoanaphylactic endophthalmitis may coexist secondary to rupture of the lens capsule in the exciting eye.<sup>11</sup>

## PREVENTION

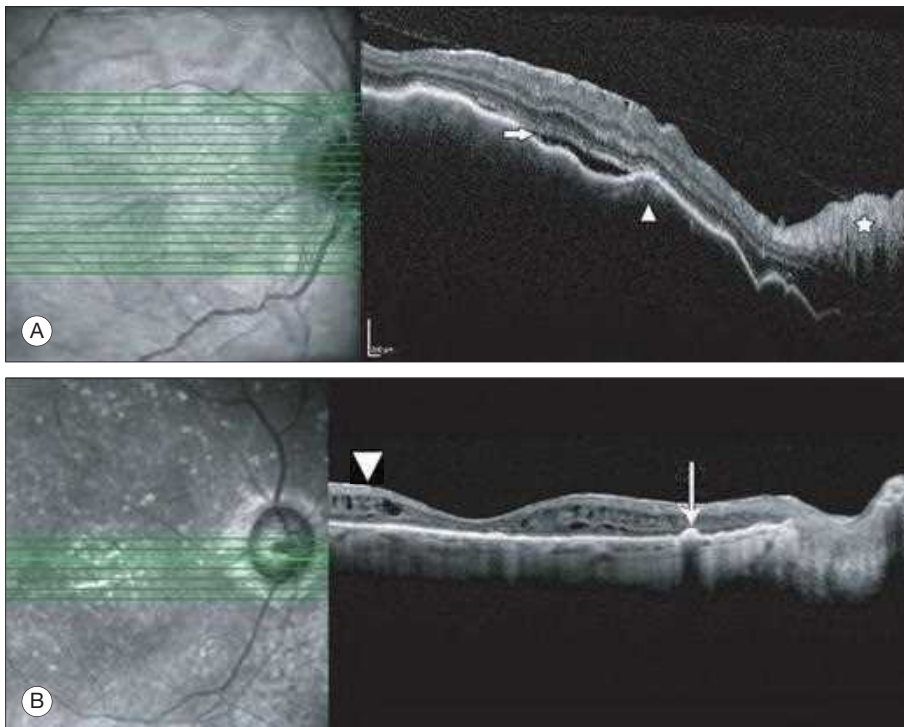
Meticulous and prompt microsurgical wound closure of penetrating ocular injuries may prevent SO. The basic principle is to save the injured eye with useful or potentially salvageable vision and to enucleate badly damaged eyes with no visual function. Once the disease process has commenced, the benefit of enucleation of the traumatized eye is a topic of controversy. Prophylactic corticosteroids treatment has no role in prevention.

## TREATMENT

SO is a sight-threatening disease with high visual morbidity. The objective of treatment is to completely and promptly suppress inflammation and to maintain control for an extended period. Topical, periocular, and systemic corticosteroids are started in severe panuveal inflammation. Pulse intravenous methylprednisolone (up to 1 g daily for 3 days), followed by oral



**Fig. 7.19.3** An active yellow-white focal retinal pigment epithelium (RPE) nodule (black arrowhead) corresponding to a histopathological Dalen–Fuchs nodule in a patient with chronic recurrent sympathetic ophthalmia. Old resolved Dalen–Fuchs nodule (black arrow) and resolved peripapillary exudative detachment (star).



**Fig. 7.19.4** Spectral-domain optical coherence tomography (SD-OCT) in sympathetic ophthalmia. (A) SD-OCT scan of acute sympathetic ophthalmia shows intraretinal edema, serous retinal detachment (arrow), peripapillary edema (star), and choroidal folds (arrowhead). (B) Posttreatment SD-OCT scan shows photoreceptor elongation (arrowhead) and loss of the inner segment/outer segment (IS/OS) hyperreflective band. A hyperreflective lesion is seen at the level of retinal pigment epithelium (arrow) with disruption of IS/OS junction, suggestive of a Dalen–Fuch nodule.

prednisone (1.5–2.0 mg/kg) may be required to suppress inflammation. Immunosuppressive therapy is added to reduce corticosteroid therapy to nontoxic levels (<7.5 mg/day) and to aim for a disease remission. Common agents used include azathioprine (2–4 mg/kg/day), mycophenolate mofetil (1–1.5 g two times daily), and methotrexate (15–25 mg/wk). Alkylating agents, such as cyclophosphamide (2 mg/kg/day) and chlorambucil (0.1–0.2 mg/kg/day) are highly useful in refractory cases.<sup>17,18</sup> Currently, cyclophosphamide and chlorambucil are rarely used since the introduction of biological agents. Biologicals, particularly anti-tumor necrosis factor agents are used in patients who do not respond to the above-mentioned conventional treatment.<sup>19</sup>

## COURSE AND OUTCOME

Although rare, SO is a serious disease that may ultimately result in blindness. The importance of early, aggressive treatment and regular follow-up cannot be overemphasized. Common complications include cataract, glaucoma, macular edema, subretinal fibrosis, retinal detachment, hypotony, and phthisis bulbi. Cataract surgery involves no unusual risks when performed during remission, and its outcomes are dependent on posterior segment complications of the disease.<sup>20</sup> Currently, there are no reliable data on the complications of glaucoma surgery and retinal surgery.

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# Idiopathic and Other Anterior Uveitis Syndromes

7.20

Olivia L. Lee

**Definitions:**

- Intraocular inflammation featuring the anterior chamber as the predominant site of inflammation.
- Also referred to as *iritis*, *iridocyclitis*, or *anterior cyclitis*.

**Key Features**

- Inflammatory cell and flare visible in the anterior chamber by slit-lamp biomicroscopy.
- Keratic precipitates, either granulomatous or nongranulomatous, may be present.

**Associated Features**

- Pain, photophobia.
- Hypopyon.
- Posterior synechiae.
- Cataract formation.

**INTRODUCTION**

Anterior uveitis is the most common form of intraocular inflammation. The diagnosis of anterior uveitis is based on clinical findings consistent with inflammation primarily located in the anterior chamber.<sup>1</sup> On slit-lamp biomicroscopy, anterior chamber cell and flare can be seen as the major indicator of inflammation affecting the iris and the ciliary body. Typically, the diagnosis is straightforward, although other conditions, such as panuveitis, endophthalmitis, and ocular tumors, can begin with a presentation mimicking anterior uveitis. Although occasionally self-limiting, in most cases anterior uveitis can be treated simply with topical corticosteroids and cycloplegic agents. However, those cases of chronic inflammation or multiple recurrent episodes can be more difficult to manage.

**EPIDEMIOLOGY AND PATHOGENESIS**

Anterior uveitis accounts for most cases of uveitis with an annual incidence of 12 cases per 100 000.<sup>2</sup> The most common association is with haplotype human leukocyte antigen (HLA) B27 (see Chapter 7.14). Depending on the population, in some series, HLA B27 is associated with up to 50% of cases of anterior uveitis,<sup>3</sup> with approximately 45% of these being associated with spondyloarthropathy.<sup>4,5</sup> However, when no identifiable etiology is attributed, the classification of idiopathic anterior uveitis is made. The lifetime cumulative incidence of idiopathic acute anterior uveitis is 0.15%.<sup>6</sup> Males and females are affected equally.

A systemic disease association, including juvenile idiopathic arthritis (JIA), sarcoidosis, tubulointerstitial nephritis and uveitis syndrome (TINU) or Behçet's disease, and HLA B27-associated conditions, should be considered. The ophthalmologist can play a role in making the diagnosis of such systemic conditions when anterior uveitis presents in a patient with no known prior diagnosis. Other ocular conditions, such as ocular ischemic syndrome, neovascular glaucoma, and pigment dispersion syndrome, can either mimic or produce anterior chamber inflammation. Trauma can also produce iritis, and when the history is indicative, careful examination for intraocular foreign body and lens capsule rupture should be performed.

Nevertheless, most cases of anterior uveitis have no specific etiology and are classified as idiopathic. If a patient tests positive for HLA B27 but

has no extraocular manifestation, the term *idiopathic anterior uveitis* should not be used. The pathogenesis of anterior uveitis in idiopathic cases is presumed to be autoimmune. Blood–aqueous barrier disruption in acute anterior uveitis has been demonstrated by laser cell and flare photometry.<sup>7</sup> Compared with healthy controls, patients with a history of idiopathic anterior uveitis have low-grade systemic inflammation, even at the time when uveitis is quiescent. Furthermore, their monocytes generate higher levels of innate immune responsiveness when stimulated *ex vivo*, suggesting these patients with uveitis but no identifiable systemic autoimmune condition have altered innate immunity that plays a role in the development of anterior uveitis.<sup>8</sup>

Anterior uveitis is presumed to be noninfectious but may be preceded by a nonocular infectious condition. Various pathogens affecting the gastrointestinal, urinary, and respiratory tracts have been implicated in triggering a bout of intraocular inflammation. The prevalence of antibodies to these pathogens is higher in patients with a history of multiple recurrences of anterior uveitis compared with those with fewer recurrences and normal controls.<sup>9</sup>

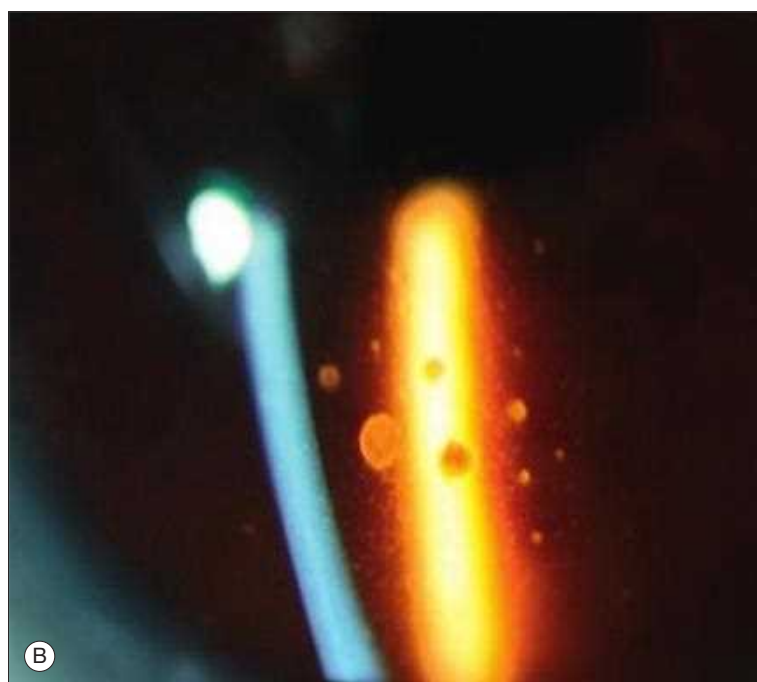
Recent evidence of viral infectious agents in the intraocular fluid of eyes with anterior uveitis has led to infectious theories of the pathogenesis of conditions previously thought to be noninfectious, such as Posner–Schlossman syndrome (PSS) and Fuchs' heterochromic iridocyclitis (FHI).<sup>10</sup> Cytomegalovirus (CMV) has been recognized to have an association with anterior uveitis in immunocompetent patients without chorioretinitis, particularly in Asia.<sup>11</sup> Identification of other viral organisms in the aqueous fluid taken from eyes with anterior uveitis, including Epstein–Barr virus, human herpesvirus, and human parechovirus, have been demonstrated by polymerase chain reaction (PCR), but the clinical implication of these findings are still unknown.<sup>12,13</sup>

**OCULAR MANIFESTATIONS**

Presenting symptoms of acute anterior uveitis include pain, redness, photophobia, and sometimes blurred vision. Some patients, particularly those with JIA, can be asymptomatic. The onset is typically acute but can also occur insidiously with exacerbating severity over the period of  $\geq 1$  week. The patient may complain of unilateral symptoms but may have asymmetrical, bilateral inflammation on examination.

Slit-lamp biomicroscopy will reveal anterior chamber cell and flare. Ciliary flush in the form of limbal vascular injection is frequently seen. Keratic precipitates on the corneal endothelium are a common finding (Fig. 7.20.1). These cellular deposits are most often localized within Arlt's triangle as a result of aqueous currents in the anterior chamber. However, viral anterior uveitis is associated with keratic precipitates in a diffuse pattern. Large, greasy keratic precipitates are granulomatous and suggestive of etiologies, such as sarcoidosis, tuberculosis, Vogt–Koyanagi–Harada syndrome, toxoplasmosis, and sympathetic ophthalmia. Stellate, nodular, and dendritic keratic precipitates are seen in infectious uveitis.<sup>14,15</sup>

Hypopyon is a collection of inflammatory cells seen occupying the inferior aspect of the anterior chamber as the exudate settles dependently as a result of gravity. The presence of a hypopyon suggests active infection but can occur with both acute uveitis and recurrent anterior uveitis. Hypopyon uveitis is seen in Behçet's disease and HLA B27-associated uveitis, as well as in rifabutin-induced anterior uveitis and in infectious conditions, such as microbial keratitis and endophthalmitis.<sup>16</sup> Fibrin may accumulate in the anterior chamber as well, causing the otherwise mobile inflammatory cells in the anterior chamber to move slowly within the aqueous humor. The

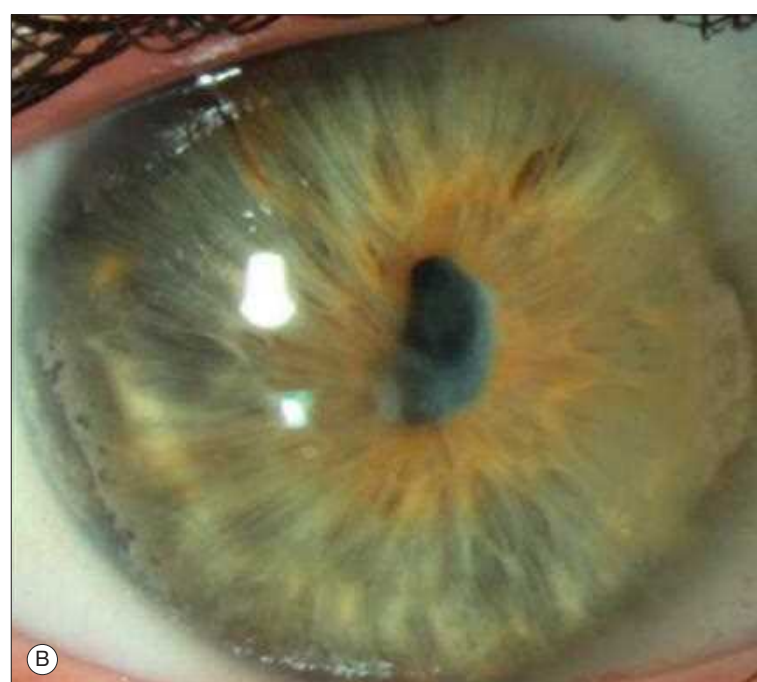
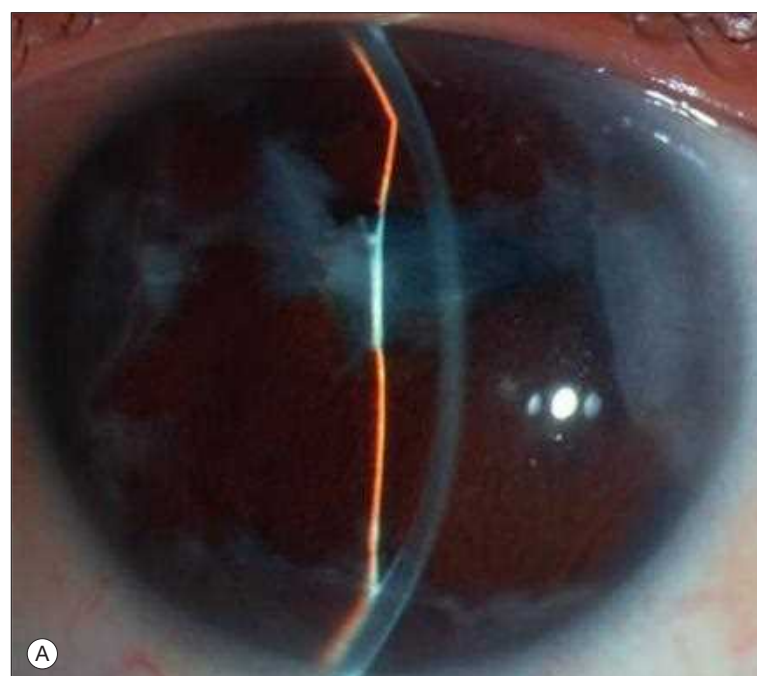


**Fig. 7.20.1 Keratic Precipitates.** Collections of inflammatory cells can be seen on the corneal endothelium. Their appearance, for example as stellate in viral uveitis (A) or “mutton fat” in granulomatous inflammation (B) can be suggestive of the etiology of anterior uveitis.

fibrin may organize into a membrane, partially or completely occluding the pupil.

Any level of intraocular pressure (IOP) can be seen during episodes of active anterior uveitis. The pressure may be low because of ciliary body shutdown and reduced aqueous production and returns to normal after resolution. In long-standing, chronic cases, intractable hypotony may occur in eyes where the ciliary body does not recover. However, elevated pressure can be seen during the acute phase of the disease, particularly with viral anterior uveitis, PSS, and uveitic glaucoma. An open angle can be blocked by inflammatory cells and fibrin, decreasing aqueous outflow. Over time, peripheral anterior synechiae formation can lead to complete angle closure and iris bombé. This is further complicated by the possibility of corticosteroid response glaucoma in a patient receiving treatment with corticosteroids. Therefore, the pathogenesis of elevated IOP in eyes with anterior uveitis can be multifactorial.

Previous episodes of anterior uveitis will lead to sequelae of anterior chamber inflammation that can be seen on examination (Fig. 7.20.2). These findings include old, pigmented, or crenated keratic precipitates; peripheral anterior synechiae; posterior synechia or remnants of broken



**Fig. 7.20.2 Sequelae of Chronic Anterior Uveitis.** As a result of chronic anterior chamber inflammation, pupillary membrane formation is seen. Synechiae are present as iridocorneal adhesions in this patient with HLA B27–associated chronic anterior uveitis (A). Band keratopathy is a common corneal finding in patients with juvenile idiopathic arthritis (JIA)–associated chronic anterior uveitis (B).

posterior synechiae on the anterior lens capsule; pupillary membrane; or occlusion pupillae. Calcific band keratopathy can be seen as deposition of calcium on the cornea within the interpalpebral zone and is indicative of long course of chronic inflammation.

## DIAGNOSIS AND ANCILLARY TESTING

The diagnosis of anterior uveitis can be made on the basis of clinical examination consistent with inflammation that affects primarily the anterior chamber but does not exclude the possibility of associated inflammatory findings, such as spillover anterior vitreous cells or cystoid macular edema. The presence of anterior chamber reaction in the form of cells and flare can be seen by slit-lamp biomicroscopy. Combined with clinical history and usual symptoms of pain, redness, and photophobia, the diagnosis is typically straightforward.

Although unnecessary for making the diagnosis, measurements of aqueous flare, made using laser flare photometry, can provide the ability to monitor anterior chamber reaction in a quantitative fashion during and



between episodes.<sup>7,17–19</sup> Anterior chamber paracentesis is a safe and useful outpatient procedure,<sup>20</sup> which can aid in the diagnosis of idiopathic anterior uveitis because it is a diagnosis of exclusion. The aqueous sample can be used for culture when an infectious etiology is suspected. However, newer techniques for aqueous humor analysis are more sensitive than culture. PCR can be performed on aqueous samples to identify a range of infectious organisms, such as CMV, herpes simplex virus (HSV), varicella zoster virus (VZV), rubella, and *Mycobacterium tuberculosis*. Furthermore, histopathology can be useful in identifying masquerade syndromes, such as leukemia, retinoblastoma, and phacoantigenic uveitis.<sup>21</sup>

## DIFFERENTIAL DIAGNOSIS

Idiopathic anterior uveitis is a diagnosis of exclusion. In some cases, the patient's history (e.g., recent cataract surgery or antecedent nonpenetrating ocular trauma) makes the diagnosis obvious. At times, review of systems or examination findings may be suggestive of a particular etiology, emphasizing the importance of a thorough medical history and careful examination. For example, a history of recurrent, alternating episodes of acute anterior uveitis in a patient with joint pain and keratoderma blennorrhagia is suggestive of HLA B27-associated anterior uveitis. A clinical diagnosis of herpetic iritis can be made with a constellation of typically associated examination findings, such as iris transillumination defects, stellate keratic precipitates, and elevated IOP. In this case, anterior chamber paracentesis for viral PCR could be performed to confirm the diagnosis. Otherwise, there is no consensus as to whether or not a single, isolated episode of anterior uveitis necessitates a systemic workup. If consistent with the clinical picture, including demographics and geographical locale, such a workup should aim at ruling out treatable infectious etiologies, such as syphilis, Lyme disease, leprosy, and tuberculosis, as well as conditions with systemic ramifications, such as HLA B27 haplotype, sarcoidosis, JIA, Behçet's disease, and TINU. Some cases of presumed idiopathic anterior uveitis are later found to be associated with a specific disease entity, particularly if extraocular symptoms present later.

## PATHOLOGY

Histological examination of the anterior uvea in experimental melanin-induced uveitis (EMIU), an animal model of anterior uveitis, reveals mononuclear cells, neutrophils and T cells.<sup>22</sup> Monocytes may be seen marginating in the iris vessels. Evidence suggests that cytokines produced by uveal macrophages may play a role in the development of uveitis.<sup>23,24</sup> Aqueous samples taken from patients with idiopathic anterior uveitis demonstrate CD4+ T cells with increased interleukin-2 receptor expression<sup>25,26</sup> consistent with findings of CD4+ T cell infiltration of the anterior uvea in EMIU, which responds to treatment with anti-CD4+ antibody.<sup>27</sup>

## TREATMENT

Corticosteroids are the mainstay of therapy for the treatment of noninfectious anterior uveitis and have both anti-inflammatory and immunosuppressive properties, irrespective of the etiology of the inflammatory response (traumatic, infectious, autoimmune, postoperative, etc.) These changes to the immune system are temporary and cease within days of discontinuation of corticosteroid use. Various topical corticosteroids are available for ophthalmic use; the more potent preparations contain acetate and penetrate intact cornea. Frequent administration is typically recommended, and patients are commonly instructed to apply this medication every 1–2 hours while awake during an acute episode of severe anterior uveitis. Once an improvement in cell and flare is observed, slow tapering of the corticosteroid medication can begin. In refractory cases, periocular or systemic corticosteroid may be required to achieve quiescence. Fortunately, topical corticosteroids for ophthalmic use have not been reported to be associated with teratogenicity, but systemic corticosteroids have been associated with the formation of orofacial clefts.<sup>28</sup> Therefore, in the setting of pregnancy, regional corticosteroid injection would minimize the potential for systemic absorption affecting the fetus.

Cycloplegic/mydriatic agents are given to prevent the formation of, and possibly break, posterior synechiae. In addition, these agents reduce pain and photophobia caused by inflammation of the ciliary muscle. If the intraocular pressure is elevated, glaucoma medication should be employed. However, if possible, prostaglandin analogues and pilocarpine should be avoided, although not contraindicated, because of the theoretic effect on the blood–aqueous barrier.<sup>29,30</sup> Topical nonsteroidal anti-inflammatory

drugs (NSAIDs) can be given for uveitic cystoid macular edema associated with chronic anterior uveitis; alternatively, or in refractory cases, periocular corticosteroid injection can be given for this indication as well.<sup>31</sup>

It is important to consider that prolonged and frequent use of topical corticosteroids is not prudent in certain situations. The risk of cataract formation and glaucoma should be considered in patients with phakia and those who react to corticosteroid, respectively. Because of the risk of amblyopia secondary to cataract formation, it is preferable to avoid  $\geq 3$  times daily dosing of topical corticosteroids in pediatric patients.<sup>32</sup> Therefore, in children with chronic anterior inflammation, such as JIA-associated uveitis, systemic treatment with a corticosteroid-sparing agent is usually necessary. In patients with chronic anterior uveitis who are unable to achieve or sustain remission after corticosteroid taper, as well as those who cannot tolerate the necessary dosage or frequency of corticosteroid required, systemic immunosuppression should be considered.

Surgical intervention is seldom recommended as a treatment for anterior uveitis because surgical trauma itself will incite further ocular inflammation. Typically, surgery to address complications of chronic uveitis is deferred until a period of quiescence has been achieved. However, surgical lens removal is the treatment of choice for active lens-induced uveitis and uveitis glaucoma hyphema (UGH) syndrome. In these conditions, removal of the phakic or pseudo-phakic lens is the definitive treatment to address the inciting cause of ocular inflammation.

## FUCHS' HETEROCHROMIC IRIDOCYCLITIS

FHI is an anterior uveitis syndrome that may present with variable signs and symptoms, often beginning insidiously. Young adults are affected, and the disease is usually unilateral, although 15% of cases are reported to be bilateral.<sup>33</sup> Patients typically do not have the usual symptoms of pain, redness, and photophobia. Typical manifestations include low-grade chronic anterior chamber reaction, iris heterochromia, stellate keratic precipitates, and bridging iris vessels. Low-grade anterior vitritis is present and may cause symptomatic floaters. Because of the subtleties of its clinical presentation, the diagnosis of FHI may be delayed,<sup>34</sup> and the patient may not become symptomatic until cataract formation becomes visually significant.

Iris heterochromia, the hallmark of this syndrome, was initially described by Fuchs in 1906<sup>35</sup> and may be noticed by the patient or family members. Iris stromal atrophy leads to the color change of the iris on the affected eye. In a patient with dark irises, the involved eye takes on a lighter color. In a patient with pale-colored eyes, reverse heterochromia occurs as the darker pigmented posterior iris becomes exposed as a result of anterior iris stromal atrophy. In a patient with bilateral FHI, heterochromia will not be evident, and characteristics of the iris, including a moth-eaten appearance with patchy areas of transillumination defects, may be the only consistent findings.

Fine, stellate keratic precipitates are commonly seen in a diffuse distribution. However, all types of keratic precipitates, including globular, infiltrating, dendritiform, stippled, cruciform, and "mutton fat" varieties, have been reported.<sup>36,37</sup> Fine neovascularization with bridging vessels over the angle are seen on gonioscopy. These vessels have a tendency to hemorrhage during anterior chamber paracentesis, a phenomenon termed "Amsler's sign."<sup>38</sup> Similarly, hyphema is expected to occur intraoperatively during cataract surgery but does not typically complicate the procedure.

Cataract is seen in over 80% of eyes with FHI and elevated IOP in 25%–60% of patients, arising either from the inflammation or from corticosteroid therapy.<sup>33,39</sup> Posterior subcapsular cataracts are most common, and patients tend to tolerate cataract extraction without complication. Glaucoma develops in 6.3%–59% of patients, and 25%–60% of those individuals require a filtering procedure during the course of treatment. Most importantly, the complications from chronic inflammation in FHI do not usually include posterior synechiae or cystoid macular edema, unlike other anterior uveitis entities.

The use of NSAIDs is not useful in the treatment of FHI, as there is little effect on the severity or course of intraocular inflammation. Treatment is directed toward the management of complications of the condition, including cataract, glaucoma, and, occasionally, visually significant vitreous opacities. The prognosis for eyes with FHI is good, with almost all eyes achieving visual acuity of 20/40 or better.<sup>40–42</sup>

Once thought to be idiopathic, there is now evidence to support that FHI is linked to rubella virus. Isolation of the organism from intraocular fluids by using PCR and reverse transcription-PCR is difficult.<sup>43</sup> Local antibody production is indicated by a Goldmann–Witmer coefficient (GWC) of  $>3$ . The presence of rubella infection in FHI eyes has been confirmed

by GWC in several studies.<sup>44-47</sup> Furthermore, epidemiological data suggest that FHI has become less common among patients born after the introduction of the US rubella vaccination program compared with foreign-born and older American populations for whom rubella vaccination was not available.<sup>48</sup>

## POSNER–SCHLOSSMAN SYNDROME

Unilateral attacks of mild nongranulomatous anterior uveitis with elevations in IOP are the hallmark of PSS. Acute attacks of glaucomatocyclitic crisis last from a few hours to several weeks and may be recurrent. Between episodes, IOP and aqueous outflow facility return to normal. Affected patients tend to be younger (age 20–50 years) with a male predilection.

Symptoms of an acute attack of PSS may include unilateral blurred vision and pain. Clinical examination reveals mild anterior chamber reaction and small- to medium-sized nongranulomatous keratic precipitates. There may also be associated corneal edema, which resolves with lowering of the IOP. IOP elevation is usually as high as 40–60 mm Hg, which results from blockage of the trabecular meshwork with mononuclear cells.<sup>49</sup>

Attacks of PSS are thought to be benign. Transient S-cone response reductions on electroretinography<sup>50</sup> and optic nerve head blood flow alterations<sup>51</sup> have been described. Mild loss of endothelial cell density, particularly with recurrent attacks, has been noted on specular microscopy.<sup>52</sup> Both mild and advanced glaucomatous optic nerve cupping and visual field loss have been reported.<sup>53,54</sup>

The exact etiology of PSS is unknown. Since it was first described, a variety of noninfectious etiological theories were proposed, including autoimmune dysregulation,<sup>55</sup> allergy,<sup>55-58</sup> and abnormality of the ciliary vasculature.<sup>59,60</sup> Infectious etiologies were not entertained initially because of the episodic nature of the acute attacks. In modern literature, evidence has emerged to support various infectious theories associated with several distinct organisms: CMV,<sup>11,15,61-63</sup> *Helicobacter pylori*,<sup>64</sup> VZV,<sup>65</sup> HSV,<sup>66</sup> and *Borrelia burgdorferi*.<sup>67</sup> Enzyme-linked immunosorbent assay of serum tested positive for *H. pylori* in 80% of patients with PSS compared with 56% in controls.<sup>64</sup> PCR of aqueous fluid has been used to confirm the presence of CMV.<sup>11,61-64</sup> The lack of PCR positivity during times of quiescence and a positive Goldmann–Whitmer coefficient, as well as therapeutic response to anti-infectives suggest a causal relationship, with the largest body of evidence supporting CMV as an etiological agent.<sup>64</sup> PSS has also been described in association with peptic ulcer disease<sup>58,69</sup> and genetic marker HLA-Bw54.<sup>68</sup>

The aim of treatment is to address the anterior segment inflammation and to lower IOP. Topical corticosteroids and ocular hypotensive medications are sufficient to control these attacks but not to prevent recurrences. Without intervention, these attacks usually resolve. However, cases of nonarteritic anterior ischemic optic neuropathy secondary to acute glaucoma associated with PSS have been reported,<sup>69,70</sup> suggesting the need to treat IOP even if it is self-limiting. IOP in PSS responds to topical hypotensives more readily compared with that in primary open-angle glaucoma; apraclonidine alone lowers IOP by 50% over a 4-hour period.<sup>71</sup> Occasionally, surgical intervention is necessary to control raised IOP.<sup>72</sup>

## DRUG-INDUCED ANTERIOR UVEITIS

Anterior uveitis can arise as a result of drug-induced ocular inflammation but the incidence is <1%.<sup>73</sup> The offending agent may have been administered systemically, topically, or intracamerally. Diagnosis of drug-induced anterior uveitis relies on suspicion on the part of the clinician with consistent time sequence between drug administration and clinical event, as well as resolution of the condition after withdrawal of the drug. The most commonly implicated drugs are intravenous or intravitreal cidofovir, systemic rifabutin, systemic sulfonamides, oral bisphosphonates, topical metipranolol, topical and intravitreal corticosteroids and, most recently, oral moxifloxacin.<sup>74-77</sup> Cidofovir causes a mild anterior chamber reaction with a fibrinous response; the anterior vitreous is involved in half the cases.<sup>78</sup> Rifabutin-induced uveitis occurs in the dose range of 200–1800 mg and is more common in immunocompromised individuals but has been reported in immunocompetent patients also.<sup>79</sup> The anterior chamber reaction is severe and fibrinous, accompanied by hypopyon that resolves with intensive topical corticosteroid therapy.<sup>80</sup> Oral moxifloxacin has been reported to be associated with bilateral anterior uveitis, pigment dispersion, transillumination defects, and atonic pupils.<sup>74-77</sup> Less frequently, other fluoroquinolones have also been implicated to cause this reaction.<sup>77</sup> The mechanism

behind ocular inflammation secondary to medication is unknown but may represent a hypersensitivity reaction.

## SCHWARTZ–MATSUO SYNDROME

Anterior segment inflammation with elevated IOP and open anterior chamber angle is caused by rhegmatogenous retinal detachment in Schwartz–Matsuo syndrome.<sup>81,82</sup> This is not a true anterior uveitis, as the anterior chamber is filled with pigmented cells representing photoreceptor outer segments.<sup>83</sup> Retinal tears or dialysis anterior to the anterior vitreous base allow rod outer segments to migrate from the subretinal space through the peripheral retinal break into the aqueous humor, thus obstructing aqueous outflow.<sup>82</sup> The condition is not responsive to corticosteroid therapy. IOP can be as high as 60–70 mm Hg and is responsive to aqueous suppressants. Upon repair of the retinal detachment, the condition resolves, and IOP normalizes.

## ELLINGSON SYNDROME

UGH syndrome, also known as *Ellingson syndrome*, was first described by Ellingson in 1978.<sup>84</sup> This form of anterior uveitis is secondary to chaffing of the uvea by an intraocular lens and is associated with elevated IOP and bleeding of uveal vessels. The syndrome was originally described with first-generation anterior chamber IOLs which led to haptic or optic contact with iris and angle structures. The size, rigidity, shape, and design of earlier IOLs caused lens movement and mechanical chaffing on the iris and angle structures.<sup>85</sup> However, UGH syndrome may also occur with sulcus IOLs and posterior chamber lenses implanted partially or completely within the capsular bag,<sup>86</sup> as well as cosmetic iris prosthetic devices<sup>87,88</sup> and Soemmering's ring.<sup>89</sup> Irritation of the uveal tissue creates pigment dispersion as well as breakdown of the blood–aqueous barrier. Iris chaffing leads to localized transillumination defects in the area of mechanical contact with the iris stroma. Release of erythrocytes, lymphocytes, and pigment into the anterior chamber result in elevated IOP as a result of clogging of the trabecular meshwork. Iris neovascularization can occur, and bleeding from these vessels result in recurrent microhyphema, hyphema, or, occasionally, vitreous hemorrhage.<sup>90</sup> Although the diagnosis of UGH is made clinically, ultrasound biomicroscopy<sup>91</sup> can aid in visualization of IOL malposition and the contact between the IOL optic and/or haptics with uveal structures. Medical management with topical corticosteroids and cycloplegic agents are used in the acute management of UGH syndrome. However, UGH syndrome is an indication for IOL explantation,<sup>92</sup> which is a definitive treatment to resolve recurrent inflammation caused by uveal irritation.

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# Pars Planitis and Other Intermediate Uveitis

John A. Gonzales, Aliza Jap, Soon-Phaik Chee

7.21

**Definition:** Intraocular inflammation primarily involving the anterior vitreous, pars plana ciliaris, and peripheral retina.

### Key Features

- Typically bilateral.
- Inflammatory cells in the anterior vitreous.
- Aggregates of inflammatory cells (snowballs) in the vitreous.
- White exudate (snowbank) on the inferior pars plana.
- Peripheral retinal vascular sheathing adjacent to exudates.
- Cystoid macular edema.
- Vitreous opacity.
- Mild or absent anterior chamber cell and flare.

### Associated Features

- Patients are generally young, with a mean age at presentation of 23–31 years, and it is uncommon in older adults.
- Floaters and blurry vision are the most common symptoms.
- Mild pain, photophobia, and redness are less common.
- Possible complications include vitreous traction, rhegmatogenous retinal detachments, neovascularization of the retina or optic disc, vitreous hemorrhage, posterior subcapsular cataract, glaucoma, inferior endophthalmitis, posterior synechiae, retinal or anterior segment neovascularization, and secondary vasoproliferative tumors.<sup>1</sup>

## INTRODUCTION

*Intermediate uveitis* (IU) is the term recommended by the Standardization of Uveitis Nomenclature working group for intraocular inflammation when the primary site of involvement is the vitreous.<sup>2</sup> It includes inflammation occurring at the pars plana and the peripheral retina. Pars planitis is a subset of IU in which snowbanks or snowballs are prominent features and there is no associated systemic or infectious disease.<sup>2</sup>

## EPIDEMIOLOGY AND PATHOGENESIS

IU is relatively uncommon, accounting for 1%–26% of all cases of uveitis,<sup>3,4</sup> with an annual incidence of 1.5–2.1 per 100 000 person years in the general population.<sup>5–8</sup> It occurs mainly in children and young adults with a mean age at presentation of 23–31 years, and it is uncommon in older adults.<sup>4</sup>

It is thought to be an autoimmune process, and there is considerable evidence to show an association between multiple sclerosis (MS) and IU. The prevalence of MS in patients with IU ranges from 7% to 16%.<sup>5,9–11</sup> Conversely, the prevalence of uveitis in patients with MS is about 1%, and in these patients, IU is the most common form of involvement.<sup>4,6</sup> Uveitis may be the presenting symptom in 25% of cases, and it may precede the diagnosis of MS by 3–9 years.<sup>10</sup> Furthermore, various studies have also found an association between human leukocyte antigens (HLAs) (in particular HLA DR15), with IU and MS.<sup>7</sup> Similarly, the association with sarcoidosis<sup>9,12</sup> as well as the involvement of family members with similar HLA typing also suggests an autoimmune mechanism.<sup>13</sup>

In some cases, an infection, such as tuberculosis (TB), syphilis, Lyme disease, cat scratch disease, or human T-lymphotropic virus type 1 infection, may be the inciting cause for the immune response.<sup>14–18</sup>

Histopathological studies of the snowbanks show glial and vascular proliferation, as well as lymphocytic infiltration of the peripheral retinal veins. The glial component comprises vitreous collagen and fibrous astrocytes, whereas lymphocytic infiltrates are composed mainly of T helper cells. These further suggest that IU is an autoimmune process. The choroid is relatively spared.<sup>13,19</sup>

## OCULAR FINDINGS AND COMPLICATIONS

IU is typically a bilateral disease (Table 7.21.1)<sup>8,20,21</sup> with a chronic, slowly progressive course and episodes of relapses in some patients.<sup>5,20</sup> As the primary site of involvement is the vitreous, the most common symptoms are blurred vision and floaters.<sup>5</sup> Pain, photophobia, and redness are less common symptoms (4%–7%),<sup>5</sup> and it may be asymptomatic especially in children (7%–25%).<sup>5,21</sup>

Although anterior chamber inflammation may be present in up to 57% of cases,<sup>5,21,22</sup> it is usually mild<sup>5,21</sup> and posterior synechiae is uncommon (6%–14%).<sup>5,8,21,22</sup> A linear configuration of keratic precipitates, similar to that seen in autoimmune endotheliopathy, has also been described in a small number of cases (Fig. 7.21.1). There may also be concomitant corneal edema.<sup>20</sup>

The predominant finding is vitritis, and the vitreous cells may coalesce to form snowballs. Another frequently seen finding is that of snowbanks, which consist of a conglomeration of inflammatory exudates at the pars plana. These snowbanks are generally found inferiorly but may extend throughout the pars plana.<sup>5,22</sup> These inflammatory changes may be associated with peripheral vascular sheathing<sup>5,9,21,22</sup> and as a result, neovascularization of the pars plana (Fig. 7.21.2), retina, or optic disc may occur.<sup>5,21,22</sup> This can lead to vitreous hemorrhage, which is more commonly seen in children,<sup>12</sup> and/or retinal detachment. However, neovascular glaucoma is rarely seen. Inferior peripheral elevations are found in about 13% of cases<sup>21,23</sup> and may be caused by retinoschisis, and/or tractional or exudative retinal detachment.

The main causes of visual loss in IU are cystoid macula edema (CME) (Fig. 7.21.3),<sup>5,8,20–22</sup> epiretinal membranes (ERMs),<sup>5,20,22</sup> and cataract formation.<sup>5,8,19,20</sup> Glaucoma is also seen in 11%–14% of cases<sup>8,20,22</sup> and may be

TABLE 7.21.1 Main Clinical Features and Complications of Intermediate Uveitis

Clinical Features	Percentage <sup>5,8,19–21</sup>
Bilaterality	>80%
Blurring of vision	74%
Floaters	61%
Vitritis/snowballs/snowbanks	63–90%
Peripheral vascular sheathing	23–90%
<b>Complications</b>	
Cystoid macula edema	20–63%
Cataract	25–83%
Epiretinal membrane	6–36%
Neovascularization	4–23%
Vitreous hemorrhage	17–24%
Optic disc swelling	12–75%
Glaucoma	11–14%
Band keratopathy	3–17%



**Fig. 7.21.1** Slit-lamp photograph of a linear arrangement of keratic precipitates in an eye with intermediate uveitis.

a direct result of chronic inflammation or secondary to corticosteroid therapy. Other complications include optic disc swelling<sup>3,20,22</sup> and band keratopathy.<sup>20,22</sup>

## DIAGNOSIS

The diagnosis of pars planitis is based on meticulous history and examination and ancillary tests to exclude infective causes and associated systemic diseases. Specifically, the history and examination should include the presence of skin lesions, which may indicate sarcoidosis, syphilis, TB, or Lyme disease. A history of fever, cough, or night sweats may suggest TB or sarcoidosis. Arthralgia may be a symptom of Lyme or Whipple's disease. If an infectious cause is suspected, the history should include travel to areas where the disease is endemic, trekking, or contact with cats, as appropriate. Patients with MS may have had previous episodes of neurological involvement, such as optic neuritis.

In addition to diagnosis, ancillary tests are also useful in assessing the severity of disease. Fundal photography and fluorescein angiography allow for objective records of extent of vitritis and/or vascular sheathing, respectively. Ultrasonography is especially useful in evaluating and monitoring the progression in eyes where examination of the posterior segment is limited by media opacity or a small pupil. Optical coherence tomography is a valuable tool in assessing macular changes, such as CME, during the course of the disease as well as during treatment.

Diagnostic tests should include complete blood count; tuberculin sensitivity test; angiotensin-converting enzyme and lysozyme levels; serology for syphilis, Lyme disease, TB, and other infectious diseases, as indicated; and chest radiography for TB and/or sarcoidosis. Magnetic resonance imaging of the brain for white matter lesions may be advisable in populations with a high prevalence of MS.

In older patients, the possibility of lymphoma should also be considered. Ocular involvement, including IU, may be the first presentation of primary central nervous system lymphoma, and the mean age of onset in these patients is about 60 years.<sup>24,25</sup> A definitive diagnosis of ocular lymphoma often requires vitreous biopsy, and if the cellular quality of the sample is inadequate for cytology, molecular analysis of immunoglobulin heavy chain (IgH) and T-cell receptor (TCR) gene arrangement, flow cytometry, or cytokine analysis of vitreous interleukin-10 (IL-10) to IL-6 ratio are useful biomarkers with high sensitivity and specificity.<sup>26,27</sup>

## MANAGEMENT

Up to one third of patients have mild inflammation and good vision and do not require treatment.<sup>4</sup> However, if visual loss results from CME, vitritis, or neovascularization, treatment should be started early, and the duration of treatment in these eyes is often prolonged.

## Medical Management

Corticosteroids are the first line of treatment and may be given via the topical, periocular, intravitreal, or systemic route. Local administration avoids the protean complications of systemic corticosteroids. However, the ocular penetration after topical applications of corticosteroids is poor, and in view of the chronic nature of IU and the limited duration of effectiveness of periocular and intravitreal medications, the injections often have to be repeated. Cataract progression and elevated intraocular pressures are common complications of intravitreal corticosteroids. In addition, periocular injections carry risks of ocular perforations, and intravitreal injections of triamcinolone or implants of sustained release formulations of corticosteroids, such as flucinolone or dexamethasone, pose risks of endophthalmitis, vitreous hemorrhage, and/or retinal detachment. If the inflammation is refractory or the patient is unable to tolerate corticosteroids, various systemic immunosuppressive/immunomodulatory agents, such as azathioprine, methotrexate, tacrolimus, mycophenolate mofetil, cyclosporine, or interferon- $\alpha$ 2a (IFN- $\alpha$ 2a,<sup>28–33</sup> may be used. With the advent of the biologicals, tumor necrosis factor (TNF) inhibitors have been used for the management of intermediate uveitis, particularly when it exhibits recalcitrance to antimetabolites or calcineurin inhibitors.<sup>34</sup> Additionally, the US Food and Drug Administration has approved the use of adalimumab for noninfectious intermediate, posterior uveitis, and panuveitis. Although TNF inhibitors (particularly adalimumab and infliximab) can be effective in managing inflammation in intermediate uveitis, given the incidence of MS in intermediate uveitis, referral to a neurologist for consideration of neuroimaging to rule out features of a demyelinating process is recommended. Anti-TNF agents can hasten the development of MS in those predisposed to developing the neurological disease or make the condition worse if it is present.<sup>35,36</sup>

In eyes with persistent CME despite having achieved control of the inflammation, in addition to supplemental local therapy with periocular or intravitreal corticosteroids, the intravitreal administration of other anti-inflammatory drugs, such as methotrexate and anti-vascular endothelial growth factors (anti-VEGF) agents have also been shown, in a small case series, as being a potential alternative treatment for refractory uveitic CME.<sup>37,38</sup> However, although these agents have a rapid effect in reducing the macular edema and in improving the visual acuity, their action is also short-lived and repeated injections may be required. Their long-term effects are also unknown, and there is concern that repeated injections of the anti-VEGF agents themselves may be associated with the occurrence of uveitis.<sup>39</sup> Somatostatin analogues, such as octreotide, IFN- $\alpha$  drugs, and long-term low-dose acetazolamide, are other potential modalities for management of CME secondary to IU.<sup>40–42</sup> Infliximab has been reported to improve CME in patients who have uveitis but no other demonstrable features of inflammation.<sup>43</sup>

## Surgical Management

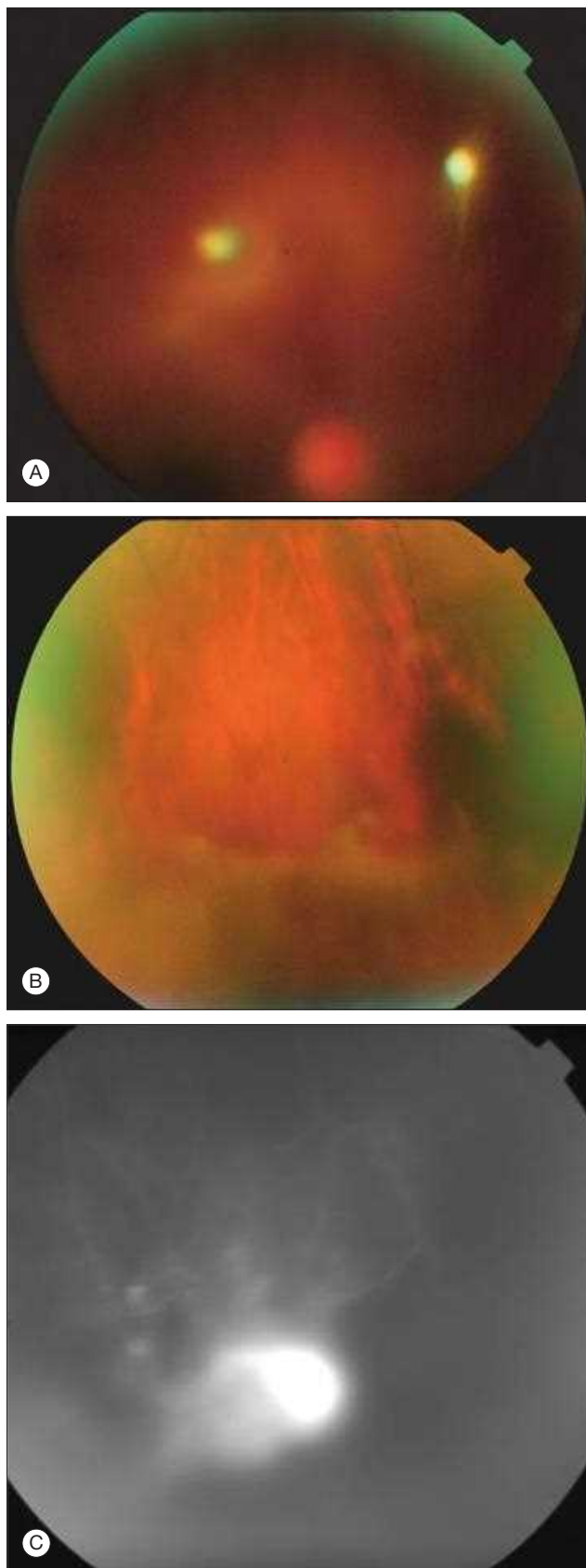
Pars plana vitrectomy in addition to its role in management of the complications of IU, such as CME, ERM, retinal detachment, or vitreous hemorrhage, has also been advocated as an alternative to immunosuppressants for the control of active inflammation. By removing inflammatory cells and membranes, it has been found to be useful in reducing visual loss from CME and ERM, as well as in reducing the requirement for immunosuppressive therapy.<sup>44–46</sup>

Cataract surgery should be undertaken when the eye has been quiet for at least 3 months; with meticulous surgery as well as perioperative immunosuppressants or intravitreal corticosteroids, as indicated, at least 79% majority of patients improve by  $\geq 2$  Snellen lines. The main causes of poor vision are posterior capsule opacification, CME, ERM, and submacular fibrosis.<sup>47</sup>

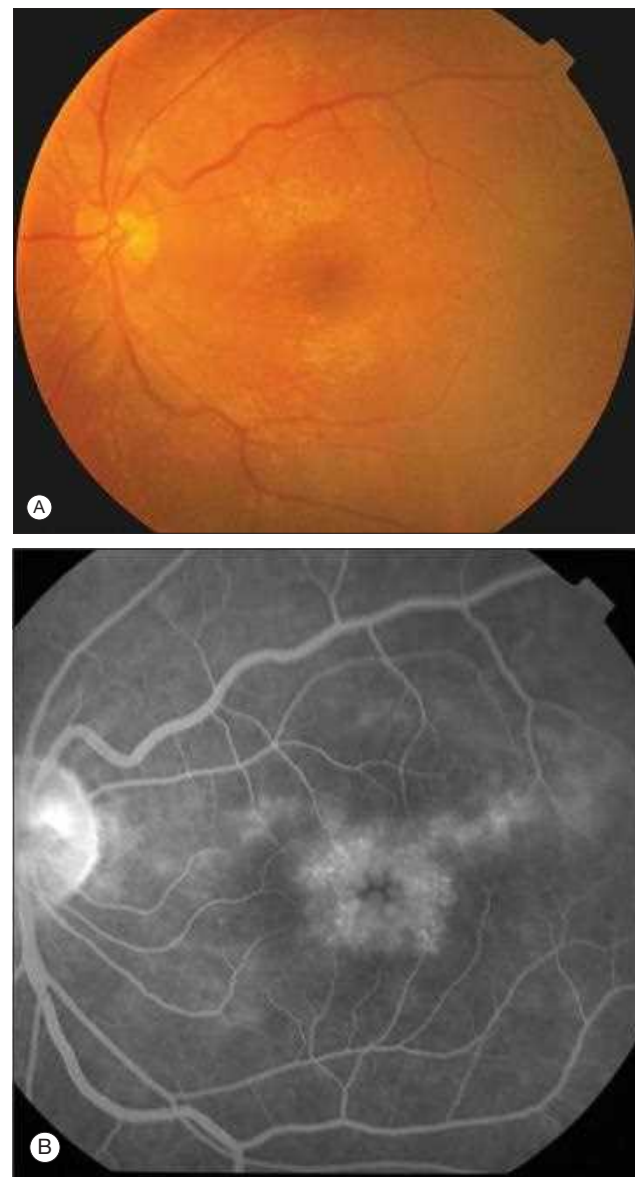
## PROGNOSIS

The prognosis for most patients with IU is generally good. The mean visual acuity after 10 years of follow-up was 20/30, with 75% achieving 20/40 or better visual acuity<sup>5,20</sup> and remission was seen in 30%–50% of patients, with younger age being associated with a better outcome.<sup>8,19,21</sup> However, children age  $< 7$  years had a less favorable outcome, with poorer vision requiring longer treatment, a lower likelihood of remission, and a higher probability of secondary glaucoma, vitreous hemorrhage, and need for cataract surgery.<sup>21</sup>





**Fig. 7.21.2** (A) Fundal photograph of an eye with sarcoidosis showing snowballs (B) and snowbanks. (C) Fluorescein angiography image of the same eye showing an area of neovascularization in the snowbank seen above.



**Fig. 7.21.3** (A) Fundal photograph and (B) fluorescein angiography image of an eye with intermediate uveitis showing cystoid macula edema.

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# Posterior Uveitis of Unknown Cause— White Spot Syndromes

7.22

Rukhsana G. Mirza, Ramana S. Moorthy, Lee M. Jampol

**Definition:** A heterogeneous group of posterior segment inflammatory disorders of unknown cause involving the outer retina, retinal pigment epithelium, choroid, or a combination of these in one or both eyes of patients in their second to sixth decades of life.

## Key Feature

- Multiple unilateral or bilateral discrete outer retinal or choroid inflammatory lesions that appear white or placoid.

## Associated Features

- Unilateral or bilateral, depending on the disease.
- Second to sixth decades of life.
- Often female predilection.
- Variable inflammatory cells in the anterior chamber and vitreous humor, depending on the disease.
- Usually self-limiting course, but variable prognosis, depending on the disease.
- Unknown cause with negative serological evaluation.

## INTRODUCTION

White spot syndromes (WSSs) are a group of diseases that affect the outer retina, retinal pigment epithelium (RPE), choroid, or a combination of these. The lesions are typically multifocal in nature. They may present in one eye or both eyes. When bilateral, they may be asymmetrical. The white spots themselves may be a variable finding. For this reason, the term *inflammatory multifocal chorioretinopathies* may be more appropriate.

Patients in the second to sixth decades of life are typically affected by these diseases. The entities covered in this chapter include birdshot chorioretinopathy (BCR), acute posterior multifocal placoid pigment epitheliopathy (APMPPE), serpiginous choroiditis (SC), relentless placoid chorioretinitis (RPC), persistent placoid maculopathy (PPM), idiopathic multifocal choroiditis (MFC)/punctate inner choroidopathy (PIC), multiple evanescent white dot syndrome (MEWDS), acute zonal occult outer retinopathy (AZOOR), and acute macular neuroretinopathy (AMN). These diseases present in a varied fashion; however, there are some similarities. Many have a female predilection. Some common presentations include blurred vision; photopsias; visual field changes, including an enlarged blind spot; and floaters. These diseases are thought to be inflammatory in nature, but iritis and vitritis are not essential findings in the diagnosis of most of these entities. These syndromes have no known cause. An autoimmune etiology has been hypothesized,<sup>1</sup> and it appears that this group of diseases occurs in families with inherited immune dysregulation that predisposes to autoimmunity.<sup>2</sup> Although some of these disorders are self-limiting and have good visual outcomes, others are associated with serious retinal and choroidal sequelae and can result in visual loss. Newer imaging modalities, such as spectral-domain optical coherence tomography (SD-OCT) and enhanced depth imaging optical coherence tomography (EDI-OCT), fundus autofluorescence (FAF), and optical coherence tomography angiography (OCTA), are shedding light on the pathogenesis and prognosis of these syndromes. Multimodal imaging now can distinguish

what were previously thought to be overlapping diseases. Acute idiopathic blind spot enlargement (AIBSE), initially described by Fletcher et al. in 1988,<sup>3</sup> has, in the past, been presented as a distinct entity within WSS. Many of the cases that were described in the literature can now be identified as “other WSS,” and we believe that an enlarged blind spot may be a feature of these “other” diseases, rather than being its own clinical entity.

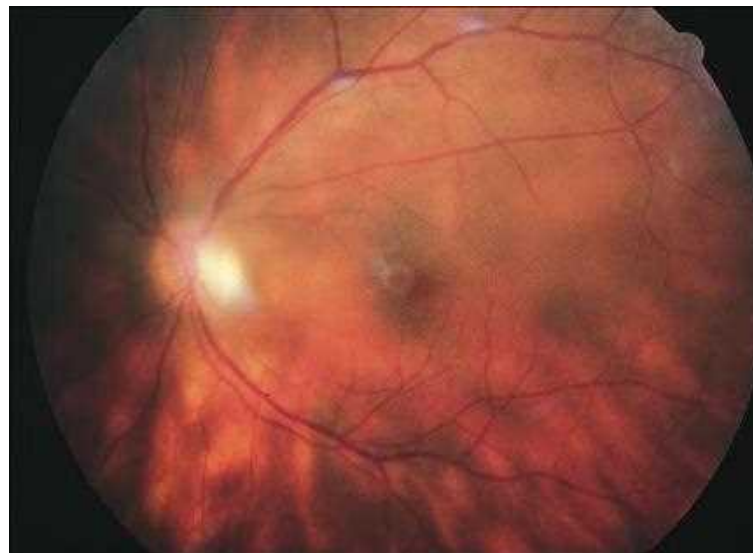
## BIRDSHOT CHORIORETINOPATHY

### Epidemiology and Pathogenesis

Birdshot chorioretinopathy (BCR) also has been called *birdshot retinochoroidopathy*<sup>4</sup> and *vitiliginous chorioretinitis*.<sup>5</sup> The preferred term *BCR* is used here because of histopathological evidence that the primary lesions of the disease are located in the choroid.<sup>6</sup> This syndrome affects healthy patients, usually women, between the third and sixth decades of life.<sup>4,6</sup> At least 90% of patients who have BCR possess the human lymphocyte antigen A\*29 (HLA-A\*29) allele compared with 7% of the general Caucasian population. Subtype HLA-A29.2 occurs most commonly in Caucasians with BCR.<sup>7</sup> This is the highest association of any HLA antigen with a human disease.

### Ocular Manifestations

Patients complain of blurred vision, floaters, central and peripheral photopsias, and, later, nyctalopia and color blindness.<sup>4-6</sup> The lesions of BCR are scattered around the optic disc and radiate to the equator in a “shotgun” pattern; they sometimes appear to follow choroidal vessels (Fig. 7.22.1). The creamy lesions are small and <1 disc diameter in size. They can be oval or round in shape and are located deep to the retina. They tend to cluster near the nerve, especially nasal and inferiorly to it.<sup>8</sup> Vitreous inflammation is present. Disc edema, narrowed retinal vessels, and cystoid macular edema (CME) are also seen.



**Fig. 7.22.1 Birdshot Chorioretinopathy.** Note the optic disc edema, vitritis, and multiple, creamy, yellow choroidal lesions in the midperiphery of the left eye.



## Diagnosis

The diagnosis of BCR can be made on the basis of history and physical findings. However, imaging is useful to delineate the disease and monitor therapy. Fluorescein angiography (FA) reveals disc staining, vascular leakage, and, often, late CME.<sup>5,6</sup> The birdshot lesions have variable appearance with this mode of imaging and generally are seen better clinically. In the late phases of angiography, these hypopigmented lesions can appear mildly hyperfluorescent. Indocyanine green angiography (ICGA) in acute disease demonstrates hypofluorescent lesions in the intermediate phase of the angiography, and the lesions are bordered by medium-to-large vessels even before apparent clinical lesions.<sup>9</sup> SD-OCT demonstrates circular patches of chorioretinal atrophy, ellipsoid zone disruption, outer retinal atrophy,<sup>10</sup> and chronic retinal thinning.<sup>11</sup> EDI-OCT shows reduction in choroidal thickness and volume with increased disease duration.<sup>12</sup> SD-OCT is also useful in monitoring CME, a common cause of vision loss in BCR.<sup>11</sup> OCTA demonstrates retinal capillary density reduction at the deep retinal capillary plexus level and may explain the development of retinal neovascularization (NV), retinal thinning, and reduction of visual function.<sup>13</sup> FAF<sup>14,15</sup> reveals more extensive hypoautofluorescent lesions than are seen clinically. In addition, perivascular linear and late macular hypoautofluorescent patterns are noted on FAF.<sup>16</sup> Electroretinography (ERG) is important in the diagnosis and management of BCR. It may show moderately to severely depressed rod and cone function. Severe cases often demonstrate an extinguished image on ERG. Results of electro-oculography (EOG) usually are normal but can be variably subnormal in some patients.<sup>5,17,18</sup> Visual field abnormalities are common in BCR. These can include peripheral constriction, enlarged blind spot, central or paracentral scotomas, and generalized diminished sensitivity.<sup>5,8</sup> Visual field testing is important in monitoring BCR.

## Differential Diagnosis

The differential diagnosis of BCR is given in [Box 7.22.1](#). Several disorders produce multiple, creamy choroidal lesions. Not many are as commonly associated with CME as is BCR. Pars planitis and chronic iridocyclitis can produce CME but are not associated with choroidal lesions. Onset of vitritis and CME in the fifth and sixth decades is characteristic of BCR. Sarcoidosis and BCR may be the most difficult to distinguish from each other.<sup>6</sup> Unilateral birdshot-type lesions with or without vitritis can be seen in newly described diseases, such as benign reactive lymphoid hyperplasia, indolent nonprogressive multifocal lesions,<sup>19</sup> and frank lymphoid tumors.

## Treatment

Photoreceptor loss is an important component of vision loss. Macular edema caused by inflammation is another reason for vision loss. Optic disc edema leading to atrophy can also be vision threatening. Corticosteroids have been the short-term mainstay of therapy for patients who have BCR. Oral, sub-Tenon's, intraocular, and the most recently described sustained-release administrations of fluocinolone acetonide<sup>20</sup> have been used. Corticosteroids carry their own systemic and local (glaucoma and cataract) risks. Therefore, corticosteroid-sparing immunomodulatory agents have been used in the long-term management of refractory cases. Systemic cyclosporine, azathioprine, mycophenolate mofetil, or low-dose methotrexate may be administered (sometimes in combination) judiciously, if necessary with the help of an oncologist, a rheumatologist, or an internist. With

the approval of the US Food and Drug Administration (FDA) for adalimumab for noninfectious posterior uveitis, second-line immunomodulatory therapy with this tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) inhibitor can also be used when first-line agents fail. Choroidal neovascularization (CNV) is rare in BCR, but anti-vascular endothelial growth factor (VEGF) therapy has been demonstrated to be useful in treatment of CNV associated with inflammatory chorioretinal disorders.<sup>21</sup> In managing BCR, close monitoring of visual acuity, Goldmann visual fields at least yearly, ERG yearly, and OCT to evaluate for integrity of photoreceptors, epiretinal membranes (ERMs), and CME are recommended.

## Course and Outcome

The long-term visual prognosis for patients with BCR is guarded. The disease is chronic and does not appear to undergo regression. Retinal vascular attenuation and chorioretinal atrophy may eventually occur. Evidence suggests that patients treated with corticosteroid-sparing immunomodulatory agents experience stabilization or, at least, deceleration of clinical and electrophysiological disease progression.<sup>17,18</sup> Chronic CME may cause permanent visual loss.<sup>6</sup>

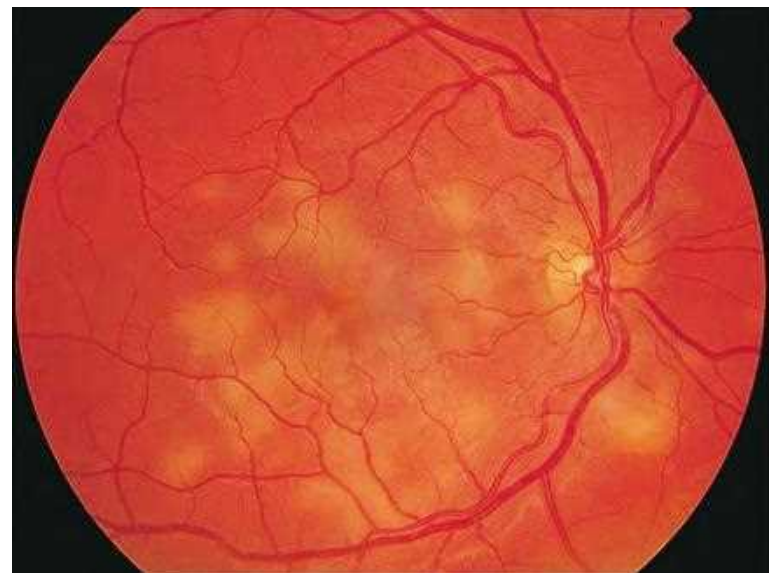
## ACUTE POSTERIOR MULTIFOCAL PLACOID PIGMENT EPITHELIOPATHY

### Epidemiology and Pathogenesis

APMPPE is a bilateral inflammatory disease that affects the choriocapillaris, RPE, and outer retina of otherwise healthy young adults, often in the second and third decades of life. Men and women are affected equally. The disease may be preceded by a viral prodrome.<sup>22</sup>

### Ocular Manifestations

Patients develop sudden, painless loss of vision in one eye or, more typically, both eyes.<sup>22</sup> Symptoms of mild meningismus, headaches, and transient hearing loss have been reported.<sup>23–25</sup> Cerebral vasculitis can occur. Ocular examination usually shows no evidence of anterior uveitis. Minimal to no vitreous cells occur.<sup>22,26</sup> Multiple, yellow, creamy-colored, flat-to-placoid (plate-like) lesions of variable size are seen and involve the posterior pole ([Fig. 7.22.2](#)).<sup>22,26</sup> In general, these lesions do not occur anterior to the equator. Fresh lesions may present over the course of a few weeks, so lesions of differing ages can be seen. These lesions can be associated with exudative detachments.<sup>24,27–32</sup> As the lesions resolve, they tend to clear centrally and they become hypopigmented. Later pigment clumping occurs. An association with retinal vasculitis and retinal vein occlusions has been reported.<sup>33,34</sup> CNV is rare.<sup>35</sup> Optic disc edema has also been noted in APMPPE.<sup>36</sup>



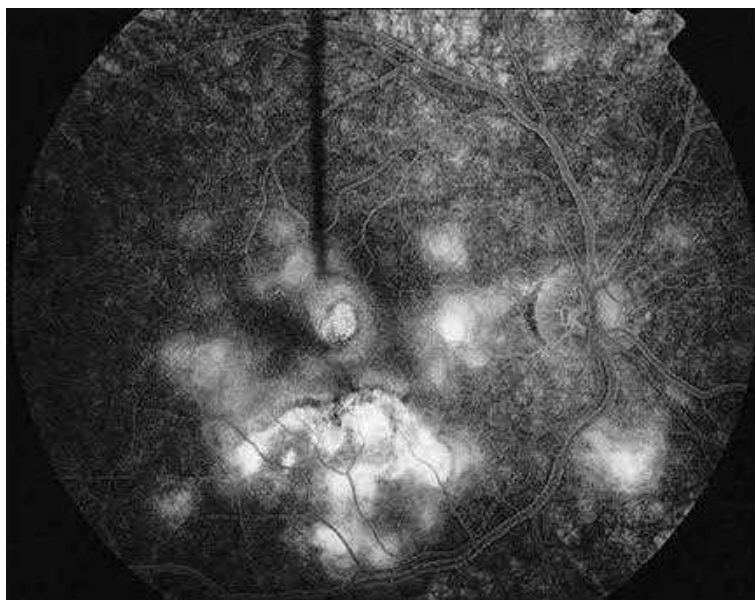
**Fig. 7.22.2 Fundus View of the Right Eye of a 17-Year-Old Man With Acute Posterior Multifocal Placoid Pigment Epitheliopathy.** Numerous creamy, white-yellow, placoid lesions are seen in the posterior pole. Note the pigmented lesion in the inferior macula that has started to heal.

### BOX 7.22.1 Differential Diagnoses in Birdshot Chorioretinopathy

- Pars planitis
- Sarcoidosis
- Chronic iridocyclitis, idiopathic
- Papilledema
- Intraocular lymphoma
- Vogt-Koyanagi-Harada syndrome
- Multifocal choroiditis
- Ocular histoplasmosis syndrome
- Syphilis
- Sympathetic uveitis
- Indolent nonprogressive multifocal choroidal lesions
- Metastasis



**Fig. 7.22.3 Hypofluorescence of Acute Lesions and Early Hyperfluorescence of Healing Lesions.** Laminar, venous-phase fluorescein angiography image of the right eye of the patient shown in Fig. 7.22.2.



**Fig. 7.22.4 Late Hyperfluorescence of Both Acute and Healing Lesions.** Late arteriovenous-phase fluorescein angiography image of the same eye as shown in Figs. 7.22.2 and 7.22.3.

## Diagnosis

APMPPE is diagnosed on the basis of clinical examination findings, time course, and imaging characteristics. The absence of substantial anterior chamber or vitreous inflammation in a young, healthy patient who has a viral prodrome with placoid fundus lesions is highly suggestive of APMPPE. FA shows early hypofluorescence of these white placoid lesions with late staining of these same lesions (Figs. 7.22.3 and 7.22.4).<sup>22</sup> ICGA shows hypofluorescent lesions in the acute phase of the disease. These areas are more numerous than the clinically seen plaques. OCTA definitively demonstrates patchy areas of choriocapillaris ischemia corresponding to the clinical lesions that improve to varying degrees with disease regression.<sup>37–39</sup> These findings confirm that the pathogenesis of APMPPE can, at least partially, be attributed to ischemia of the choriocapillaris.<sup>37</sup> OCT shows disruption of the external limiting membrane (ELM), inner segment/outer segment (IS/OS) junctions, and the ellipsoid zone in the outer retina, with areas of hyperreflectivity in the photoreceptor layer corresponding to the placoid lesions.<sup>40,41</sup> RPE disruption, restoration of the ELM, and increase in photoreceptor volume occur as the lesions begin to heal.<sup>40</sup> In our experience, the outer retinal elements can regenerate in this disease, likely signifying an improved prognosis in these patients.<sup>40</sup> FAF is useful in delimiting RPE involvement in this disease.<sup>42</sup> Laboratory

### BOX 7.22.2 Differential Diagnoses in Acute Posterior Multifocal Placoid Pigment Epitheliopathy

Serpiginous choroidopathy  
Relentless placoid chorioretinitis  
Persistent placoid maculopathy  
Choroidal vasculitis (lupus, polyarteritis nodosa)  
Syphilitic retinitis  
Harada's disease  
Tuberculosis, sarcoid, fungal disease  
Outer retinal toxoplasmosis  
Viral or bacterial retinitis  
Choroidal metastasis  
Lymphoma

evaluation of these patients is usually unrewarding (except for the findings of protein and cells in cerebrospinal fluid [CSF], and rare hematuria) and usually not necessary. Cerebral involvement should dictate neurological consultation because deaths resulting from this have been reported.

## Differential Diagnosis

The differential diagnoses of APMPPE are listed in Box 7.22.2. Primarily, other white spot diseases should be considered. Specifically, SC should be considered in recurrent/chronic cases and RPC should be thought of in severe, persistent, and recurrent cases. The creamy lesions of APMPPE are unique but occasionally may be confused with Harada's disease, metastatic tumors, viral retinitis, syphilis, and toxoplasma retinochoroiditis. In APMPPE, however, the creamy lesions are flat and are not associated with significant vitritis. Healed APMPPE usually leaves behind variable pigmentary changes in the posterior pole. The scars may be difficult to differentiate from other inactive inflammatory conditions. Failure to show healing with concomitant RPE changes is suggestive of an alternative diagnosis, such as RPC or lymphoma.

## Systemic Associations

Cerebral vasculitis and CSF pleocytosis have been reported in patients who have APMPPE.<sup>23–26</sup> Rarely, this may be fatal. Acute nephritis occurred concurrently with APMPPE in one patient.<sup>43</sup> Serological evidence of mumps<sup>44</sup> and adenovirus type 5 infection has been documented.<sup>45</sup>

## Pathology

The etiology and the histopathology are unknown. Various theories exist. Some authors believe that a vascular insult involving the choroid possibly leads to some choroidal ischemia causing RPE damage and thus affects photoreceptors. However, it is also possible that the primary site of inflammation is in the outer retina and that this affects the choroid. It is likely that some trigger, either inflammatory or infectious, incites this process. In addition, some individuals may be more prone to this insult.<sup>46</sup> Delayed-type hypersensitivity<sup>47</sup> and a thrombotic process of the choroid have also been postulated.<sup>48</sup>

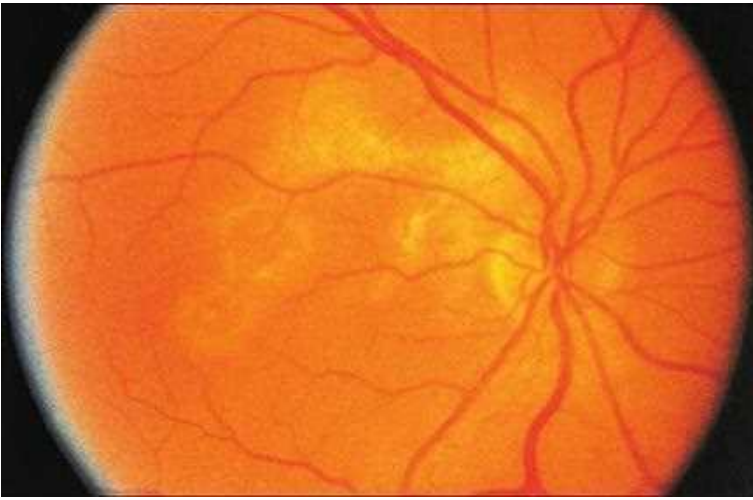
## Treatment

Usually, no treatment is necessary; the disease is self-limiting. Some ophthalmologists use systemic corticosteroids, although there is no definitive evidence that corticosteroids speed visual recovery or improve the visual outcome.<sup>49</sup> Rarely, CNV can develop. Anti-VEGF agents have been found useful.<sup>21</sup>

## Course and Outcomes

In most patients, APMPPE runs a self-limiting course of 2–6 weeks. Visual acuity is usually diminished during the early part of the disease and may vary from 20/20 (6/6) to 20/400 (6/120), depending on the location of the placoid lesions. In most patients, vision improves to near-normal levels during the first 2–3 weeks after the onset of symptoms. Patients, however, may continue to complain of difficulty with reading or of scotomas in the central visual field. The placoid lesions resolve over a period of 2–6 weeks. Significant macular RPE mottling and alterations remain after the resolution of these placoid lesions.<sup>22</sup> There are reported cases of





**Fig. 7.22.5 Fundus View of the Right Eye of a 57-Year-Old Woman With Early Serpiginous Choroiditis.** A peripapillary serpentine lesion extends into the fovea. Visual acuity is 20/60 (6/18).

persistent, chronic, or recurrent APMPE in which severe RPE alterations may occur.<sup>50</sup> This can result in severe vision loss. Recurrent cases must be distinguished from SC. Chronic cases probably represent RPC. CNV is an uncommon complication of APMPE but has been reported.<sup>51</sup> Permanent disruption of Bruch's membrane and the choriocapillaris occurs less frequently in APMPE than with SC.

## SERPIGINOUS CHOROIDITIS

### Epidemiology

SC has also been called *helicoid peripapillary chorioretinal degeneration*, *geographical helicoid peripapillary choroidopathy*, and *geographical choroidopathy*. Our current understanding of this rare disease is limited. The condition affects healthy patients from the second to seventh decades of life. Men and women are affected equally.<sup>52</sup> It is usually bilateral, recurrent, and progressive. This disease affects the outer retina and RPE, perhaps associated with impaired circulation in choriocapillaris and inner choroid.<sup>53–55</sup>

### Ocular Manifestations

Although a bilateral disease, the patient usually presents with unilateral symptoms when a lesion affects the fovea. Patients may experience paracentral or central scotomata with vision loss. Ocular examination may reveal some inflammatory response in the anterior chamber or vitreous humor.<sup>56</sup> Serpiginous lesions are geographical gray or gray-yellow areas that begin either in the peripapillary region or macula and eventually affect both eyes. Unlike in APMPE, usually one eye is active at a time, with one or a few foci. New lesions usually appear at the edges of healed scars. The disease has a progressive, stepwise course. Often, these lesions progress in a centripetal, helicoid, or serpentine-like fashion from the peripapillary area or macula into the remainder of the posterior pole (Fig. 7.22.5).<sup>52,57</sup> With time, these lesions become atrophic, with disappearance of the RPE, choriocapillaris, and choroid.<sup>53</sup> In patients who have macular SC, the initial lesions are seen in the macula.<sup>58</sup> Subretinal hemorrhage and serous retinal detachment as a result of CNV can occur in eyes with SC.<sup>59</sup>

### Diagnosis

Diagnosis is established on the basis of typical clinical appearance. FA demonstrates early hypofluorescence and late hyperfluorescence of active lesions. ICGA also shows hypofluorescent active and healed lesions. Atrophic lesions show diffuse loss of pigment, choroidal vessels, and late staining on FA. Retinal vascular staining may occur adjacent to active lesions. Associated CNV shows late leakage and often arises from the borders of old scars.<sup>59</sup> The individual lesions may resemble APMPE and RPC, but the clinical setting and course distinguish these diseases in most patients. SD-OCT has shown hyperreflective outer retina, with disruption of ellipsoid zone in acute lesions and eventual retinal thinning and RPE atrophy with resolution.<sup>60,61</sup> OCTA demonstrates multiple small geographical areas of inner choroidal/choriocapillaris nonperfusion within active lesions that improve with treatment.<sup>62</sup> Older atrophic lesions are marked by decreased

### BOX 7.22.3 Differential Diagnoses in Serpiginous Choroiditis

Acute multifocal placoid pigment epitheliopathy  
Relentless placoid chorioretinitis  
Persistent placoid maculopathy  
Birdshot choroidopathy  
Multifocal choroiditis  
Presumed ocular histoplasmosis  
Tuberculous (serpiginous) choroiditis  
Sarcoidosis  
Antiphospholipid antibody syndrome  
Toxoplasmosis  
Syphilis  
Posterior scleritis  
Choroidal ischemia (vascular diseases, such as systemic lupus erythematosus, polyarteritis nodosa, toxemia of pregnancy, disseminated intravascular coagulopathy, thrombotic thrombocytopenic purpura, and malignant hypertension)

or absent inner choroidal vessels.<sup>54</sup> FAF has been effective in illustrating new lesions as hyperautofluorescent, appearing at the edge of old lesions, which are hypoautofluorescent.<sup>63</sup> Furthermore, FAF seems to be useful in distinguishing tuberculosis (TB)-related disease from SC. TB lesions that mimic SC appear more stippled compared with the more homogeneous lesions of SC.<sup>63</sup>

Laboratory evaluation of these patients is unrevealing. An association of serpiginous choroiditis and TB has been suggested. However, treatment of patients without TB with antimicrobial agents has made no difference in the disease course in these patients.<sup>53</sup>

### Differential Diagnosis

The differential diagnoses for SC are listed in Box 7.22.3. Other white spot syndromes, especially APMPE, RPC, and PPM should be considered. The peripapillary scarring seen in SC may be difficult to differentiate from inactive MFC and ocular histoplasmosis syndrome. However, serpentine centripetal progression and chronic, relapsing time course are characteristic of SC. Tuberculous SC can also resemble SC; however, it is associated with more vitritis and more multifocal lesions involving the periphery. SC has larger lesions and is more likely to be associated with the optic nerve.<sup>64</sup>

### Pathology

The few eyes with SC studied histopathologically showed extensive loss of RPE, with destruction of the overlying retina and lymphocytic infiltration of the choriocapillaris and other areas of the choroid.<sup>53</sup> The pathogenesis remains unknown. Autoimmune, infectious, vascular, and degenerative etiologies have been postulated.

### Treatment

Because of the relapsing and progressive nature of this disease, therapy is aimed at treating acute episodes as well as at preventing recurrences that can lead to foveal involvement. Corticosteroids are a mainstay of treatment and have been given via multiple routes of administration (oral, sub-Tenon's, intravenous, intravitreal injections and via an implant). Aggressive management with corticosteroids is useful in treating acute attacks but not in preventing recurrence. Treatment with other immunosuppressive therapy may be necessary for long-term management of SC. Cyclosporine, azathioprine, and other cytotoxic agents have been used to treat SC.<sup>53</sup> Because these medications have associated potential systemic side effects, they should be used in consultation with a rheumatologist, an internist, or an oncologist. In addition, systemic TNF- $\alpha$  inhibitors, such as adalimumab, may be used in relentless or recalcitrant cases in conjunction with the previously mentioned corticosteroid-sparing immunomodulatory agents. However, these agents should be used only after tuberculous SC has definitively been ruled out because these agents are contraindicated in latent or active TB. CNV is common in this disease, and there are reports of response to anti-VEGF injection.<sup>21</sup> CME can develop in SC, and treatment success has been reported with the use of oral acetazolamide.<sup>65</sup>



## Course and Outcomes

Many cases of SC are progressive, and foveal destruction may occur. Central visual acuity is lost in  $\geq 20\%$  of eyes with SC.<sup>53</sup> Central vision loss also can occur as a result of CNV. Long-term immunosuppressive therapy may prevent vision loss.<sup>66</sup>

## RELENTLESS PLACOID CHORIORETINITIS

### Epidemiology

RPC is a rare, often bilateral ocular inflammatory disease of unknown etiology affecting patients between the second and sixth decades of life.<sup>67</sup> This disease resembles both APMPE and SC but is distinguished by its time course and retinal distribution. The term *ampiginous* has been used to describe similar cases. Men and women are equally affected in RPC. When seeking treatment, patients complain of decreased vision, pericentral scotomas, photopsias, floaters, and, rarely, pain.

### Ocular Manifestations

Varying numbers of anterior chamber and vitreous cells may be seen. Active retinal lesions are creamy white and located at the level of the outer retina. They may be smaller than those of APMPE ( $\frac{1}{2}$  disc area). The lesions can be active bilaterally and may affect the mid- and far periphery prior to involvement of the posterior pole, unlike APMPE or SC.<sup>67</sup> Many of these lesions heal over weeks, resulting in chorioretinal atrophy. However, progressive increase in size of subacute lesions and development of new lesions occurs in all patients. The hallmark of the disease is the eventual presence of  $\geq 50$  lesions can occur throughout the fundus. These lesions eventually can involve the macular region and acutely result in visual loss, metamorphopsia, or scotoma. Subretinal fluid may be seen in association with the acute lesions. When these lesions heal, visual acuity is often preserved even with macular involvement.<sup>67</sup>

### Diagnosis

Diagnosis is based on clinical appearance of retinal lesions and prolonged clinical course, unless shortened by immunosuppression. APMPE and SC are the main considerations. FA show early hypofluorescence and late staining of lesions as in APMPE and SC. Similarly, ICGA shows hypofluorescence in the areas corresponding to the clinical lesions. SD-OCT demonstrates retinal photoreceptor disruption in the ellipsoid zone surrounding the areas of central subretinal fluid in early lesions and RPE atrophy with patchy hyperplasia and rarefaction of the ellipsoid zone as lesions heal.<sup>68</sup> OCTA demonstrates multifocal areas of inner choroidal ischemia, which improve with treatment but recur in adjacent and noncontiguous areas.<sup>37</sup> FAF of early lesions demonstrate three concentric zones with a central round area of dense hypoautofluorescence, surrounded by a narrow ring of hyperautofluorescence, which, in turn, is surrounded by a faint wider ring of hypoautofluorescence.<sup>68</sup> Over time, these lesions contract on FAF and become more hyperautofluorescent with central hypoautofluorescent RPE hyperplasia. Laboratory evaluation is not helpful. No consistent systemic association has been found.

### Differential Diagnosis

See Box 7.22.4.

#### BOX 7.22.4 Differential Diagnoses in Relentless Placoid Chorioretinitis

Acute posterior multifocal placoid pigment epitheliopathy  
Serpiginous choroiditis  
Persistent placoid maculopathy  
Multifocal choroiditis  
Viral retinitis  
Choroidal vasculitis (e.g., systemic lupus erythematosus, polyarteritis nodosa)  
Neoplastic infiltration of the choroid  
Syphilis  
Sarcoid  
Tuberculosis

## Treatment

In the original report on RPC, glucocorticoids, antiviral agents, and cyclosporine all were tried to treat patients. Immunosuppression did appear to halt disease activity.<sup>67</sup> With glucocorticoid treatment, healing and improvement in visual acuity are observed; however, the disease can recur despite the use of glucocorticoids. Corticosteroids have been used in combination with azathioprine or cyclophosphamide as well.<sup>69</sup> The best treatment for this condition remains unknown.

### Course and Prognosis

Growth of subacute lesions and appearance of new lesions occurs from 5–24 months after initial diagnosis. Relapses are common. Eventually, most patients develop  $\geq 50$  (sometimes hundreds) of healed lesions in the periphery and posterior pole. The long-term visual prognosis appears to be good.<sup>67</sup> Central vision is generally preserved. Intensive immunosuppression may shorten the course of the disease, but relapses occur on tapering of medication.

## PERSISTENT PLACOID MACULOPATHY

### Epidemiology and Pathogenesis

PPM is a recently recognized, bilateral, symmetrical entity primarily affecting patients in the sixth and seventh decades of life.<sup>70,71</sup> The etiology is unknown, and no consistent systemic associations have been found.

### Ocular Manifestations

Patients report decreased vision and photopsias in both eyes. All patients demonstrate a well-delineated, jigsaw-patterned, whitish, plaque-like lesion involving the fovea and not contiguous with the disc. Satellite lesions may be seen. PPM resembles macular SC. Although the fovea is involved in PPM, vision may be remarkably good (20/25–20/50). The whitish lesion persists in the macula for months and may be replaced by pigment mottling or atrophy. Many patients develop CNV within months to years that may be multifocal, with severe vision loss resulting from disciform scarring.<sup>70</sup>

FA demonstrates early hypofluorescence of the macular lesions with partial filling in the late phases. There is no leakage unless CNV is present. ICGA demonstrates persistent hypofluorescence of macular lesions throughout the study, with visible large choroidal vessels observed within the lesions.<sup>70</sup> SD-OCT shows hyporeflectivity of the outer retina and ellipsoid zone disruption early,<sup>72,73</sup> with variable loss of the outer retina in long-standing disease.<sup>73</sup> OCTA demonstrates hypoperfusion of the choriocapillaris that persists, although with some improvement, despite treatment.<sup>37,72</sup> FAF may show stippled hyperautofluorescence early and hypoautofluorescence correlating to RPE damage in the later stages.<sup>71</sup>

### Differential Diagnosis

The differential diagnosis includes macular SC, APMPE, RPC, syphilitic placoid chorioretinitis, and diseases that cause choroidal ischemia (e.g., systemic lupus erythematosus, polyarteritis nodosa, disseminated vascular coagulopathy, thrombotic thrombocytopenic purpura, and malignant hypertension). CNV occurs less frequently in macular SC than in PPM. Syphilitic placoid chorioretinitis is generally associated with clinical signs of inflammation as a result of the infectious etiology (Box 7.22.5).

#### BOX 7.22.5 Differential Diagnoses in Persistent Placoid Maculopathy

- Macular Serpiginous Choroiditis
- Acute posterior multifocal placoid pigment epitheliopathy
- Relentless placoid chorioretinitis
- Syphilis
- Diseases that cause choroidal ischemia
  - Systemic lupus erythematosus
  - Polyarteritis nodosa
  - Disseminated intravascular coagulopathy
  - Thrombotic thrombocytopenic purpura
  - Malignant hypertension

## Treatment

Oral corticosteroids may be of some benefit in the acute phase of the disease to improve initial visual loss but do not prevent the eventual development of CNV and disciform scarring. CNV has been treated with anti-VEGF agents, with good results, as described in a report.<sup>74</sup> Reports have suggested that photodynamic therapy (PDT) has not been of benefit.

## Course and Outcome

Patients may retain good vision despite the entire macula being involved with a white lesion for months to years. The long-term prognosis, however, is sometimes poor because many patients eventually develop subfoveal CNV and lose central vision. Some eyes lose vision to pigmentary degeneration, atrophy, and mottling.

## MULTIFOCAL CHOROIDITIS/PUNCTATE INNER CHOROIDOPATHY

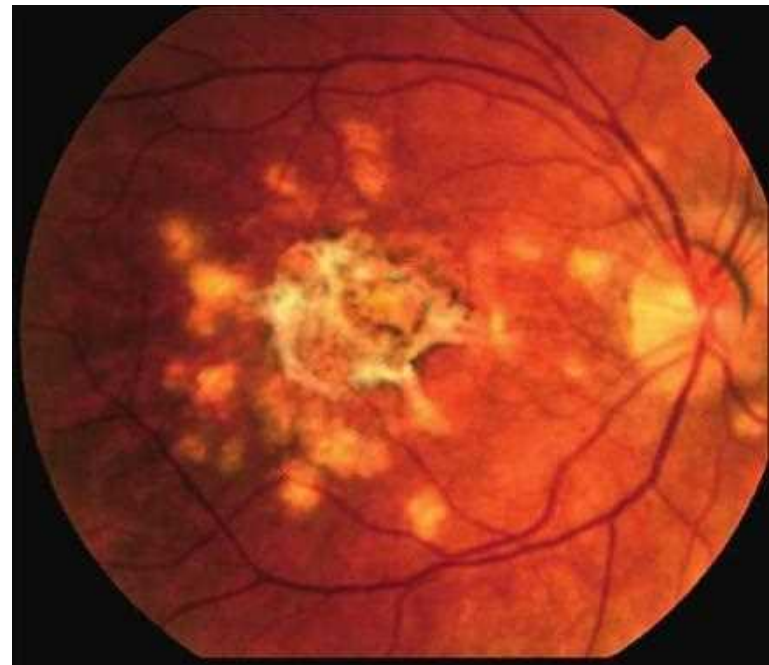
MFC and PIC are considered the same entity by many retina specialists and have been classified as the same disease process by Jampol et al.<sup>75,76</sup> Multimodal imaging has supported this classification.<sup>75,77,78</sup> Historically, the term *PIC* was used when lesions were limited to the posterior pole, and *MFC* was used when lesions extended to the periphery as well. Some lesions also have significant fibrosis associated with them. The term *subretinal fibrosis and uveitis syndrome* has been used in the past<sup>79</sup> when significant fibrosis was present. We consider fibrosis as a feature of the same disease and not a separate entity. In this chapter, the term MFC/PIC or MFC will be used. It should further be clarified that the MFC discussed in this chapter is the idiopathic type. MFC can be secondary to other processes, including infectious (TB, syphilis, fungal/presumed ocular histoplasmosis syndrome [POHS], viral infections) and noninfectious etiologies (sarcoidosis).

## Epidemiology

MFC along with PIC is a common inflammatory disease that occurs predominantly in women with myopia between their second and sixth decades of life. Most cases are bilateral when diagnosed or become bilateral.<sup>80,82</sup> MFC and PIC are characterized by inflammation at the level of the RPE and outer retina, so “choroiditis” may be a misnomer.

## Ocular Manifestations

Patients present with decreased visual acuity in one eye or both eyes. Photopsias may be present (often temporal), and patients may be symptomatic with an enlarged blind spot. There is a variable amount of anterior segment inflammation and vitritis; however, this is not essential to diagnosis. When there is a significant amount of vitritis, the term *multifocal choroiditis and panuveitis* has been used. These patients are commonly seen by uveitis specialists, but we consider these part of the spectrum of the same disease. The optic discs generally are normal, but the peripapillary RPE often is disrupted. An area of fibrosis in the shape of a “napkin ring” may surround the disc. Acute lesions are yellowish to gray in color and located at the level of the RPE and outer retina; they range in size from 50 to 1000 microns. Serous detachment of the retina may accompany active lesions. The lesions may vary in number from several to hundreds. They occur in the posterior pole, peripapillary region, and midperiphery with often a clustering in the nasal retina. They can occur in linear clusters or as streak lesions.<sup>83</sup> Older lesions appear atrophic and “punched out,” with variable amounts of pigment. RPE metaplasia with associated fibrosis may be seen, and this fibrosis can bridge the space between scars (Fig. 7.22.6).<sup>80</sup> Some cases show evanescent white lesions resembling MEWDS. Those can resolve without scarring. Peripapillary and macular CNV occurs in more than one third of eyes.<sup>81</sup> CNV may occur in up to 70% of eyes from healed scars. If CNV occurs in the macula or near the fovea, serious vision loss may result.<sup>84,85</sup> CNV may be the presenting sign of disease. MFC may also present with more diffuse photoreceptor loss distinct from focal lesions,<sup>86</sup> which we have described as MFC with chorioretinal atrophy.<sup>87</sup> The chorioretinal atrophy can be diffuse, multizonal, or zonal.<sup>86</sup> Previously, these cases may have been classified in the past as being part of Gass’s AZOOR complex<sup>88</sup> but now can be distinguished by using multimodal imaging.



**Fig. 7.22.6 Punctate Inner Choroidopathy.** White, punctate chorioretinal lesions in the macula with overlying serous retinal detachment of the fovea in the right eye of a 20-year-old woman with myopia. (Courtesy Richard R. Ober.)

## Diagnosis

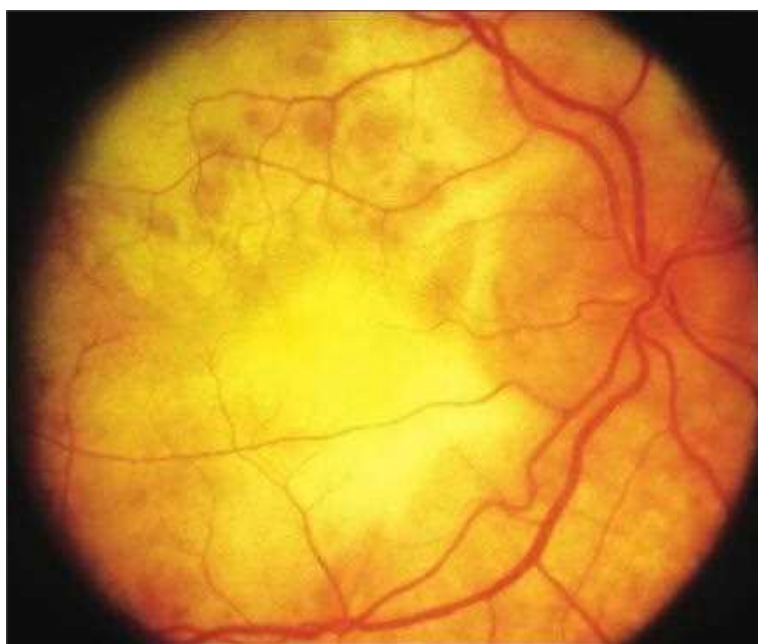
Diagnosis is made on the basis of clinical examination findings, although imaging is helpful. In the acute stage, the lesions appear hypofluorescent on FA. Later, these lesions stain. In the healed phase, the lesions atrophy and show a window defect. Peripapillary or subfoveal CNV may be seen. CME may be seen in the late phases of angiography in some patients.<sup>80</sup> ICGA shows hypofluorescent lesions that may cluster around the optic disc; these lesions often are far more numerous than those seen on FA or clinical examination. SD-OCT shows an elevation of the RPE corresponding to active lesion with loss of the ellipsoid layer, outer photoreceptor damage, choroidal thickening, and subretinal material that may erupt through the RPE with an intact Bruch’s membrane.<sup>89</sup> This can potentially normalize with treatment, or there can be persistent outer retinal atrophy. OCTA has been somewhat useful in distinguishing inflammatory lesions from CNV.<sup>90–92</sup> FAF can show diffuse zone of peripapillary and/or multiple posterior-pole hyperautofluorescent acute lesions, even in areas that appear clinically uninvolved, and that can resolve with treatment.<sup>89,93</sup> In our experience, numerous hypoautofluorescent lesions not associated with clinical lesions have been seen, and these also resolved in the healing phase.<sup>94</sup> Punched-out lesions appear hypoautofluorescent persistently and may enlarge with time. ERG results are usually normal, or mildly attenuation is seen; however, in severe cases, it may be extinguished. The EOG result is normal.<sup>80</sup> Visual field testing may reveal an enlarged blind spot and, rarely, other abnormalities. Evanescent white spots may be seen, but these may resolve with or without treatment and with or without scarring. These can resemble MEWDS.

## Systemic Associations

An association between MFC and systemic infection by Epstein–Barr virus has been suggested.<sup>95</sup> A second investigation could not confirm this. Some patients who have MFC also have known sarcoidosis or are diagnosed later with sarcoidosis. These cases may be indistinguishable from the group with idiopathic etiology. Often, the sarcoid lesions predominate in the inferior retina.

## Course and Outcomes

MFC waxes and wanes, but progressive loss of vision may take place. Episodes can resolve spontaneously or with the help of immunosuppressants. In ≈25% of cases, the disease takes a more aggressive course, with more inflammation and CNV. CNV is the most common cause of vision loss.<sup>85,96</sup> Macular disciform scarring may develop. Severe cases of subretinal fibrosis may develop (Fig. 7.22.7).<sup>80,81</sup> Loss of photoreceptors with more widespread



**Fig. 7.22.7** Fundus View of the Right Eye of a Patient Who Has Progressive Subretinal Fibrosis and Uveitis Syndrome. Note the extensive submacular fibrosis.

#### BOX 7.22.6 Differential Diagnoses in Multifocal Choroiditis /Punctate Inner Choroidopathy

- Multiple evanescent white dot syndrome
- Presumed ocular histoplasmosis syndrome
- Sarcoidosis
- Vogt–Koyanagi–Harada syndrome
- Sympathetic ophthalmia
- Myopic degeneration maculopathy
- Serpiginous choroiditis
- Infectious etiologies: viral (herpes simplex virus, herpes zoster virus, Epstein–Barr virus, cytomegalovirus, Coxsackievirus)
  - Bacterial (syphilis, tuberculosis, *Borrelia burgdorferi* infection, septic choroiditis, metastatic endophthalmitis)
  - Fungal (histoplasmosis, cryptococcosis, coccidiomycosis, candidiasis)
  - Protozoal (toxoplasmosis, *Pneumocystis carinii* infection)
  - Helminthic (diffuse unilateral subacute neuroretinitis)
- Neoplastic: intraocular lymphoma

chorioretinal atrophy may be seen. ERMs and CME are other causes of vision loss.<sup>96</sup>

### Differential Diagnosis

The differential diagnoses for MFC/ PIC are listed in Box 7.22.6. Evanescent lesions may resemble MEWDS. MFC and POHS have many similarities in their punched-out lesions involving the posterior pole as well as the periphery. Additionally, peripapillary changes and CNV can be seen in both these entities. Classically, MFC has some degree of intraocular inflammation, but this is not necessary. Clinically distinct features of MFC include multiple, small, white lesions that cluster in the macula, nasal retina, or equator. Furthermore, the presence of acute and inactive lesions, growth of lesions, subretinal fibrous metaplasia, and bridging tissue is more characteristic of MFC.<sup>97</sup>

### Treatment

The goal of treatment is to manage inflammation and its complications (CME and CNV). MFC can present with significant anterior and posterior inflammation. Corticosteroids (topical, periocular, intraocular, and systemic) are used. Corticosteroid-sparing immunomodulatory agents become necessary when corticosteroids are not tolerated or recurrence is frequent. TNF- $\alpha$  inhibitors, such as adalimumab, can also be used in conjunction

with these corticosteroid-sparing immunomodulatory agents in particularly recalcitrant cases. CNV is primarily managed with anti-VEGF injections. Other management strategies for CNV include thermal laser, if extrafoveal, and very rarely PDT. Generally, this is done in conjunction with management of inflammation. Immunosuppressive agents may be most effective in the early stages of CNV development.<sup>98</sup> Spontaneous involution of CNV can occur. No treatment may be necessary if the lesions are not sight threatening. Therapy of the diffuse photoreceptor damage occasionally seen is uncertain.

## MULTIPLE EVANESCENT WHITE DOT SYNDROME

### Epidemiology and Pathogenesis

MEWDS is an inflammatory chorioretinopathy that affects predominantly young, healthy women in their second to fourth decades of life. A flu-like illness often precedes the eye symptoms in about one half of the patients.<sup>99</sup>

### Ocular Manifestations

Patients with MEWDS have acute, unilateral, painless visual loss.<sup>99</sup> Rarer bilateral MEWDS that is asymmetrical has been reported.<sup>100</sup> Patients often complain of a scotoma and associated shimmering photopsias, often in the temporal visual field. Ocular findings include a variable number of small, white spots at the level of the deep retina. These are concentrated in the paramacular area and less prominent beyond the vascular arcades (Fig. 7.22.8). A characteristic granular appearance to the fovea is usually present acutely, and the fovea usually does not return to a normal appearance (see Fig. 7.22.8).<sup>99</sup> In atypical cases, this may be the only presenting feature.<sup>101</sup> Variable amounts of vitritis and optic disc edema are present. Retinal vascular sheathing may also be seen. Rarely, a progressive geographical circummacular discoloration or white lesion can be the presenting sign.<sup>102</sup> Mild pigmentary changes may develop with the resolution of the white spots. Choroidal scarring resembling MFC is possible in some patients. Rarely, CNV can develop and may be the presenting sign.<sup>103</sup> About 10% of cases may show recurrences.<sup>100</sup>

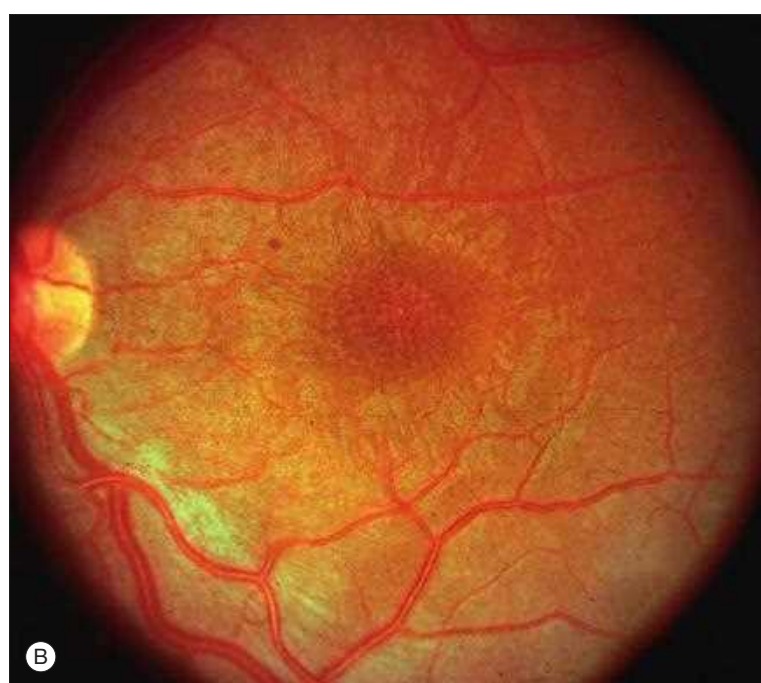
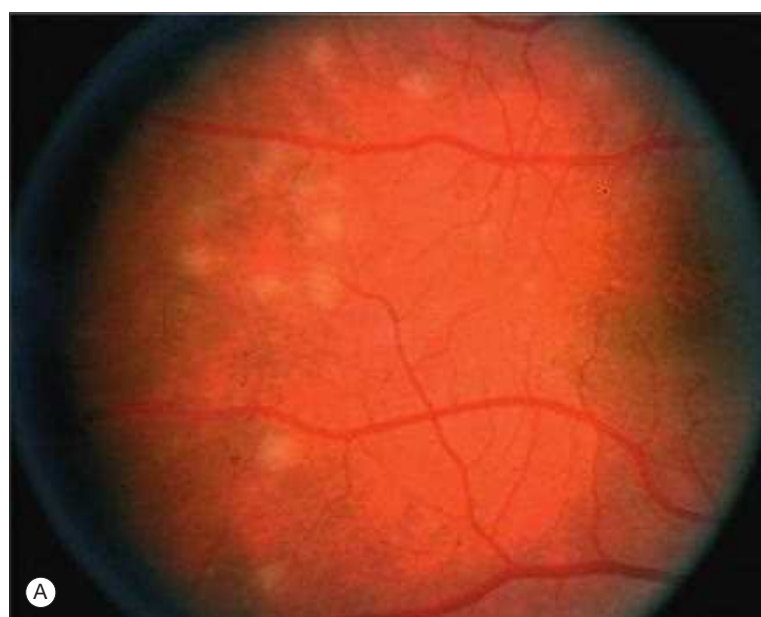
### Diagnosis

Diagnosis is made clinically. Visual field testing may reveal enlargement of the blind spot.<sup>99,104</sup> FA may reveal leakage from disc capillaries and late retinal punctate staining, characteristically in the shape of a wreath (Fig. 7.22.9).<sup>99,104</sup> Leakage in the macula in a noncystoid pattern may be seen. ICGA demonstrates multiple hypofluorescent (more than are clinically seen or detected on fluorescein) areas in the posterior pole.<sup>105</sup> Dots on spots are seen (see below), and OCTA shows no abnormalities in the superficial or deep choroidal or retinal circulation.<sup>106</sup> SD-OCT shows hyper-reflective multifocal debris at the ellipsoid layer, with dome-shaped protrusions of the hyperreflectant material from the ellipsoid layer toward the outer nuclear layer corresponding to the location of perifoveal dots seen with photography.<sup>107,108</sup> The larger confluent “spots” are hyporeflective and localized to the level of the ellipsoid zone, with disruption of the IS/OS junction.<sup>106</sup> All these changes resolve spontaneously. In addition, although lesions typically occur unilaterally, photoreceptors can rarely have abnormalities bilaterally.<sup>109</sup> FAF shows hypofluorescent spots and dots in greater numbers than clinically seen.<sup>110,111</sup> ERG may reveal a profoundly decreased a-wave amplitude and early receptor potential amplitudes in the acute phase of the disease, suggesting widespread photoreceptor dysfunction.<sup>112</sup> During the recovery, these amplitudes return to normal. In addition, prolonged regeneration kinetics of the RPE also are present in the acute phases of the disorder.<sup>112</sup> The exact mechanisms of visual loss in MEWDS are not understood well but probably represent photoreceptor dysfunction.

### Differential Diagnosis

Diagnosing MEWDS can be challenging because of the transient nature of clinical findings. MFC may have evanescent white spots. Lymphoma may produce white lesions. Sarcoidosis and diffuse unilateral subacute neuroretinitis should also be considered. In young healthy patients presenting with unilateral vision loss (often with an abnormal fovea), MEWDS must be considered because it may present after the white spots have subsided<sup>113,114</sup> (Box 7.22.7).





**Fig. 7.22.8 (A) Right Eye of a Woman With Multiple Evanescent White Dot Syndrome.** Note the multiple white spots throughout posterior pole and (B) the granular appearance of the fovea.

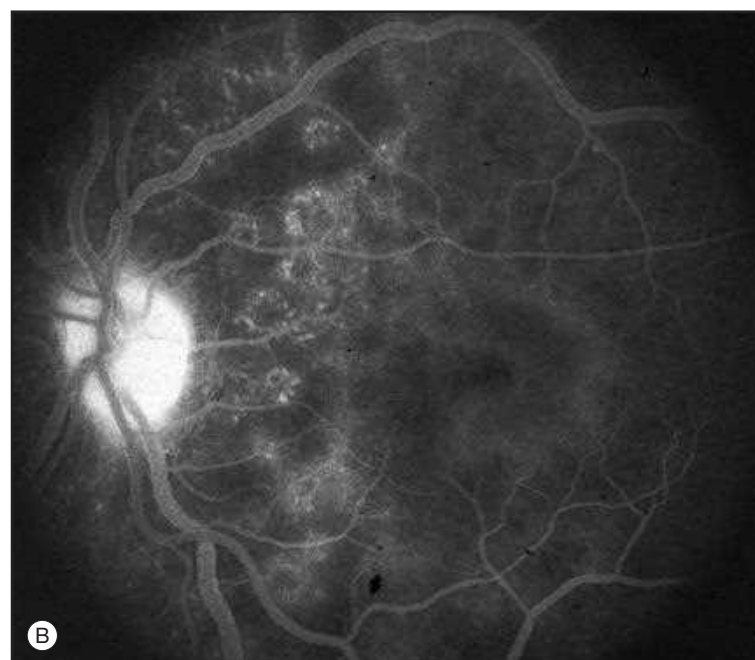
## Course and Outcomes

Because MEWDS has a self-limiting course, no specific treatment is indicated.<sup>99</sup> The white dots fade, and disc edema gradually resolves, usually within 2–6 weeks of the onset of symptoms and ocular findings. Visual acuity gradually returns to baseline levels. The temporal scotoma and photopsias may take considerably longer to improve (several months).<sup>99</sup> Recurrences have been reported.<sup>100</sup> Visual prognosis is good, even among patients who have recurrences. A very rare association with AZOOR has also been reported.<sup>115</sup> OCT can be helpful to monitor the course of the disease. The recovery of photoreceptors is a good prognosticator. CNV, although rare, can affect the prognosis negatively.

## ACUTE ZONAL OCCULT OUTER RETINOPATHY

### Epidemiology

Although AZOOR is often included in the WSS, no clinical white spots are observed in this condition. AZOOR is a disorder that predominantly affects young, healthy women in their second to fourth decades of life.<sup>116</sup> Patients develop photopsia and complain of a dense scotoma related to outer retinal dysfunction. The condition may be unilateral or bilateral.



**Fig. 7.22.9** Late hyperfluorescent leakage from disc capillaries and late punctate staining, characteristically in the shape of a wreath, with diffuse late leakage in a nonpetaloid fashion in (A) early- and (B) late-phase fluorescein angiography image of the left eye of a patient with multiple evanescent white dot syndrome.

### BOX 7.22.7 Differential Diagnoses in Multiple Evanescent White Dot Syndrome

- Multifocal choroiditis/punctate inner choroidopathy
- Lymphoma
- Sarcoidosis
- Diffuse unilateral subacute neuroretinitis
- Infectious retinitis

Systemic autoimmune diseases have been noted in some patients with AZOOR.<sup>2,117</sup>

## Ocular Manifestations and Diagnosis

On initial examination, the fundus appears normal. Narrow retinal vessels and depigmentation of the RPE are found within months of onset of symptoms. These correspond to zones of visual field loss. Often, there is a sharp demarcation between normal retina and abnormal retina that has a curvilinear appearance. The scotoma is often contiguous with the disc. The eyes are usually quiet, but some vitreous cell may be present. In a possible variant of classic AZOOR, called *acute annular outer retinopathy*,

**BOX 7.22.8 Differential Diagnoses in Acute Zonal Occult Outer Retinopathy**

Hereditary retinal diseases (retinitis pigmentosa)  
 Cancer-associated retinopathy/melanoma-associated retinopathy  
 Autoimmune retinopathies (without cancer)  
 Diffuse unilateral subacute neuroretinitis  
 Optic neuropathies (Leber's optic neuropathy)

a gray-white line is visible between normal and abnormal retina.<sup>118</sup> The abnormal retina becomes atrophied, as seen in classic AZOOR.

FA findings typically are normal during the early phases of the disorder. Once RPE changes occur, pigment mottling and window defects develop in the involved areas. ICGA demonstrates a trizonal pattern in late-stage AZOOR with a normal appearance outside the AZOOR line (zone 1), minimal late leakage in the subacute area (zone 2), and hypofluorescence with choriocapillaris atrophy (zone 3).<sup>119</sup> SD-OCT shows disruption of the ellipsoid zone and interdigitation line (cone outer segment tips) with thickened outer plexiform layer (OPL) and loss of the outer nuclear layer (ONL). With healing, RPE atrophy and persistent loss of the ONL and ellipsoid zone are seen. In subacute or chronic AZOOR lesions, a trizonal pattern is seen with a normal appearance outside the AZOOR line (zone 1), drusen-like multifocal subretinal deposits (zone 2), and photoreceptor, RPE, and choroidal atrophy (zone 3).<sup>119,120</sup> FAF imaging reveals hypoautofluorescence in areas of severe involvement and hyperautofluorescence at the margins of these areas.<sup>121</sup> Again, a trizonal pattern is present in older lesions with normal autofluorescence in zone 1, speckled hyperautofluorescence with in the AZOOR lesion (zone 2), and hypoautofluorescence with choroidal atrophy (zone 3).<sup>119</sup> The outer retinal dysfunction can be documented by using visual field testing, which shows large, superior, temporal, and, occasionally, central zones of visual field loss. The scotomas often increase in size within a few days to months and may stabilize or progress. Visual field loss often occurs in both eyes but can be asymmetrical. Some improvement has been reported. Focal ERG reveals abnormalities in the area of the scotoma. Full-field ERG shows moderate to severe reduction in a-wave amplitude.<sup>122</sup> EOG testing is usually abnormal. Laboratory evaluation, including testing for antiretinal antibodies, is not helpful.

**Differential Diagnosis**

The differential diagnoses for AZOOR are listed in [Box 7.22.8](#).

**Course and Outcome**

Patients may show progression or recurrences with new areas of involvement. No specific treatment for AZOOR has been established. Glucocorticoids, immunosuppression, and antiviral agents have been tried but have not been proven to be efficacious. Although most patients retain visual acuity of better than 20/40 (6/12), permanent and occasionally severe visual field loss can occur.

Gass used the term *AZOOR complex*<sup>88</sup> to include MEWDS, AIBSE, AMN, PIC, and MFC. He felt that similarities existed in the demographics of these entities as well as in their effects on the outer retina. Multimodal imaging can now usually distinguish one disease from the other.

**ACUTE MACULAR NEUORETINOPATHY****Epidemiology and Pathogenesis**

AMN occurs in the second to fourth decades of life.<sup>123</sup> The disease process may be unilateral or bilateral. Rarely, there may be recurrences in one or both eyes. A history of a viral prodrome, trauma, or drug use (sympathomimetics) has been noted.<sup>124</sup> Many vascular causes have now been described.<sup>125</sup> Patients complain of decreased vision, paracentral scotomas, or both. The exact cause of AMR remains unknown. Newer imaging modalities have shown that the middle retina and the outer retina are involved.<sup>126–131</sup> Fawzi et al. found that the disease starts at the level of the

**BOX 7.22.9 Differential Diagnoses in Acute Macular Neuroretinopathy**

Multiple evanescent white dot syndrome  
 Paracentral acute middle maculopathy  
 Old inner retinal infarcts  
 Post-blunt ocular injury retinal thinning

outer plexiform layer and then rapidly involves the outer retina.<sup>132</sup> Multimodal imaging has indicated that a deep retinal vascular insult may cause this entity. It is important to discuss the retinal vascular anatomy to better understand AMN. OCTA has confirmed that there are three capillary layers of the retina in the posterior pole (a fourth is found along the temporal arcades).<sup>133</sup> The innermost layer is the superficial plexus (SCP), followed by the intermediate (ICP) and then the outermost layer, called the *deep capillary plexus* (DCP). A vascular insult to the SCP creates a cotton wool spot, whereas an insult to the ICP will result in a deeper defect called paracentral acute middle maculopathy (PAMM). Finally, vascular compromise to the DCP causes AMN.

**Diagnosis**

Ophthalmoscopy reveals one to several small, circular, oval, or petaloid dark lesions that surround the fovea. These may appear darker red or brown than the surrounding normal macula. Diagnosis usually is made on the basis of the clinical course and appearance of the lesion. The lesions are best seen on red-free photographs, infrared reflectance (IR) images, or OCT images. FA and ICGA results are normal. OCTA, however, may demonstrate areas of flow deficits in the deep retinal vascular plexus corresponding to the macular lesion(s) in the enface and B-scan images. Initial SD-OCT shows a hyperreflective band involving the OPL and ONL, with associated disruption of the ellipsoid and interdigitation zones. Over several weeks, there is improvement in hyperreflectivity, but punctate hyperreflective areas persist within the OPL and ONL. Thinning of the ONL occurs.<sup>132</sup> The ellipsoid and interdigitation zones are partially restored ([Fig. 7.22.10](#)).<sup>134</sup> Infrared SLO and near-infrared FAF images highlight the lesions well.<sup>132,134</sup> These, along with OCT images, show rapid changes over the first few weeks of disease. Very subtle pigmentary changes involving the RPE have been suggested to cause the reddish AMN lesions.<sup>132</sup> Visual field testing often reveals paracentral scotomas that correspond to the shape and location of the macular lesions. Electrophysiological testing results, except those of multifocal ERG, are normal.

**Differential Diagnosis**

The differential diagnoses for AMN are listed in [Box 7.22.9](#).

AMN should be further distinguished from PAMM. Sarraf et al. coined the term PAMM in 2013.<sup>127</sup> These patients also present with acute scotomas, and gray or reddish lesions may be seen clinically. However, multimodal imaging shows an insult to the ICP rather than to the DCP. PAMM has been found in other vascular disorders, such as diabetes and vein occlusions.<sup>131</sup>

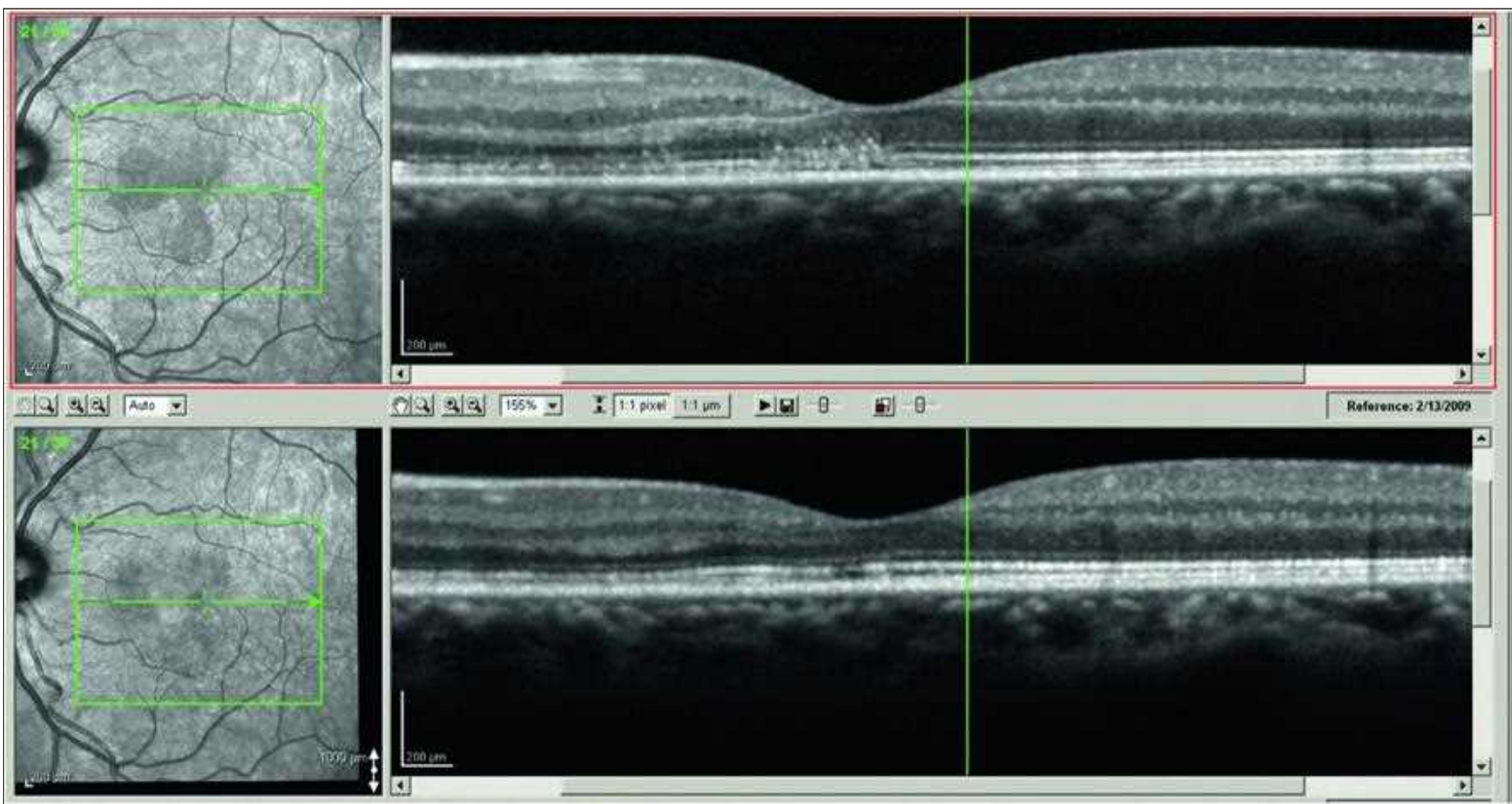
**Course and Outcomes**

No treatment is known for AMN, but the active lesions are usually self-limiting. Visual acuity may improve, and the paracentral scotomas may decrease in size; however, resolution of symptoms may take months. The acute retinal lesions fade but do not resolve completely, and loss of the ONL is seen. PAMM and AMN can be distinguished by using multimodal imaging, and these entities are being increasingly recognized.

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**Fig. 7.22.10 Acute Macular Neuroretinopathy (AMN).** Infrared reflectance (IR) and optical coherence tomography (OCT) at baseline (*top*) shows wedge-shaped, dark lesions on IR. OCT shows outer nuclear layer (ONL) hyperreflectivity and disruption of the inner segment/outer segment (IS/OS), and OS/RPE lines. The 14-month follow-up (*bottom*) shows fading of the lesion on IR. OCT shows normal reflectivity of the ONL, with focal thinning in the areas that were previously involved. The IS/OS lines have completely normalized, but the OS/RPE lines remain absent in the regions of the original AMN lesion. OCT evidence of OS/RPE disruption and ONL thinning, as well as the fading IR lesion, may be long-term markers. (Courtesy Amani Fawzi, MD, Northwestern University.)

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## Masquerade Syndromes: Neoplasms

7.23

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**Definition:** Simulation of an inflammatory condition by a neoplastic process.

## Key Features

- Usually bilateral but may have asymmetrical involvement.
- Cells in aqueous or vitreous humor or both.
- With primary central nervous system (CNS) lymphoma: subretinal pigment epithelium lesions, CNS involvement, patients typically >50 years of age.

## Associated Features

- May respond initially to corticosteroids, but eventually becomes “corticosteroid resistant”.
- Older age or known history of malignancy elsewhere.
- Usually a lack of inflammatory features, such as keratic precipitates and synechiae, but not universally.

## INTRODUCTION

Masquerade syndromes are a rare group of disorders that mimic ocular inflammatory disease. They can be infectious or neoplastic, but they commonly refer to a neoplastic process. The term “masquerade syndrome” was first used in ophthalmology by Theodore in 1967 to describe a conjunctival carcinoma that presented as chronic conjunctivitis.<sup>1</sup> Neoplastic masquerade syndromes constitute a minority of cases (2.3%) in uveitis clinics.<sup>2</sup> Early recognition of masquerade syndromes is critical, as infectious masquerade syndromes are potentially curable, and recognition of neoplastic masquerade syndromes can be life-saving.

## PRIMARY NEOPLASMS

## Primary Intraocular (Vitreoretinal) Lymphoma

Primary intraocular lymphoma (PIOL), renamed as primary vitreoretinal lymphoma (PVRL), is a subset of primary central nervous system lymphoma (PCNSL). It is typically an extranodal non-Hodgkin's, diffuse large B-cell lymphoma (DLBCL), which presents in the eye with or without simultaneous central nervous system (CNS) involvement.<sup>3,4</sup> Various studies have reported that 56%–90% of patients with PVRL have or will develop CNS disease, whereas 15%–25% of patients with PCNSL present with or ultimately develop PVRL.<sup>3</sup> In contrast to systemic DLBCL and similar to PCNSL, extracerebral dissemination is very rare. PVRL is a challenging malignancy with high rates of morbidity and mortality. It affects patients in their sixth to seventh decades. The incidence is higher in men, and there is no racial predilection. PVRL is bilateral in approximately 80%–90% of patients but can be unilateral at presentation. The incidence of PVRL is approximately 380 persons/year in the United States.<sup>5,6</sup>

PVRL typically masquerades as chronic intermediate uveitis that is unresponsive or poorly responsive to corticosteroids. Patients present with blurred vision and floaters; vitreous cells (usually in sheets); vitreous haze; multifocal, elevated, cream-colored, subretinal infiltrates; and, less commonly, anterior chamber inflammation, keratic precipitates, exudative retinal detachment, or retinal pigment epithelium (RPE) detachments (Fig. 7.23.1). Clinically, PVRL can mimic autoimmune or infectious uveitides, such as sarcoidosis, tuberculosis, viral retinitis, Behçet's disease, Vogt-Koyanagi-Harada disease, and toxoplasmosis, often leading to delayed

diagnosis.<sup>7,8</sup> Human immunodeficiency virus (HIV)-associated PCNSL, which occurs in younger patients, should also be considered in the differential diagnosis. The incidence of PCNSL in HIV is 2%–6%, at least 1000 times more than the rate for the average population. It occurs with low CD4 counts (<50–100) and is closely related to Epstein-Barr virus (EBV).<sup>3,6</sup>

## Diagnosis

Definitive diagnosis of PVRL requires identification of malignant lymphoma cells in ocular specimens. Specimens for diagnosis include vitreous, aqueous, or chorioretinal biopsy. It is essential to collaborate with the ocular pathologist to optimize specimen handling.<sup>9</sup> CNS involvement can lead to neurological deficits, including hemiparesis, ataxia, neuropsychiatric symptoms, and behavioral changes.<sup>10</sup> Therefore, magnetic resonance imaging (MRI) and lumbar puncture with cerebrospinal fluid cytology is crucial, even if patients are asymptomatic (Fig. 7.23.2). Brain biopsy may be necessary in select cases.

Chorioretinal biopsy and diagnostic enucleation demonstrate that lymphoma cells are located between the RPE and Bruch's membrane, but these cells may invade the vitreous and the retina. A complete diagnostic vitrectomy in the eye with more “vitritis” and worse vision is recommended. Undiluted fresh vitreous (1–2 mL) should be placed into cell culture medium and immediately transported for processing. Cytology reveals atypical lymphoid cells with scanty basophilic cytoplasm and large, irregular nuclei with prominent (or multiple) nucleoli (Fig. 7.23.3). Reactive T lymphocytes, necrotic cells, fibrin, and debris are often present.<sup>3,9</sup>

Immunohistochemistry or flow cytometry is helpful in determining monoclonality. Most PVRL specimens stain positively for B-cell markers and show restricted expression of either  $\kappa$ - or  $\lambda$ -chain. T-cell markers help identify rare cases of T-cell lymphoma.<sup>3</sup> Demonstration of rearrangement of the immunoglobulin heavy chain (*IgH*) or *TCR* gene by using microdissection and polymerase chain reaction also indicates monoclonality. A high ratio of interleukin-10 (IL-10) (a cytokine secreted by B cells) to IL-6 (proinflammatory cytokine) is suggestive of PVRL and a ratio >1 has a reasonably high sensitivity and specificity but is not diagnostic.<sup>3,9</sup>

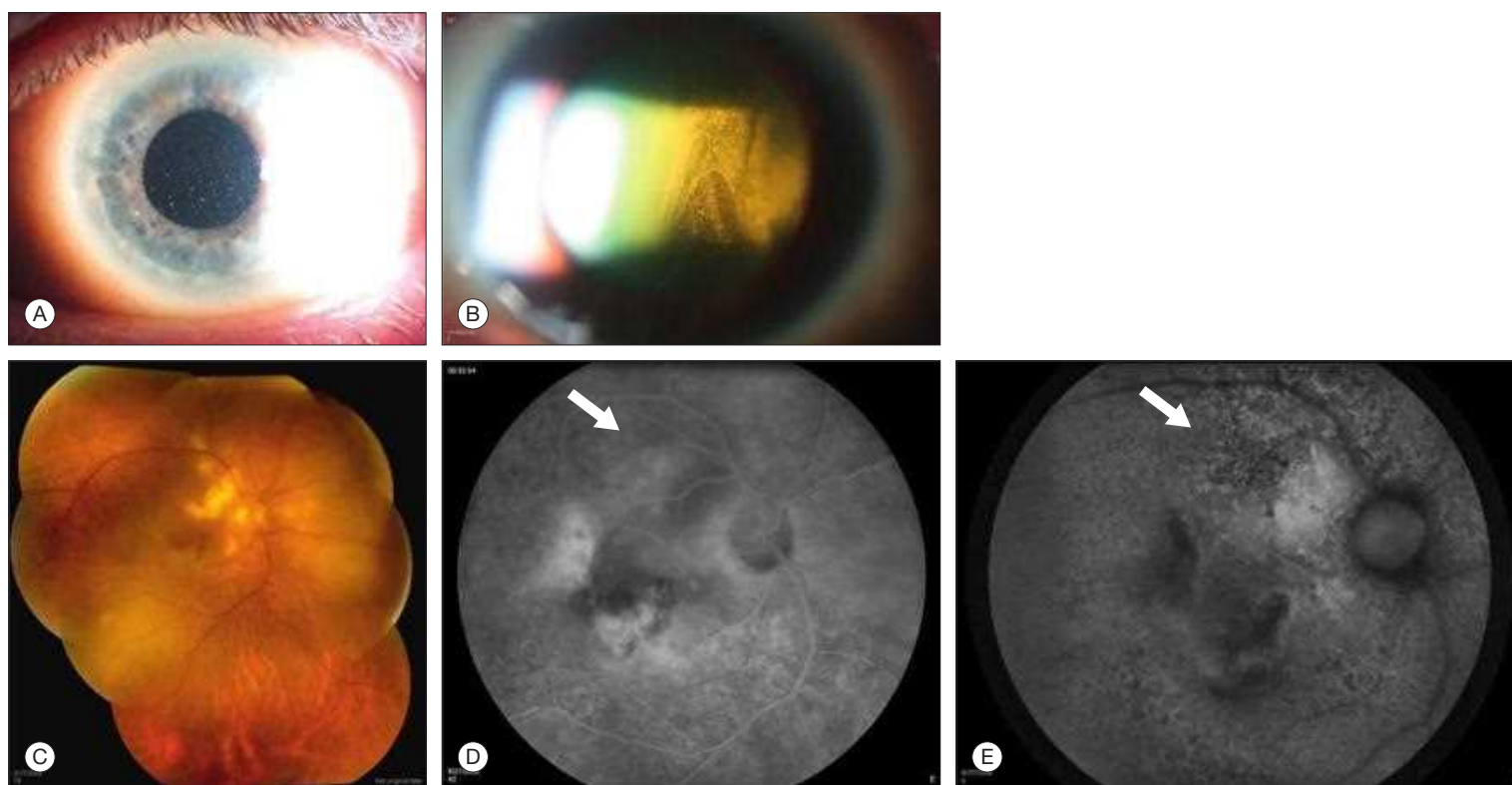
False-negative results can occur as a result of improper handling and processing of specimens, corticosteroid use, or simply because of paucity of neoplastic cells in the specimen. A quick taper of corticosteroids preoperatively should be considered. Repeated diagnostic vitrectomies may be required in some cases when more neoplastic cells break through the retina.

Multimodal imaging with fundus photography, fundus autofluorescence (FAF), fluorescein angiography (FA), and optical coherence tomography (OCT) may aid in diagnosis and follow-up.<sup>11,12</sup> The most frequent FA finding in PVRL is a “leopard spot” pattern of granular hypofluorescence, reported in 43%–61% of eyes in a published series, which characteristically correlates with the yellow infiltrates apparent on examination. FAF is also associated with a granular appearance in PVRL. Areas seen as hypofluorescent on FA correspond to hyperautofluorescent spots on FAF. Following treatment of PVRL, patchy hypofluorescence caused by RPE atrophy can occur in areas of prior activity. Abnormalities visualized at the subretinal or RPE level are the most commonly reported OCT findings of PVRL and have ranged in frequency from 41.7% to 75% of eyes. These can include subretinal hyperreflective nodules, RPE irregularities, subretinal fluid, and separation of the RPE from Bruch's membrane. Less commonly, intraretinal hyperreflective infiltrations and disruption of the ellipsoid zone have also been reported.

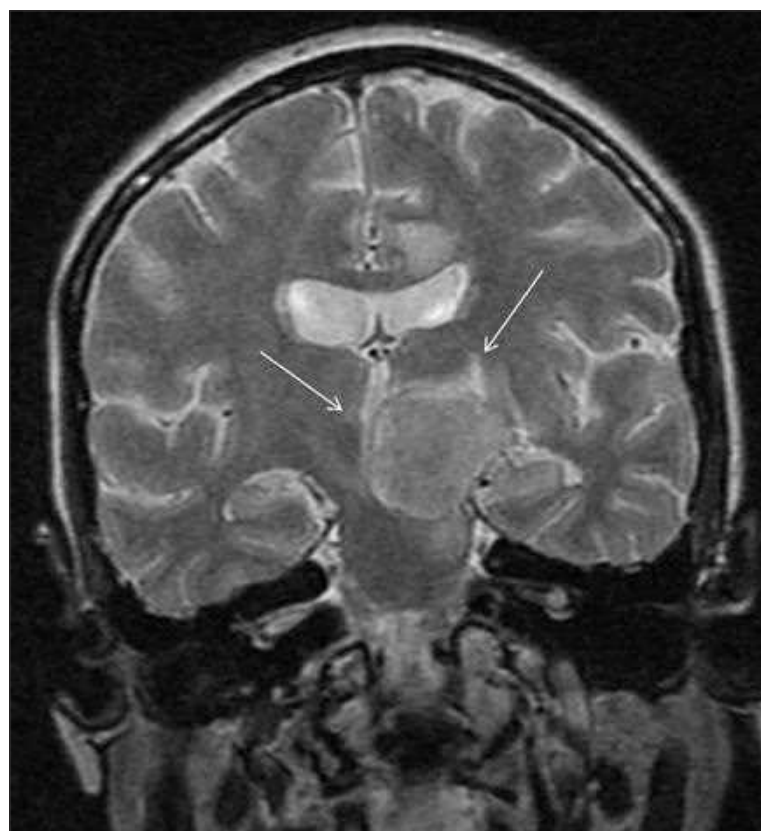
## Treatment

The diagnosis and treatment of PCNSL/PVRL require a multidisciplinary approach and is best achieved in large centers that have experience. Median survival without specific therapy is 1.9–3.3 months.<sup>13</sup> PCNSL is





**Fig. 7.23.1** Diffuse stellate-like keratic precipitates (A) and vitreous cells in “sheets” in a patient with primary vitreoretinal lymphoma (PVRL) (B). Multiple, elevated, creamy subretinal lesions along the superior arcade and the optic nerve on fundus photography (C) correspond to the early blockage outlined by arrows on fluorescein angiography (D). There is also punctate hyper- and hypofluorescence surrounding the lesions reminiscent of a “leopard spot” pattern outlined by arrows both on fluorescein angiography (FA) and autofluorescence (E).



**Fig. 7.23.2** Central nervous system (CNS) involvement in a patient with primary vitreoretinal lymphoma/primary central nervous system lymphoma (PVRL/PCNSL) with multiple enhancing lesions with the largest  $\approx 2.5$ -cm homogenous spherical lesion (arrows) centered in the left hypothalamus.

sensitive to chemotherapy and radiotherapy (RT), but the outcomes are still poor compared with other lymphomas. Most therapies used for systemic lymphoma have been ineffective for PCNSL. With the exception of stereotactic biopsy, surgical tumor resection is not done in the treatment of PCNSL. RT had been the standard of care until 1990s. Since then, high-dose methotrexate (MTX) with or without RT has been the mainstay

of therapy with an overall survival of 24–40 months. In addition to MTX, cytarabine, Ara-C, glucocorticoids, and temozolomide are also used. Rituximab, an anti-CD20 monoclonal antibody, is now used in combination with chemotherapy, although its role in PCNSL is still uncertain despite its effectiveness in other lymphomas.<sup>14</sup> The roles of intrathecal chemotherapy and stem cell transplantation remain unclear. Intravitreal methotrexate (400  $\mu\text{g}$  in 0.1 mL) or rituximab (1 mg in 0.1 mL), alone or in combination, or ocular RT can be administered for isolated ocular recurrences or to supplement systemic therapy in PVRL.<sup>3</sup> Overall survival in patients with PVRL is 58 months, with the majority of recurrences occurring in the CNS. Local ocular therapy will not prevent CNS recurrences, and patients should be monitored closely with regular MRIs, neurological and ocular examinations. The long-term prognosis for patients with PCNSL remains poor. Multiple factors, including age, performance status, neurological function, and the number and location of lesions, can influence survival in patients with PCNSL.<sup>7,14</sup>

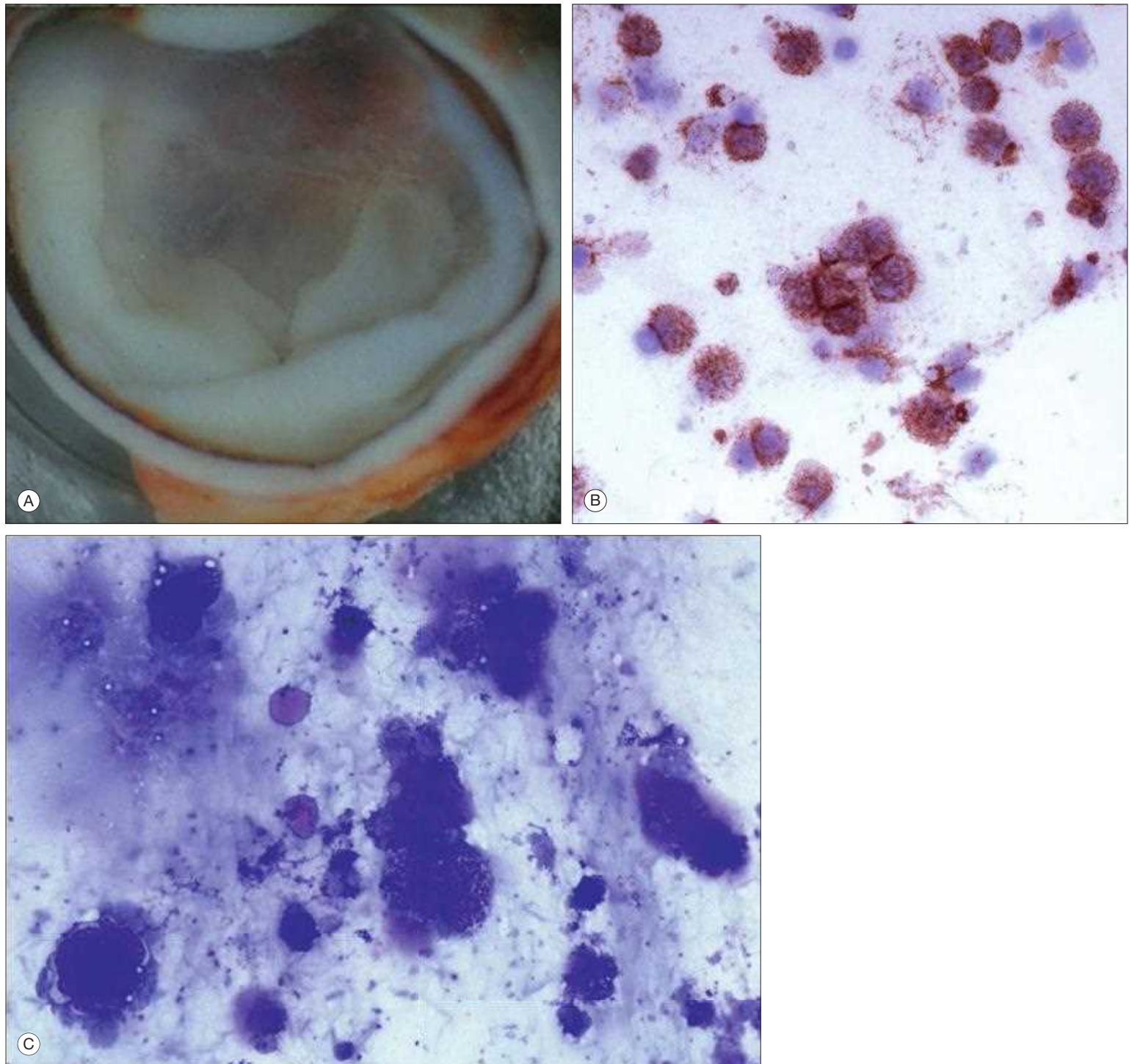
### Primary Choroidal Lymphomas and Lymphoid Hyperplasia

First described in 1920, primary choroidal lymphomas are typically extranodal marginal zone, mucosa-associated lymphoid tissue (MALT) lymphomas.<sup>3</sup> They are rare and are not associated with CNS disease. Because they are typically low-grade B-cell lymphomas with an indolent clinical course, they were previously termed “uveal or intraocular pseudo-tumor” and “reactive lymphoid hyperplasia.” Recent studies have confirmed that lymphoid hyperplasia is, indeed, a lymphoma.<sup>15</sup> Early diagnosis is usually based on multifocal creamy choroidal infiltrates, choroidal thickening on ultrasonography, and extraocular extension leading to orbital mass or salmon-colored conjunctival mass. It carries a favorable prognosis, with very low rates of systemic metastasis, and frequently responds to corticosteroids or low-dose RT.<sup>15</sup>

Posttransplantation lymphoproliferative disorders (PTLDs), potentially fatal complications of chronic immunosuppression, are extranodal non-Hodgkin’s lymphoma (NHL) of large-B-cell type. Its pathogenesis is closely related to EBV and the degree of immunosuppression.

### Melanoma

Ocular melanoma is the most frequent neoplasm of the eye, with a 5.1 per 1000000 annual incidence in the United States, arising from the uveal



**Fig. 7.23.3** Gross photograph of an enucleated eye with primary vitreoretinal lymphoma (PVRL) with retinal thickening and subretinal tumor infiltration (A). Photomicrograph showing immunohistochemical staining of lymphoma cells from the vitreous with positive staining for CD-20, a B-cell marker (B), and large lymphoma cells with scanty basophilic cytoplasm and large hypersegmented nuclei and prominent nucleoli (Giemsa stain) (C).

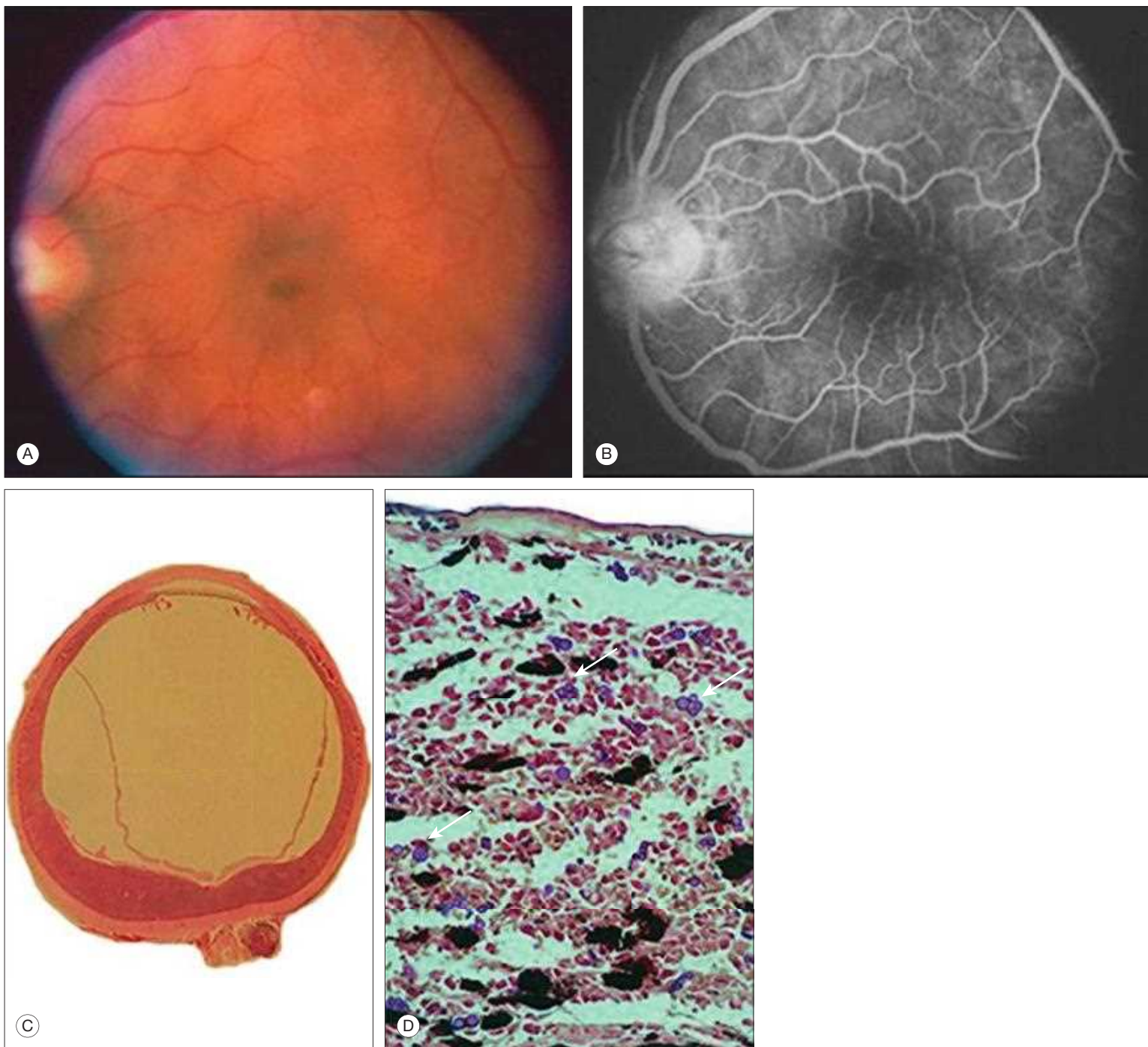
tract in 97% of cases.<sup>16</sup> It mainly affects white patients in their early 60s, and approximately 5% of uveal melanomas present with ocular inflammation with iridocyclitis or with dilated episcleral vessels (“sentinel vessels”) that can be misdiagnosed as scleritis. Focal choroidal mass can mimic a choroidal granuloma, sectoral cataract, posterior scleritis, secondary glaucoma, or retinal detachment. Ultrasonography shows characteristic low internal reflectivity. The most common sites for metastases are the liver, lungs, and skin. All patients require metastatic evaluation prior to therapy. Treatment includes radiation (brachytherapy, external beam radiotherapy, and transpupillary thermotherapy), or surgery (transscleral partial choroidectomy, transretinal endoresection, and enucleation). Adjuvant therapy may consist of RT or systemic therapy, such as chemotherapy, immune therapy, hormone therapy, biological therapy, or target therapy. Prognosis is fair, with a 5-year survival of approximately 50%–80%, but this largely depends on the nature of melanoma.<sup>16,17</sup>

### Other Primary Neoplasms

A small percentage of retinoblastomas (RBs) (1%–3%) can present as ocular inflammation with a shifting pseudo-hypopyon and vitritis. Patients are typically young children with diffuse infiltrating retinoblastoma. Computed tomography (CT) may not be helpful because of lack of calcification. Aqueous aspiration should be avoided if RB is suspected because of the risk of tumor spread.<sup>18</sup>

Juvenile xanthogranuloma (JXG), a benign cutaneous fibrohistiocytosis of infancy, is characterized by reddish-yellow nodules of the skin, eye and rarely viscera. Yellowish iris nodules can masquerade as inflammatory granuloma. Anterior chamber cells, heterochromia, iris thickening, and spontaneous hyphema can masquerade as pediatric anterior uveitis. Histopathology illustrates large foamy histiocytes and Touton giant cells. Prognosis is often favorable, with good response to topical, local, or systemic corticosteroids.<sup>19</sup>





**Fig. 7.23.4** Fundus photograph of a patient with choroidal mucosa-associated lymphoid tissue (MALT) lymphoma shows deep multifocal faintly creamy choroidal infiltrates in the posterior pole (A) showing mild staining in corresponding areas on fluorescein angiography (FA) (B). The gross photograph of another typical choroidal MALT lymphoma shows diffuse choroidal infiltration (C). The photomicrograph of the choroidal lymphoma in the patient (A–B) shows Dutcher bodies (arrows) admixed with numerous atypical lymphocytes in the choroid (D).

## SECONDARY NEOPLASMS AND METASTASES

### Lymphoma and Leukemia

Secondary lymphomas represent metastatic systemic lymphoma and are usually confined to the choroid. Metastatic lymphomas are less of a diagnostic challenge because most patients have a known history at presentation. They often exhibit creamy choroidal/subretinal infiltrates (Fig. 7.23.4). Diffuse choroiditis, retinal vasculitis, or necrotizing retinitis may be present. Ocular adnexa and anterior segment can also be affected causing hypopyon and anterior uveitis. The most common metastatic lymphoma involving the choroid is DLBCL. Average survival in these patients is <3 years after ocular diagnosis. Most orbital/adnexal lymphomas are MALT lymphomas with good prognosis (10-year survival ≈80%).<sup>3,20</sup>

Less frequently, multiple myeloma, extramedullary plasmacytoma, lymphoplasmacytic lymphoma/immunocytoma (including Waldenström's macroglobulinemia), B-cell chronic lymphocytic leukemia, and, very rarely, intravascular lymphoma can also lead to similar findings.<sup>3,21</sup> Peripheral T-cell lymphomas, a rare group of disorders with generally poor prognosis,

and mycosis fungoides (cutaneous T-cell lymphoma) are rarely responsible for ocular involvement and not only typically present with anterior segment or external involvement but can also cause vitritis, exudative RD, papilledema, and even PVRL. Adult T-cell leukemia/lymphoma is caused by human T-lymphotropic virus-1, a retrovirus endemic in Japan, Caribbean islands, and central Africa. It can present with retinal vasculitis, subretinal infiltrates, macular edema, vitritis, anterior uveitis, keratopathy, or episcleritis.<sup>22</sup> Patients with leukemia can present with retinal hemorrhages, cotton wool spots, Roth spots, retinal microaneurysms, or neovascularization. It can also cause vitritis, exudative RD, pseudo-hypopyon, hyphema, and iris heterochromia. Differentiation between PVRL and metastatic lymphoma/leukemia is critical from a therapeutic standpoint because the former requires chemotherapy that crosses the blood–brain barrier.

### Metastatic Carcinoma

Uveal metastases, particularly to the choroid, are the most common intraocular malignancies in adults. Most common primaries are lung and breast cancers. In the case of breast carcinoma, >90% patients have a



known primary history, whereas this is not the case with regard to lung carcinoma. Common findings are bilateral choroidal involvement; multifocal gray-yellow, relatively flat lesions that can be associated with vitritis; exudative RD or a “leopard spot” pattern; and papilledema. Most patients also have CNS metastasis and have a poor prognosis, with an average survival of <1 year.<sup>23</sup>

## Metastatic Melanoma

Metastatic melanoma to the eye is extremely rare and can involve the uvea or the orbit. It can manifest as exudative RD or RPE detachments, clumps of pigmented or nonpigmented vitreous cells, hyphema, neovascular glaucoma, or vitelliform retinopathy. Prognosis is very poor.<sup>24</sup>

## Paraneoplastic Syndromes

Paraneoplastic autoimmune retinopathy can masquerade as uveitis. Patients can present with photopsiae, nyctalopia, photoaversion or dyschromatopsia, vision loss, mild vitritis, and, less frequently, macular edema, but the fundus can look normal in the early stage. Later, vascular attenuation, optic nerve pallor, and RPE disturbances may ensue. Electroretinography (ERG) and visual field testing show scotomas and decreased cone and rod responses. Cancer-associated retinopathy (CAR) is most commonly associated with oat cell carcinoma of the lung. Anti-recoverin antibody is the characteristic autoantibody, but is not unique to CAR. Melanoma-associated retinopathy (MAR) is a complication of metastatic cutaneous melanoma. ERG findings are characteristic with negative b-wave and relatively preserved photopic responses. Responsible autoantibody targets TRPM1 channel on ON-bipolar cells. Typically, retinopathy precedes cancer in CAR, whereas it follows the diagnosis of melanoma by months to years in MAR. Therapy is aimed at treating the underlying malignancy. Local or systemic corticosteroids, intravenous immunoglobulin and plasmapheresis have been tried.<sup>25,26</sup>

Bilateral diffuse uveal melanocytic proliferation, a very rare paraneoplastic syndrome that occurs in patients with occult carcinoma, is characterized by multiple subtle subretinal reddish-brown lesions, which show

hyperfluorescence on angiography, exudative RD, thickening of the uvea, mild uveitis, and rapidly progressive cataracts. Histopathology shows melanocytic hyperplasia.<sup>27</sup>

## CONCLUSIONS

The most important step in the diagnosis of neoplastic masquerade syndromes is clinical suspicion. A thorough history, systemic review, and careful ophthalmic examination aided by appropriate ancillary testing are required. Early recognition of the malignancy is crucial for both vision-saving and life-saving outcomes, which can be achieved through a multidisciplinary approach.

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# Malignant Intraocular Neoplasms

James J. Augsburger, Zélia M. Corrêa, Jesse L. Berry

## 8.1

**Definition:** Spectrum of intraocular tumors composed of malignant neoplastic cells capable of destroying normal intraocular tissues by expansion and invasion, extending outside the eye, and/or spawning extraophthalmic metastatic tumors.

### Key Features

- Shape:
  - Most appear as discrete nodular tumors (e.g., primary uveal melanoma, medulloepithelioma, intraocular metastases, some retinoblastomas, occasional primary intraocular lymphoma).
  - May vary substantially among the different malignant tumor types (e.g., many posterior uveal melanomas [about 20%] exhibit a mushroom-like three-dimensional shape; most subretinal pigment epithelium infiltrates in primary vitreoretinal lymphoma exhibit a geographic basal configuration; most metastatic choroidal tumors exhibit a broad base but limited thickness and are more likely to be multinodular than most other tumor types).
  - Some appear as ill-defined infiltrates in the vitreous (e.g., primary vitreoretinal lymphoma, intraocular leukemia, retinoblastoma with vitreous seeding), some of which have no associated discrete intraocular tumor(s).
  - Some (e.g., diffuse posterior uveal melanoma, diffuse posterior uveal lymphoma, some cases of diffuse intraocular retinoblastoma) appear as broad-based (i.e., largest basal diameter >15 mm) but relatively thin tumors (i.e., having a maximal thickness <20% of the tumor's largest basal diameter).
  - Uveal melanomas in the ciliary body can assume a ring shape.
- Color:
  - Most primary uveal melanomas are brown to gray (although nearly 15% are clinically amelanotic).
  - Most retinoblastomas are white (although some of a pink to orange color depending on the density of superficial retinal capillaries in the tumor).
  - Most metastatic carcinomas to the choroid are pale yellow to nearly white (although some, such as thyroid carcinoma, renal cell carcinoma, carcinoid tumors, and choriocarcinoma tend to be red to pink to orange and most metastatic skin melanomas are golden brown to dark brown).
  - Most medulloepitheliomas are off-white.
  - Most subretinal pigment epithelium infiltrates of primary vitreoretinal lymphoma are pale yellow to golden.
- Laterality/Focality:
  - Primary uveal melanomas and medulloepithelioma are almost exclusively unilateral and unifocal.
  - Retinoblastoma, uveal metastases, and primary vitreoretinal lymphoma may be unilateral and unifocal but may also occur bilaterally and/or multifocally.
- Growth:
  - Most untreated malignant intraocular tumors enlarge progressively.
  - Stable size may occur in dormant posterior uveal melanoma, retinomas, and metastatic uveal carcinomas in patients being treated by an effective systemic chemo- or immunotherapy.
  - Some malignant intraocular tumors (primary uveal melanomas, retinoblastoma, medulloepitheliomas) can extend outside the eye by invasive spreading.

### INTRODUCTION

A malignant intraocular neoplasm is a tumor (three-dimensional mass) that is present inside an eye and is composed of abnormal cells exhibiting features such as nuclear atypia and pleomorphism, prominent nucleoli, and abnormal nucleus-to-cytoplasm ratio sufficient to warrant their classification as malignant (cancer) cells by pathologists. These cancer cells can arise from previously normal cells that were present in their tissue of origin (*primary malignant intraocular neoplasms*), develop by intraocular invasion of cancer cells that arise from extraocular tissues adjacent the eye (e.g., conjunctiva, orbit) (*secondary malignant intraocular neoplasms*), or occur by hematogenous metastasis from a nonophthalmic primary malignant neoplasm remote from the eye (*metastatic malignant intraocular neoplasms*). Readers should note that many authors (and the ICDM coding system) lump secondary tumors and metastatic malignant intraocular neoplasms, as we define them, together under the term “secondary” and fail to address the distinction between these subtypes.

Some malignant neoplasms and neoplasias (nontumorous accumulations of malignant cells within a tissue) that metastasize to the eye, most notably the hematological neoplasias (leukemia and its variants), and some primary malignant ocular neoplasms (most notably primary vitreoretinal lymphoma and diffuse infiltrating retinoblastoma) frequently produce ill-defined infiltrates of intraocular tissues (e.g., vitreous, retina, optic disc) rather than discrete solid neoplastic tumors.

### PRIMARY MALIGNANT INTRAOCULAR NEOPLASMS

#### RETINOBLASTOMA

Retinoblastoma is a primary malignant intraocular neoplasm that arises from immature retinal cells (retinoblasts) within the developing retina. As retinoblasts mature and differentiate into adult cells, they lose their potential to give rise to retinoblastoma. Because of this, the vast majority of cases of active retinoblastoma are identified in children under the age of 6 years. Retinoblastoma is the most common primary malignant intraocular neoplasm in children worldwide.<sup>1</sup>

Almost all retinoblastoma tumors that have been studied cytogenetically exhibit inactivating mutations or deletions of both copies of the *RB1* tumor suppressor gene, which is located on the short arm of chromosome 13 (region q14) within all tumor cells.<sup>2</sup> These cytogenetic alterations can develop by chance in both copies of chromosome 13 within previously normal retinoblasts. Such occurrence is extremely uncommon in spite of the large number of retinoblasts that are present in the developing eye. Such genetic alterations usually give rise to unilateral unifocal retinoblastoma.

In contrast, these cytogenetic alterations can develop within retinoblasts that have a congenital mutation or deletion of the relevant segment of one of the two chromosomes 13 in some or all cells of the developing retina. All cells will be affected when the *RB1* tumor suppressor gene is defective and inherited from an affected parent (familial retinoblastoma) or when a mutation occurred early in embryogenesis prior to cellular differentiation into the neural epithelial precursors of the retina.<sup>2</sup> These cells can give rise to retinoblastoma if the normal *RB1* tumor suppressor gene also undergoes a chance mutation of chromosome 13q14 or a deletion of that portion or all of chromosome 13. Some cells will have a congenital chromosomal mutation or deletion of chromosome 13q due to an event in a precursor cell to some but not all of the retinoblasts in one or both eyes. In such





**Fig. 8.1.1** Asymmetric White Pupil (Leukocoria) of Both Eyes Due to Intraocular Retinoblastoma.



**Fig. 8.1.3** Massive Conjunctival Chemosis as Presenting Feature of Advanced Intraocular Retinoblastoma Associated With Massive Tumor Necrosis.



**Fig. 8.1.2** Small-Angle Left Exotropia as Presenting Feature of Retinoblastoma of Left Eye.



**Fig. 8.1.4** Massive Proptosis of Right Eye Due to Orbital Extension of Retinoblastoma.

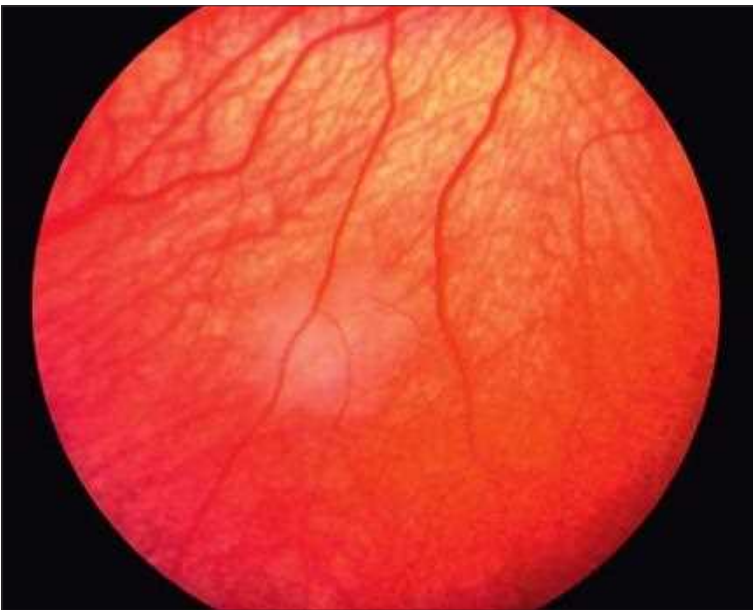
cases, the mutation or deletion of chromosome 13q will not be present in the precursor cells that give risk to spermatocytes or oocytes; consequently, such cases will not be heritable even though the affected child may have multifocal retinoblastoma in one or both eyes. These variations in heritability lead to two forms of retinoblastoma: the *heritable* form, seen in 40% of patients, with a mutation in all cells of the body and a presentation, most often, with bilateral tumors, multifocal tumors, or both; and the *somatic* form, wherein both mutations are present only in the tumor tissue and the child usually manifests unilateral unifocal disease. However, 10%–15% of patients who present with unilateral retinoblastoma may still harbor the germline mutation. In view of this, blood testing for a germline mutation (or mosaicism) is advised for all children with retinoblastoma.<sup>2</sup>

The cumulative lifetime incidence of retinoblastoma in most ethnic and racial groups has been estimated to be approximately one case in 15 000–20 000 individuals.<sup>3</sup> As mentioned above, almost all active cases of retinoblastoma occur in children under the age of 6 years. Survivors of bilateral or known familial retinoblastoma who subsequently have children run nearly a 50% chance that any child they have will develop retinoblastoma.<sup>2</sup> Because many more children with bilateral and familial retinoblastoma are cured now than was possible in prior generations, the frequency of hereditary retinoblastoma may be increasing in the general population.

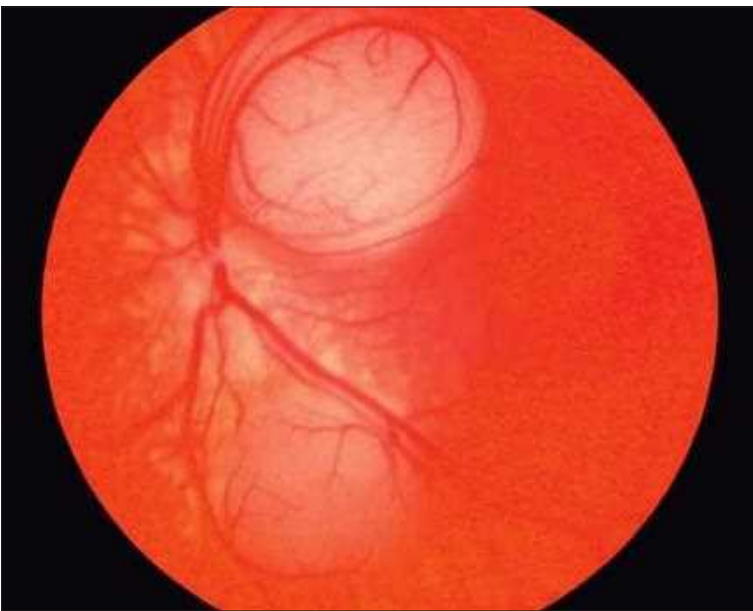
The clinical features of retinoblastoma differ substantially depending on the extent of ocular involvement at the time of initial detection. The most common presenting feature of retinoblastoma reported by parents of an affected child is that of a white appearance or glow of the pupil in one or both eyes (leukocoria) (Fig. 8.1.1). The second most common presenting feature is ocular misalignment (strabismus) (Fig. 8.1.2). Congestive ocular signs (Fig. 8.1.3) are quite uncommon except in very advanced cases. However, some children (principally ones in underdeveloped countries with poor access to healthcare professionals) do not have their

retinoblastoma identified until the eye is grossly hyperemic with profound chemosis or even proptosis (due to posterior extraocular extension of tumor to the orbit) (Fig. 8.1.4).<sup>4,5</sup>

Children suspected of having or developing retinoblastoma because of a positive family history of the disease should be screened for retinoblastoma shortly after birth and (if this baseline examination does not reveal any retinoblastoma) periodically thereafter during at least the first 2 years of life. In these children, retinoblastoma tumors that are detected are usually relatively small and predominantly intraretinal. In contrast, children who develop nonfamilial retinoblastoma are frequently not diagnosed until their intraocular tumors are much larger and the eye demonstrates leukocoria, strabismus, or both. Very small intraretinal tumors (i.e., ones that are  $\leq 1$  mm in diameter) appear as smudgy translucent to off-white intraretinal lesions (Fig. 8.1.5). Slightly larger tumors appear more opaque white but exhibit prominently dilated and tortuous retinal blood vessels and a fine network of superficial capillaries that frequently give the tumor a slightly pink appearance (Fig. 8.1.6). Still larger intraretinal tumors are likely to show a surrounding cuff of serous subretinal fluid and limited tumor seeding extending into the overlying vitreous or subretinal fluid (Fig. 8.1.7). Massive intraocular tumors (generally defined as larger than 15 mm in diameter) frequently grow outwardly toward the choroid and become associated with a bullous nonrhegmatogenous retinal detachment (*exophytic* growth pattern), inwardly toward the vitreous to appear as a fuzzy white mass associated with prominent vitreous seeding (*endophytic* growth pattern), or both (mixed growth pattern). In some advanced cases, tumor seeding by retinoblastoma is so extensive that the clouding of the vitreous obscures many of the features of the underlying tumor (Fig. 8.1.8) or associated subretinal fluid is so turbid that the underlying retinal tumor is difficult to visualize. In some cases, the retina is infiltrated diffusely by a fluffy white accumulation of tumor cells without formation of any discrete



**Fig. 8.1.5** Small Intraretinal Retinoblastoma Appears as a Poorly Defined Translucent Retinal Lesion.



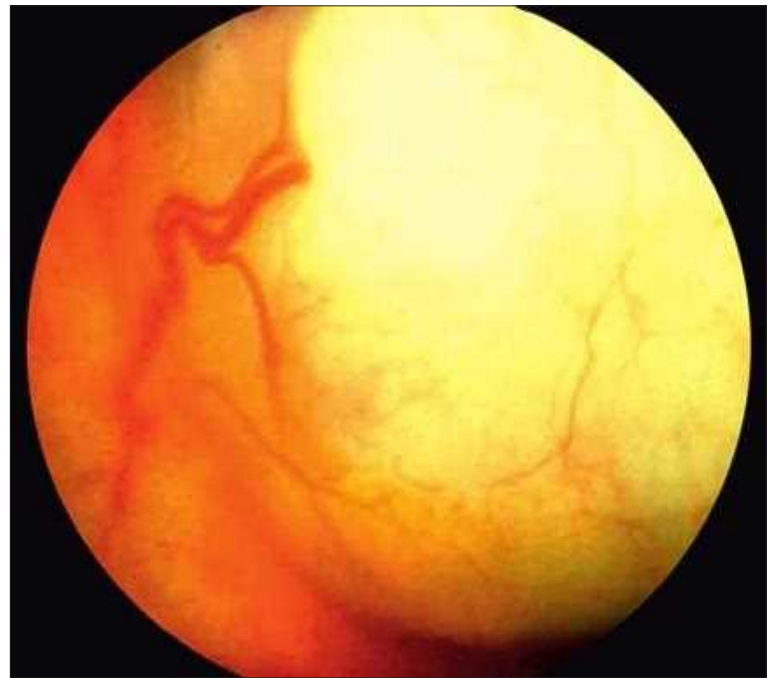
**Fig. 8.1.6** Two Discrete Intraretinal Retinoblastoma Tumors Supplied by Retinal Vasculature.

retinal tumor or tumors (diffuse infiltrating growth pattern)<sup>6</sup> (Fig. 8.1.9). In rare cases, retinoblastoma tumor seeds extend from the vitreous into the aqueous and enter the anterior chamber (Fig. 8.1.10). Advanced intraocular cases also frequently develop iris neovascularization, which can cause abrupt change in color of the iris noted by the child's parents, secondary glaucoma, and buphthalmos.

Occasionally, a retinoblastoma tumor undergoes spontaneous growth arrest to form a lesion known clinically as *retinoma*.<sup>7</sup> The typical retinoma is partly calcific with an associated pale gray to dull pink soft tissue component (Fig. 8.1.11). The lesion does not have prominent feeder and drainer retinal blood vessels that are characteristic of active retinoblastoma tumors. A limited area of chorioretinal atrophy is sometimes evident underlying or surrounding such lesions. Some lesions of this type transform to active retinoblastoma later in life, and such transformations are likely to explain many if not most reported adult cases of retinoblastoma.

Rarely, an advanced case of intraocular retinoblastoma undergoes spontaneous necrosis followed by shrinkage of the affected eye (*phthisis bulbi*).<sup>7</sup> While some of these cases result in total destruction of all viable retinoblastoma, others have persistent active tumor that involves the retrobulbar optic nerve or orbit and leads ultimately to a progressive orbital tumor, intracranial extension, and metastasis.

Ocular B-scan ultrasonography allows confirmation of most discrete retinoblastoma tumors and usually reveals hyperreflective intralesional dots



**Fig. 8.1.7** Relatively Large Intraretinal Retinoblastoma Tumor Associated With Prominent Feeder and Drainer Retinal Blood Vessels. Smaller intralesional blood vessels can also be appreciated.

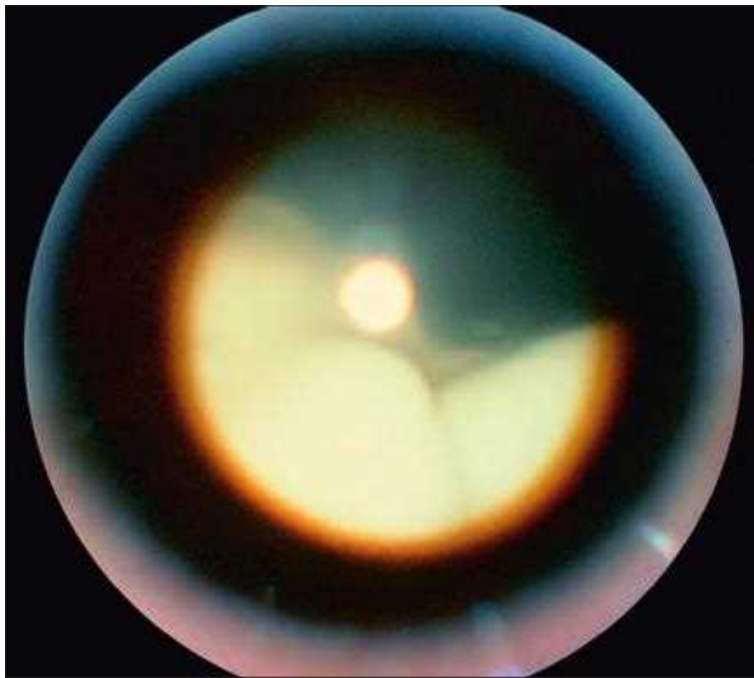


**Fig. 8.1.8** Prominent Vitreous Seeds of Retinoblastoma Partly Obscuring Underlying Retinal Tumor.

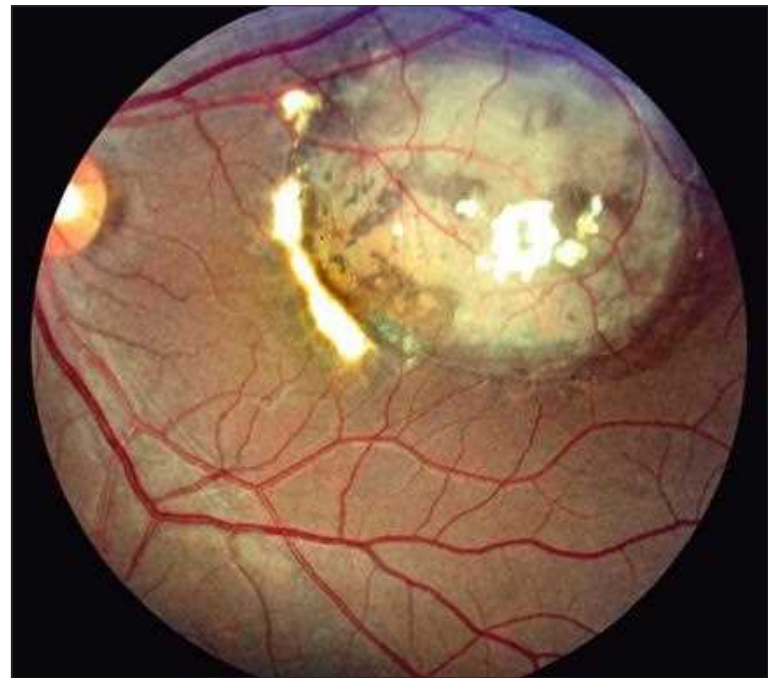
(foci of intratumoral calcification) that are nearly pathognomonic of retinoblastoma (Fig. 8.1.12). However, eyes with diffuse infiltrating retinoblastoma frequently show no discrete tumor nodules or foci of intralesional calcification.<sup>6</sup> In cases with advanced vitreous seeding or bullous retinal detachment, B-scan can identify the underlying retinal tumor(s) and allow approximate measurement of the individual tumors. In eyes with massive involvement by retinoblastoma, ocular ultrasonography is of limited value for evaluating the retrobulbar optic nerve and orbital soft tissue for involvement by tumor (because the intralesional calcification usually reduces the quality of the orbital images).

Computed tomography (CT) scanning of the orbits and brain can be performed to identify discrete retinal tumors containing foci of calcification, evaluate the optic nerve and orbit, and evaluate the brain in children with suspected retinoblastoma (Fig. 8.1.13). This method of evaluation is not generally advocated in centers where magnetic resonance imaging (MRI) is available for children with suspected bilateral or familial retinoblastoma (who are known to be susceptible to radiation-induced second

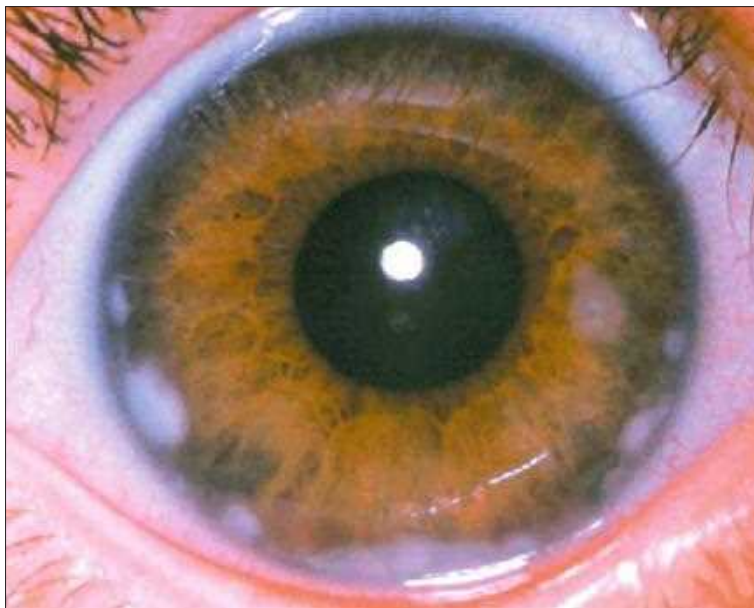




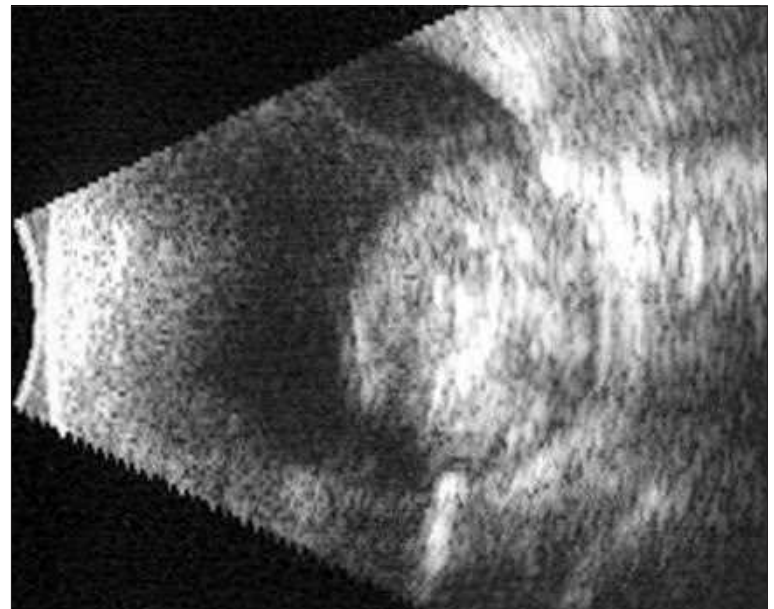
**Fig. 8.1.9** Diffuse Retinal Infiltration by Retinoblastoma (Diffuse Infiltrating Growth Pattern). No discrete mass or foci of intralesional calcification was appreciated on B-scan ultrasonography (not shown).



**Fig. 8.1.11** Spontaneously Arrested Retinoblastoma (Retinoma) in an Adult Who Fathered a Child With Bilateral Active Retinoblastoma.



**Fig. 8.1.10** Multifocal White Implantation Tumors on Iris in Retinoblastoma.



**Fig. 8.1.12** B-Scan Ultrasound Image of Nodular Retinoblastoma Showed Multiple Dense Intralesional Echoes Consistent With Calcific Foci.

malignant neoplasms in the field of radiation therapy) because of the relatively high level of radiation exposure associated with this testing.

MRI of the orbits and brain (Fig. 8.1.14) also identifies discrete intraocular retinoblastoma tumors, detects massive optic nerve invasion by tumor and transscleral orbital tumor extension, and permits identification of any associated brain lesions without subjecting the patient to relatively high doses of ionizing radiation.<sup>8</sup>

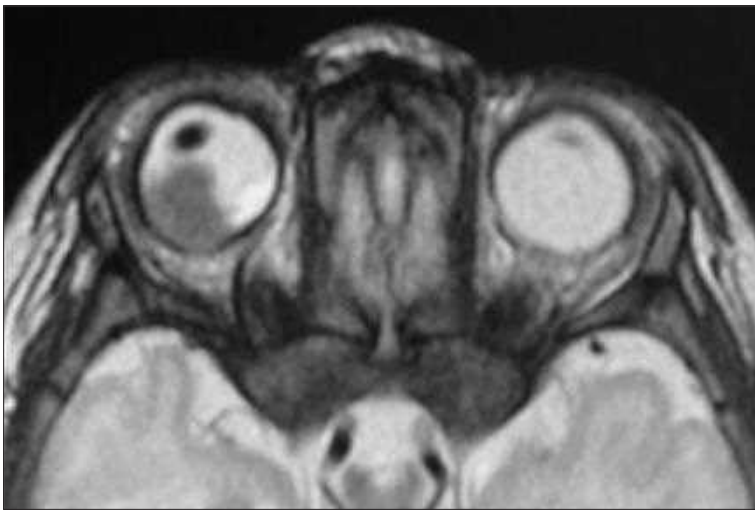
Some children who have bilateral or familial retinoblastoma develop a retinoblastoma-like neoplasm in the pineal region of the brain (pineoblastoma).<sup>9</sup> The association of bilateral retinoblastoma and pineoblastoma (sometimes referred to as ectopic intracranial retinoblastoma) is known as *trilateral retinoblastoma*. MRI is effective for identifying this type of brain tumor when it is present.<sup>10</sup>

Children with clinically diagnosed or suspected retinoblastoma are usually evaluated by baseline ophthalmic examination under anesthesia to ascertain the number, size, and location of discrete retinal tumors in each eye and the presence and extent of features such as serous retinal detachment, vitreous seeding, and subretinal seeding. Fundus mapping and (if available) intraoperative fundus photography are performed to document the clinical findings in each eye, justify classification of the extent of intraocular retinoblastoma, and serve as a baseline for comparison with



**Fig. 8.1.13** Computed Tomography Scan of Unilateral Retinoblastoma of Right Eye Showing Sizeable Intraocular Tumor That Is Almost as White as Bone Due to Intralesional Calcification.





**Fig. 8.1.14 T2-Weighted Magnetic Resonance Image of Eyes and Orbits in Child With Unilateral Retinoblastoma of Right Eye Demonstrating a Lesion That Is Hypointense to the Vitreous on T2 Imaging.**

subsequent findings if a treatment intended to be eye preserving is provided. The extent of intraocular retinoblastoma is classified today in most retinoblastoma centers using the International Classification of Intraocular Retinoblastoma (ICIR).<sup>11</sup>

Initial treatment options for retinoblastomas range from primary enucleation of one or both eyes to no treatment at all (in the case of retinoma).<sup>12</sup> Factors influencing the treatment recommendation for intraocular retinoblastoma include age of the affected patient, clinically assessed activity versus inactivity (retinoma) of the tumors, extent of abnormalities attributable to active intraocular retinoblastoma (ICIR group) in each affected eye, the unilaterality versus bilaterality of involvement, and absence versus presence of trilateral retinoblastoma. Enucleation is generally recommended for advanced (ICIR group D or E) unilateral nonfamilial retinoblastoma,<sup>13</sup> whereas intravenous multidrug chemotherapy with a carboplatin-based regimen is commonly recommended for bilateral advanced intraocular retinoblastoma or bilateral retinoblastoma with macular involvement in each eye.<sup>14</sup> With increasing frequency in recent years, unilateral cases of retinoblastoma and occasional bilateral cases are treated by selective ophthalmic artery infusion chemotherapy,<sup>15</sup> most commonly using melphalan. Occasional patients with ICIR group A or B retinoblastoma are managed by focal treatments alone (transscleral cryotherapy,<sup>16</sup> focal laser therapy,<sup>17,18</sup> episcleral plaque radiotherapy<sup>19</sup>) without any concurrent chemotherapy. Many cases are treated by more than one method (combined modalities therapy; e.g., selective ophthalmic artery infusion chemotherapy plus local consolidation using cryotherapy, laser therapy, or both). Since 2012, vitreous seeding has been treated in some centers by intravitreal injection of one or more chemotherapeutic drugs,<sup>20</sup> most commonly melphalan, topotecan, or both. Intravitreal injection of chemotherapeutic drugs is not recommended as the initial or only treatment for any category of retinoblastoma, and extreme care must be taken to avoid any exteriorization of active intraocular retinoblastoma associated with this treatment.<sup>21</sup> External beam radiation therapy to both eyes of bilaterally affected children or the better eye of bilaterally affected children following enucleation of the worse eye, once the standard of care for such cases, is no longer advocated as initial therapy in most retinoblastoma centers because of the recognized potential for ionizing radiation to stimulate subsequent development of nonretinoblastoma “second malignant neoplasms” in the head and neck tissues that were in the field of radiation.<sup>22</sup> However, it is still used occasionally in attempt to salvage eyes that continue to harbor active retinoblastoma in spite of prior intensive systemic and local therapies.<sup>12,22</sup>

Children who are found to have pineoblastoma in association with their retinoblastoma (trilateral retinoblastoma) are treated with an aggressive regimen of intravenous chemotherapy, excision or focal radiation therapy to the residual central nervous system (CNS) tumor, and frequently by subsequent bone marrow transplantation.<sup>23</sup>

Children who have optic nerve invasion by retinoblastoma or orbital involvement by tumor are also treated by intravenous chemotherapy plus enucleation with debulking of the residual orbital tumor or external beam radiation therapy to the affected orbit.<sup>24</sup>

Children who have intracranial extension of retinoblastoma or metastasis of retinoblastoma are also managed by intensive intravenous chemotherapy, intrathecal chemotherapy, and subsequent bone marrow

transplantation (if the active retinoblastoma can be eradicated).<sup>25</sup> Unfortunately, a substantial proportion of children who develop intracranial extension or metastasis of retinoblastoma or intracranial pineoblastoma ultimately die of that cancer in spite of these aggressive interventions intended to eradicate it. In contrast, the vast majority (approximately 90%–95%) of children with clinically intraocular retinoblastoma at the time of diagnosis and initial treatment are cured of their cancer if appropriate treatment is provided.<sup>4</sup>

## PRIMARY UVEAL MELANOMA

Primary uveal melanoma is a malignant neoplasm that arises from previously normal melanocytes or nevus cells (slightly atypical but nonmalignant uveal melanocytes) within the uveal tract. While it has the potential to extend transclerally to the orbit, its principal danger is its potential to metastasize hematogenously to other organs, most notably the liver.<sup>26</sup> Most deaths attributable to primary uveal melanoma occur as a result of liver failure induced by metastatic tumors to that organ.<sup>27</sup>

The principal recognized risk factors for occurrence of primary posterior uveal melanoma are older patient age, white race, and presence of congenital ocular melanocytosis.<sup>26,28</sup> Primary uveal melanoma affects approximately one in 2000–2500 persons during their lifetimes. The annual incidence of primary uveal melanoma is less than one new case per million persons per year under the age of 20 years, approximately 7–8 new cases per million persons per year during the age range 55–65 years, and approximately 30–50 new cases per million persons per year during the age range 75–85 years. Light-skinned persons, particularly those of northern European extraction, have the highest risk for development of primary uveal melanoma, whereas dark-skinned persons have a very low risk for development of such tumors. Individuals with congenital ocular melanocytosis have a substantially increased likelihood of developing primary uveal melanoma in the involved eye.

Unlike retinoblastoma, primary uveal melanoma is almost exclusively a unilateral unifocal neoplasm. Also unlike retinoblastoma, primary uveal melanoma infrequently affects more than one individual in a family. However, individuals who are members of families that have an inheritable mutation in the BAP1 gene have been shown to be at increased risk for familial uveal melanoma as well as familial skin melanoma, renal cell carcinoma, and other malignant neoplasms.<sup>29</sup>

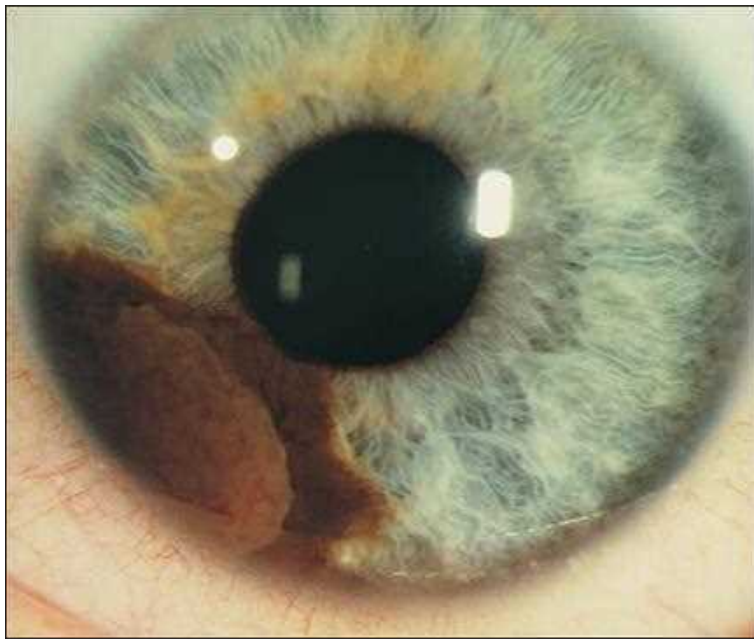
In most primary uveal melanoma cells that have been studied cytogenetically, mutations or deletions of several different chromosomes (principally chromosome 3, 8, 6, and 1) and of genes *GNAQ* and *GNA11* have been identified.<sup>30,31</sup> The mutations in *GNAQ* and *GNA11* appear to be necessary preliminary steps in the process that leads to development of uveal melanoma, but these gene mutations do not appear to have any prognostic significance with regard to emergence of metastasis.<sup>32</sup> In contrast, partial or complete deletion of one chromosome 3 (monosomy 3) has been shown to be of major prognostic significance. Patients having a primary uveal melanoma composed of tumor cells with monosomy 3 have a much higher probability of developing distant metastasis than those having disomy 3 of the tumor cells.

Although these prognostic markers do not aid in diagnostic or therapeutic management, many clinicians use this information to guide screening protocols aimed at the liver for the detection of metastatic disease, as discussed further in this chapter.

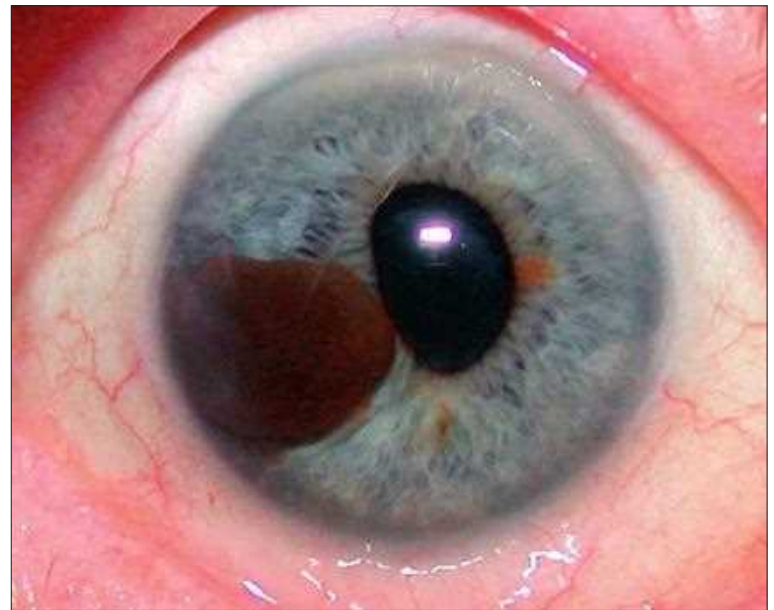
Primary uveal melanomas are divided conventionally into anterior and posterior subgroups. Anterior uveal melanomas are tumors that involve the iris, ciliary body, or both. Posterior uveal melanomas are those that involve the choroid alone or the choroid and ciliary body together. Occasional primary uveal melanomas involve all three portions of the uvea (i.e., choroid, ciliary body, and iris) simultaneously. Tumors of this type are usually grouped with the posterior uveal melanomas. This subdivision is a practical one that reflects relevant differences in clinical presentation, management, and outcomes.

## Primary Anterior Uveal Melanoma

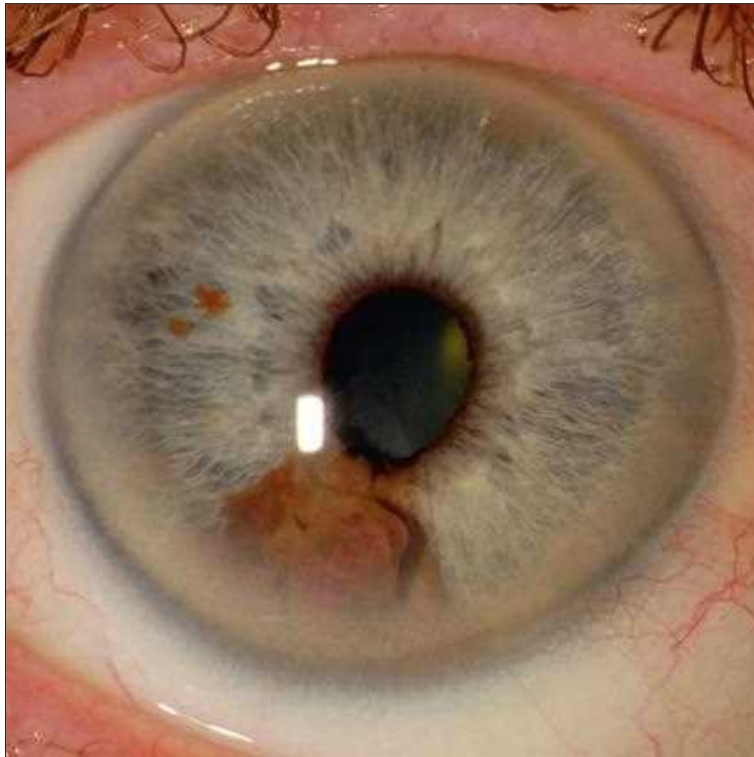
Primary anterior uveal melanomas that involve the iris are frequently noted by the patient or family member as a newly apparent spot on the iris of one eye.<sup>33</sup> Because they are visible to the patient, such tumors tend to be detected at a substantially younger age and at substantially smaller size on average than those involving the ciliary body or choroid. Tumors that involve the ciliary body frequently interfere with the zonule or indent and displace the crystalline lens and thereby cause blurring of vision in the affected eye. Some patients with an anterior uveal melanoma will report



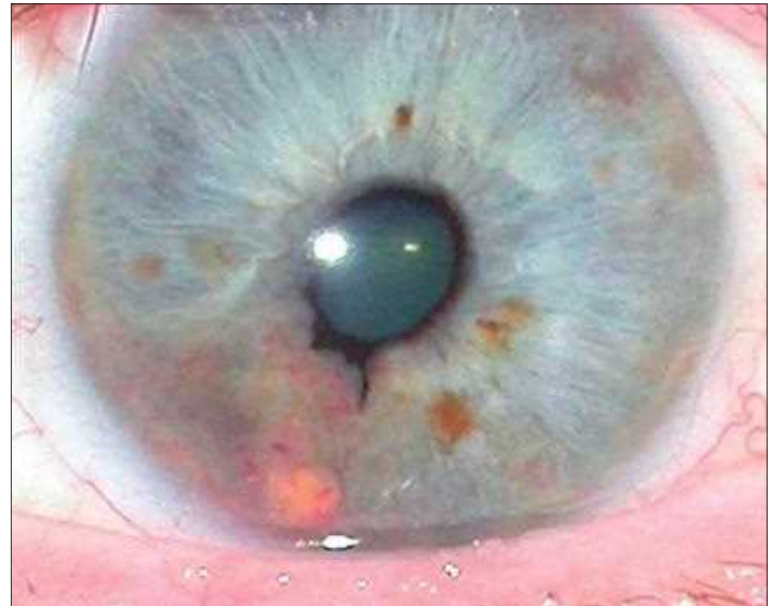
**Fig. 8.1.15** Darkly Melanotic Primary Uveal Melanoma of Iris and Angle.



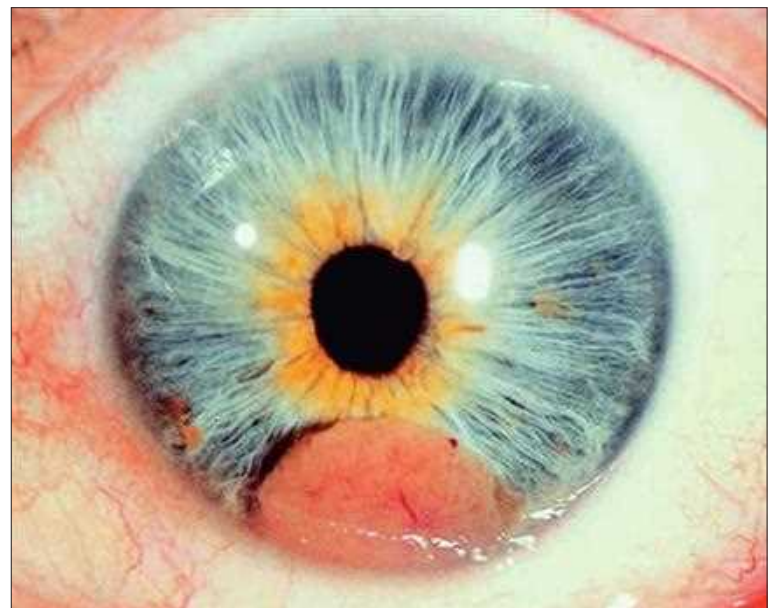
**Fig. 8.1.17** Nodular Darkly Melanotic Iris Melanoma Preventing Pupillary Dilation Due to Iris Replacement.



**Fig. 8.1.16** Pale Vascularized Uveal Melanoma of Iris Causing Mild Pupillary Peaking and Limited Ectropion Iridis.



**Fig. 8.1.18** Iris Melanoma Causing Pupillary Peaking and Ectropion Iridis.

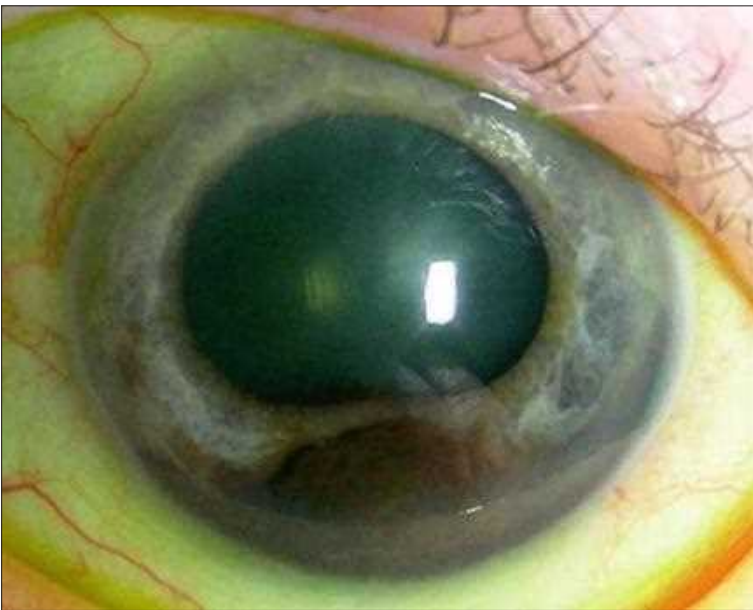


**Fig. 8.1.19** Nodular Pale Iris Melanoma Having Prominent Intralesional Blood Vessels.

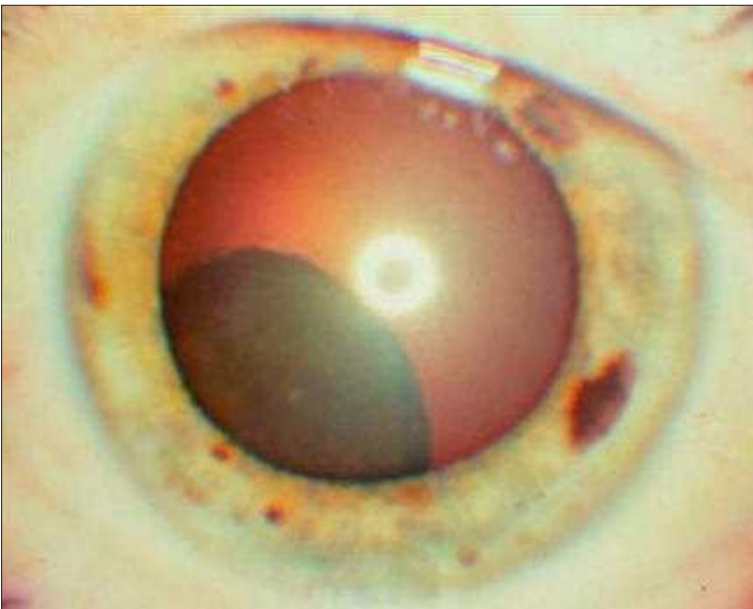
eye pain due to shedding of melanoma cells from the tumor that clogs the trabecular meshwork, thereby causing an abrupt rise in intraocular pressure.

Iris melanoma appears as a melanotic iris tumor in most cases (Fig. 8.1.15). The tumor is usually focally nodular but can be diffuse. Most iris melanomas that have ever spawned metastasis have been larger than 5 mm in diameter and larger than 1.5 mm in thickness<sup>34</sup> (determinable by ultrasound biomicroscopy). There is considerable size overlap between larger iris nevi and smaller iris melanomas, however, and differentiation between the two is frequently impossible clinically. The tumor replaces the normal iris stroma and frequently causes the pupil to be peaked toward the lesion (most evident prior to pupillary dilation) (Fig. 8.1.16), splinted (prevented from dilating in the sector of involvement) after mydriatic drops have been administered (Fig. 8.1.17), or both. Ectropion iridis is also commonly associated with such tumors (Fig. 8.1.18). Prominent blood vessels are commonly evident within the tumor, especially if it is hypomelanotic or amelanotic (Fig. 8.1.19), and spontaneous hyphema from such blood vessels is an occasional presenting feature of such lesions. While some





**Fig. 8.1.20** Ill-Defined Darkly Melanotic Iris Melanoma Showing Discohesive Shedding of Tumor Cells That Have Become Matted in the Peripheral Iris and Angle.



**Fig. 8.1.21** Ciliary Body Melanoma Visible as Dark Retrolenticular Tumor Against Red Reflex After Pupillary Dilation.

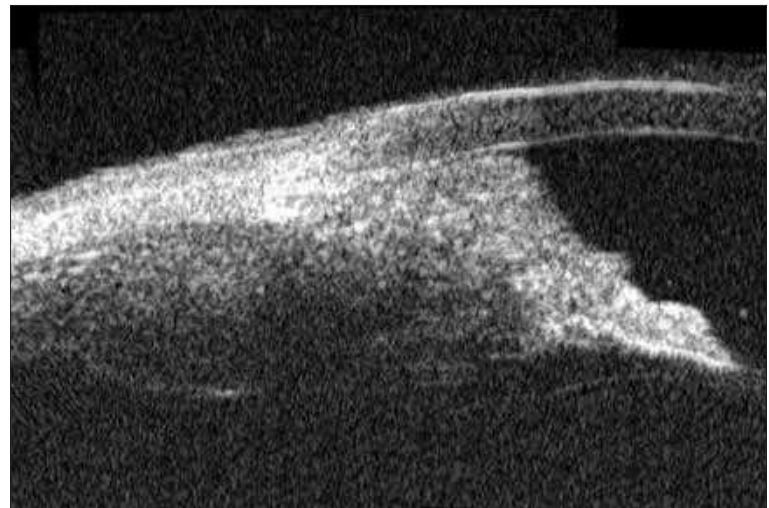
iris melanomas remain cohesive, many become discohesive and shed tumor cells into the aqueous humor. These tumor cells can form satellite lesions by implantation on the adjacent iris stroma, become matted on the trabecular meshwork (causing elevated intraocular pressure), or both (Fig. 8.1.20).

An anterior uveal melanoma confined to the ciliary body (ciliary body melanoma) is not generally evident on slit-lamp biomicroscopy of the anterior ocular segment prior to pupillary dilation but commonly shows up as a solid dark retrolenticular mass visible in the “red reflex” of the fundus following pupillary dilation (Fig. 8.1.21). Because of its hidden location behind the iris, the typical ciliary body melanoma is at least 3 mm thick when first detected. The tumor is frequently apposed to the crystalline lens in its equatorial region, and the lens is often clouded focally adjacent to that apposition. Prominent epibulbar blood vessels are frequently evident in the sclera overlying the ciliary body tumor. Transillumination of the eye usually shows a well-defined shadow corresponding to the ciliary body tumor (Fig. 8.1.22). Ultrasound biomicroscopy confirms the solid soft tissue nature of the tumor (Fig. 8.1.23).

An anterior uveal melanoma involving both the iris and ciliary body (iridociliary melanoma) will be evident in its anterior aspect on slit-lamp biomicroscopy and gonioscopy. A characteristic feature of such tumors is



**Fig. 8.1.22** Ocular Transillumination Image Showing Dark Shadow of an Underlying Ciliary Body Melanoma.



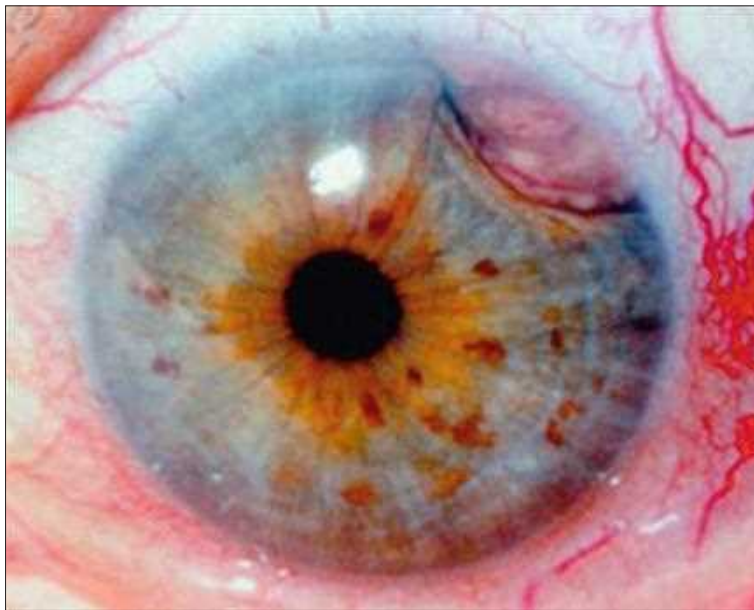
**Fig. 8.1.23** Ultrasound Biomicroscopic Image of Anterior Ocular Segment Showing Nodular Iridociliary Melanoma.

the presence of a furrow in the iris around the anterior aspect of the tumor (Fig. 8.1.24). Iridociliary melanomas occasionally extend circumferentially around several clock hours of the anterior ocular segment to form what has been termed “ring melanoma.” A ciliary body or iridociliary melanoma will occasionally extend transsclerally through vascular or neural foramina in the anterior sclera to form one or more acquired dark episcleral patches or nodules of extrascleral tumor extension (Fig. 8.1.25).

If the clinical diagnosis is not in doubt, treatment may be undertaken without a confirmatory biopsy of the tumor, but for borderline lesions classified clinically as large anterior uveal nevus versus small iris melanoma or alternative tumor type, biopsy of the tumor by methods such as fine-needle aspiration, suction cutting of a portion of the tumor using a vitrector, or conventional incisional techniques may be used to confirm the diagnosis pathologically prior to initiating treatment.<sup>35</sup>

Management options for anterior uveal melanomas include surgical excision<sup>36</sup> (iridectomy, iridocyclectomy, or cyclectomy—usually reserved for cohesive-appearing tumors), plaque radiotherapy,<sup>37</sup> and enucleation<sup>33</sup> (usually reserved for eyes that are blind and painful, have extensive seeding of the trabecular meshwork with secondary glaucoma, or contain a tumor that involves more than one quadrant of anterior segment).





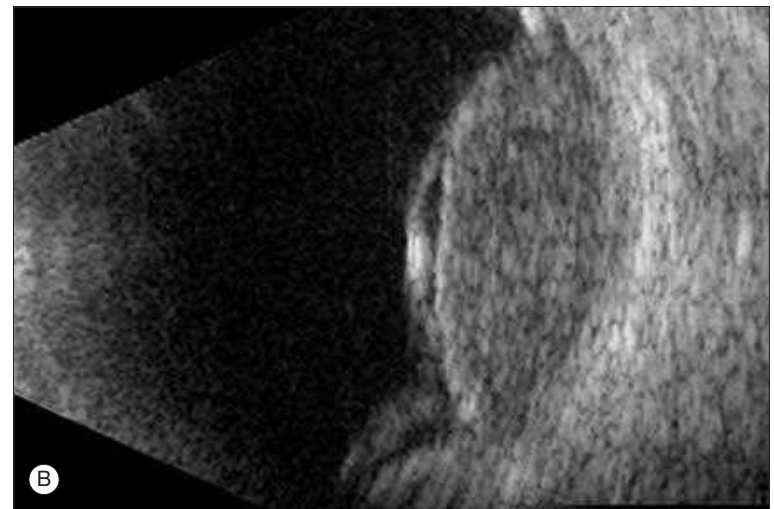
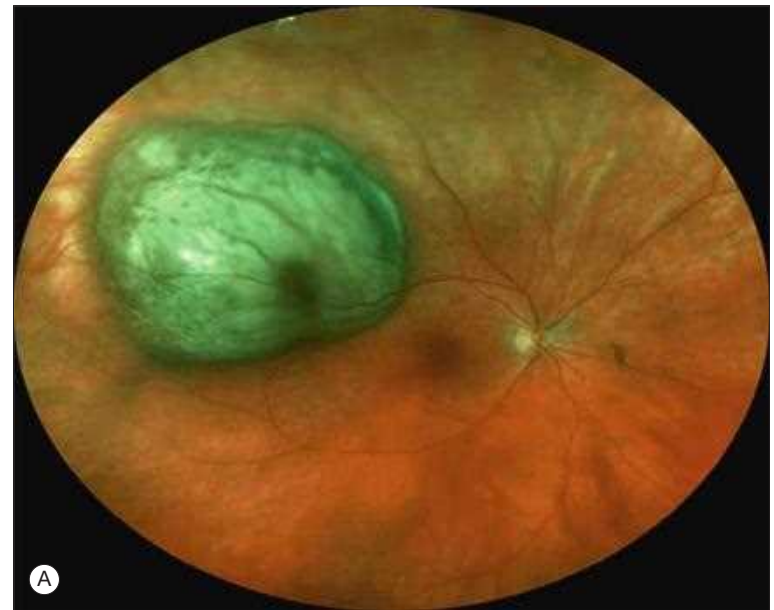
**Fig. 8.1.24** Iridociliary Melanoma Showing Retraction Furrow in Iris Along Its Anterior Margin.



**Fig. 8.1.25** Limited Anterior Transscleral Extension of Iridociliary Melanoma.

### Primary Posterior Uveal Melanoma

Posterior uveal melanomas that involve the choroid (choroidal melanomas) generally appear as dark brown to golden brown choroidal tumors. Several discrete clinical growth patterns are recognized. The most common growth pattern is the oval dome-shaped tumor (Fig. 8.1.26). The tumor generally has a base that is larger than 5 mm in largest diameter and a maximal thickness larger than 2.5 mm. Many tumors that are substantially larger exhibit this same growth pattern. In general, the thickness of such tumors tends to be approximately half the basal diameter of the tumor. The most characteristic growth pattern (albeit not the most frequent) is the *mushroom-shaped tumor* (Fig. 8.1.27). This three-dimensional shape is due to tumor eruption through Bruch's membrane to form an extruded sub-retinal nodule projecting from the dome-shaped tumor base. The eruption is frequently eccentric from the tumor base and is occasionally multifocal. The apical eruption may be relatively small compared with the tumor base, approximately the same size as the tumor base, or substantially larger than the tumor base when the tumor is detected (Fig. 8.1.28). In this latter case, B-scan ultrasonography may be performed to confirm the cross-sectional shape of the tumor. Some choroidal melanomas exhibit an irregular geographic base and one or more accentuated tumor nodules (*irregular growth pattern*) (Fig. 8.1.29), and others exhibit a broad base associated with a maximal thickness that is smaller than or equal to 20% of its largest basal diameter (*diffuse growth pattern*; Fig. 8.1.30).

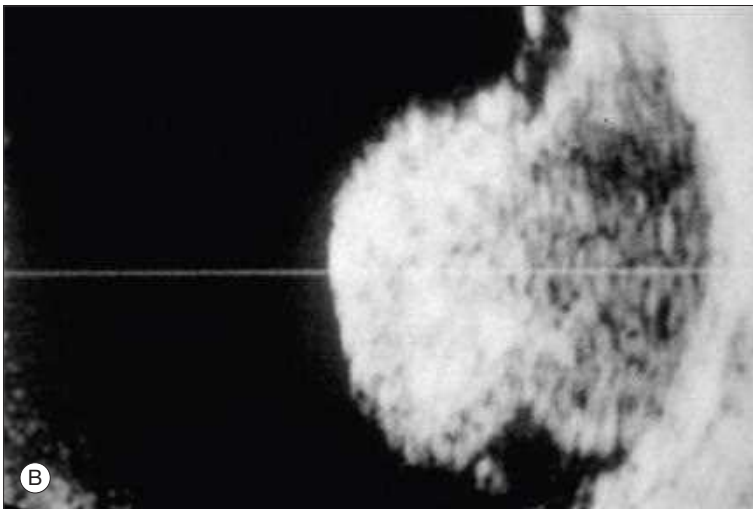
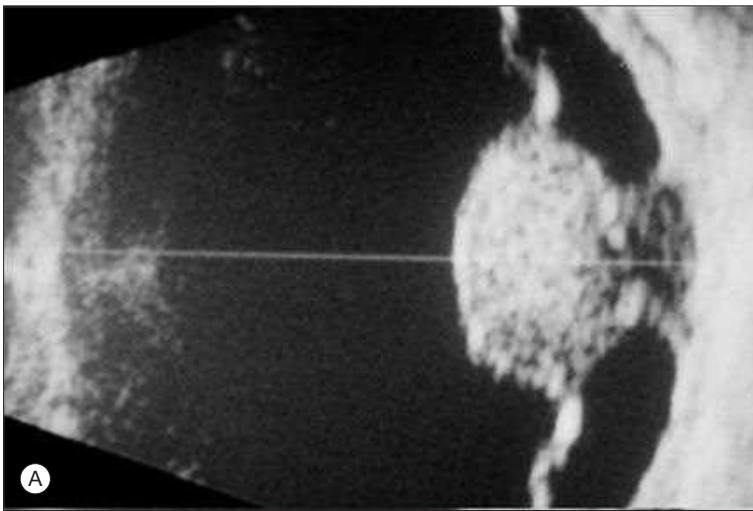


**Fig. 8.1.26** Choroidal Melanoma Exhibiting Typical Smoothly Nodular Dome Shape. (A) Clinical appearance of tumor. (B) Corresponding B-scan ultrasonographic image showing bluntly biconvex cross-sectional shape and relatively low internal sonoreflectivity of tumor.

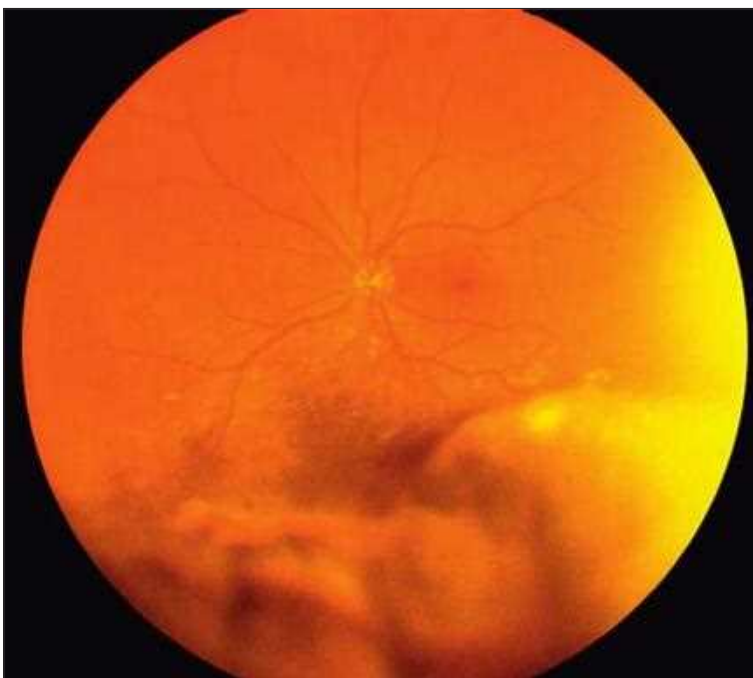


**Fig. 8.1.27** Choroidal Melanoma Exhibiting Eccentric Darkly Melanotic Eruption Through Bruch's Membrane.

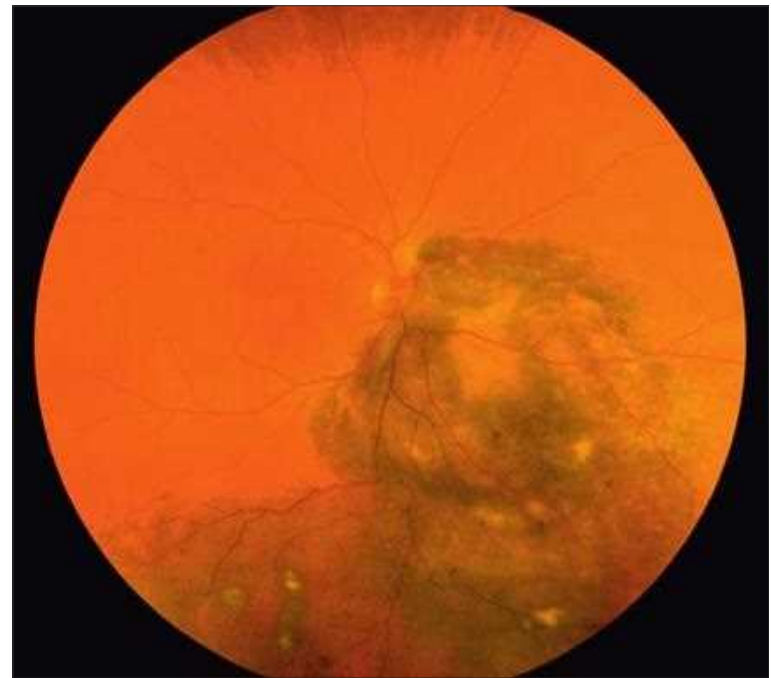
Most choroidal melanomas that are left untreated for any reason (including uncertainty about the clinical diagnosis) exhibit progressive enlargement that is usually evident within 1–3 months. Smaller growing choroidal melanomas frequently exhibit prominent clumps of orange pigment (lipofuscin) on their surface (Fig. 8.1.31) as an indicator of active enlargement,<sup>38,39</sup> and most choroidal melanomas develop a serous retinal



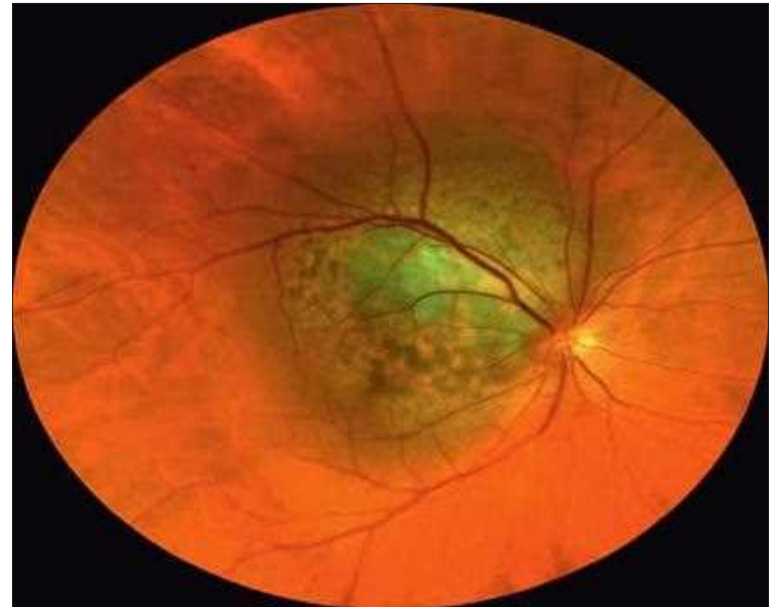
**Fig. 8.1.28 B-Scan Ultrasonographic Images of Choroidal Melanoma That Have Erupted Through Bruch's Membrane.** (A) Tumor with small base and relatively large apical cap. (B) Tumor with a biconvex cross-sectional base and relatively large apical cap. Note that the base of each tumor is relatively hyporeflective while the apical cap is more brightly sonoreflective.



**Fig. 8.1.29 Choroidal Melanoma Exhibiting Thin Geographic Darkly Melanotic Base With Multiple Superimposed Foci of Nodular Accentuation.**



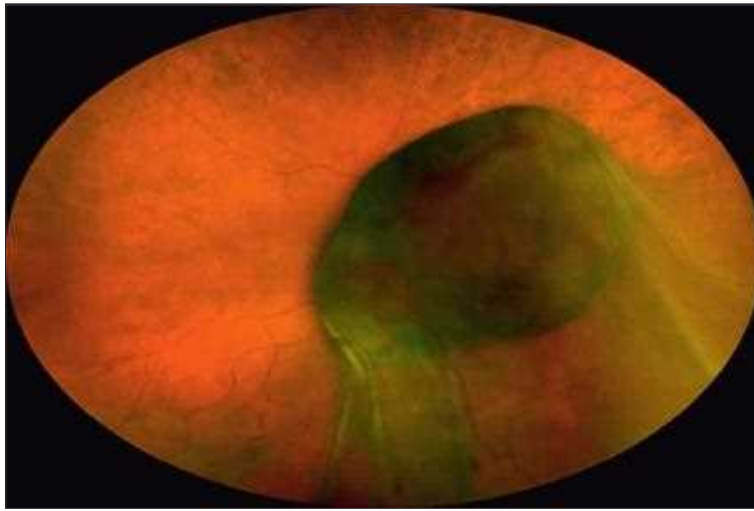
**Fig. 8.1.30 Choroidal Melanoma Exhibiting Diffuse Growth Pattern.** The maximal thickness of this broad-based choroidal tumor was only 2 mm.



**Fig. 8.1.31 Small Darkly Melanotic Macular-Juxtapapillary Choroidal Melanoma Exhibiting Prominent Slumps of Orange Pigment (Lipofuscin) on Its Surface.**

detachment over and around the tumor (Fig. 8.1.32) that increases in extent as the tumor enlarges.<sup>39</sup> This nonrhegmatogenous retinal detachment can become total and bullous in association with larger choroidal tumors. For reasons that are not obvious, some nodular choroidal melanomas enter a phase during which the tumor exhibits prominent clinical features of chronicity (numerous prominent drusen, disruption of the overlying retinal pigment epithelium [RPE] with clumping and intraretinal invasion by RPE epithelial pigment, fibrous metaplasia of the RPE overlying the tumor, absence or a minimal amount of orange pigment on the surface of the tumor, and absence or a limited amount of overlying and surrounding serous subretinal fluid)<sup>40</sup> (Fig. 8.1.33) and remain dormant for months to years or enlarge to a limited extent during such an interval.<sup>40</sup> Clinical follow-up studies of such tumors have shown them to be associated with a much lower risk of metastasis and metastatic death than are actively enlarging choroidal melanomas of similar size.<sup>40</sup> Choroidal melanomas that arise adjacent to the optic disc or extend to or around the optic disc frequently show signs of optic disc invasion or compression (Fig. 8.1.34), and those that erupt through Bruch's membrane frequently show apical retinal invasion (Fig. 8.1.35) that may be focal or extensive. Hypomelanotic choroidal melanomas frequently exhibit prominent intralesional

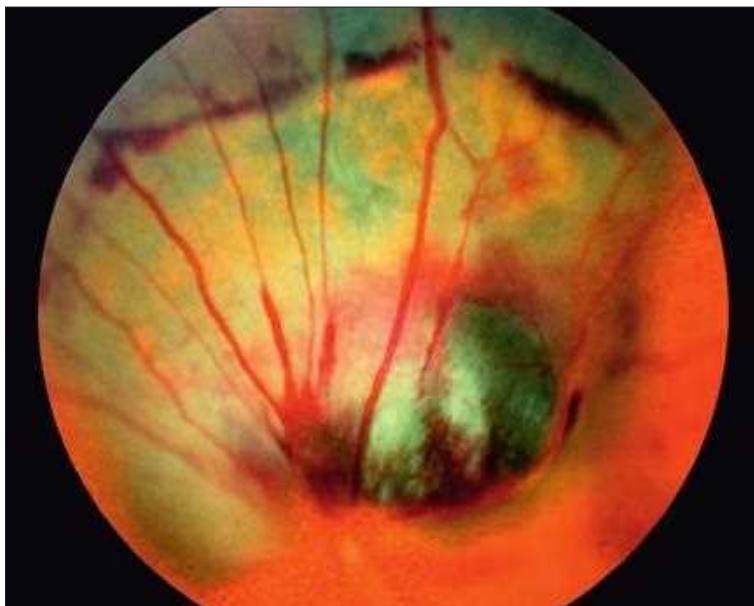




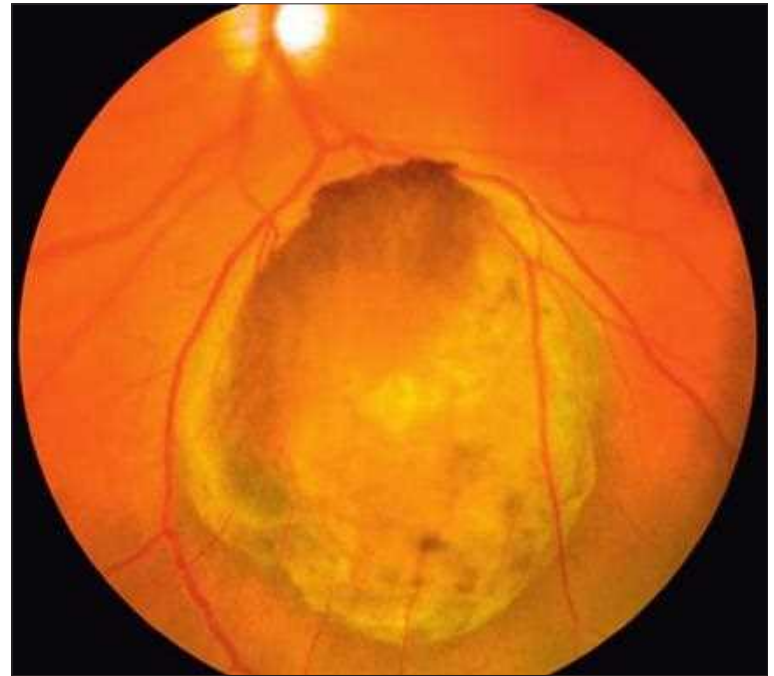
**Fig. 8.1.32** Nodular Mushroom-Shaped Choroidal Melanoma Associated With Partial Serous Retinal Detachment.



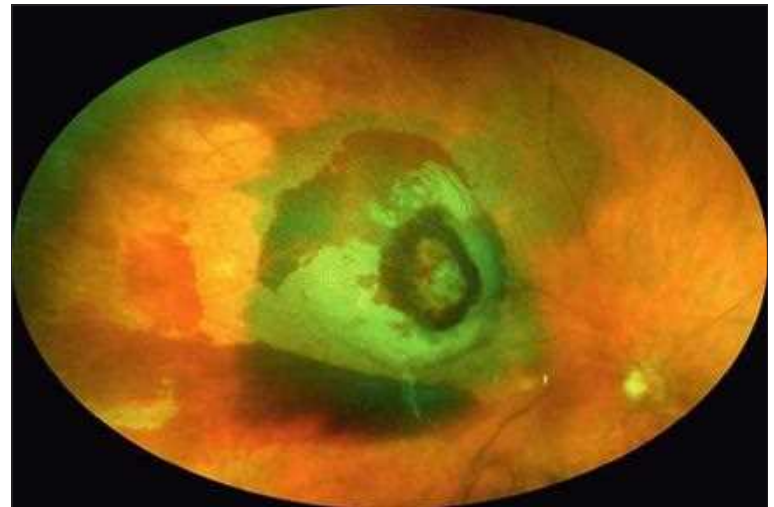
**Fig. 8.1.33** Dormant Choroidal Melanoma. Note prominent disruption of overlying retinal pigment epithelium with clumping and intraretinal invasion by black retinal pigment epithelial pigment.



**Fig. 8.1.34** Juxtapapillary Choroidal Melanoma Invading Optic Disc.



**Fig. 8.1.35** Choroidal Melanoma With Prominent Apical Retinal Invasion by Brown Tumor Cells.



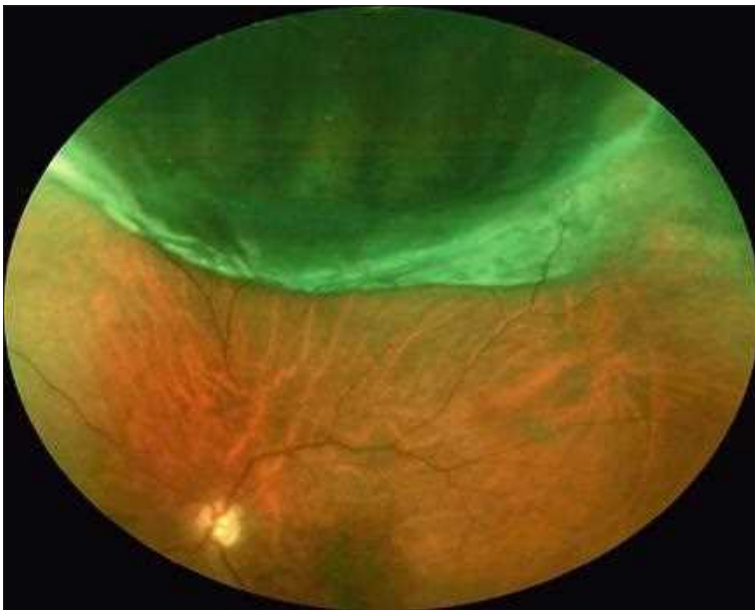
**Fig. 8.1.36** Choroidal Melanoma That Has Erupted Through Bruch's Membrane Exhibiting Intraretinal, Subretinal, and Intravitreal Bleeding.

choroidal blood vessels that can be demonstrated well by fluorescein angiography or indocyanine green angiography. Spontaneous subretinal and intravitreal bleeding is frequently associated with tumors that have erupted through Bruch's membrane (Fig. 8.1.36) or invaded the optic disc and retina but is extremely uncommon in choroidal melanomas exhibiting the dome-shaped, diffuse, or irregular growth pattern.

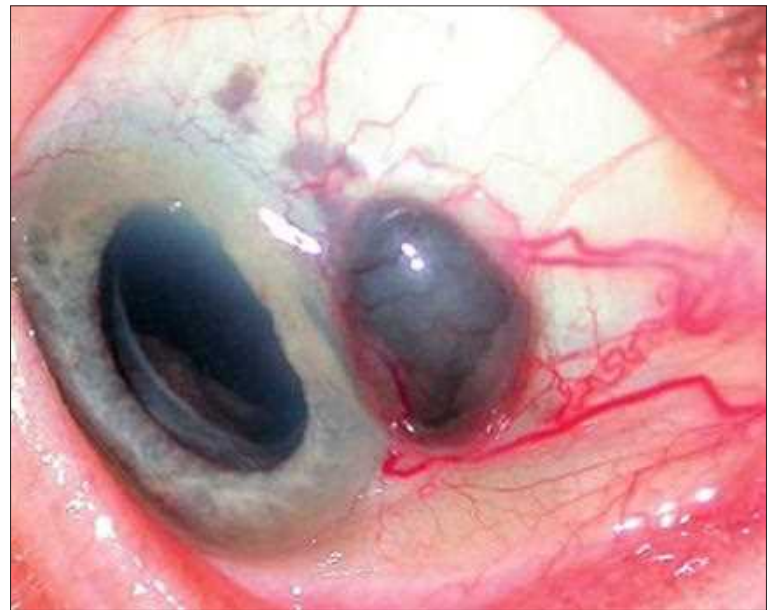
Small choroidal melanomas (generally regarded as tumors  $\leq 10$  mm in diameter and  $\leq 5$  mm in maximal thickness) may be asymptomatic if they are extramacular but are usually associated with blur and flashes if located in the macula. Larger choroidal melanomas are usually associated with blur, flashes, and a recognized visual field defect corresponding to the location of the tumor and the extent of associated retinal detachment. Vitreous hemorrhage from a choroidal melanoma generally causes the symptom of dark floaters.

Posterior uveal melanomas that involve both the choroid and ciliary body (ciliochoroidal melanomas) tend to be much larger when they are first detected than those confined to the choroid. Symptomatic ciliochoroidal melanomas are frequently larger than 15 mm in largest basal diameter and larger than 8 mm in maximal thickness when first identified, whereas asymptomatic peripheral ciliochoroidal melanomas detected on routine fundus examination tend to be substantially smaller. The ora serrata is pushed centrally over the crest of the posterior uveal tumor and is therefore evident without scleral depression on indirect ophthalmoscopy (Fig. 8.1.37). Prominent dilated epibulbar blood vessels (sentinel blood vessels)





**Fig. 8.1.37** Ciliochoroidal Melanoma Displacing the Ora Serrata Centrally on Its Crest.



**Fig. 8.1.39** Nodular Darkly Melanotic Extraocular Extension of a Primary Iridociliary Melanoma.



**Fig. 8.1.38** Prominent Epibulbar "Sentinel" Blood Vessels Overlying the Anterior Portion of a Ciliochoroidal Melanoma.



**Fig. 8.1.40** Ocular Transillumination Image Showing Shadow Cast by Ciliochoroidal Melanoma.

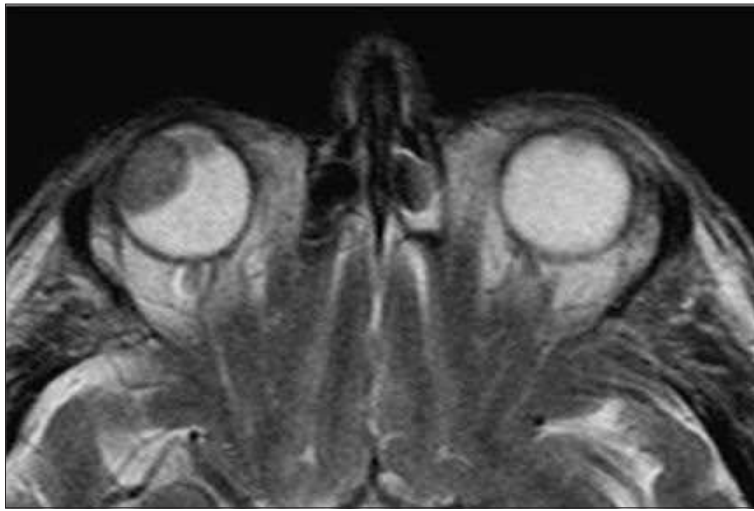
are frequently evident over the ciliary body portion of the tumor (Fig. 8.1.38), and transscleral tumor extension develops over the anterior portion of the tumor in some cases (Fig. 8.1.39). Clinical ocular transillumination shows a dark shadow corresponding to the ciliary body extent of the tumor (Fig. 8.1.40).

Most relevant diagnostic information about the intraocular tumor (size, color, intraocular location, growth activity of the tumor, and absence versus presence and extent of invasive features) is determinable by indirect ophthalmoscopy and fundus biomicroscopy.<sup>39</sup> Documentary fundus photography is helpful for patient education about the posterior uveal melanoma and may reveal some features of the intraocular tumor not recognized during fundus examination. However, B-scan ocular ultrasonography is generally regarded as the most important ancillary diagnostic study in patients with a solid intraocular tumor of the posterior ocular segment. This imaging method confirms the soft tissue nature of the tumor, reveals its cross-sectional shape, and provides estimates of the dimensions of the tumor that supplement the ophthalmoscopic and ocular transillumination findings. It also identifies posterior scleral invasion and transscleral tumor extension (Fig. 8.1.41) when they are present and permits assessment of spontaneous vascular pulsations within the tumor during dynamic imaging.

When a melanotic choroidal or ciliochoroidal tumor is larger than 10 mm in diameter and larger than 5 mm in thickness and exhibits



**Fig. 8.1.41** B-Scan Ultrasound Image of Ciliochoroidal Melanoma Showing Nodular Posterior Extraocular Extension of Tumor.



**Fig. 8.1.42 T2-Weighted Magnetic Resonance Image of Ciliochoroidal Melanoma Showing Hypointensity of Intraocular Tumor Compared With the Bright (Hyperintense) Vitreous.**

characteristic clinical features or when a smaller melanotic choroidal or ciliochoroidal tumor exhibits prominent invasive clinical features, there is usually little if any doubt about the clinical diagnosis (unless the optical media are cloudy or opaque) and virtually no need for a confirmatory biopsy of the tumor to establish a pathological diagnosis prior to treatment. However, for tumors smaller than 5 mm in diameter and smaller than 2.5 mm in thickness, there can be considerable uncertainty about the clinical diagnosis. This doubt stems in large part from the substantial size overlap that exists between larger benign choroidal nevi and small choroidal melanomas and the substantially higher frequency of choroidal nevus than of choroidal melanoma in the general population.<sup>41</sup> In such cases, the physician managing the patient needs to inform the patient about the recognized potential benefits versus potential risks and limitations of (1) assuming the tumor to be a malignant melanoma and treating it without pathological confirmation of the diagnosis, (2) assuming the tumor to be a large benign choroidal nevus and leaving it untreated but arranging for regular periodic follow-up to monitor for active tumor enlargement, and (3) performing a diagnostic fine-needle aspiration biopsy of the choroidal tumor to establish a cytopathological diagnosis that can then be used to direct subsequent tumor management and arrange for intervention in accordance with the patient's informed decision.

In some patients with a suspected primary posterior uveal melanoma, vitreous hemorrhage, a mature cataract, or a hemorrhagic retinal detachment may preclude a satisfactory clinical view of the fundus mass. In such cases, a supplemental imaging study of the affected eye (e.g., high-resolution MRI without and with contrast) may be able to identify the tumor and characterize it as consistent or inconsistent with uveal melanoma (Fig. 8.1.42). However, in patients with clear optical media and satisfactory ophthalmoscopic evaluation of the fundus and complete ultrasonographic evaluation of the eye, such a supplemental study adds minimally to diagnostic accuracy.

Patients with primary posterior uveal melanoma are advised routinely to undergo a baseline systemic "staging" evaluation intended to identify or rule out metastatic tumors in the sites where such tumors are most likely to occur (liver, lungs, bones of the chest and abdomen, and skin).<sup>42</sup> The currently recommended evaluation consists of a general physical examination (principally to detect cutaneous metastases, jaundice, and hepatomegaly, if present), blood testing for liver enzyme levels (likely to be elevated if the liver is involved extensively), and CT scans of the chest and abdomen with contrast. In many European centers, ultrasounds of the liver are performed instead of CT scanning. In some centers, MRI of the chest and abdomen and even positron emission tomography (PET)/CT scanning are used as alternatives to CT scanning. Unless the patient has recent-onset neurological or psychiatric symptoms, baseline imaging of the brain is not recommended.

Provided that baseline systemic staging shows no worrisome lesions suggestive of metastasis, treatment is directed toward elimination or destruction of the primary intraocular tumor. The principal treatment options for posterior uveal melanoma at present<sup>26</sup> are enucleation (indicated for blind, severely painful eyes secondary to the intraocular tumor), eyes containing an extremely large intraocular tumor (generally regarded to be a tumor >16 mm in diameter, >10 mm in thickness or both), and

eyes with a circumpapillary choroidal tumor or optic disc invasion) and focal radiation therapy (the most commonly employed methods being I-125 plaque radiotherapy<sup>43</sup> and gamma knife and proton beam irradiation<sup>44</sup>) for posterior uveal melanomas smaller in size than those prompting enucleation and not invading the optic disc. These focal radiation therapy methods have been shown to yield virtually the same rate of cure as enucleation when applied to comparable, appropriately selected cases (principally posterior uveal melanomas ≤16 mm in diameter and ≤10 mm thick not involving the macula or optic disc and not associated with extrascleral tumor extension).<sup>45-47</sup> While these radiation therapy methods usually destroy the intraocular tumor and preserve the treated eye, vision in that eye is frequently impaired and may be lost completely (usually after a period of months to years) because of radiation-induced side effects on the optic disc and retina, secondary (usually neovascular) glaucoma, or both. Alternative management options employed in certain centers include transscleral en bloc tumor resection<sup>48</sup> (principally reserved for relatively young and healthy patients without retinal invasion, optic disc invasion, or macular involvement) and vitrector endoresection of the intraocular tumor<sup>49</sup> (usually performed following focal tumor irradiation to minimize the risk of intraocular dissemination or extraocular implantation of viable tumor cells during the procedure<sup>48,50</sup>). Long-duration exposure, relatively low power, large spot size transpupillary infrared laser therapy (frequently referred to as transpupillary thermotherapy, TTT) has been employed extensively in several centers to treat selected small melanocytic choroidal tumors in the large nevus versus small melanoma category over the past three decades,<sup>51</sup> but long-term studies have shown such treatment as single modality therapy to be associated with an extremely high probability of local tumor relapse and occasional instances of transscleral tumor extension to the orbit.<sup>52</sup> Because of this, TTT is not generally recommended today except as a supplement to focal radiation therapy.<sup>53</sup>

In most centers today, prognostic testing of tumor cells is performed in conjunction with treatment of the intraocular tumor in virtually all patients (unless the patient had a biopsy of the tumor prior to treatment for diagnostic or confirmatory reasons and underwent prognostic testing of the tumor cells at that time).<sup>54</sup> In patients undergoing focal radiation therapy, direct transscleral or indirect transvitreal fine-needle aspiration biopsy of the choroidal or ciliochoroidal tumor for gene expression profiling or chromosomal analysis is performed immediately prior to tumor irradiation.<sup>55</sup> In patients managed by enucleation or tumor resection, fresh tumor cells are harvested immediately after globe or tumor removal for prognostic gene expression profile testing (DecisionDx-UM test<sup>56,57</sup>) and classification (GEP class 1 [favorable], GEP class 2 [unfavorable]) or chromosomal mutation studies (e.g., multiplex ligation-dependent probe amplification,<sup>30</sup> [MLPA] or microsatellite analysis<sup>38</sup> [loss of heterogeneity testing]) and classification (disomy 3 [favorable], monosomy 3 [unfavorable]). Current evidence shows such prognostic testing to be superior to any individual clinical or histopathological factor or combination of such factors for dividing patients into relatively high risk versus relatively low risk for future emergence of distant metastasis.

Regardless of how the primary intraocular tumor was treated, the patient with a posterior uveal melanoma must be considered at risk for future emergence of metastatic tumors. Prognostic testing of the tumor cells as outlined in the preceding paragraph helps the clinician subdivide patients into those having higher versus lower risk of metastasis, and this information is currently being used in many centers to influence how frequently and how intensively (i.e., which components of a surveillance regimen are employed) a given patient is re-evaluated systemically following ocular tumor treatment.<sup>57</sup> At present, there is no adjuvant therapy that has been proven in randomized clinical trials to prevent or delay emergence of metastatic tumors compared with no treatment at all.<sup>59</sup> If a patient with primary uveal melanoma is identified as having metastatic melanoma during follow-up (either by periodic surveillance testing or by symptom-prompted testing), that patient's prognosis for long-term survival is currently poor. Although there is great current interest in targeted therapy for individual patients based on that patient's particular constellation of genetic abnormalities within the tumor cells,<sup>60,61</sup> no method of chemotherapy, immunotherapy, or molecular pathway modifier therapy has been shown to date to improve survival of patients with metastatic uveal melanoma significantly compared with no treatment at all.<sup>62</sup>

## Primary Intraocular Lymphoma

Primary intraocular lymphoma is an unusual form of malignant non-Hodgkin's lymphoma that appears to arise independently in one or both eyes of occasional individuals. Because lymphoid cells are not



present normally in the eye (except within the intravascular blood), the source of these malignant lymphoid cells is unknown.<sup>63,64</sup> Two principal clinical types of primary intraocular lymphoma are currently recognized. *Primary vitreoretinal lymphoma* is characterized by malignant lymphoid cell infiltrates, usually of B-cell lineage, involving the vitreous, retina, and subretinal pigment epithelial space of one or both eyes with limited if any involvement of the uvea.<sup>65,66</sup> This form of primary intraocular lymphoma is associated with antecedent, concurrent, or subsequent primary CNS lymphoma in approximately 80% of cases. *Primary uveal lymphoma* is characterized by focal or diffuse uveal infiltration by malignant lymphoid cells with limited involvement of the retina and vitreous in most cases.<sup>67,68</sup> This form of primary intraocular lymphoma is almost always unilateral. Approximately 30% of patients with this form of primary intraocular lymphoma ultimately develop systemic non-Hodgkin's lymphoma.

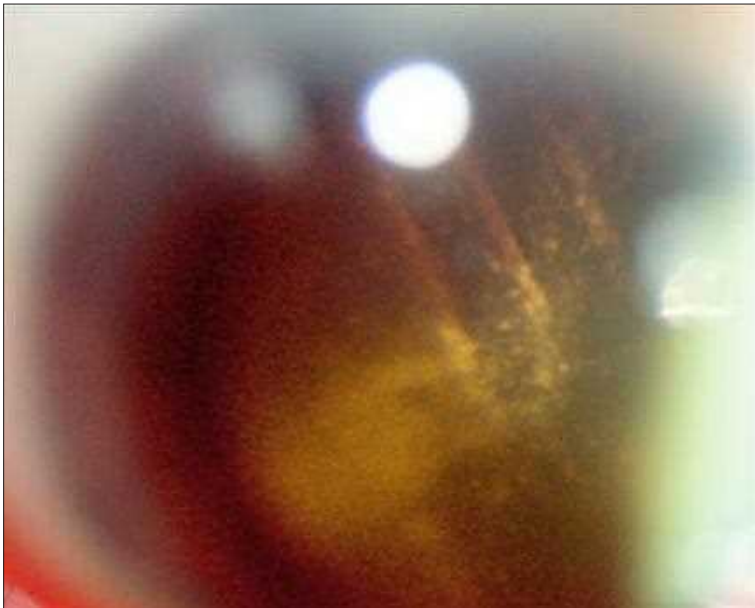
### Primary Vitreoretinal Lymphoma

The typical clinical features of primary vitreoretinal lymphoma are prominent cellular infiltrates of the vitreous (Fig. 8.1.43), geographic off-white to pale yellow accumulations of lymphoid cells under the RPE (Fig. 8.1.44), and patchy ill-defined retinal infiltrates (Fig. 8.1.45). The typical affected patient is over 60 years of age with a slight female predominance. The abnormal intraocular features are usually bilateral, although not necessarily present simultaneously, and may be substantially asymmetrical. Affected patients frequently report blur and floaters if vitreous cells are

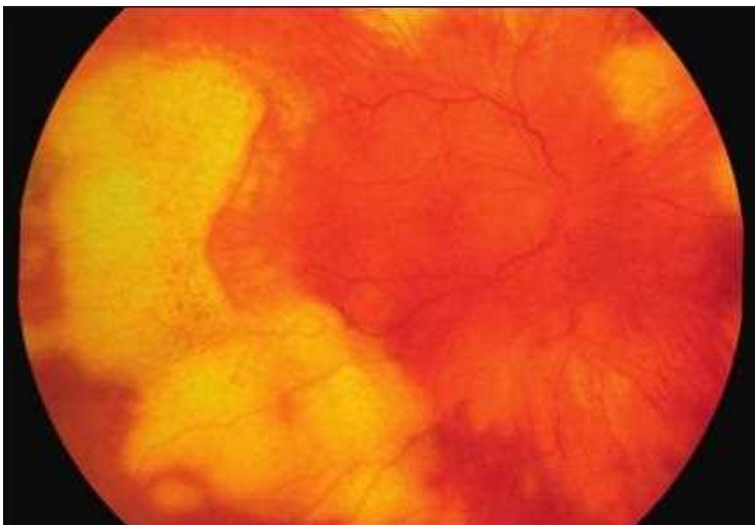
prominent and visual blurring and field loss if retinal and subretinal infiltrates predominate. Some patients have prominent vitreous cells without retinal or subretinal infiltrates, and a few have prominent subretinal tumors or infiltrates with few if any vitreous cells. Patients may report a history of prior CNS lymphoma. Patients without such a history and their spouses or family members should be queried about recent changes in affect, slurred speech, or other neurological or psychological symptoms that might indicate undiagnosed CNS involvement. All patients with clinically suspected vitreoretinal lymphoma should be evaluated by CNS imaging (MRI or CT scanning with contrast) to identify any clinically detectable CNS lesions and lumbar puncture for CNS cytology should be performed prior to any ocular intervention in patients found to have suspicious foci in the brain on CNS imaging or exhibiting new neurological or psychological symptoms even if the CNS imaging is negative. Provided that these studies are negative, posterior vitrectomy with cytopathological and immunocytochemical analysis of the obtained intravitreal cells<sup>69,70</sup> (and lymphoid cell flow cytometry, if possible) should be performed on patients with a prominent cellular infiltration of the vitreous to establish a pathological diagnosis that can be used to direct subsequent patient evaluation and management. Occasionally, the obtained cells will be predominantly monoclonal by immunocytochemical analysis and consistent with malignant lymphoid cells cytopathologically. In such cases, most ophthalmic pathologists are comfortable classifying those cells as consistent with vitreoretinal lymphoma. Frequently, however, most of the intact cells recovered from the vitrectomy fluid appear to be mature lymphocytes rather than clearly malignant lymphoid cells and exhibit some polyclonality on immunostaining. The key to diagnosis in such cases is the presence of numerous necrotic tumor cells in the background. Necrotic cells are not a feature of inflammatory cell infiltrations of the vitreous but are an almost consistent feature in cases of lymphoma. In patients with prominent geographic subretinal pigment epithelial infiltrative tumors but few if any vitreous cells, transvitreal fine-needle aspiration biopsy can be performed to obtain tumor cells and thereby establish a pathological diagnosis.<sup>71</sup>

In cases with an established diagnosis of primary vitreoretinal lymphoma but no evident active CNS lymphoma, a course of intravitreal injections of methotrexate (typical dose per injection 400 mcg/0.1 mL) can be used to eliminate the active intraocular lymphoma.<sup>72</sup> In patients unwilling to undergo such injections or unable to return for the repeated injections in the course of treatment, low-dose fractionated external beam radiation therapy can be performed on the affected eye or eyes to eradicate the intraocular lymphoma.<sup>73</sup> Fortunately, most intraocular lymphomas respond favorably to these methods of treatment.

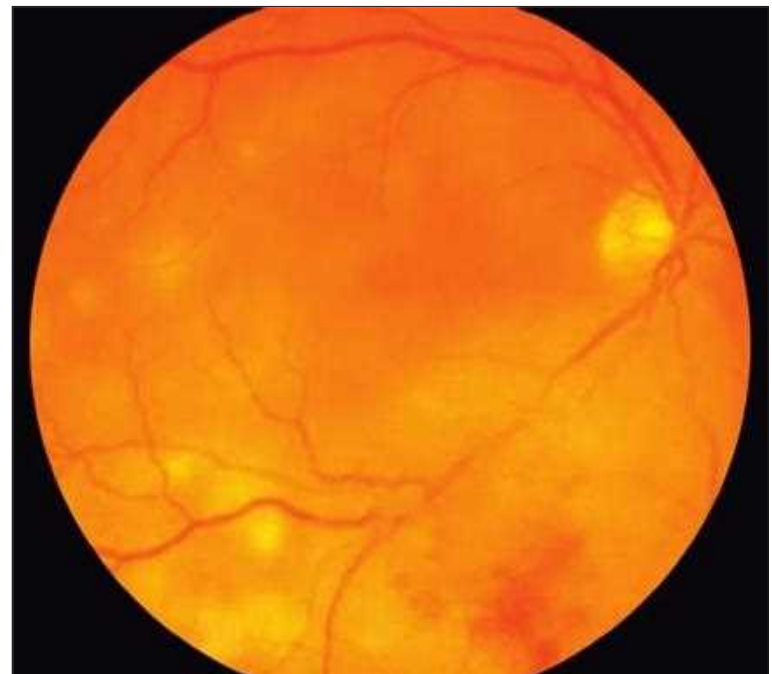
Patients with primary vitreoretinal lymphoma must be monitored for possible development of lymphoma in a previously unaffected eye, local relapse of vitreoretinal lymphoma in a treated eye, or development of new neurological symptoms suggestive of emerging CNS lymphoma.



**Fig. 8.1.43** Slit-Lamp Biomicroscopic Image Showing Prominent Cells in Anterior Vitreous in an Eye With Primary Vitreoretinal Lymphoma.



**Fig. 8.1.44** Widefield Fundus Image of Primary Vitreoretinal Lymphoma Showing Multiple Characteristic Geographic Subretinal Pigment Epithelial Infiltrates.



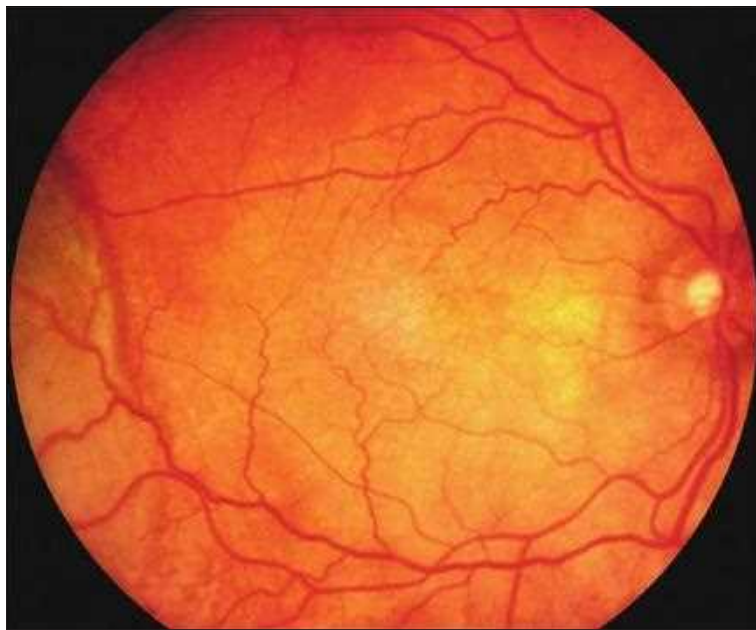
**Fig. 8.1.45** Combined Intraretinal and Subretinal Infiltrates in an Eye With Primary Vitreoretinal Lymphoma.



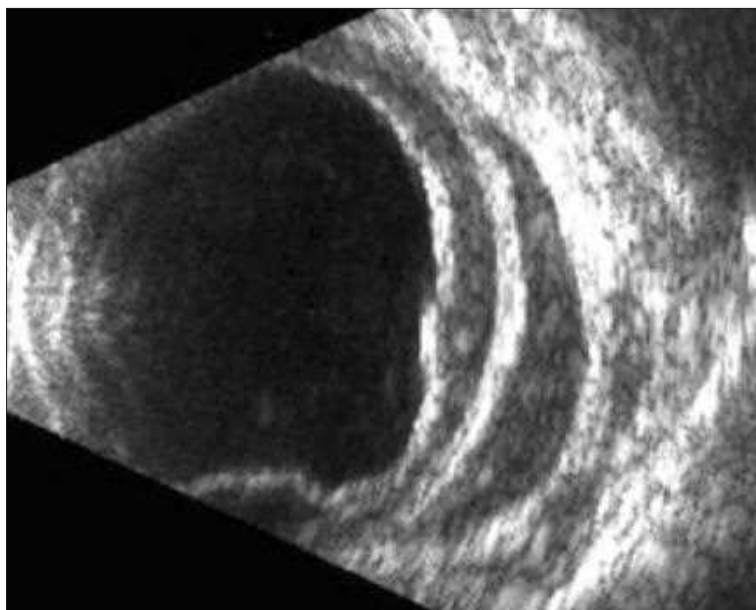
Patients with confirmed primary CNS lymphoma are managed currently in most oncology centers by multidrug intravenous methotrexate-based chemo-immunotherapy and intrathecal methotrexate.<sup>74</sup> Although the median survival time of patients with primary vitreoretinal lymphoma seems to be improved somewhat in recent years using such a regimen for CNS involvement, most affected patients still ultimately die of their lymphoma.

## Primary Uveal Lymphoma

Primary uveal lymphoma is characterized principally by localized or diffuse uveal infiltrates of malignant lymphoma cells, also usually of B-cell lineage. When the choroid is involved diffusely, it exhibits a diffuse creamy thickening with areas of focal accentuation (Fig. 8.1.46). A few cells are frequently present in the vitreous, and aqueous lymphoid cells and cellular deposits on the endothelium of the cornea are also present in some cases. B-scan ultrasonography of eyes with diffuse posterior uveal involvement shows diffuse thickening of the choroid (Fig. 8.1.47), sometimes in associated with a limited serous retinal detachment and crescentic hypochoic extrascleral lesions from lymphomatous proliferation. While such patients



**Fig. 8.1.46** Diffuse Creamy Thickening of Posterior Uvea With Nodular Accentuation Just Temporal to the Macula in an Eye With Primary Uveal Lymphoma.



**Fig. 8.1.47** B-Scan Ultrasound Image of an Eye With Diffuse Uveal Lymphoma Showing Generalized Choroidal Thickening and a Hypochoic, Crescentic, Retroscleral Accumulation of Tumor Cells.

are unlikely to report a prior history of CNS lymphoma or new neurological symptoms suggestive of possible CNS involvement, they are likely to report a prior or concurrent history of systemic lymphoma. If diffuse uveal lymphoma is suspected, the patient should undergo imaging of the chest and abdomen as well as baseline CNS imaging. The intraocular diagnosis can be confirmed by fine-needle aspiration biopsy<sup>71</sup> or incisional biopsy of the thickened uvea<sup>75</sup> in such patients. As long as there is no evident systemic or CNS lymphoma, the affected eye should generally be treated by low- to moderate-dose fractionated external beam radiation therapy. Treated patients should be monitored for signs of local tumor relapse or emergence of systemic lymphoma.

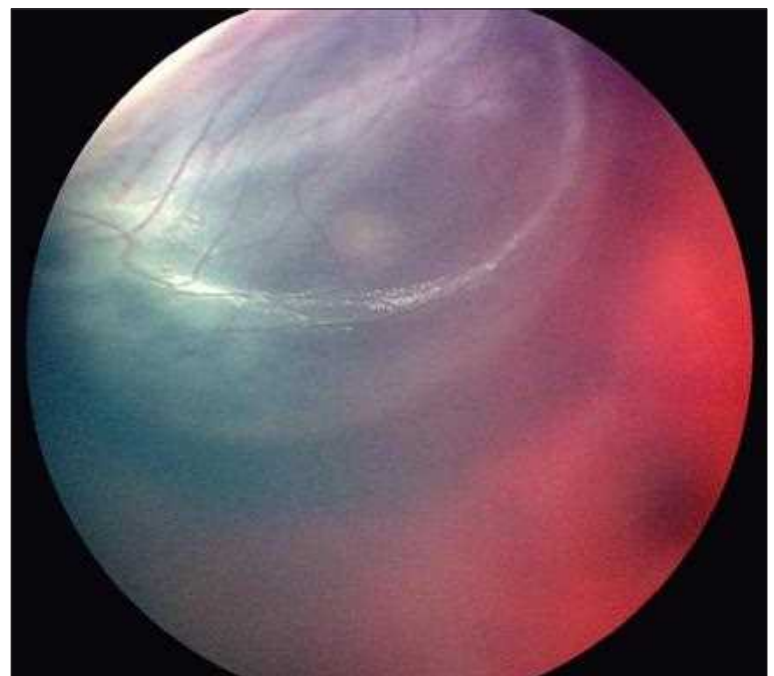
## MEDULLOEPITHELIOMA

Medulloepithelioma is an uncommon primary intraocular malignant neoplasm that arises from neuroectodermal cells that give rise to the epithelia of the ciliary body. The cells that comprise most medulloepitheliomas frequently appear rather bland without any pronounced nuclear pleomorphism or prominent nucleoli. The tumors that comprise medulloepithelioma are graded as benign versus malignant largely on the basis of whether the tumor has invaded and replaced adjacent tissues.<sup>76</sup>

Characteristic histopathological features of classic medulloepitheliomas are the formation of pseudorosettes composed of atypical neuroepithelial cells and the presence of associated neuroepithelial cysts containing vitreous.<sup>76,77</sup> In most cases, the tumor cells retain features of the neuroepithelium from which they arose. In some cases, however, some of the tumor cells exhibit differentiation into tissues not present normally in the eye (e.g., cartilage).<sup>78</sup> In cases such as these, the tumor is frequently classified pathologically as a “teratoid” medulloepithelioma. The tumors vary widely in terms of how atypical the component cells are. Medulloepitheliomas that exhibit substantial invasion and replacement of adjacent tissues are generally categorized as malignant, whereas those not exhibiting such features are commonly categorized as benign.<sup>76</sup> In spite of how the individual tumor is classified pathologically, medulloepitheliomas are associated with an extremely low potential to spawn metastasis or cause metastatic death.

The classic intraocular medulloepithelioma develops in the ciliary body and appears as an off-white to pink mass associated with small to relatively large neuroepithelial cysts on its surface (Fig. 8.1.48). Occasional tumors of this type arise in the iris (Fig. 8.1.49), retina, or even optic disc (Fig. 8.1.50).<sup>79</sup>

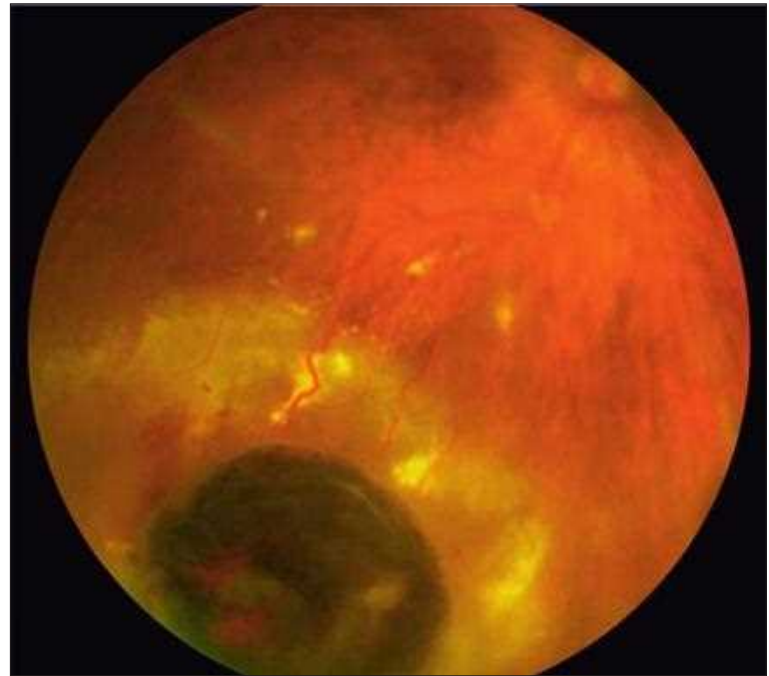
Most intraocular medulloepitheliomas occur sporadically in individuals without other known abnormalities, but occasional individuals with medulloepithelioma have been shown to be affected by constitutional mutations in the *DICER1* gene.<sup>80</sup> These individuals are at risk for development of an otherwise rare pulmonary neoplasm known as



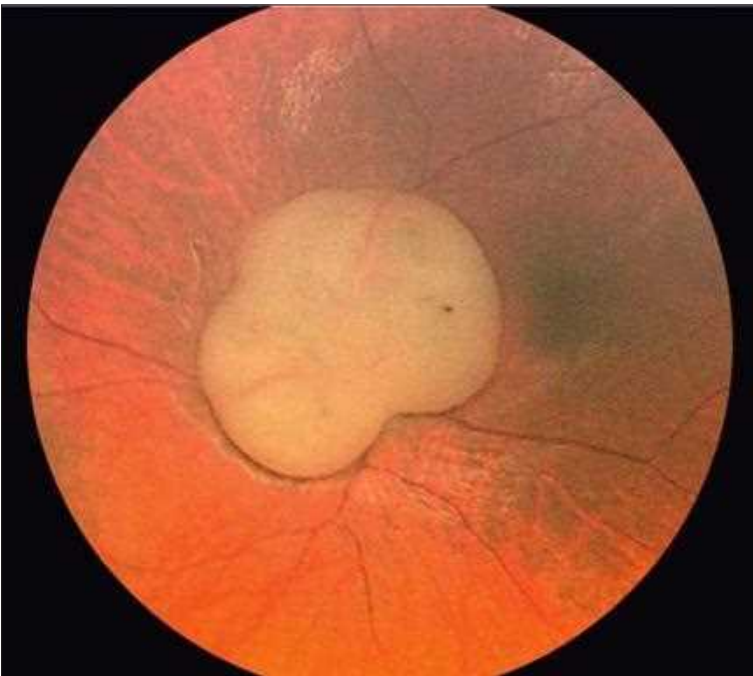
**Fig. 8.1.48** White Ciliary Body Medulloepithelioma Having a Prominent Cystic Component.



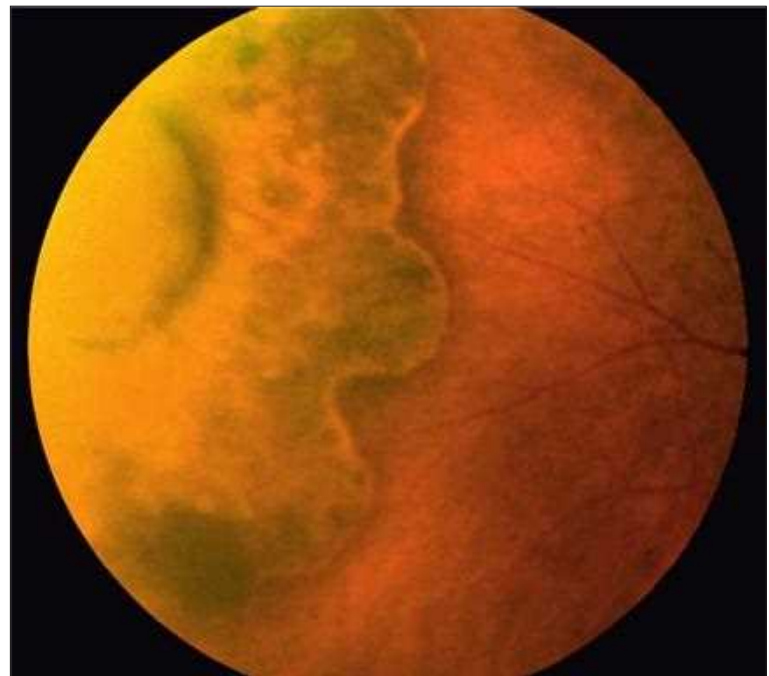
**Fig. 8.1.49** Iris Medulloepithelioma Appears as a Pale Vascularized Iris-Angle Tumor.



**Fig. 8.1.51** Isolated Adenocarcinoma of Retinal Pigment Epithelium Appears as a Nodular Black Tumor Projecting Through the Sensory Retina Associated With Exudative Retinopathy and Intraretinal Blood.



**Fig. 8.1.50** Nodular Off-White Medulloepithelioma Arising From Optic Disc.



**Fig. 8.1.52** Adenocarcinoma of Retinal Pigment Epithelium Arising From Congenital Hypertrophy of Retinal Pigment Epithelium (CHRPE). Note the well-defined smoothly curved flat margin of underlying CHRPE lesion.

pleuropulmonary blastoma and other systemic neoplasms, often at a relatively young age.

If medulloepithelioma of the iris, ciliary body, or both is suspected when the tumor is quite small, it can be excised successfully by transscleral en bloc resection,<sup>81</sup> but most larger ciliary body medulloepitheliomas and those involving the retina and optic disc eventually (if not initially) come to enucleation.

## ADENOCARCINOMAS OF INTRAOCULAR NEUROECTODERMAL EPITHELIAL LAYERS

Primary intraocular adenocarcinomas (acquired malignant neoplasms arising from neuroectodermal tissues that exhibit pseudoglandular features histopathologically) can arise from the iris pigment epithelial layers, the neuroepithelial layers of the ciliary body, and the RPE. These tumors cannot be distinguished clinically from primary epithelial adenomas (acquired, benign tumors). Fortunately, each of these tumor types is extremely uncommon. The typical adenocarcinoma of the iris pigment epithelium appears as a progressively enlarging black tumor invading and replacing the iris stroma. The typical adenocarcinoma of the nonpigmented

ciliary epithelium appears as a white to pink tumor replacing the ciliary body, and the typical adenocarcinoma of the pigmented ciliary epithelium appears as a black tumor involving the ciliary body. The adenocarcinoma of the RPE can arise de novo from previously normal-appearing RPE or occasionally from the hypertrophied RPE cells that comprise a congenital hypertrophy of the retinal pigment epithelium (CHRPE). The isolated adenocarcinoma of the RPE<sup>82</sup> typically appears as a focally invasive dark brown to black tumor associated with surrounding hemorrhagic and exudative subretinal fluid (Fig. 8.1.51). The adenocarcinoma of the RPE arising from CHRPE<sup>83</sup> appears similar to the isolated tumor but exhibits the classic features of CHRPE in addition to the tumor nodule (Fig. 8.1.52).

If adenocarcinoma of one of these neuroectodermal layers is suspected clinically, it can sometimes be excised successfully by transscleral en bloc resection.<sup>83</sup> However, most confirmed cases have been treated by enucleation.<sup>82</sup> Fortunately, such neoplasms appear to pose minimal risk for extraocular extension and virtually no risk of metastasis.



## PRIMARY NONOPHTHALMIC MALIGNANT NEOPLASMS METASTATIC TO THE EYE

A wide variety of primary nonophthalmic malignant neoplasms can give rise to metastatic intraocular tumors that reach the eye by hematogenous dissemination. Most of the nonophthalmic malignant neoplasms that give rise to such intraocular tumors are carcinomas, and most of these are adenocarcinomas.<sup>84</sup> The most common anatomic sites of origin of the underlying primary malignant neoplasm, in decreasing order of frequency, are breast, lung, colon, other gastrointestinal sites, and kidney.<sup>84</sup> Skin melanoma occasionally gives rise to metastatic intraocular tumors,<sup>85</sup> and these tumors generally appear darker in color than those that arose from other cancer types. Some systemic malignant lymphomas also metastasize to the eye,<sup>86,87</sup> where they appear similar to metastatic carcinomas.

The most common site of intraocular involvement by metastatic tumors is the choroid,<sup>84</sup> but other intraocular tissues can be affected, including (in decreasing order of frequency) the iris, ciliary body, optic disc, retina, and vitreous.<sup>84</sup> The classic metastatic choroidal tumor appears as a round to oval off-white to golden discoid tumor having homogeneous coloration and no visible intralesional blood vessels (Fig. 8.1.53). The tumor is frequently associated with overlying and surrounding serous subretinal fluid that is out of proportion to the size of the choroidal lesion. Prominent intratumoral, intravitreal, and subretinal bleeding is extremely uncommon with most types of metastatic cancer to the eye. While some patients (approximately 20% of all cases in most reported large series of cases) exhibit multiple tumors of different sizes in one or both eyes (Fig. 8.1.54), the vast majority of patients (approximately 80%) with an intraocular metastatic tumor exhibit a single tumor in one eye at presentation (Fig. 8.1.55). The choroidal tumor in patients who were known to have their cancer prior to detection of a choroidal metastasis and were treated with systemic chemotherapy prior to their ophthalmic diagnosis frequently show partial regression of their choroidal tumor with prominent clumping of the overlying RPE on the surface of the tumor, giving the lesion a “leopard-spotted” appearance (Fig. 8.1.56).

Ultrasonography is frequently helpful in the differential diagnosis of metastatic choroidal tumors (Fig. 8.1.57). In contrast to choroidal melanomas, most metastatic carcinomas are substantially more sonoreflective (bright) internally, more likely to be broad based (Fig. 8.1.57A) in comparison with their thickness, and more likely to be multinodular (Fig. 8.1.57B).

Metastatic carcinomas to the iris<sup>88</sup> appear as white to pink, frequently irregular, discohesive tumors that have a tendency to bleed spontaneously, shed tumor cells into the aqueous humor, or both (Fig. 8.1.58). Such tumors often cause a painful abrupt rise in intraocular pressure in the affected eye.

Metastatic tumors to the optic disc<sup>84</sup> generally appear as discohesive white to pale yellow infiltrates of the disc (Fig. 8.1.59) associated with abrupt onset and progressive worsening of vision in the affected eye.

Metastatic tumors to the retina<sup>89</sup> generally appear as smudgy discohesive infiltrates, frequently associated with extravasated intraretinal blood and exudates (Fig. 8.1.60). When the source cancer for metastasis to the eye is cutaneous malignant melanoma, the intraocular tumor is more likely to be dark in color and more likely to involve the retina than the typical carcinoma metastatic to the eye (Fig. 8.1.61).

If the affected patient has other concurrent metastatic tumors more amenable to biopsy than the ocular tumor, those extraocular tumors can be sampled to confirm the diagnosis pathologically. However, if the eye is the only suspected site of involvement, fine-needle aspiration biopsy of the intraocular tumor can be performed to confirm the suspected intraocular diagnosis.<sup>90,91</sup>

Treatment of the patient depends on whether the eye is the only site of metastasis and whether one or both eyes are affected. In patients with multisystem metastasis including one or both eyes, a chemotherapy or

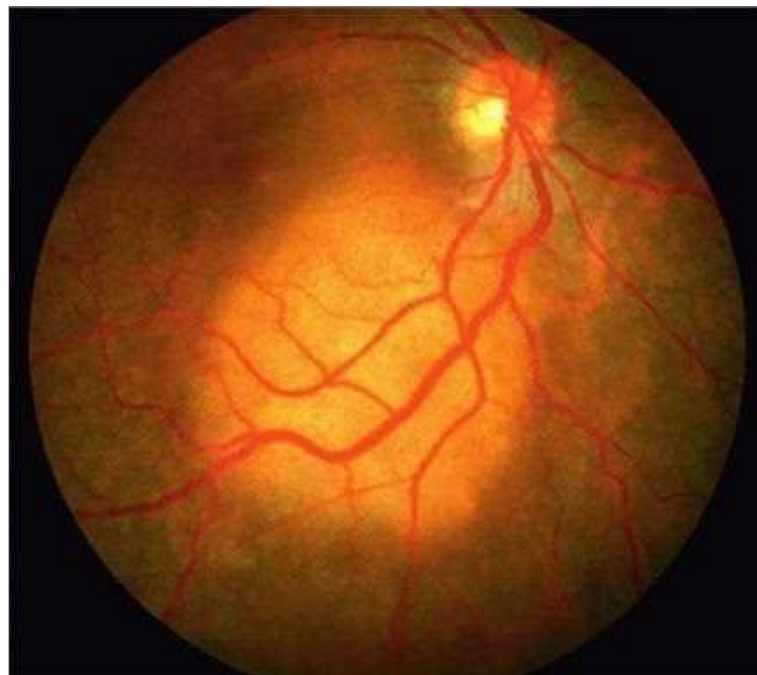


Fig. 8.1.53 Classic Appearance of Individual Metastatic Carcinoma to Choroid.

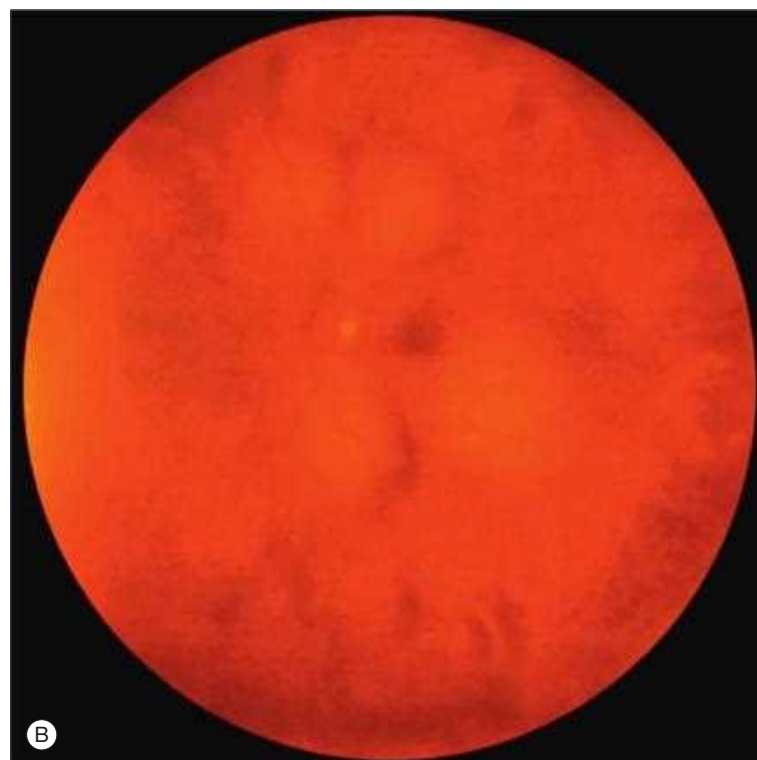
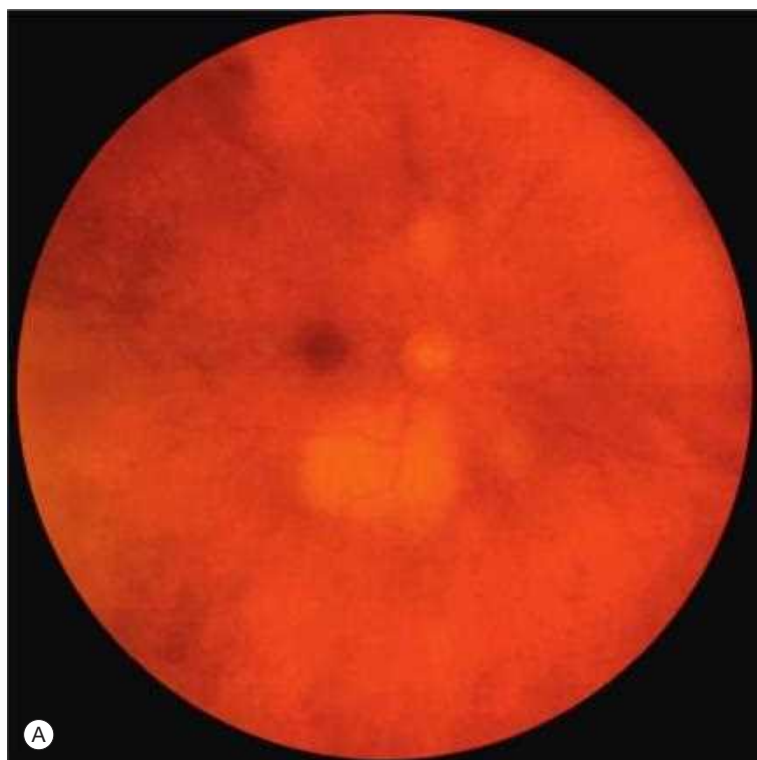
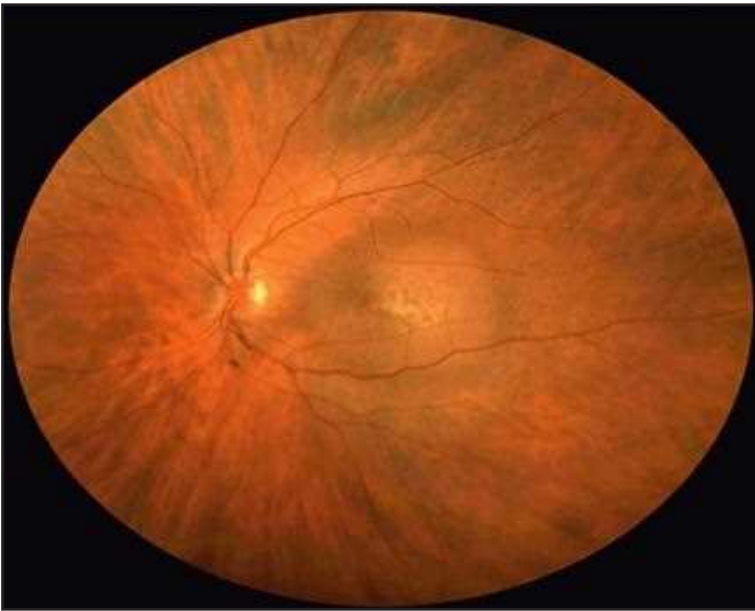
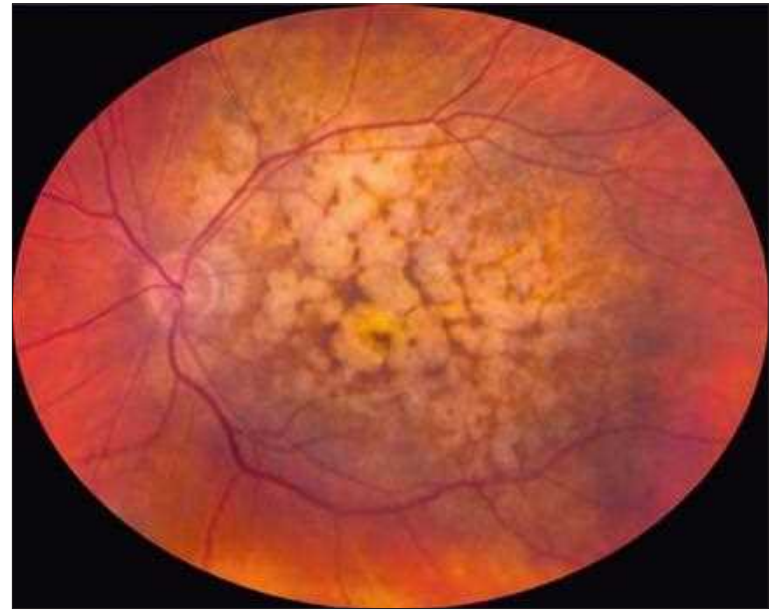


Fig. 8.1.54 Equator Plus Wide-Angle Fundus Photos Showing Multiple Pale Metastatic Choroidal Tumors in the Right Eye (A) and Left Eye (B) of a Patient.

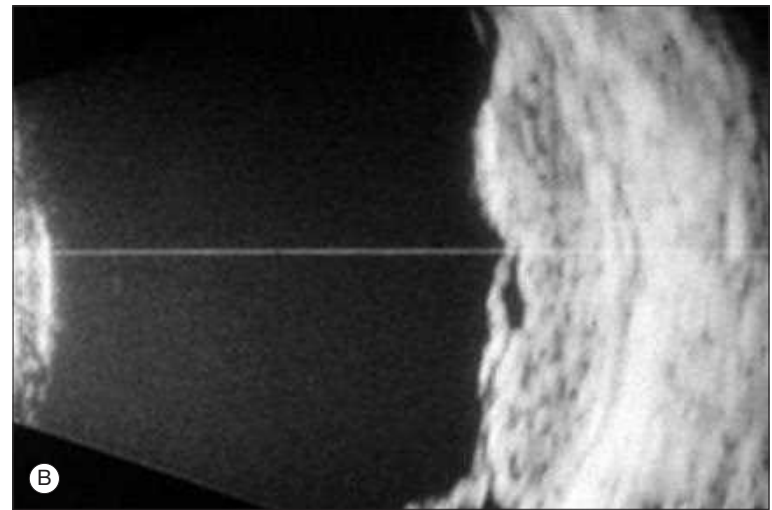
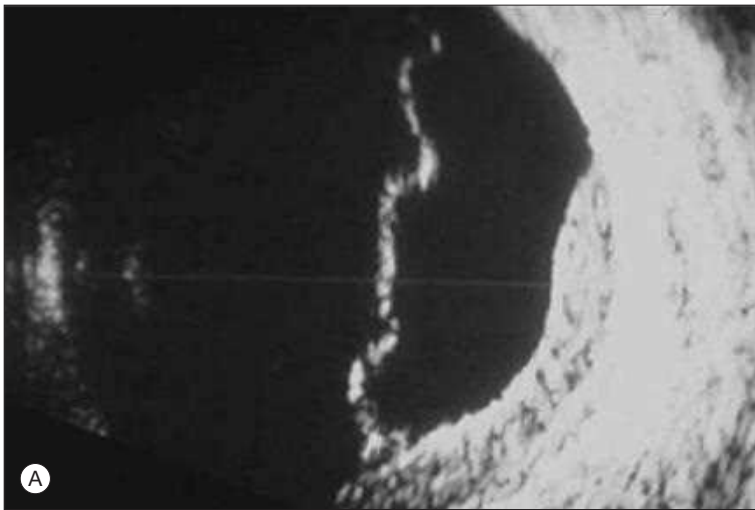




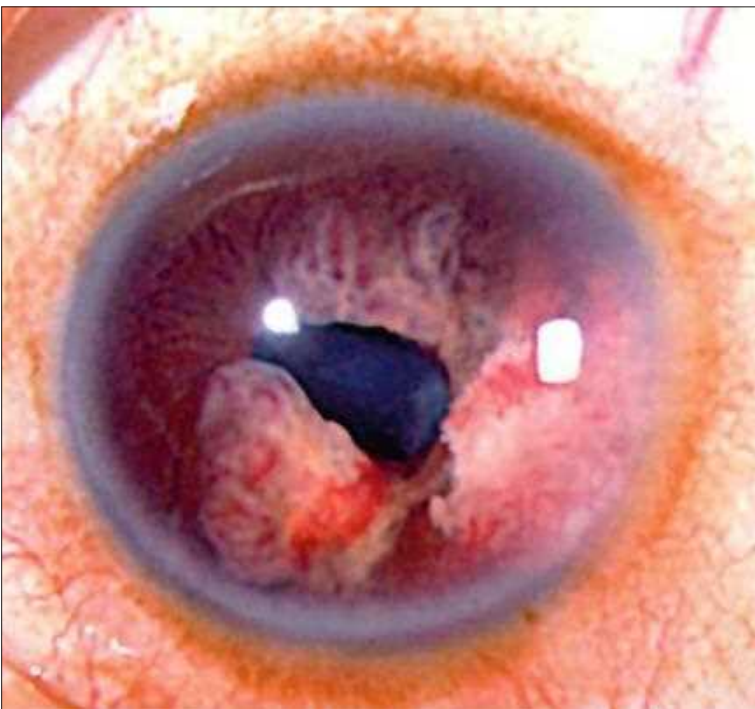
**Fig. 8.1.55** Wide-Angle Fundus Photo Showing Solitary Choroidal Metastatic Tumor.



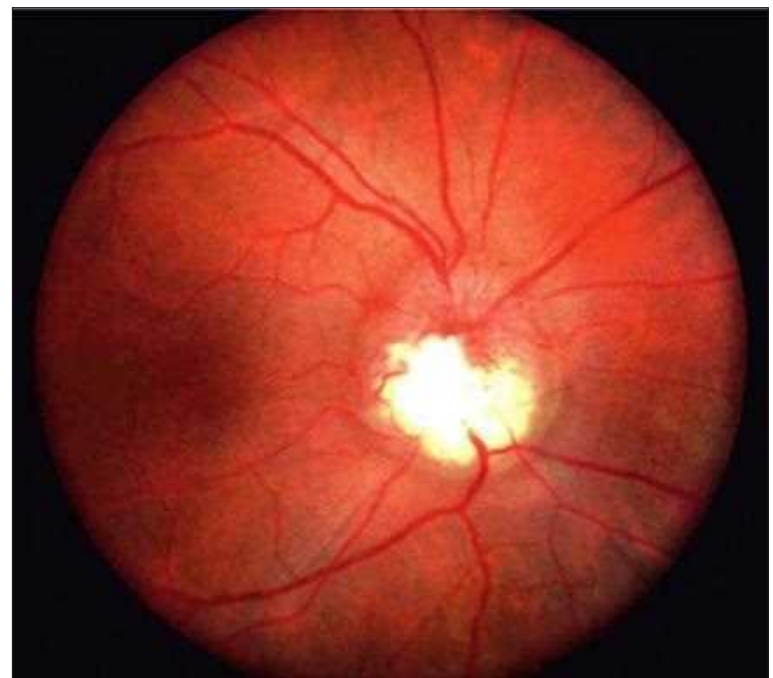
**Fig. 8.1.56** Partly Regressed Metastatic Choroidal Tumor Showing "Leopard Spots" of Retinal Pigment Epithelial Clumping on Its Surface.



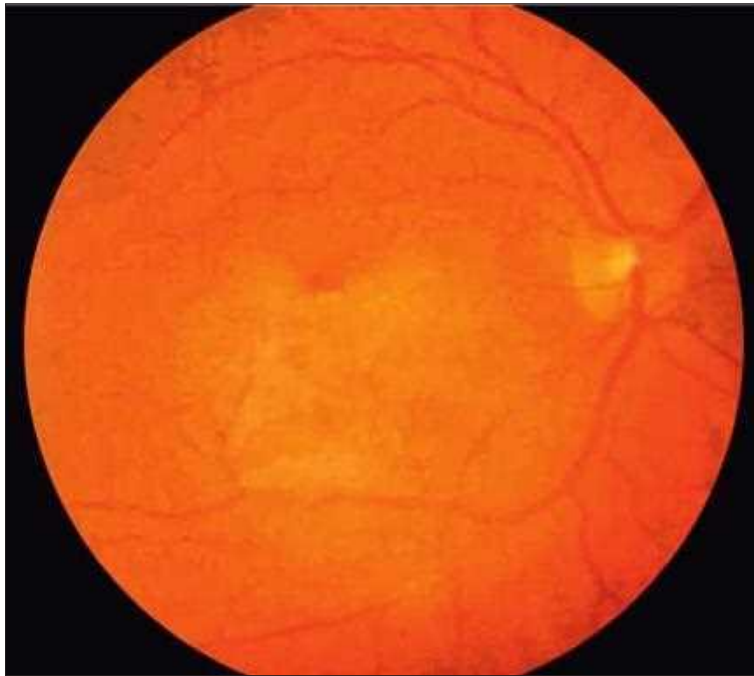
**Fig. 8.1.57** B-Scan Images of Metastatic Choroidal Tumors. (A) Thin but broad-based choroidal tumor conforming to curvature of sclera with associated bullous serous retinal detachment. (B) Nodular metastatic choroidal tumor with associated serous retinal detachment.



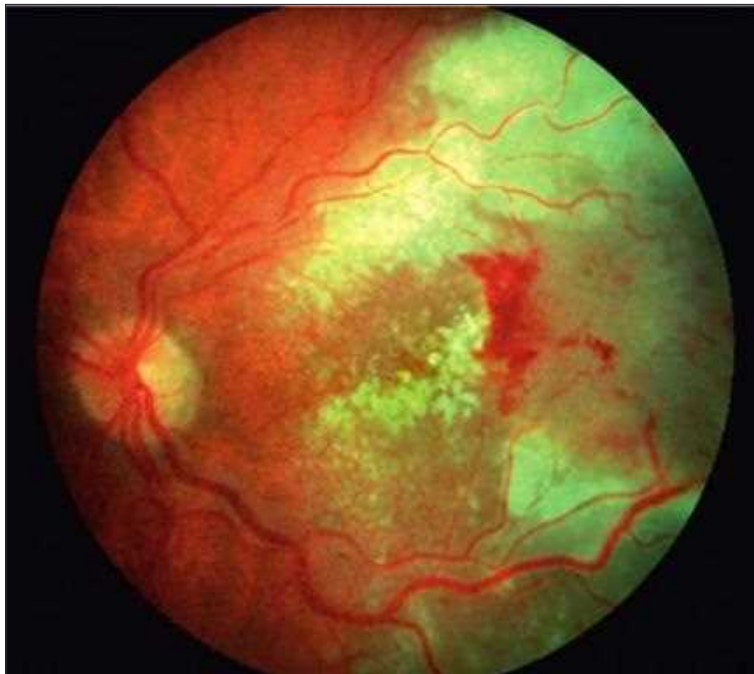
**Fig. 8.1.58** Metastatic Carcinoma to Iris From Lung Cancer Primary Site. Two discrete tumors are evident in this eye.



**Fig. 8.1.59** Infiltrative Metastatic Carcinoma to Optic Disc.



**Fig. 8.1.60** Ill-Defined Metastatic Carcinoma Involving Posterior Retina.

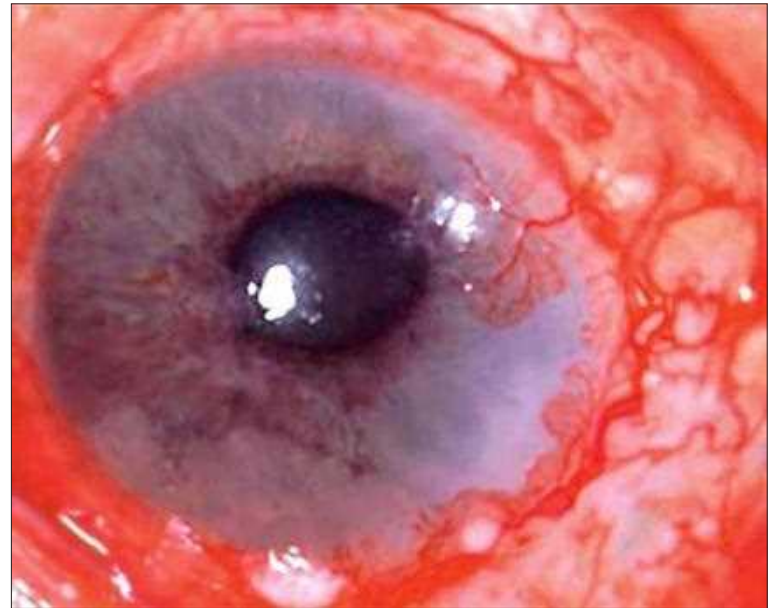


**Fig. 8.1.61** Primary Cutaneous Melanoma Metastatic to Retina Causing Localized Hemorrhagic-Exudative Retinopathy.

immunotherapy regimen appropriate to the primary cancer type<sup>92</sup> is typically initiated. If visual acuity is impaired as a result of the metastatic ocular disease, palliative external beam radiation therapy to the affected eye or eyes<sup>93</sup> is commonly provided. If a solitary metastatic tumor is present in only one eye, a focal destructive treatment such as I-125 plaque radiotherapy<sup>94</sup> can be used to eradicate the tumor. In recent years, some intraocular metastatic tumors have been treated successfully by intraocular injections of anti-VEGF drugs.<sup>95</sup> Unfortunately, patients who experience metastatic cancer to the eye generally have a poor prognosis for more than a few months of survival.<sup>96</sup>

## SECONDARY MALIGNANT INTRAOCULAR NEOPLASMS

Occasional patients who have a primary eyelid, conjunctival, orbital, or paranasal sinus malignant neoplasm will develop a secondary malignant



**Fig. 8.1.62** Primary Squamous Cell Carcinoma of Conjunctiva Invading Eye. Note smudgy off-white tumor cells in anterior chamber.



**Fig. 8.1.63** B-Scan Ultrasound Image Showing Diffuse Choroidal Involvement by Primary Paranasal Sinus Lymphoma That Invaded the Orbit and Eye Secondarily.

intraocular neoplasm by intraocular invasion from that adjacent site. Intraocular tumors of this type are much less common than metastatic tumors to the eye but should be recognized as a distinct category of intraocular malignant neoplasms. The conjunctival tumors most likely to invade the eye secondarily are conjunctival squamous cell carcinomas<sup>97</sup> and mucoepidermoid carcinomas<sup>98</sup> (Fig. 8.1.62). The intraocular tumor portion of the tumor is frequently obscured by the overlying conjunctival mass but can usually be demonstrated by ultrasound biomicroscopy if it is suspected clinically. The orbital tumor most likely to invade the eye is malignant lymphoma arising in the orbit or paranasal sinuses (Fig. 8.1.63).<sup>99</sup> The intraocular tumors of these types can occasionally be eliminated by trans-scleral resection or focal radiation therapy, but secondary enucleation of the affected eye is performed in many of these patients.

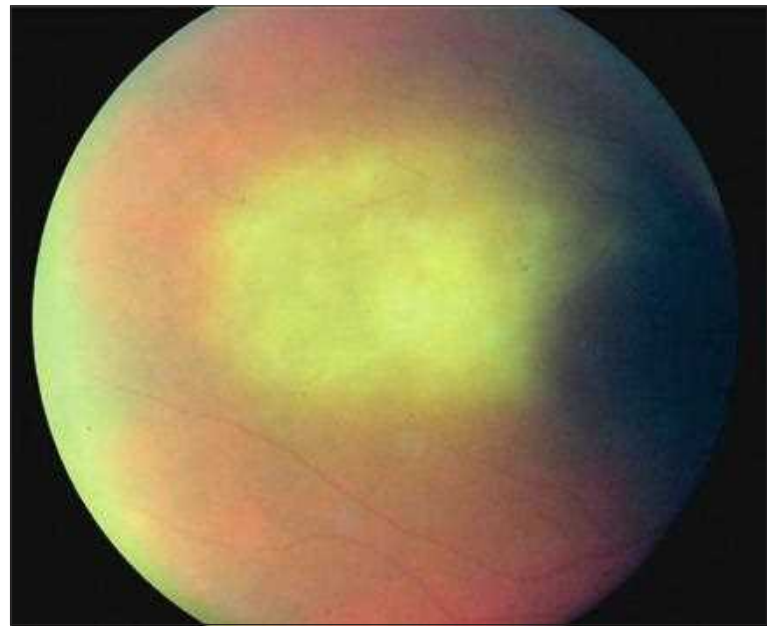
## HEMATOLOGICAL NEOPLASIAS INVOLVING THE EYES

Leukemias of different clinical, pathological, and cytogenetic varieties all have presence of malignant neoplastic cells in the circulating blood as a

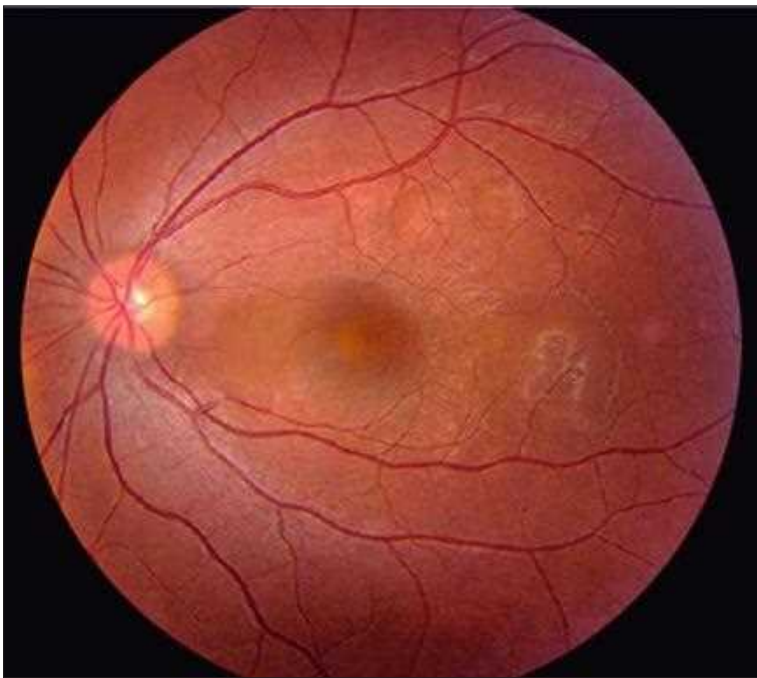




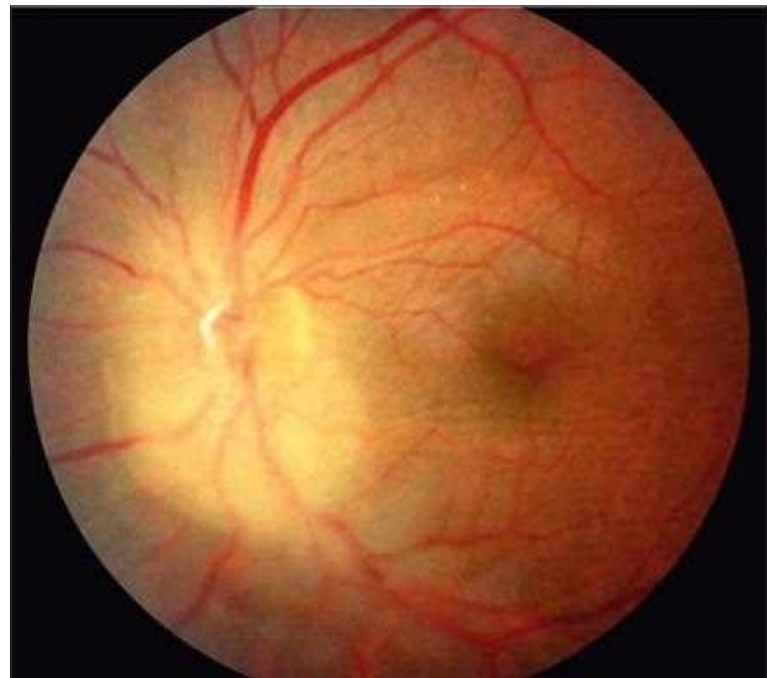
**Fig. 8.1.64** Chronic Myelogenous Leukemia Causing Neoplastic Pseudo-Hypopyon as Initial Manifestation of Disease Relapse.



**Fig. 8.1.66** Leukemic Infiltration of Retina.



**Fig. 8.1.65** Diffuse Leukemic Infiltration of Choroid Giving Rise to Serous Retinal Detachment of the Macula. Similar Findings Were Evident in the Fellow Eye of This Patient.



**Fig. 8.1.67** Optic Disc Infiltration by Leukemic Cells.

common feature. Some of these neoplastic cells can exit the bloodstream in the eye and form infiltrative tumors in various intraocular tissues including the iris (Fig. 8.1.64), choroid (Fig. 8.1.65), retina (Fig. 8.1.66), optic disc (Fig. 8.1.67), and vitreous (Fig. 8.1.68).<sup>100-104</sup> Leukemic patients are also susceptible to secondary microbial infections attributable to impaired immunity caused by their disease or its treatment. These patients can experience endogenous retinal or subretinal abscesses and microbial endophthalmitis (Fig. 8.1.69).<sup>105</sup> Leukemic patients also tend to have impaired coagulation attributable to features of their disease including hypofibrinogenemia and absence of sufficient circulating platelets.

The most common intraocular lesions associated with leukemia are retinal hemorrhages, which tend to be multifocal and are sometime extensive (Fig. 8.1.70). Patients with forms of leukemia associated with very high white blood cell counts frequently develop dilation and tortuosity of the retinal veins and secondary macular retinal edema (Fig. 8.1.71). Some of these leukemic patients develop peripheral retinal capillary bed occlusions and subsequent peripheral retinal neovascularization with preretinal intravitreal bleeding.<sup>106</sup> Frank and sometimes bilateral retinal venous occlusions can also occur. Occasional patients with leukemia develop a serous

macular retinal detachment in each eye as a presenting clinical feature (see Fig. 8.1.65).<sup>107,108</sup> Relatively few patients with leukemia in most large series actually develop infiltrative intraocular tumors composed of leukemic cells.<sup>102</sup>

When a patient with a history of leukemia or concurrent active leukemia who appears to have infiltrative leukemic versus microbial lesions in one or both eyes is encountered, the managing ophthalmologist must advise the patient about the differential diagnosis and the potential benefits versus potential risks and limitations of (1) assuming the lesions to be leukemic and advising treatment for the presumed leukemia, (2) assuming the intraocular lesions to be microbial infiltrates and advising systemic treatment for the presumed type of infection, or (3) admitting the uncertainty of the ocular diagnosis and arranging for fine-needle aspiration biopsy or vitrectomy with cytopathological and microbiological testing of the obtained specimen to establish a definitive diagnosis that can then be used to direct subsequent patient management.<sup>105</sup> Treatment for leukemic infiltrates in the eye consists of systemic multidrug chemotherapy appropriate for the type of leukemia followed by bone marrow transplantation in patients whose leukemia can be eradicated.





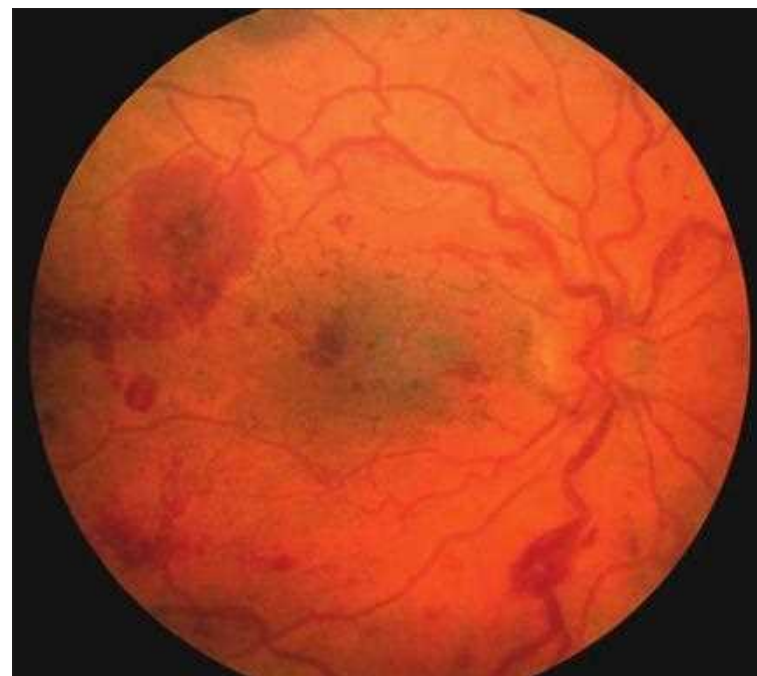
**Fig. 8.1.68** Diffuse Leukemic Cellular Clouding of Vitreous as the First Sign of Relapse of Acute Myelocytic Leukemia in a Teenage Boy.



**Fig. 8.1.70** Multiple Intraretinal Hemorrhages, Many Having a White Center, and Globular Preretinal Hemorrhage in Leukemic Patient. Similar features were noted in the fellow eye of this patient.



**Fig. 8.1.69** Retinal Abscess Due to Nocardiosis in a Patient With Hairy Cell Leukemia.



**Fig. 8.1.71** Prominently Dilated Tortuous Retinal Veins and Multiple Retinal Hemorrhages in a Patient With Chronic Myelogenous Leukemia and White Blood Cell Count Over 100 000 Cells/Mm<sup>3</sup>.

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# Benign Intraocular Neoplasms, Hamartomas, and Choristomas

## 8.2

James J. Augsburger, Zélia M. Corrêa, Amy C. Scheffler

**Definition:** Spectrum of intraocular tumors composed of minimally to moderately atypical but nonmalignant neoplastic cells capable of expanding to a limited extent, impairing vision of the affected eye by various mechanisms, and, depending on cell type, possibly giving rise to malignant intraocular neoplasms.

### Key Features

- Wide spectrum of tumor size, color, laterality, focality, and shape.
- Cells of origin:
  - Derived from cells that were once pluripotential.
  - Some are acquired lesions (e.g., uveal nevi, retinal astrocytomas, retinal capillary hemangiomas, circumscribed choroidal hemangiomas, choroidal osteomas).
  - Some are congenital (e.g., iris choristomas, combined hamartoma of retina).
  - The mechanism by which cells of mesodermal origin in the uveal tract give rise to bone that comprises choroidal osteomas is currently unknown.
- Growth pattern:
  - Most benign intraocular neoplasms, hamartoma, and choristomas do not exhibit growth after initial diagnosis.
  - Many lesions (larger choroidal nevi, circumscribed choroidal hemangiomas, choroidal osteomas) do enlarge to a limited extent long term.
  - Some (e.g., retinal capillary hemangiomas) enlarge progressively and achieve substantial size.
- May produce visual loss by a variety of mechanisms of visual loss including:
  - Choroidal neovascularization.
  - Macular edema.
  - Subretinal fluid.
  - Tractional retinal detachment.
  - Epiretinal membrane.
  - Vitreous hemorrhage.
  - Replacement of the normal retinal tissue.

### INTRODUCTION

A *benign intraocular neoplasm* is an acquired (noncongenital) tumor (three-dimensional mass) that develops inside an eye and is composed of slightly atypical but nonmalignant cells of a type that exists normally in the eye. A tumor of this type can enlarge, usually to a limited extent over an extended period, but has limited if any potential for malignant transformation.

An *intraocular hamartoma* is a congenital tumor composed of normal cells and nonmalignant tissue that exist normally in their intraocular location but are present in an excessive amount. This type of tumor is commonly referred to as an overgrowth of normal tissue. A tumor of this type can enlarge, usually to a limited extent during an extended period, but has an extremely limited potential for malignant transformation.

An *intraocular choristoma* is a congenital tumor composed of normal cells and nonmalignant tissue that do not exist normally in its intraocular tissue location. A tumor of this type can enlarge, usually to a limited extent during an extended period, but has virtually no recognized potential for malignant transformation.

Some noninflammatory cellular intraocular tumors (e.g., choroidal osteoma) do not fall neatly into any one of these categories but will also be discussed in this chapter.

### BENIGN INTRAOCULAR NEOPLASMS

#### UVEAL NEVUS

The uveal nevus is a benign neoplasm composed of slightly atypical but nonmalignant uveal melanocytes. This tumor is extremely uncommon in infants and young children but becomes progressively more common in older age groups.<sup>1,2</sup> Over 10% of white individuals over the age of 50 years have at least one uveal nevus in one eye. Given this frequency, the uveal nevus is unquestionably the most common primary intraocular neoplasm one encounters in humans. Once detected, the uveal nevus can enlarge to a limited extent, usually over an extended period.<sup>3</sup> Most such tumors are 1 mm or smaller in thickness, but some achieve a thickness that can be substantially larger than 3 mm.<sup>4</sup> The uveal nevus is believed to have a limited potential for malignant transformation to uveal melanoma.<sup>5,6</sup> Cytogenetically, virtually all uveal nevi exhibit mutations in genes *GNAQ* or *GNAI1*,<sup>2</sup> and these mutations are believed to be necessary for malignant transformation.<sup>7</sup>

Uveal nevi conventionally are divided into anterior and posterior subgroups. *Anterior uveal nevi* involve the iris or iris and ciliary body together, and *posterior uveal nevi* involve the choroid, ciliary body, or both.

#### Anterior Uveal Nevus

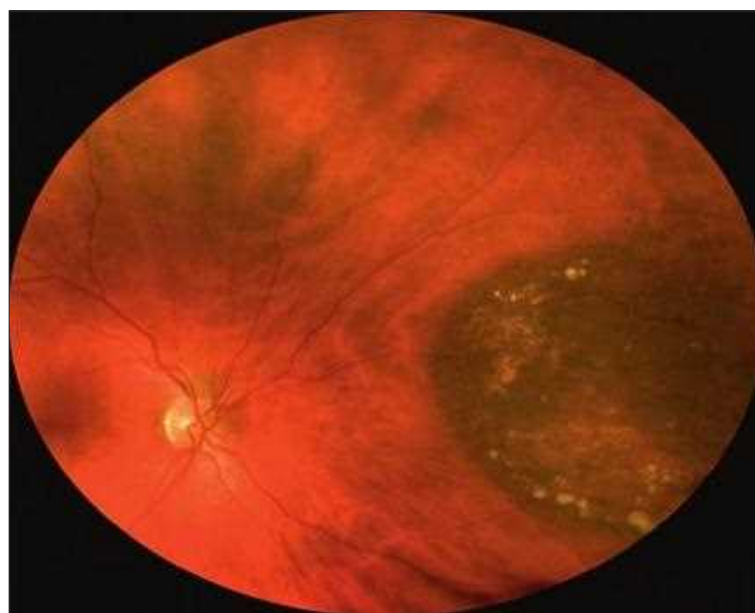
Uveal nevi of the iris or iris and ciliary body are frequently noted by the patient as a newly developed melanotic lesion of the iris. They rarely cause any visual symptoms or secondary ocular problems. The typical anterior uveal nevus is a thin bland melanotic lesion of the iris stroma that does not exhibit any prominent internal blood vessels or produce any satellite lesions or pigment dispersion (Fig. 8.2.1).<sup>8,9</sup> The classic iris nevus is 3 mm or smaller in largest basal diameter and 0.5 mm or smaller in maximal thickness. Nevi larger than 1 mm in thickness can cause limited pupillary peaking toward the lesion and limited ectropion iridis. Gonioscopy typically shows a slightly bumpy surface but limited thickness of the lesion. Ultrasound biomicroscopy can be used to measure the thickness of the tumor and determine its internal sonorefectivity, and ocular transillumination can be used to detect involvement of the anterior ciliary body.

#### Posterior Uveal Nevus

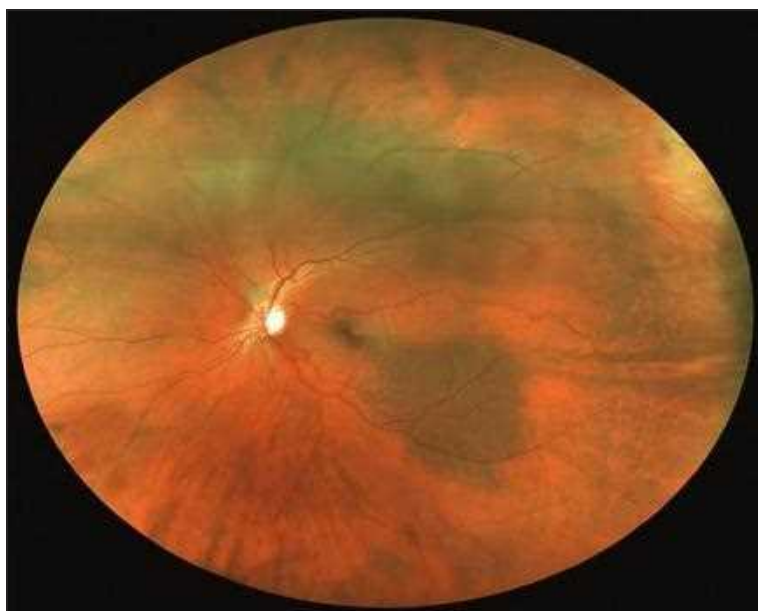
Most nevi of the choroid or choroid and ciliary body are asymptomatic and detected on routine eye examination in an adult individual.<sup>2</sup> If the nevus develops in the macular region, it can cause some visual blurring and distortion related to degeneration of the overlying photoreceptors, accumulation of limited shallow serous subretinal fluid, or (rarely) secondary choroidal neovascularization.<sup>10</sup> The typical choroidal nevus appears as a gray-brown choroidal tumor that has bland homogeneous coloration and flat margins that blend imperceptibly into the surrounding normal choroid (Fig. 8.2.2). The classic choroidal nevus is 5 mm or smaller in largest basal diameter and 1 mm or smaller in maximal thickness. Some choroidal nevi achieve substantially larger dimensions, and these nevi can be impossible to distinguish clinically from small choroidal melanomas. Benign choroidal nevi can exhibit small clumps of orange pigment (lipofuscin) on



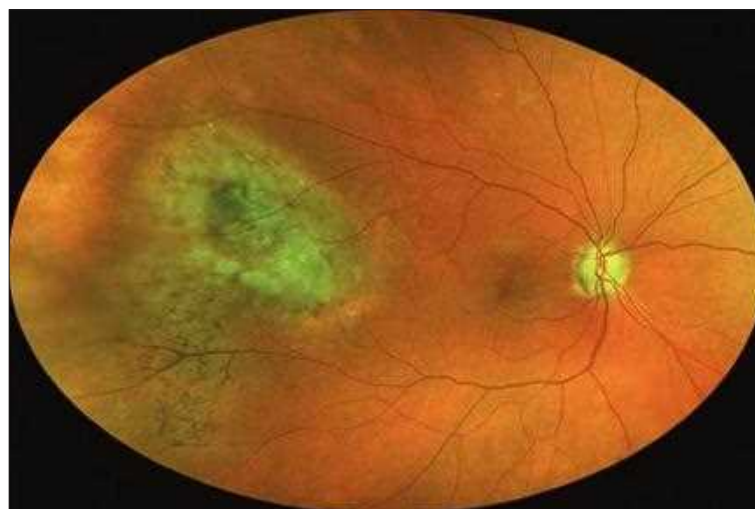
**Fig. 8.2.1** Typical Iris Nevus Appears as Thin Melanotic Lesion Limited to Inner Surface of Iris Stroma.



**Fig. 8.2.3** Choroidal Nevus Exhibiting Numerous Surface Drusen Indicative of Chronicity and Probable Dormancy.



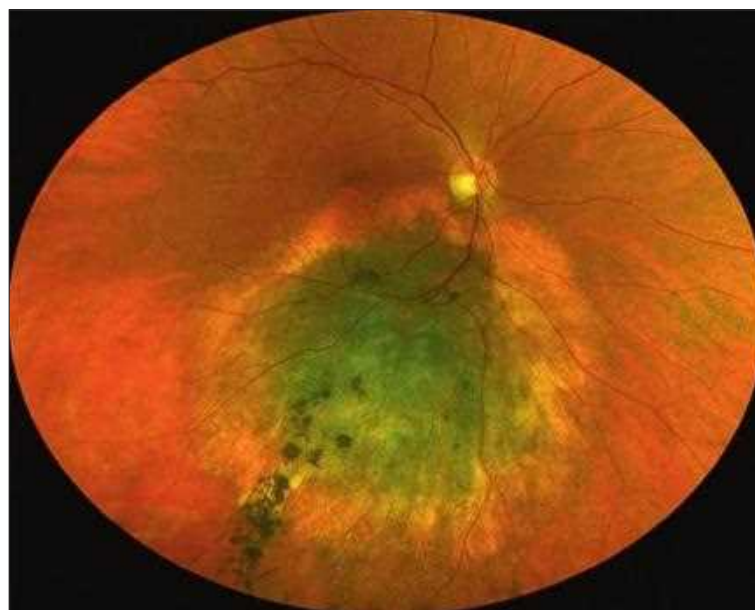
**Fig. 8.2.2** Typical Choroidal Nevus Appears as a Bland Localized Darkly Melanotic Choroidal Lesion  $\leq 1$  mm in Maximal Thickness.



**Fig. 8.2.4** Choroidal Nevus Exhibiting Extensive Disruption and Clumping of Overlying Retinal Pigment Epithelium. This lesion was 1.75 mm thick but shows no clumping of orange pigment or associated subretinal fluid.

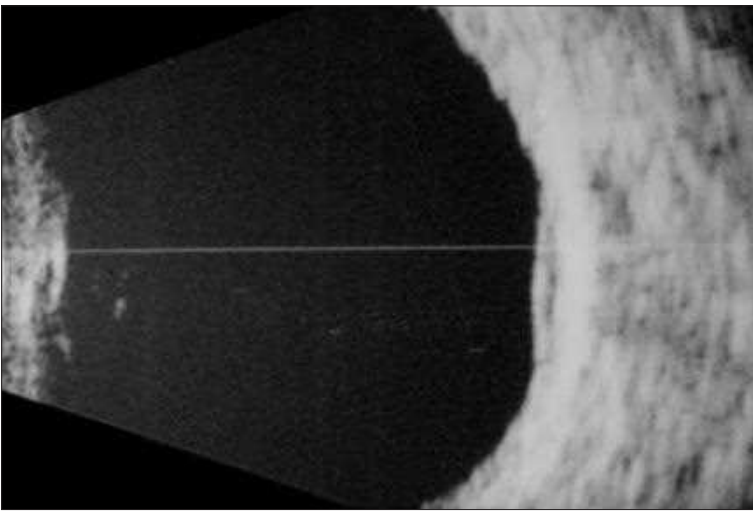
their inner surface,<sup>3</sup> but prominent clumps of orange pigment visible on indirect ophthalmoscopy are rare. As mentioned above, larger choroidal nevi frequently exhibit a limited amount of shallow overlying or surrounding serous subretinal fluid that may be evident only with testing such as optical coherence tomography (OCT) or autofluorescence imaging of the fundus. However, a prominent accumulation of serous subretinal fluid over and around the tumor that is evident on indirect ophthalmoscopy is uncommon. Choroidal nevi larger than 5 mm in diameter and larger than 1 mm in thickness frequently exhibit prominent drusen on their inner surface (Fig. 8.2.3), and some exhibit degeneration of the overlying retinal pigment epithelium with clumping and intraretinal migration by black retinal pigment epithelial pigment, a whitish patch of overlying fibrous metaplasia of the retinal pigment epithelium, or both (Fig. 8.2.4).<sup>3</sup> Occasional choroidal nevi exhibit a golden orange discoloration of the marginal portion of the tumor that gives the tumor a halo-like appearance (Fig. 8.2.5). Such *halo nevi* of the choroid and nevi associated with prominent drusen and retinal pigment epithelial abnormalities generally have a favorable long-term prognosis.

B-scan ultrasonography of eyes containing a choroidal nevus typically shows the lesion as a relatively thin, moderately sonoreflective choroidal mass that has a smooth, fusiform cross-sectional shape with tapering margins that blend imperceptibly into the surrounding normal choroid (Fig. 8.2.6).

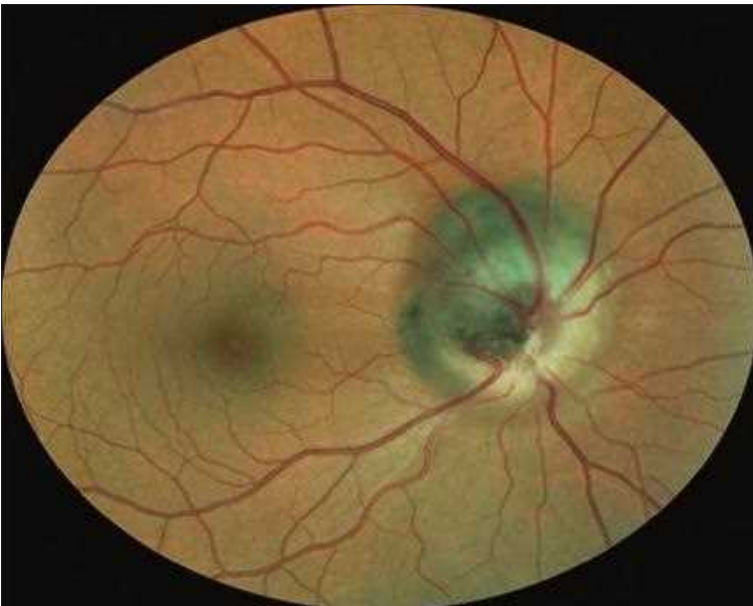


**Fig. 8.2.5** Halo-Type Choroidal Nevus Exhibiting Golden Orange Discoloration of the Peripheral Aspect of the Centrally Melanotic Lesion.





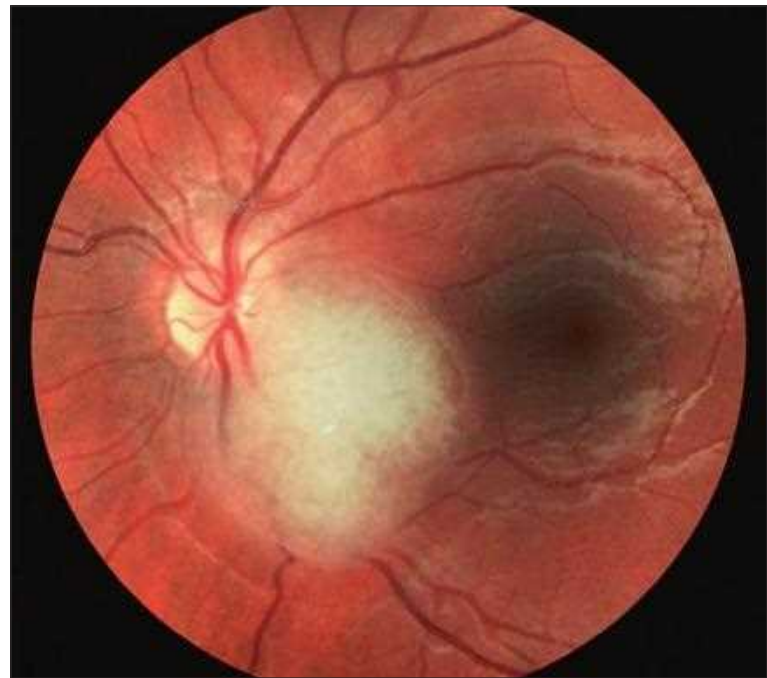
**Fig. 8.2.6 B-Scan Ultrasound Image of Slightly Elevated Choroidal Nevus.** The Tumor Appears Fusiform in Cross-Sectional Shape and Exhibits Moderately High Internal Sonoreflectivity.



**Fig. 8.2.7 Classic Melanocytoma of Optic Disc in an Asymptomatic Teenager.**

A special subtype of choroidal nevus is the melanocytoma of the optic disc.<sup>11</sup> A melanocytoma is a form of uveal nevus composed of benign magnocellular nevus cells that contain densely packed intracytoplasmic melanin granules. Such nevi occur throughout the fundus but cannot be distinguished clinically from spindle cell nevi.<sup>12</sup> For some reason, such tumors have a tendency to develop in the choroid adjacent to the optic disc or within the optic disc and grow into the substance of the disc to form a characteristic clinical lesion. The typical optic disc melanocytoma is an elevated dark brown tumor that invades the optic disc tissue, surrounds or covers the neural tissue and blood vessels of the optic disc, and causes generalized swelling of the optic disc (Fig. 8.2.7). Such tumors are commonly found in younger persons than are extrapapillary choroidal nevi and are more likely to be detected in non-white persons. Such tumors can cause an enlarged blind spot and peripheral visual field defects but rarely cause profound visual loss. They can enlarge slowly and to a limited extent, usually over many years, but appear to have extremely limited malignant potential.

The frequency of malignant transformation of uveal nevi to uveal melanomas is a subject of considerable controversy.<sup>5</sup> Many if not most ophthalmologists equate documented enlargement of a clinically diagnosed uveal nevus with malignant transformation of that lesion.<sup>6,13</sup> As mentioned earlier, however, virtually all true uveal nevi are acquired tumors and not congenital. To become evident clinically, a uveal nevus must grow. Thus, growth of a small melanocytic uveal nevus (at least that which is limited in extent and not associated with development of any clinically apparent invasive features) should not be equated with malignant transformation. To our knowledge, no case of a uveal nevus with unequivocal pathological



**Fig. 8.2.8 Retinal Astrocytoma Appears as an Off-White Inner Retinal Tumor Overlying the Retinal Blood Vessels.**

evidence of benign features determined by cytopathological or histological examination of a biopsy specimen of that tumor prior to documented enlargement has ever been shown to be a uveal melanoma following limited enlargement. At the same time, circumstantial evidence for malignant transformation comes from two histopathological series of posterior uveal melanomas in which “nevus cells” were identified at the base of the tumor in over 70% of cases.<sup>13</sup> If a tumor diagnosed as a uveal nevus enlarges enough to be reclassified as a possible uveal melanoma, biopsy of the tumor by a method such as fine-needle aspiration biopsy with cytopathological analysis and classification of tumor cells can be performed to establish a pathological diagnosis that can then be used to justify subsequent patient management.<sup>14</sup>

## RETINAL ASTROCYTOMA

The retinal astrocytoma is an acquired benign intraocular neoplasm that arises from previously normal retinal astrocytes.<sup>15</sup> This tumor is commonly referred to as retinal astrocytic hamartoma by many authors, but there is little evidence that any of these tumors are congenital in nature. There are two clinical and pathological subtypes of retinal astrocytoma: the typical retinal astrocytoma that is characteristic of tuberous sclerosis<sup>16</sup> and the isolated giant cell astrocytoma.<sup>17</sup>

The *typical retinal astrocytoma* associated with tuberous sclerosis is a localized off-white retinal tumor arising from the retinal nerve fiber layer (Fig. 8.2.8). Small tumors of this type appear as translucent patches or opalescent lesions overlying and obscuring the larger retinal blood vessels that pass beneath them. Larger tumors of this type appear as opaque white nodules that can have a lumpy surface making them appear like “rock candy” or a “white mulberry” (Fig. 8.2.9). Although such tumors can exhibit a limited retinal vascular blood supply, they do not tend to attract dilated tortuous retinal feeder and drainer blood vessels like those encountered in retinoblastoma. In individuals with tuberous sclerosis, such lesions start to appear around the end of the first decade of life and are frequently multifocal in each eye (Fig. 8.2.10).<sup>16</sup> Identical tumors that are unilateral and unifocal develop in occasional individuals who have no other clinical evidence of tuberous sclerosis. Lesions of this type tend to enlarge to a limited extent, usually over an extended period, but have limited if any malignant potential. Systemic treatment by mTOR inhibitors for tuberous sclerosis appears to reduce the likelihood and extent of growth of such retinal tumors.

The *giant cell astrocytoma* is a unilateral unifocal tumor that develops from the retina in young adult individuals, most of whom do not have tuberous sclerosis.<sup>17</sup> The tumor replaces the retina and can achieve relatively large size, frequently in association with development of a progressive nonrhegmatogenous retinal detachment (Fig. 8.2.11). Tumors of this type are frequently misdiagnosed as amelanotic uveal melanomas, and the



correct diagnosis is often not recognized until the eye had been removed and the tumor studied histopathologically.

## RETINAL CAPILLARY HEMANGIOMA

The retinal capillary hemangioma (sometimes referred to as retinal hemangioblastoma or von Hippel tumor) is an acquired benign retinal tumor composed of foamy retinal cells and a dense matrix of abnormal retinal blood vessels. This tumor is the characteristic fundus lesion of von Hippel–Lindau disease.<sup>18</sup> The typical retinal capillary hemangioma appears as a spherical bright red retinal tumor associated with prominent dilated tortuous retinal feeder and drainer blood vessels (Fig. 8.2.12). The tumor characteristically gives rise to exudative subretinal fluid that gradually involves more of the retina as the lesion enlarges (Fig. 8.2.13). In patients with von Hippel–Lindau disease, such lesions generally develop multifocally in each eye. This situation is commonly referred to as *retinal capillary hemangiomatosis*.<sup>18</sup> These tumors not only cause progressive exudative retinal detachment but somehow stimulate development of contracting vitreoretinal bands that lead to progressive tractional retinal detachment

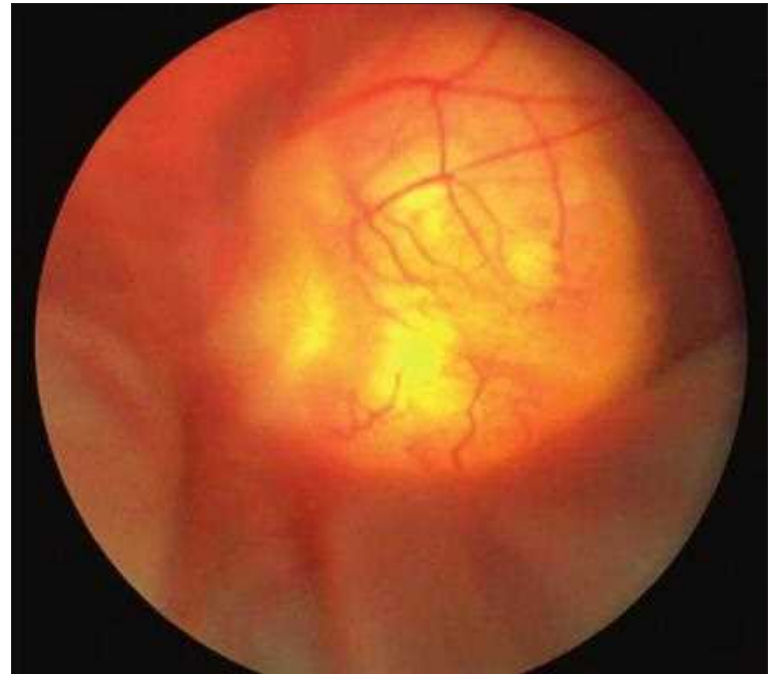
(Fig. 8.2.14). Identical tumors that are usually unifocal and unilateral also occur sporadically in individuals without von Hippel–Lindau disease. In some patients, retinal capillary hemangiomas arise on the optic disc (Fig. 8.2.15).<sup>19</sup> In such cases, prominent feeder and drainer retinal blood vessels may not be evident.

Fluorescein angiography shows rapid filling of the feeding retinal arteriole, nearly instantaneous hyperfluorescence of the entire hemangioma, and rapid filling of the draining retinal vein (Fig. 8.2.16). The tumor typically shows intense late hyperfluorescence due to dye leakage through its walls.

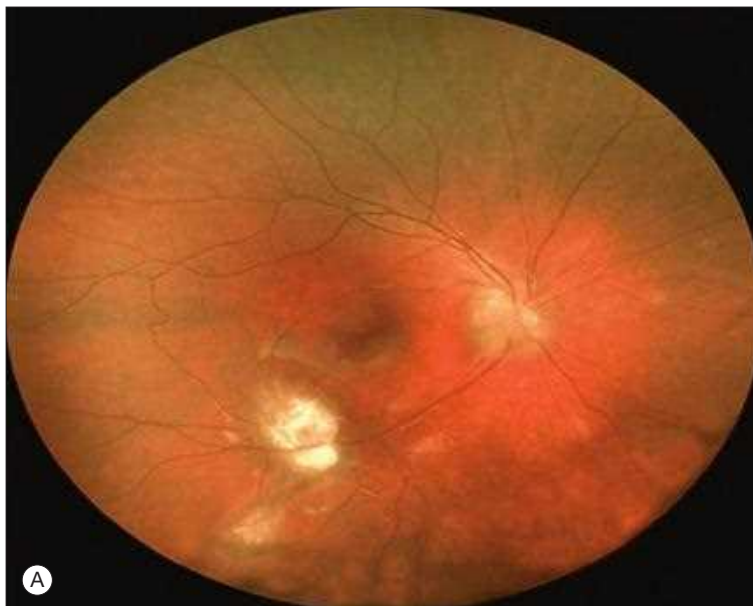
If a retinal capillary hemangioma is identified when it is small (i.e., <3 mm in diameter) and not associated with a bullous exudative or tractional retinal detachment, it can be destroyed by transpupillary laser photocoagulation or transscleral cryotherapy. If a retinal capillary hemangioma is associated with an exudative but not a tractional retinal detachment, intravitreal antivascular endothelial growth factor (VEGF) drug therapy may be able to lessen the detachment and enable subsequent successful obliteration of the tumor by laser photocoagulation or cryotherapy. If the tumor is associated with a tractional retinal detachment, the most appropriate therapy seems to be endoresection of the tumor or tumors combined



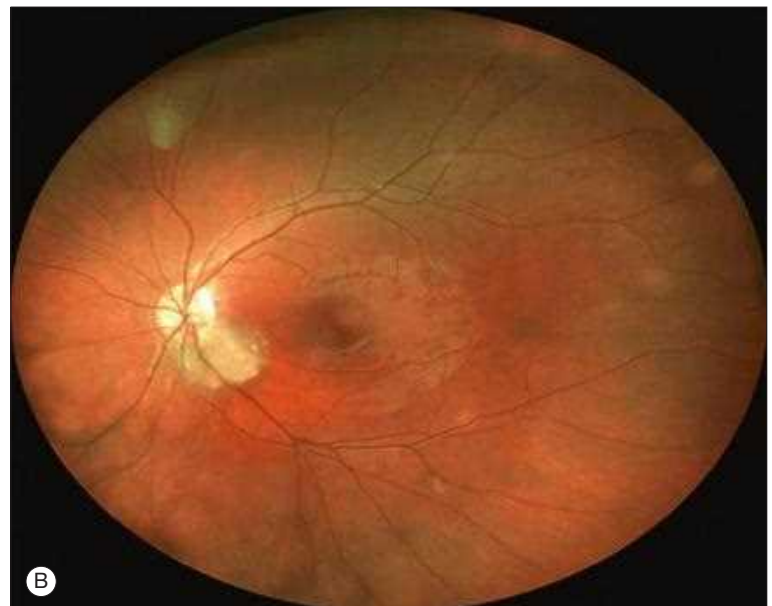
**Fig. 8.2.9** Retinal Astrocytoma Exhibiting “Rock Candy” or “White Mulberry” Features.



**Fig. 8.2.11** Isolated Giant Cell Astrocytoma of Retina Associated With Bullous Serous Secondary Retinal Detachment.

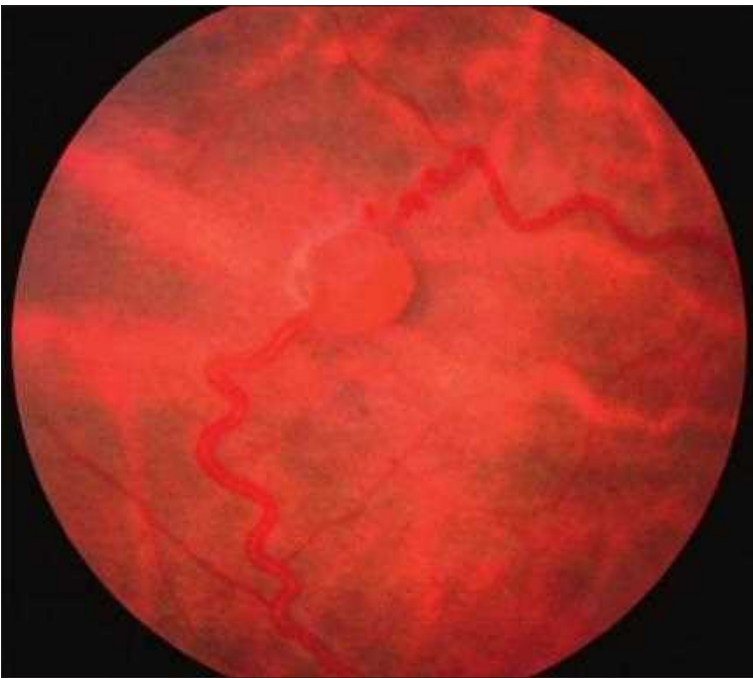


(A)

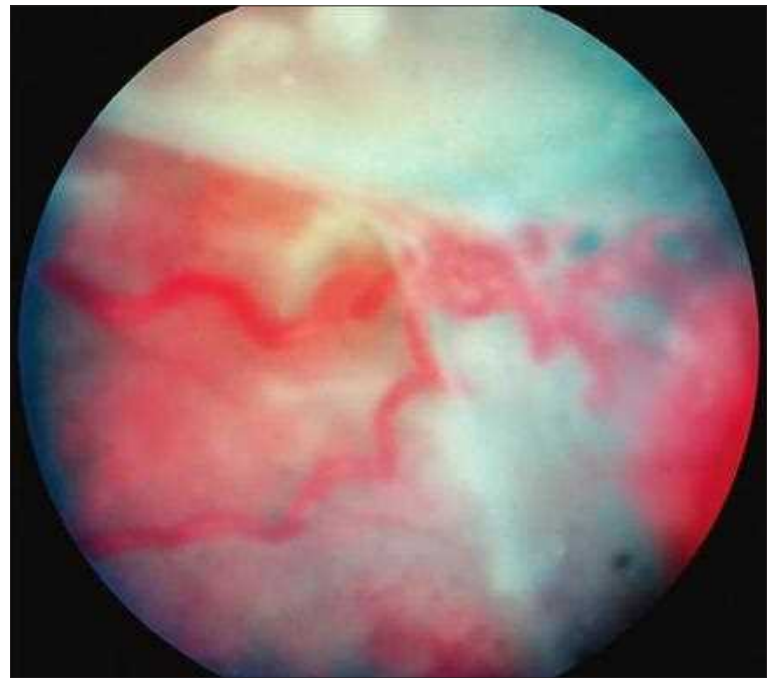


(B)

**Fig. 8.2.10** Multifocal Bilateral Retinal Astrocytomas of Differing Sizes in an Individual With Tuberous Sclerosis. (A) Right eye fundus. (B) Left eye fundus.



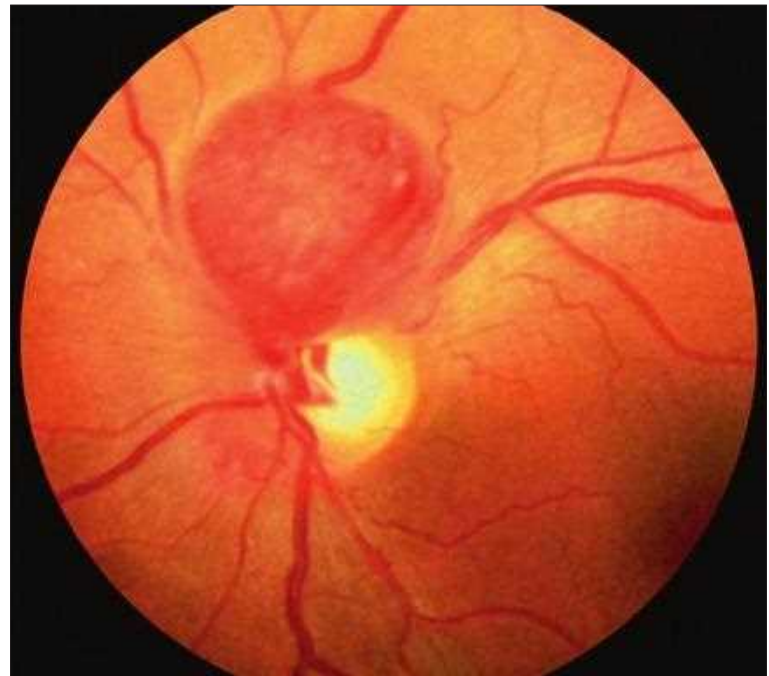
**Fig. 8.2.12** Typical Small Intraretinal Capillary Hemangioma With Dilated-Tortuous Feeder and Drainer Blood Vessels.



**Fig. 8.2.14** Retinal Capillary Hemangioma Associated With Prominent Vitreoretinal Membranes and Tractional Retinal Detachment.



**Fig. 8.2.13** Medium-Size Retinal Capillary Hemangioma Causing Exudative Retinopathy Adjacent to the Lesion.



**Fig. 8.2.15** Discrete Retinal Capillary Hemangioma on Optic Disc.

with pars plana vitrectomy and silicone oil injection. If a retinal capillary hemangioma develops on or adjacent to the optic disc, posterior vitrectomy with endophotocoagulation or endoresection of the tumor is frequently the best method to prevent progressive exudative-tractional retinal detachment and loss of the eye.

### UVEAL LEIOMYOMA

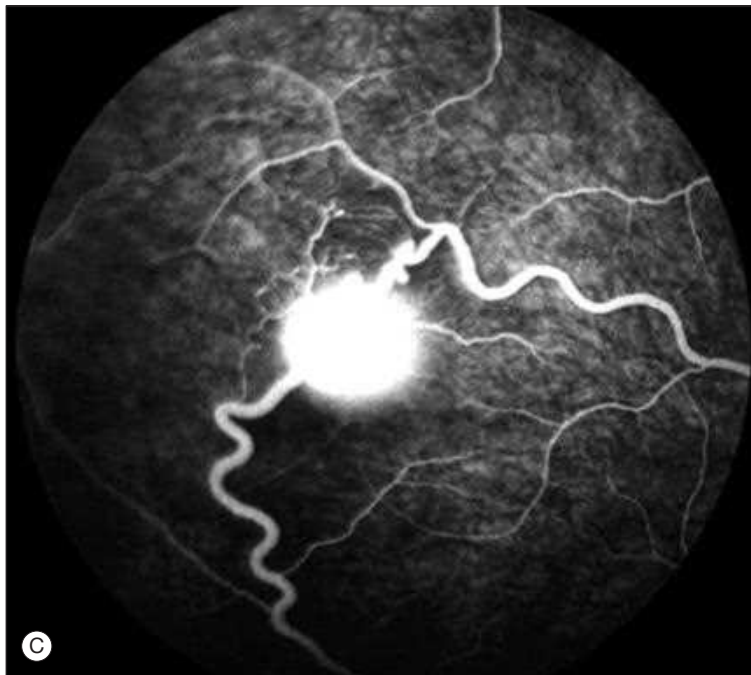
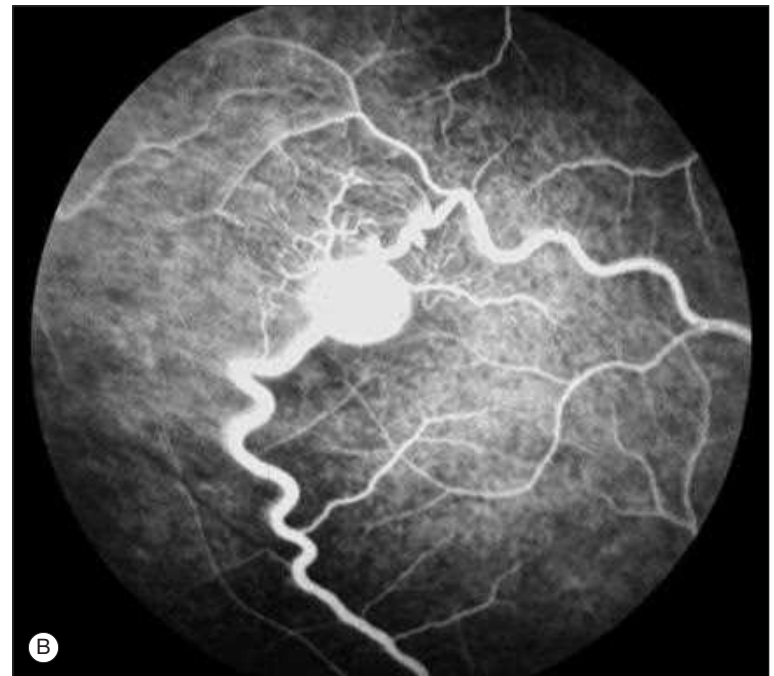
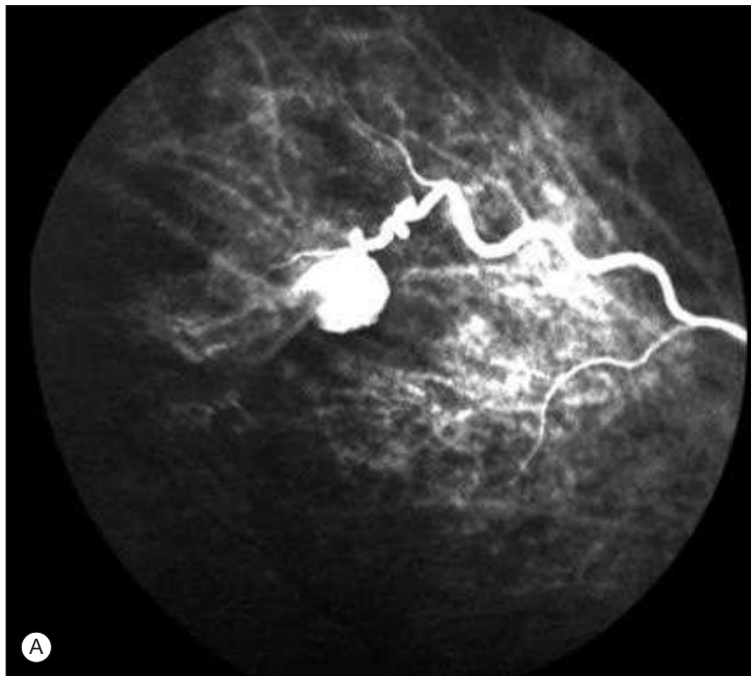
The uveal leiomyoma is a benign acquired neoplasm that develops from cells with smooth muscle differentiation that exist within the uveal tract, most commonly in the ciliary body or iris.<sup>20,21</sup> The typical iris tumor appears as a slowly enlarging tan stromal mass that cannot be distinguished clinically from a hypomelanotic iris melanoma. The typical ciliary body tumor appears as an off-white to heterogeneously pigmented retroiridic mass evident on indirect ophthalmoscopy or fundus biomicroscopy (Fig. 8.2.17). Such tumors do not tend to attract prominent epibulbar blood vessels but

otherwise appear similar to ciliary body melanomas. Tumors of this type develop more frequently in women than in men and are usually detected in individuals in the 40–60-year-old age range.

### UVEAL NEURILEMOMA

The uveal neurilemoma is a benign acquired neoplasm that develops from the Schwann cells investing sensory fibers of the trigeminal nerve within the uveal tract.<sup>22</sup> Most tumors of this type develop in the choroid.<sup>23</sup> The typical choroidal neurilemoma appears as a discoid amelanotic choroidal tumor (Fig. 8.2.18). The retina is typically attached over and around such tumors, even ones that have attained reasonably large size. Some choroidal blood vessels can usually be visualized within such tumors, but these blood vessels do not appear to be of irregular caliber and course or grossly leaky in the way that those of primary uveal melanoma are. Most such tumors that have been encountered have been misdiagnosed as choroidal melanomas and treated as such.





**Fig. 8.2.16 Fluorescein Angiogram of Retinal Capillary Hemangioma Shown in Fig. 8.2.12.** (A) Retinal arterial filling phase frame. (B) Full retinal venous filling phase frame. (C) Recirculation phase frame.

## ADENOMAS OF INTRAOCULAR NEUROECTODERMAL EPITHELIAL TISSUES

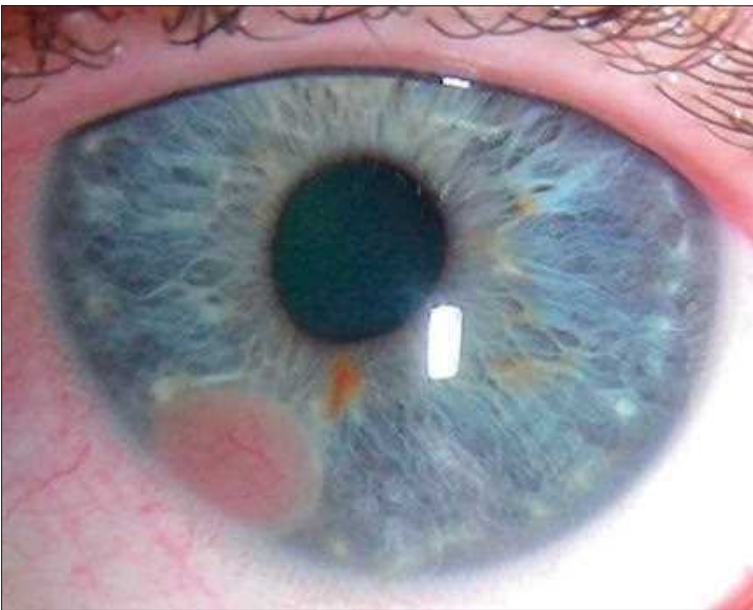
Benign adenomas can develop from the pigment epithelium of the iris, the epithelial layers of the ciliary body, and the retinal pigment epithelium.<sup>24-26</sup> Each of these benign acquired neoplasms is extremely rare. Adenomas of the iris pigment epithelium generally appear as black nodular tumors that replace the overlying iris stroma gradually (Fig. 8.2.19). Adenomas of the retinal pigment epithelium appear as well-defined black nodular tumors underlying the sensory retina (Fig. 8.2.20). Adenomas of the ciliary epithelial layers appear white when they arise from the nonpigmented ciliary epithelium and black when they arise from the pigmented ciliary epithelium. The most common of these tumors is the adenoma of the nonpigmented ciliary epithelium (Fuchs' adenoma), which is frequently noted in autopsy eyes as an incidental finding. Most of these tumors are small and do not warrant any treatment unless they are progressive.

## INTRAOCULAR HAMARTOMAS

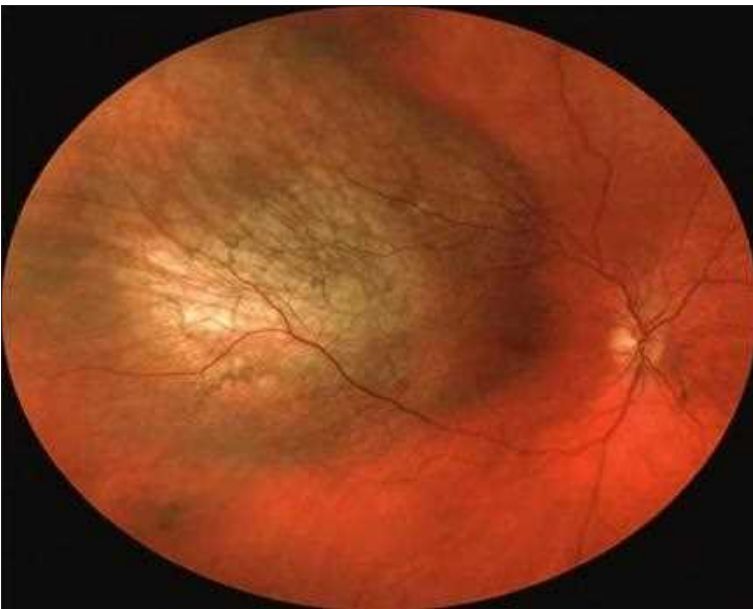
### CIRCUMSCRIBED CHOROIDAL HEMANGIOMA

The circumscribed choroidal hemangioma is generally categorized as a choroidal blood vessel hamartoma in spite of the fact that very few such lesions have ever been identified congenitally.<sup>27</sup> The tumor is composed entirely of a localized overgrowth of choroidal blood vessels of various calibers associated with a loose connective tissue stroma. The typical tumor appears as an oval to round discoid reddish orange choroidal mass that is located entirely posterior to the equator (Fig. 8.2.21). The posterior margin of virtually all circumscribed choroidal hemangiomas is located within 3 mm of the nearest margin of the optic disc, foveola, or both.<sup>28</sup> The classic circumscribed choroidal hemangioma is detected in individuals between the ages of 35 and 45 years, although larger tumors are more likely to be identified at a substantially younger age. The tumor is frequently





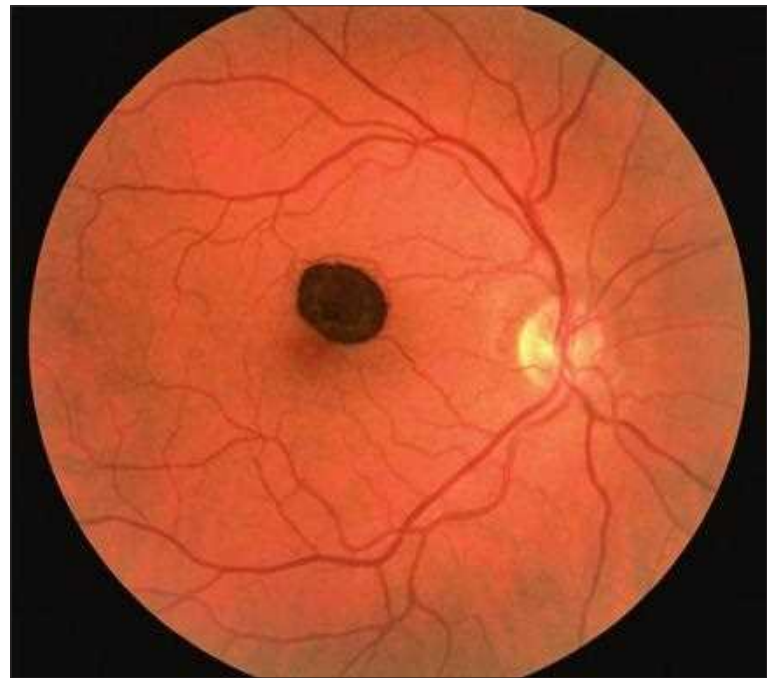
**Fig. 8.2.17** Leiomyoma of Iris (Confirmed by Postexcision Histopathology).



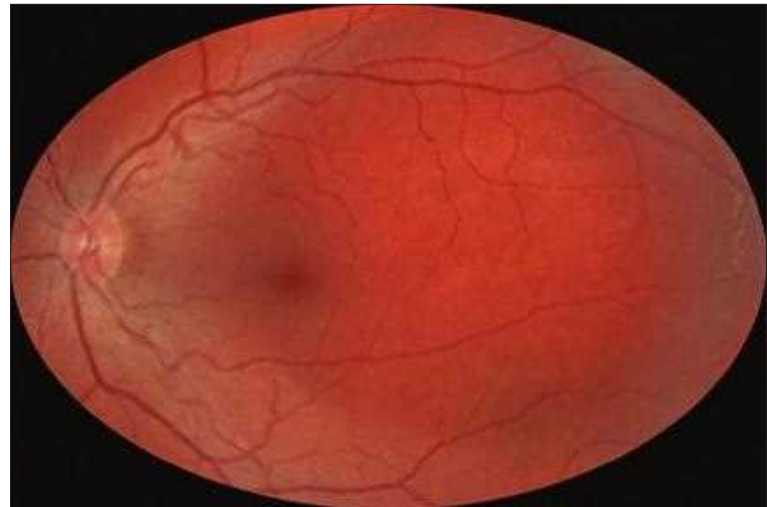
**Fig. 8.2.18** Choroidal Neurilemoma (Confirmed by Transscleral Incisional Biopsy).



**Fig. 8.2.19** Adenoma of the Iris Pigment Epithelium Prior to Microsurgical Excision. Note black color and cohesive character of tumor.



**Fig. 8.2.20** Focal Adenoma of the Retinal Pigment Epithelium in the Macula. Optical coherence tomography confirmed outer retinal location of tumor.

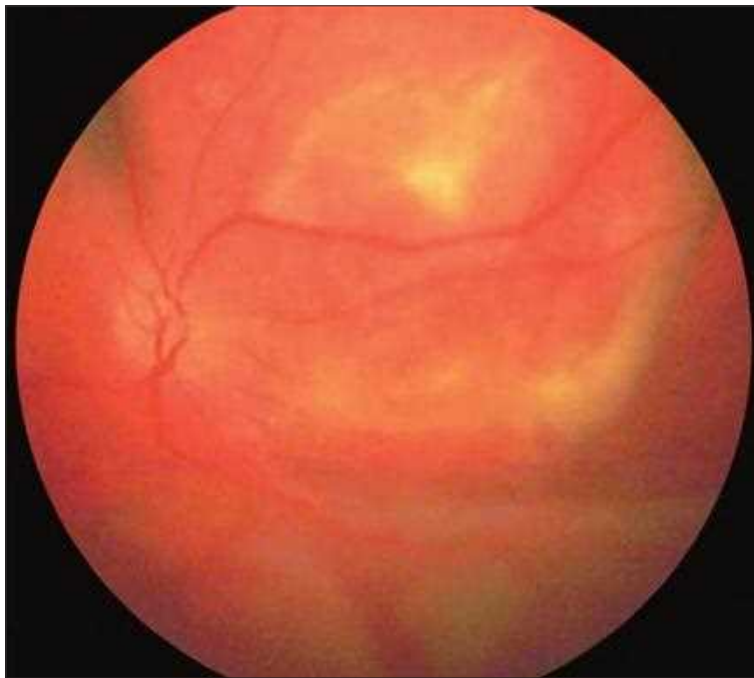


**Fig. 8.2.21** Classic Circumscribed Choroidal Hemangioma Appears as an Ill-Defined Reddish Choroidal Tumor. In virtually all cases, the posterior margin of the tumor is located within 2 disc diameters from the fovea, nearest optic disc margin, or both.

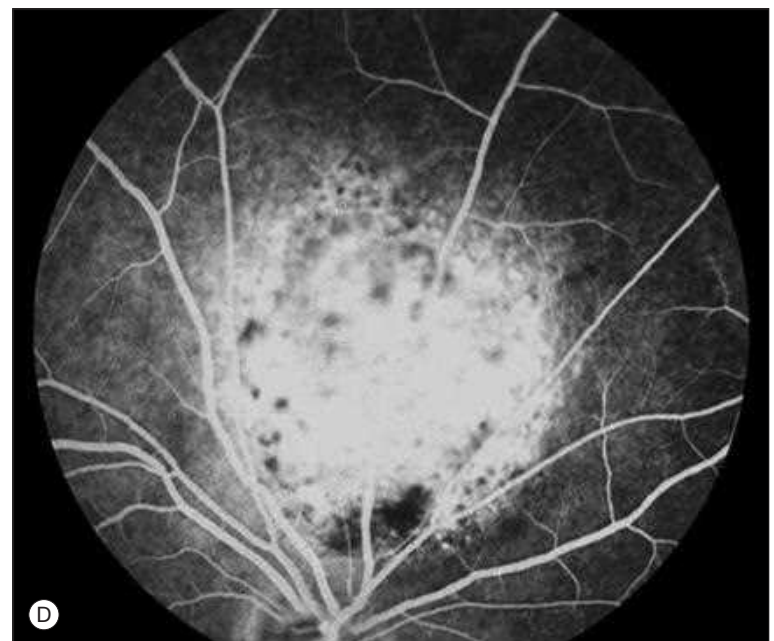
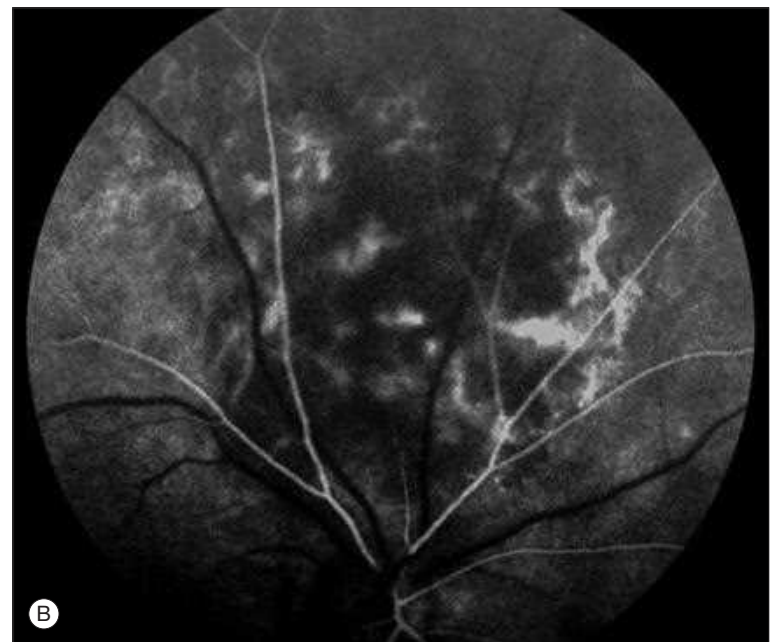
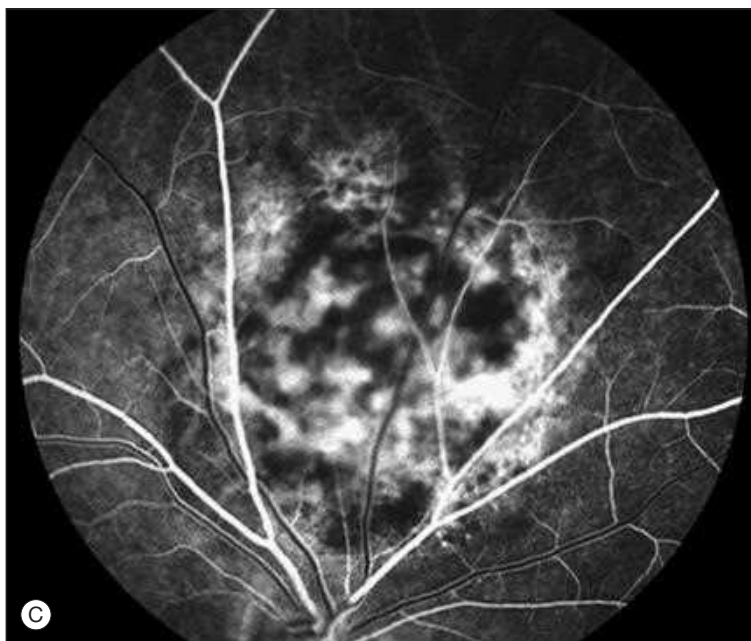
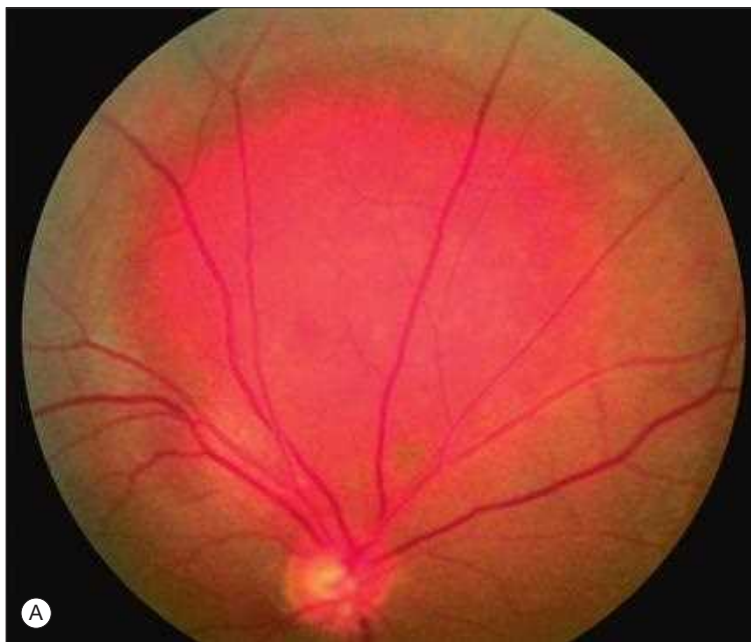
associated with a slowly progressive serous retinal detachment that can become bullous and total in some eyes with a larger tumor (Fig. 8.2.22).

Circumscribed choroidal hemangioma is generally confirmed by a combination of fluorescein or indocyanine green fundus angiography and B-scan ocular ultrasonography. Fluorescein angiography generally shows relatively rapid filling and late smudgy staining of the hemangioma (Fig. 8.2.23). Indocyanine green angiography generally shows better definition of the full extent of the hemangioma in the early to intermediate frames than does fluorescein angiography, and it also reveals late central washout of the dye that is characteristic of this type of tumor and rarely if ever encountered with other tumor types (Fig. 8.2.24). B-scan ocular ultrasonography of circumscribed choroidal hemangioma shows a fusiform to biconvex cross-sectional shape of the tumor and moderately bright internal sonorefectivity of the tumor (Fig. 8.2.25).

Photodynamic therapy is generally regarded as the treatment of choice for smaller visually symptomatic circumscribed choroidal hemangiomas.<sup>29</sup> This treatment usually gets the tumor to flatten partially and eliminates the associated serous subretinal fluid. Larger circumscribed choroidal hemangiomas associated with a bullous retinal detachment can be treated by low-dose episcleral plaque radiotherapy, proton beam irradiation, or conventional fractionated external beam radiation therapy.<sup>27</sup> This treatment induces partial flattening of the choroidal tumor and gradual reabsorption

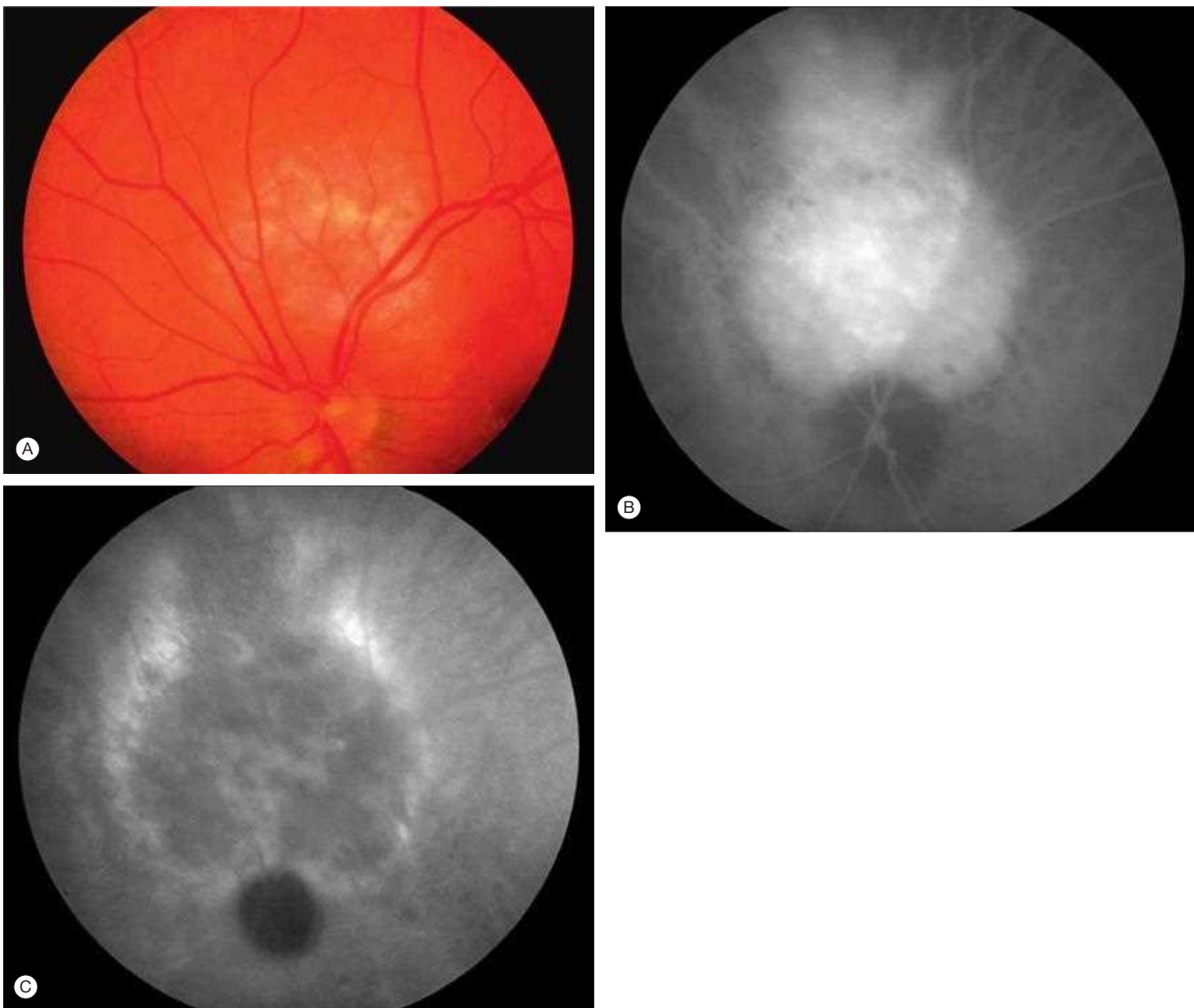


**Fig. 8.2.22 Relatively Large Circumscribed Choroidal Hemangioma Associated With Bullous Secondary Retinal Detachment.** Note white fibrous metaplasia of the retinal pigment epithelium on the surface of the tumor.

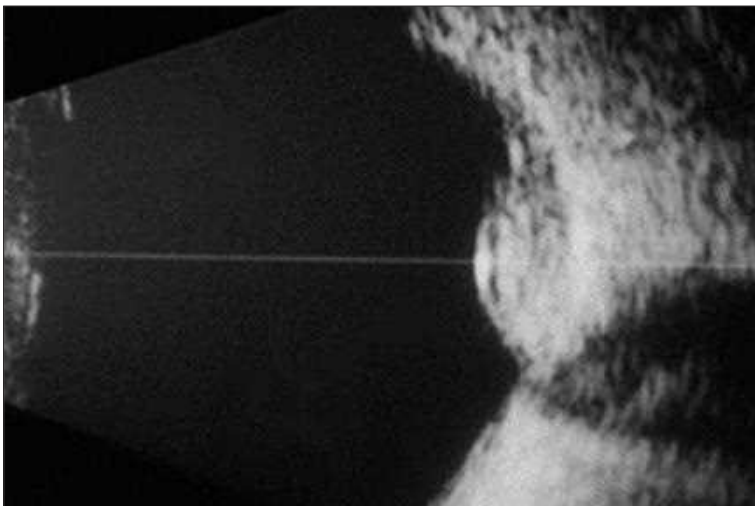


**Fig. 8.2.23 Fluorescein Angiogram of Circumscribed Choroidal Hemangioma.** (A) Color image of tumor. (B) Retinal arterial filling phase frame. (C) Retinal laminar venous filling phase frame. (D) Full venous filling phase frame.



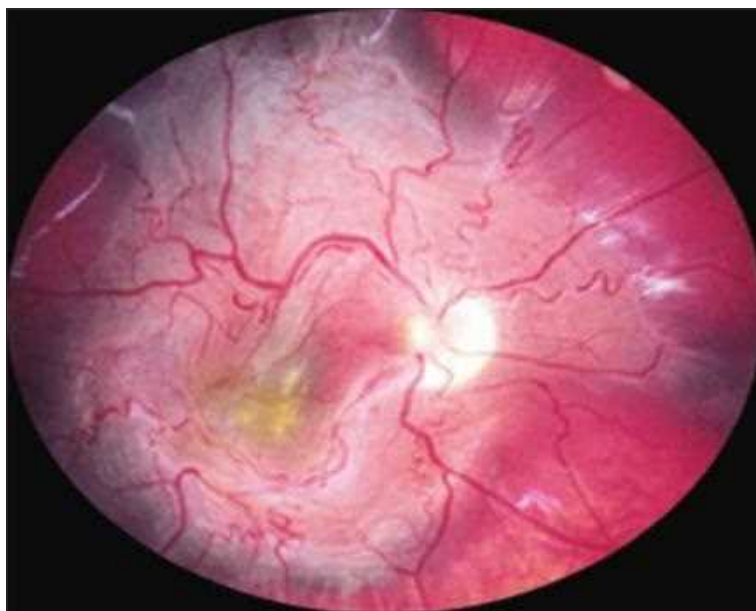


**Fig. 8.2.24 Indocyanine Green Angiogram of Circumscribed Choroidal Hemangioma.** (A) Color image of tumor. (B) Generalized hyperfluorescence of tumor about one minute after dye injection. (C) Central hypofluorescence with persistent marginal hyperfluorescence approximately 30 minutes following dye injection.



**Fig. 8.2.25 B-Scan Ultrasonography of Circumscribed Choroidal Hemangioma Shows Biconvex Cross-Sectional Shape of the Tumor, Moderately High Internal Sonorefectivity of the Tumor, and Presence of Associated Overlying Serous Retinal Detachment.**





**Fig. 8.2.26** Classic Combined Hamartoma of the Retina Appears as a Circumpapillary Retinal Lesion Having a Dark Gray Peripheral Marginal Component and Prominent Whitish Gliotic Inner Retinal Portion.

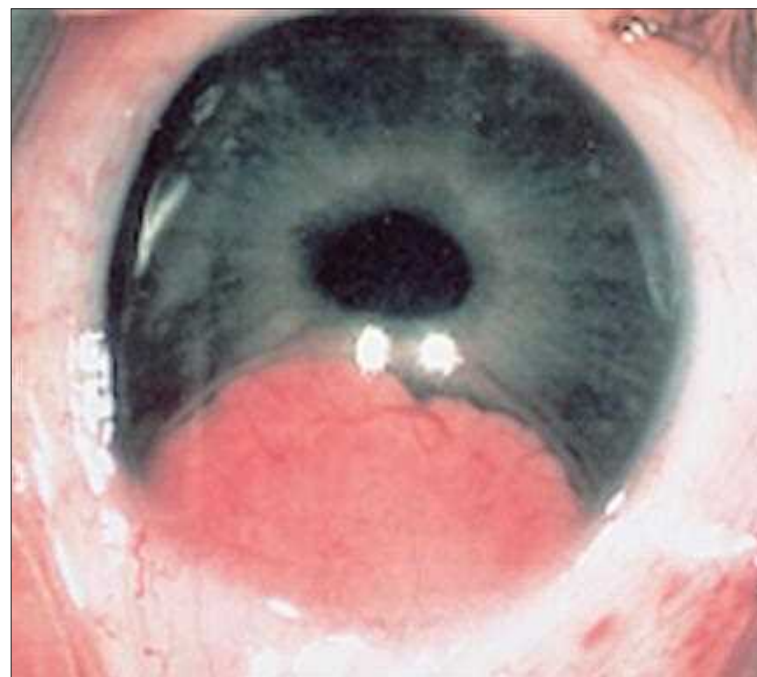


**Fig. 8.2.27** Peripheral Combined Hamartoma of Retina.

of the subretinal fluid. Fortunately, the circumscribed choroidal hemangioma has no recognized malignant potential.

### COMBINED HAMARTOMA OF THE RETINA

The combined hamartoma of the retina is a rare congenital hamartoma consisting of a focally abnormal overgrowth of disorganized retinal tissue.<sup>30,31</sup> The classic lesion appears as an irregular tumor with gray to black retinal pigment epithelial tissue at its base, whitish superficial gliosis, and angulated retinal blood vessels within the lesion (Fig. 8.2.26). Most such lesions develop on or adjacent to the optic disc, but occasional lesions with identical features have been documented in peripheral fundus locations (Fig. 8.2.27). The lesion exhibits remodeling of its shape over time but rarely enlarges to any clinically significant extent. This lesion is found most frequently in individuals with neurofibromatosis (NF) type 2 but also occurs in some persons with NF-1 and those without NF. This lesion shares many of the same clinical features as acquired vitreoretinal fibrosis due to some inciting event. Posterior vitrectomy with removal of vitreoretinal membranes causing tractional retinal detachment has been



**Fig. 8.2.28** Nodular Pink Congenital Tumor of Iris and Angle Prior to Microsurgical Resection.

reported in some individuals believed to have combined hamartoma of the retina<sup>32</sup> but is not usually beneficial in genuine cases. The principal risks of this lesion are marked visual impairment when the lesion involves the macula and its potential for clinical misdiagnosis as a choroidal melanoma or retinoblastoma, prompting enucleation. This lesion has no recognized malignant potential.

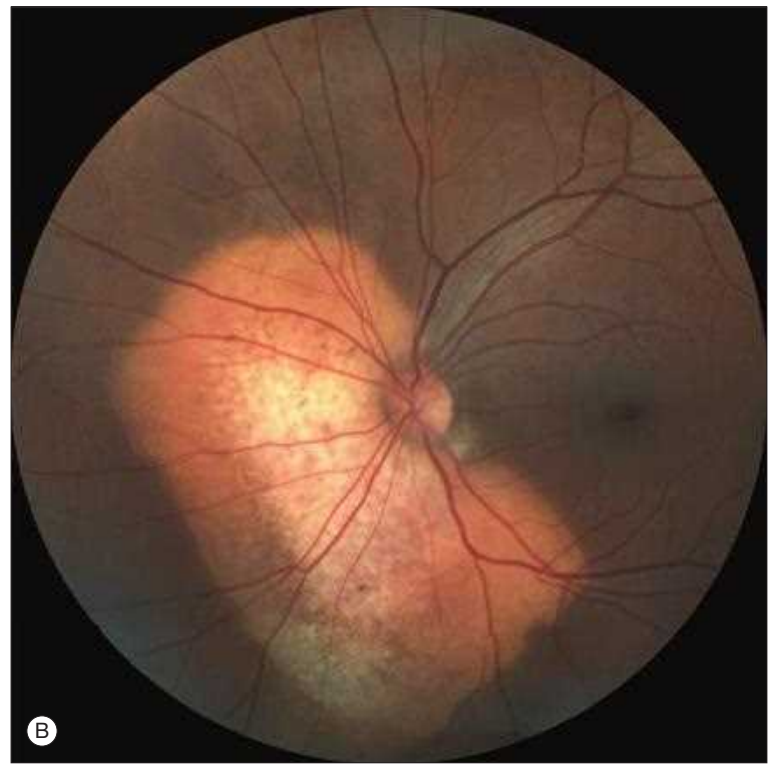
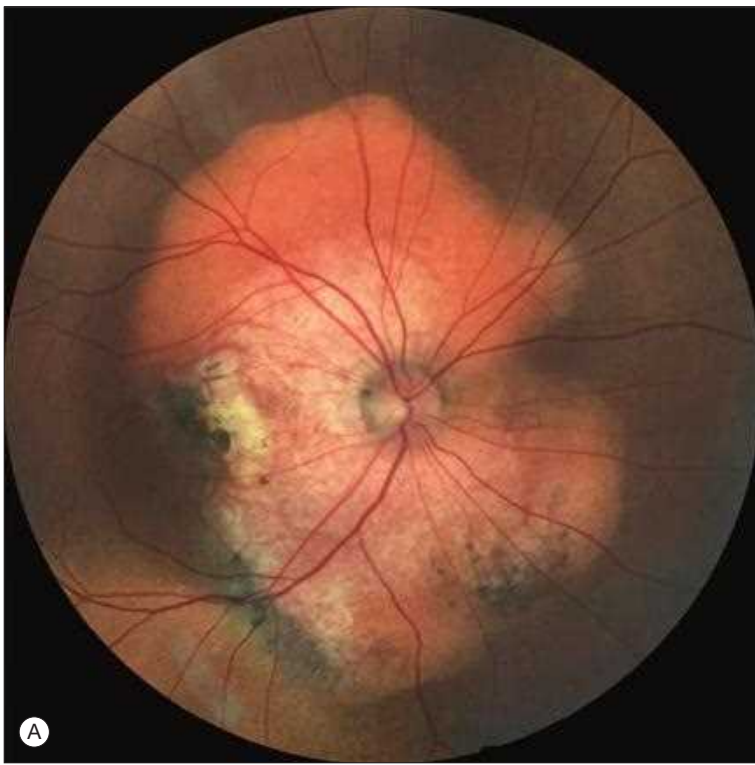
### INTRAOCULAR CHORISTOMAS

Several types of congenital intraocular choristomas have been reported, including ones consisting of lacrimal gland tissue,<sup>33</sup> thyroid gland tissue,<sup>34</sup> and brain tissue (glioneuroma).<sup>35</sup> The classic intraocular choristoma involves the iris and appears as a pink to off-white mass replacing a portion of the iris (Fig. 8.2.28). If an iris choristoma is suspected, it can be biopsied or excised to confirm the diagnosis. However, most cases have come to enucleation.

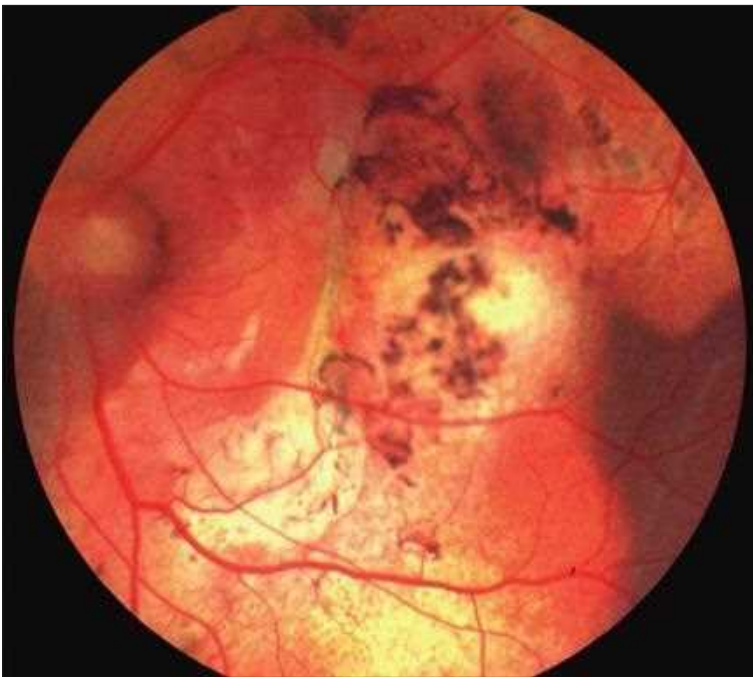
### BENIGN CELLULAR TUMORS OF UNCERTAIN CATEGORY

#### CHOROIDAL OSTEOMA

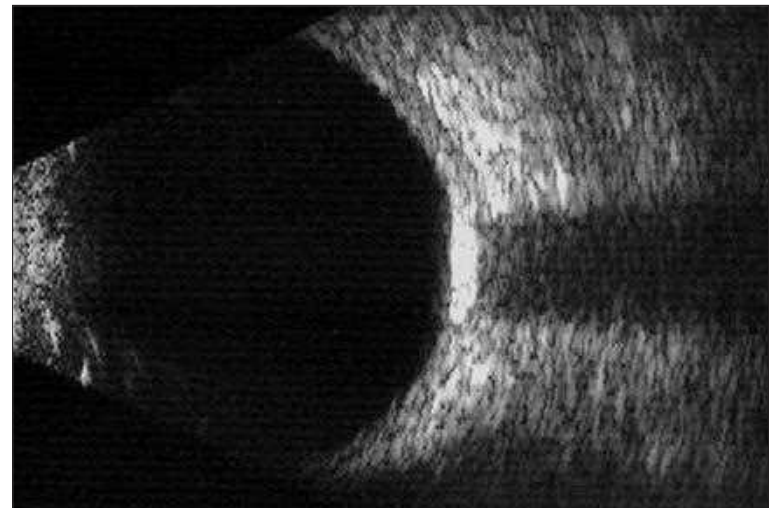
The choroidal osteoma is a benign acquired tumor consisting of mature bone that develops within the posterior choroid.<sup>36</sup> Although the presence of benign tissue of a type that does not exist normally within the choroid suggests that this tumor is a choristoma, no congenital tumor of this type has ever been documented. Most lesions of this type do not get diagnosed until the end of the first decade of life, and many are not detected until the second or third decade of life. The vast majority (approximately 90%) of such tumors occur in women, and they occur bilaterally in about 20% of cases. The typical choroidal osteoma appears as a posterior off-white to golden plate-like choroidal lesion with well-defined, smoothly curved margins (Fig. 8.2.29). Almost all documented tumors of this type involve the juxtapapillary choroid, and many extend partly or completely around the optic disc and through the fovea. The overlying retinal pigment epithelium is frequently disrupted with clumping of black pigment and patchy white fibrous metaplasia of the retinal pigment epithelium on the surface of the lesion (Fig. 8.2.30). Secondary choroidal neovascularization develops overlying many tumors of this type, with localized hemorrhagic or exudative detachment of the retina as a result.<sup>37</sup> The bony character of the tumor can be documented by ocular ultrasonography, which shows plate-like hyperreflective tissue that shadows the eye wall and orbital tissues behind



**Fig. 8.2.29 Classic Choroidal Osteoma Affecting Both Eyes of a Young Adult Woman.** Note well-defined smoothly curved margins and golden-orange color of each lesion. (A) Right eye fundus. (B) Left eye fundus.



**Fig. 8.2.30 Long-Standing Macular Choroidal Osteoma Causing Disruption of the Overlying Retinal Pigment Epithelium and Sensory Retina in the Macula.**



**Fig. 8.2.31 B-Scan Ultrasonography of Choroidal Osteoma Showing Dense Plate-Like Lesion That Shadows the Sclera and Orbital Soft Tissues Behind It.**



**Fig. 8.2.32 Computed Tomography Scan of a Patient With Bilateral Extensive Choroidal Osteoma Showing Posterior Plate-Like Bone-Dense Posterior Eye Wall Lesion Bilaterally.**

it (Fig. 8.2.31), or CT scanning, which shows a plate of bone-dense tissue within the posterior choroid (Fig. 8.2.32).

Photodynamic therapy has been reported to cause “decalcification” of the treated portion of some choroidal osteomas but does not eliminate or prevent progression of the lesion.<sup>38</sup> Intravitreal anti-VEGF drug therapy can be used to treat secondary choroidal neovascularization with exudative-hemorrhagic retinal detachment that develops over some lesions. In most cases, the visual prognosis for the affected eye is poor. Limited, slowly progressive enlargement of choroidal osteomas has been documented by multiple examiners. Fortunately, this tumor has no recognized malignant potential.

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# Non-Neoplastic Intraocular Lesions and Disorders Simulating Malignant Intraocular Neoplasms

## 8.3

James J. Augsburger, Zélia M. Corrêa, Cassandra C. Brooks

**Definition:** Spectrum of non-neoplastic lesions and disorders that are frequently mistaken for malignant intraocular neoplasms.

### Key Features

Clinical features resembling one or more of the following malignant intraocular neoplasms:

- Primary uveal melanoma.
- Extraophthalmic cancer metastatic to eye.
- Primary intraocular lymphoma.
- Retinoblastoma.

### INTRODUCTION

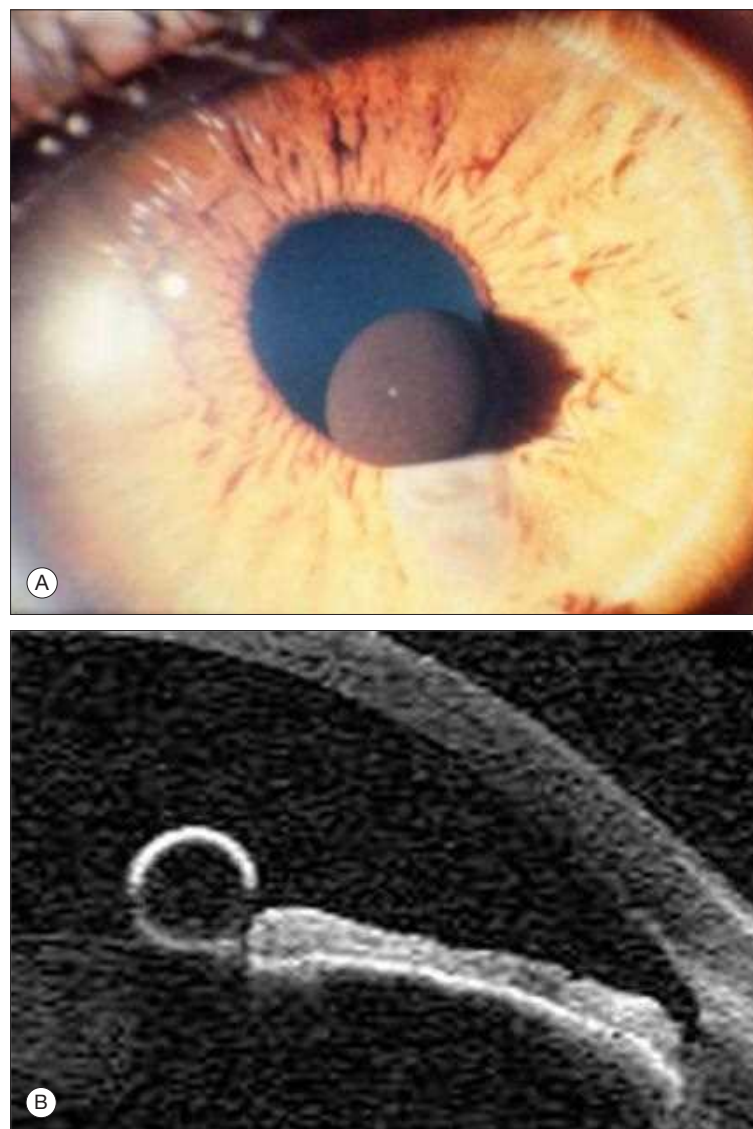
The lesions and disorders discussed in this chapter are all non-neoplastic lesions and disorders that (in certain clinical presentations) can be mistaken for one or more of the four intraocular malignant neoplasms listed in the Key Features. The chapter is subdivided into (1) lesions and disorders simulating malignant intraocular neoplasms of the anterior ocular segment, (2) lesions and disorders simulating malignant intraocular neoplasms of the posterior ocular segment other than retinoblastoma (i.e., posterior uveal melanoma, metastatic cancer to the posterior segment, and intraocular lymphoma), and (3) lesions and disorders simulating the different clinical forms of retinoblastoma.

### NON-NEOPLASTIC LESIONS AND DISORDERS SIMULATING MALIGNANT INTRAOCULAR NEOPLASMS OF THE ANTERIOR OCULAR SEGMENT

#### NEUROEPITHELIAL CYSTS OF IRIS AND CILIARY BODY

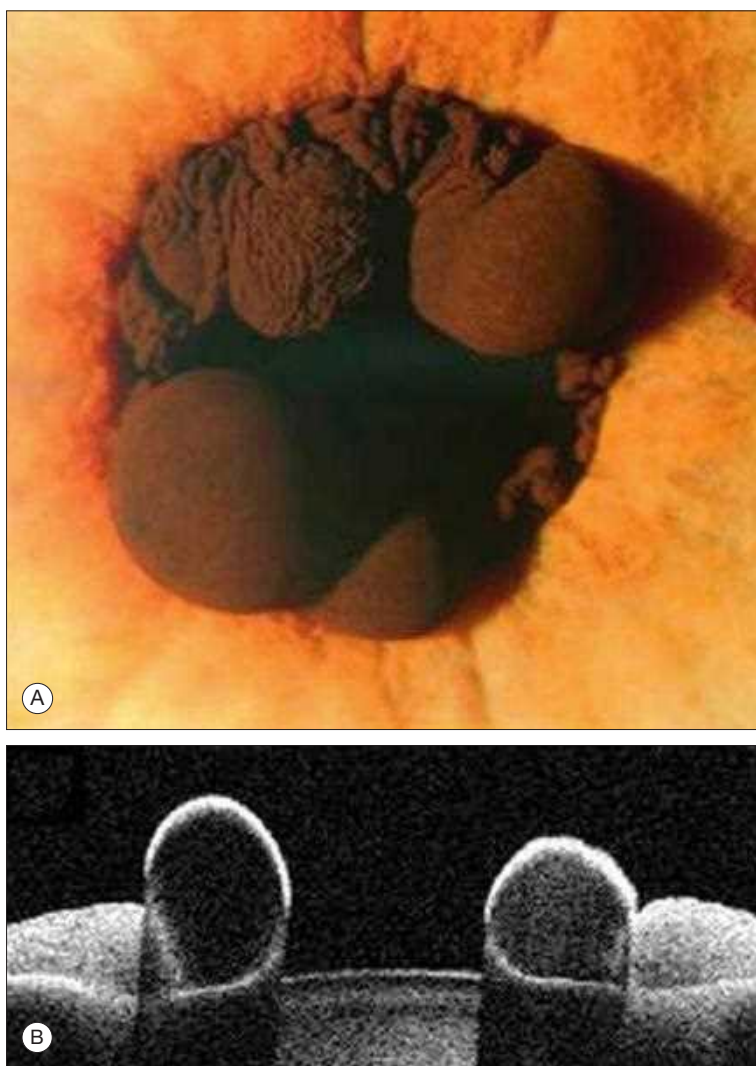
Neuroepithelial cysts of the iris and ciliary body are thin-walled spheres filled with clear serous fluid.<sup>1</sup> The wall can be formed by the iris pigment epithelium (IPE), resulting in a dark brown color, or by anterior ciliary body neuroepithelium (CBNE), resulting in a translucent appearance. The cause of such cysts is unknown in most cases. Neuroepithelial cysts that occur as isolated lesions without an associated underlying cause are referred to as idiopathic cysts. Three principal varieties are encountered clinically based on the site of the lesion.

**Pupillary zone cysts of the iris pigment epithelium** are evident at the pupillary margin prior to pupillary dilation. They can be solitary (Fig. 8.3.1) or multifocal (Fig. 8.3.2), in which case the term *iris flocculi* is commonly applied. They do not distort the pupil or interfere with pupillary dilation. Ultrasound biomicroscopy (UBM) or anterior segment optical coherence tomography (AS-OCT) can be used to confirm the cystic nature of these lesions. **Peripheral neuroepithelial cysts of the iris** appear as smooth anterior bulges in the peripheral iris evident on slit-lamp biomicroscopy and



**Fig. 8.3.1 Cyst of Pupillary Zone of Iris Pigment Epithelium.** (A) Color image of cyst. (B) Ultrasound biomicroscopic image of cyst shown in A.

gonioscopy (Fig. 8.3.3). The anteriorly displaced iris stroma appears unremarkable. Focal iridocorneal apposition corresponding to the location of the cyst is frequently present. Occasionally, transpupillary retroillumination of the iris at the slit lamp will reveal a faint focal transillumination defect corresponding to the cyst. Gonioscopy following wide pupillary dilation can sometimes show the smooth wall of the cyst. However, UBM and AS-OCT are the currently preferred methods for confirming the cystic lesion, as opposed to a solid tumor, as the primary cause of the iris bulge (Fig. 8.3.3B). These studies frequently reveal multiple cysts when only one



**Fig. 8.3.2 Multifocal Cysts of Pupillary Zone of Iris Pigment Epithelium (Iris Flocculi).** (A) Color image of *iris flocculi*. (B) Ultrasound biomicroscopic image of iris cysts shown in A.

was suspected on ophthalmic physical examination. **Midzonal cysts of the iris pigment epithelium** are not evident on slit-lamp examination prior to pupillary dilation but appear as a dark brown retroiridic ridge-shaped mass projecting in front of the lens when the pupil is widely dilated (Fig. 8.3.4A). The overlying iris stroma appears normal. The cyst can appear bilobed (Fig. 8.3.4B) or multilobed. Cysts of this type are commonly mistaken for ciliary body melanomas. AS-OCT or UBM confirms the cystic nature of the lesion in such cases (Fig. 8.3.4C) and rules out a solid iridic or ciliary body melanoma.

### EPITHELIAL INCLUSION CYST OF IRIS

An epithelial inclusion cyst of the iris is a thick-walled spherical or irregularly shaped structure containing relatively turbid fluid in which discrete particles are suspended.<sup>2</sup> The wall of the cyst is composed of conjunctival epithelial cells, and the intracavitary particles are desquamated ocular surface squamous epithelial cells. The ocular surface epithelium is embedded in the iris either as a congenital malformation of the eye or as a result of eye wall perforation (which may be surgical or nonsurgical trauma). This type of cyst is an off-white to bluish gray mass that replaces the iris stroma and distorts the architecture of the iris and shape of the pupil (Fig. 8.3.5A). Such lesions can be mistaken for amelanotic anterior uveal melanoma or a nonophthalmic primary malignant neoplasm metastatic to the iris. UBM shows the thick wall of the cyst and suspended intracavitary squamous epithelial cells (Fig. 8.3.5B).

### ANTERIOR SCLERAL STAPHYLOMA

In some patients with prior focal ocular injury, scleral inflammation, or ischemia, a focal area of bluish brown scleral thinning (Fig. 8.3.6) will

develop.<sup>3</sup> The intraocular pressure can cause the thinned portion of the eye wall to bulge externally. Anterior staphylomas frequently are mistaken for ciliary body melanomas with extraocular extension. Ocular transillumination generally reveals bright transillumination rather than a dark shadow corresponding to the bulge. UBM confirms thinning of the eye wall and absence of any underlying uveal or neuroectodermal mass.

### IRIDOCORNEAL ENDOTHELIAL SYNDROME

The iridocorneal endothelial (ICE) syndrome is a developmental disorder of the eye characterized by acquired nontraumatic corneal edema, progressive abnormalities of the iris, and elevated intraocular pressure.<sup>4,5</sup> Three subcategories of ICE syndrome are commonly recognized: essential iris atrophy, the iris nevus syndrome (Cogan–Reese syndrome), and Chandler’s syndrome. Only the first two of these entities are relevant to this discussion. In **essential iris atrophy**, the spontaneous development of high peripheral anterior synechiae (PAS) occurs, leading to progressive thinning with eventual hole formation of the iris 180° opposite the original adhesions (Fig. 8.3.7).<sup>5</sup> The pupil is gradually displaced toward the PAS. This condition is usually unilateral and most commonly affects middle-aged to older women. AS-OCT or UBM can be used to rule out an iridic or ciliary body melanoma. In **iris nevus syndrome**, multiple focal dark brown to almost black bumps of melanotic iris tissue develop on the anterior surface of the iris. These bumps are due to melanotic tissue projecting through small defects in an abnormal basement membrane (Fig. 8.3.8).<sup>4</sup> In most cases, the presence of shiny basement membrane tissue on the anterior surface of the iris and the multifocal nature of the iris lesions allow one to distinguish this condition from diffuse iris melanoma. AS-OCT or UBM will show absence of any solid ring melanoma of the peripheral iris or anterior ciliary body.

### INFLAMMATORY TUMOR OF IRIS OR CILIARY BODY

Occasionally individuals will develop a microbial inflammatory tumor of the iris or ciliary body (e.g., tuberculoma,<sup>6</sup> fungal granuloma<sup>7</sup>) due to hematogenous dissemination of micro-organisms to that portion of the uvea. Others will develop various nonmicrobial inflammatory tumors (most commonly sarcoid granulomas<sup>8</sup> and lesions of juvenile xanthogranuloma<sup>9,10</sup>) in the iris or ciliary body (Fig. 8.3.9). Lesions of these types are usually unilateral but can be bilateral. They are characterized by prominent inflammatory cells in the anterior chamber, keratic precipitates, posterior synechiae with resultant pupillary distortion, and occasionally hypopyon. Such inflammatory tumors can easily be mistaken for nonophthalmic primary cancers metastatic to the anterior uvea.

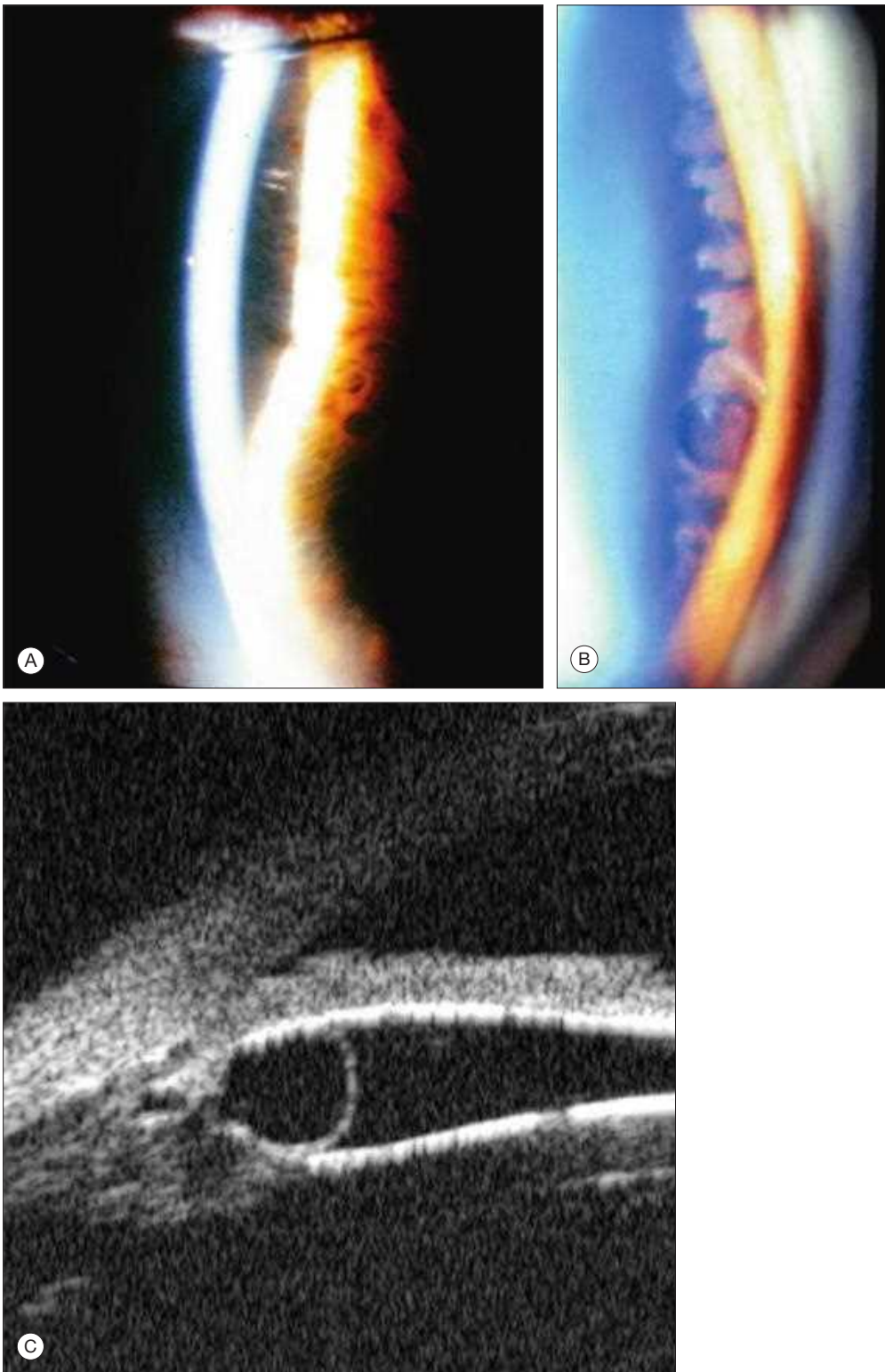
### IRIS FOREIGN BODY

Occasionally intraocular foreign bodies simulate an anterior uveal melanoma (Fig. 8.3.10).<sup>11,12</sup> The patient generally recalls a prior ocular injury but is frequently unaware that any foreign body perforated the eye wall. Slit-lamp biomicroscopy shows a localized mass of the peripheral iris associated with focal iridocorneal adhesion. An entry wound is frequently not evident. UBM can show the presence of a dense hyperreflective body within the mass.<sup>13</sup>

### ADVANCED CATARACT SIMULATING CILIARY BODY MELANOMA ON B-SCAN ULTRASONOGRAPHY

When B-scan ultrasonography (US) is performed on some eyes with an advanced opaque cataract and peripheral fundus imaging is attempted from across the eye, the US beam can pass through the posterior aspect of the enlarged cataractous lens and thereby form a cross-sectional image that appears to show a ciliary body mass (Fig. 8.3.11).<sup>14</sup> In most cases, the same finding can be demonstrated in all quadrants of the eye. At the same time, ocular transillumination demonstrated no ciliary body shadow and UBM demonstrates the enlarged lens.





**Fig. 8.3.3 Cyst of Peripheral Zone of Iris Pigment Epithelium.** (A) Slit-lamp biomicroscopic image showing smooth anterior bulge in peripheral iris corresponding to location of the cyst. (B) Ultrasound biomicroscopic image showing thin-walled cyst containing clear fluid. (C) Ultrasound biomicroscopic image of typical peripheral zone cyst of iris pigment epithelium.

## NON-NEOPLASTIC LESIONS AND DISORDERS SIMULATING MALIGNANT INTRAOCULAR NEOPLASMS OF THE POSTERIOR OCULAR SEGMENT OTHER THAN RETINOBLASTOMA

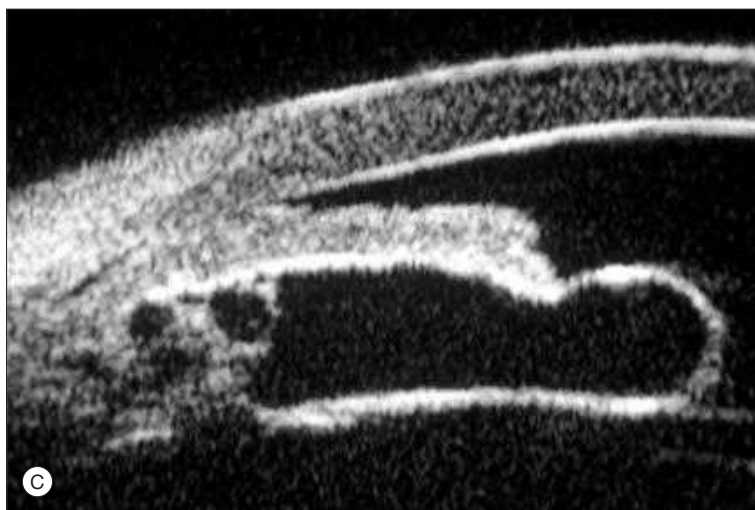
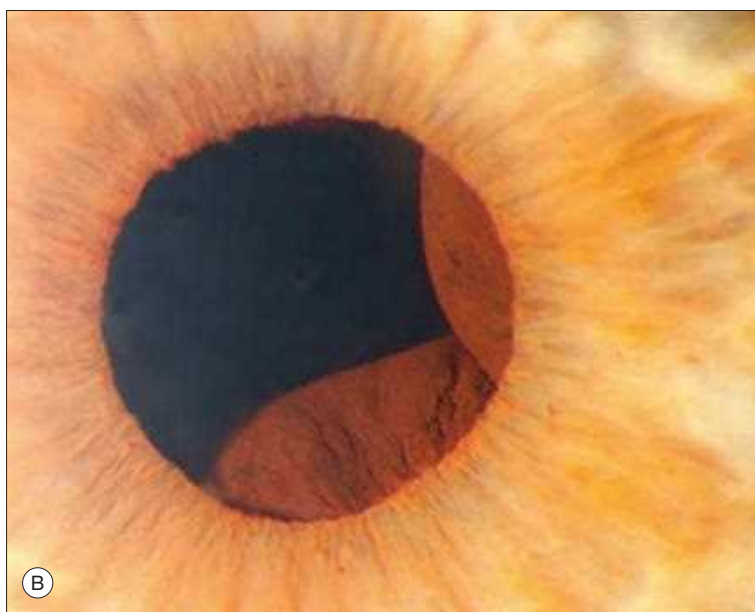
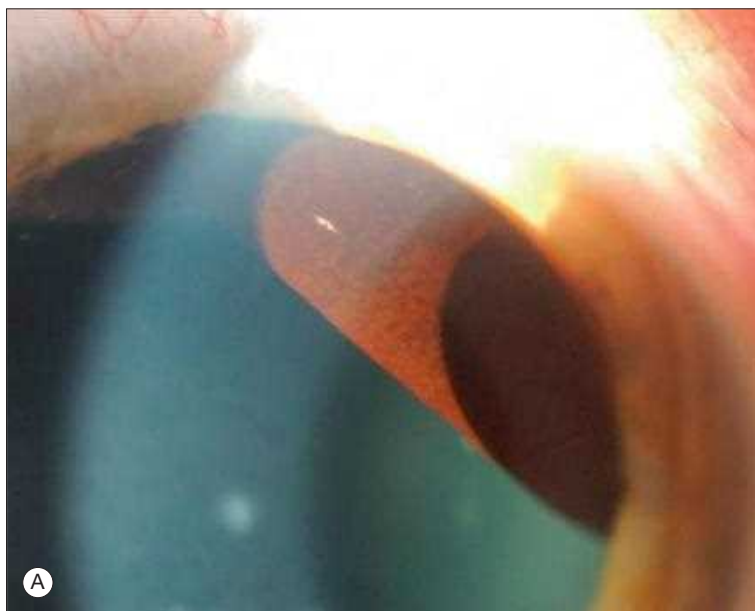
### CONGENITAL HYPERTROPHY OF RETINAL PIGMENT EPITHELIUM

Congenital hypertrophy of retinal pigment epithelium (CHRPE) is a non-neoplastic birthmark lesion of the fundus localized to the retinal pigment epithelium (RPE).<sup>15</sup> The RPE cells comprising this lesion are generally taller than normal and densely packed with intracytoplasmic melanin granules. The lesion has a well-defined margin and black to dark gray-brown color. Although the typical unifocal CHRPE lesion is 3 mm

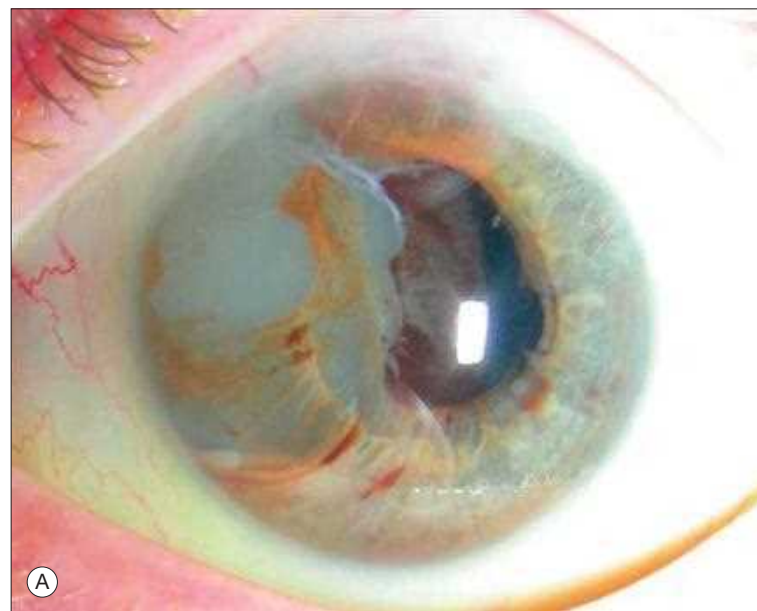
or smaller in diameter, some are substantially larger (Fig. 8.3.12). Because of their dark color, larger CHRPE lesions are frequently suspected to be choroidal melanomas, particularly if a cataract is present that degrades the clarity of the fundus view. B-scan ocular ultrasonography demonstrates a flat or insignificantly elevated lesion. Rarely, one of these lesions spawns an adenocarcinoma of the RPE.<sup>16,17</sup> Because of this, such lesions should be monitored periodically.

### FOCAL RETINAL PIGMENT EPITHELIAL HYPERPLASIA

Patients who suffer blunt trauma or localized intraocular inflammation sometimes develop a localized area of RPE hyperplasia that can be somewhat thickened (Fig. 8.3.13).<sup>18,19</sup> The lesion generally appears as an irregular, poorly defined mass consisting of localized nodular accumulation



**Fig. 8.3.4 Cyst of Intermediate Zone of Iris Pigment Epithelium.** (A) Solitary cyst appearing as dark ridge-like mass between posterior surface of iris and anterior lens capsule following wide pupillary dilation. (B) Bilobed cyst of intermediate zone of iris pigment epithelium evident following pupillary dilation. (C) Ultrasound biomicroscopic image showing retroiridic cyst projecting into the pupil following pupillary dilation.

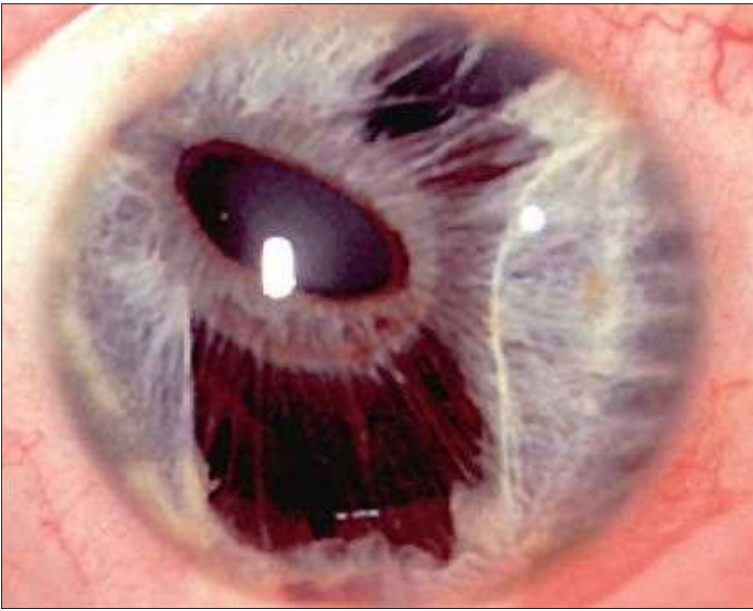


**Fig. 8.3.5 Epithelial Inclusion Cyst of Iris (Stomal Cyst).** (A) Opalescent cyst replacing portion of iris stroma. (B) Ultrasound biomicroscopic image showing thick-walled bilobed cyst containing numerous particles (desquamated epithelial cells) in the intracavitary fluid.



**Fig. 8.3.6 Anterior Scleral Staphyloma Appears as a Subconjunctival Bluish Gray Ridge-Shaped Protrusion of the Sclera.**

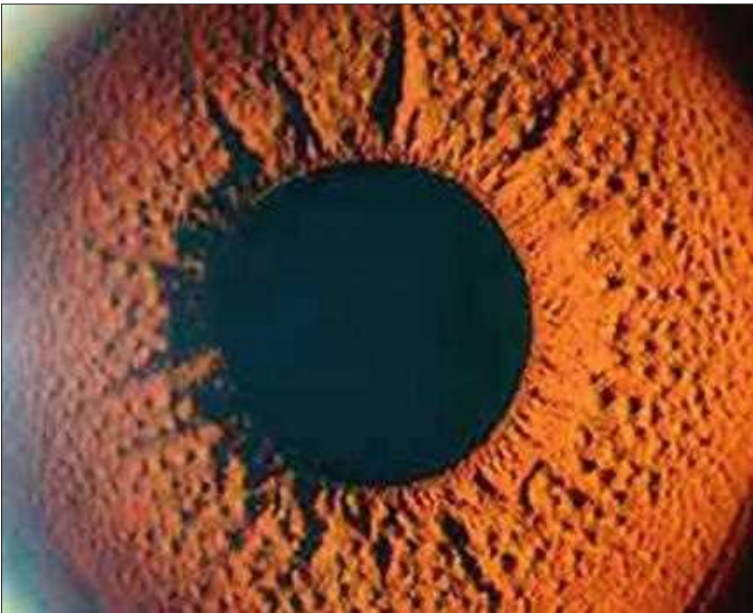




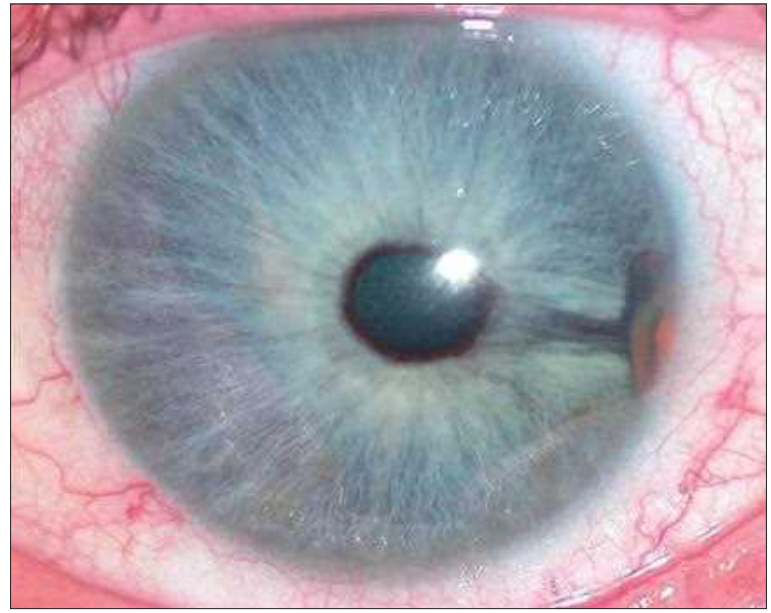
**Fig. 8.3.7 Essential Iris Atrophy.** The pupil is ovoid in shape and drawn toward the limbus superonasally, with prominent holes evident in the iris stroma.



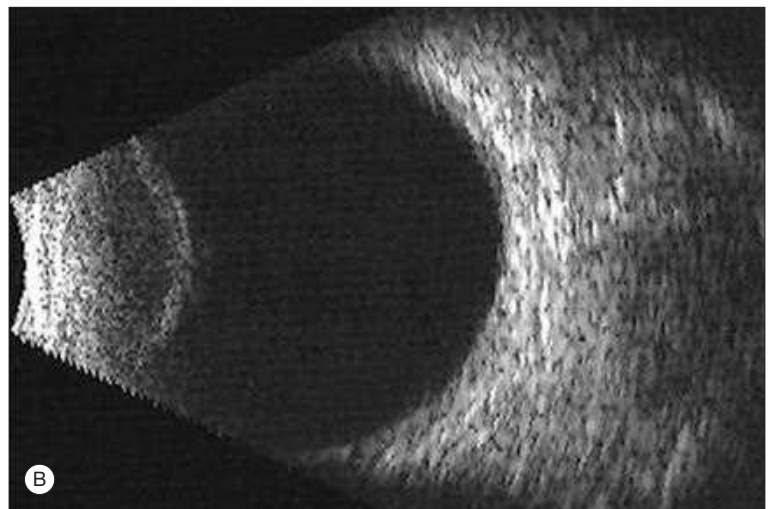
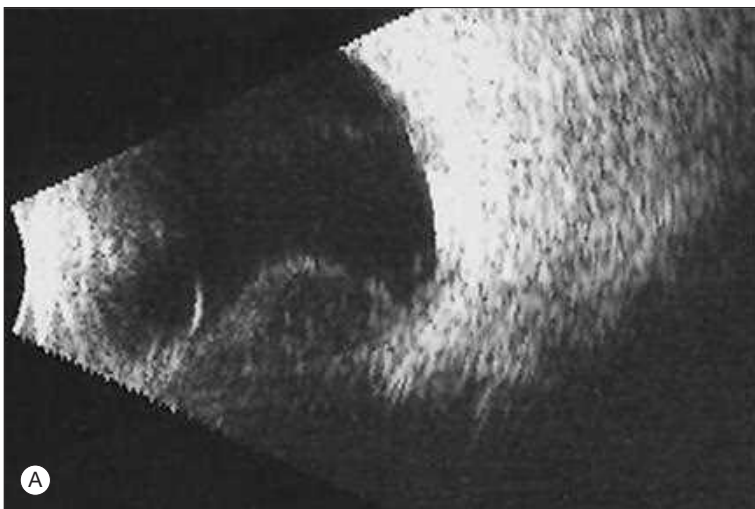
**Fig. 8.3.9 Inflammatory Tumor of Iris (Sarcoid Granuloma).** Note the multiple associated keratic precipitates in this eye.



**Fig. 8.3.8 Iris Nevus Syndrome.** The inner surface of the iris appears to have multiple tiny nodular melanotic protrusions or tufts.

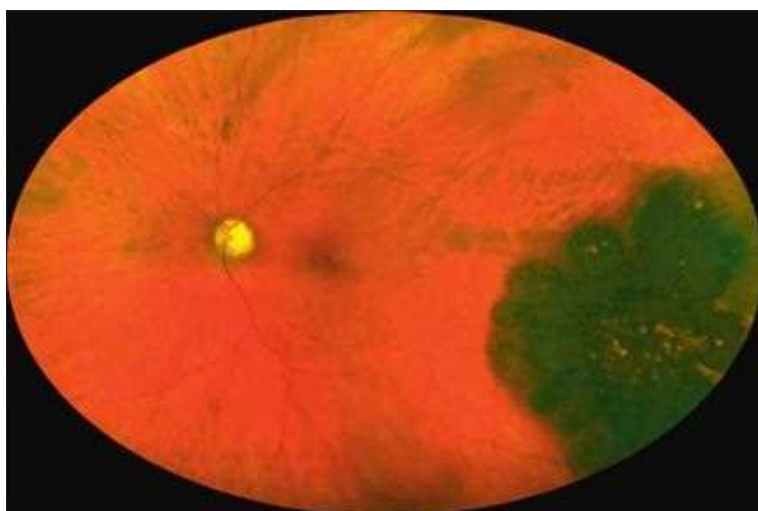


**Fig. 8.3.10 Encapsulated Iris Foreign Body Following Prior Ocular Injury.**



**Fig. 8.3.11 B-Scan Ultrasonographic Images of Advanced Cataract Suggesting the Presence of a Ciliary Body Neoplasm.** (A) Anteroposterior slice through cataract. (B) Transverse slice through cataract.





**Fig. 8.3.12** Large Peripheral Unifocal Congenital Hypertrophy of the Retinal Pigment Epithelium (CHRPE).

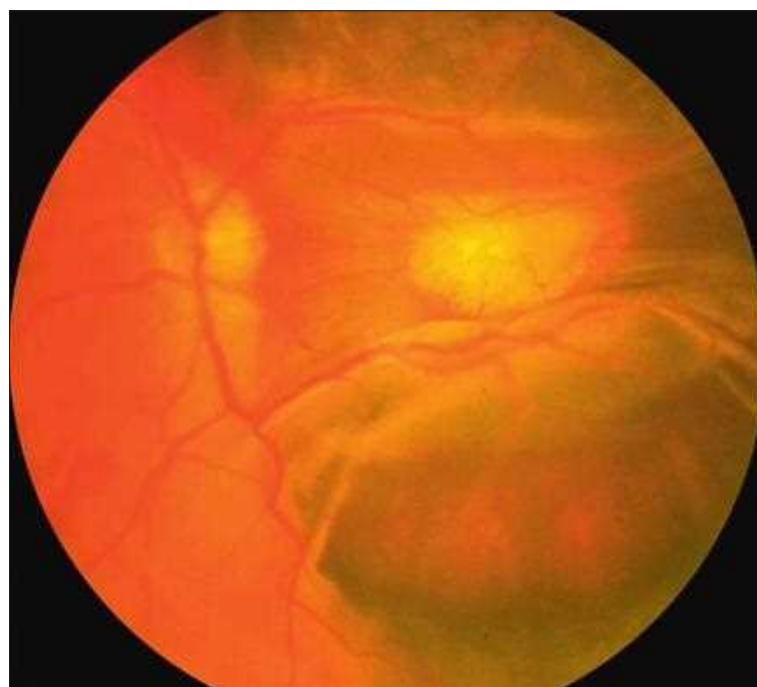


**Fig. 8.3.13** Focal Retinal Pigment Epithelial Hyperplasia in Macular Region. Note Black Color and Irregular Margins of Lesion.

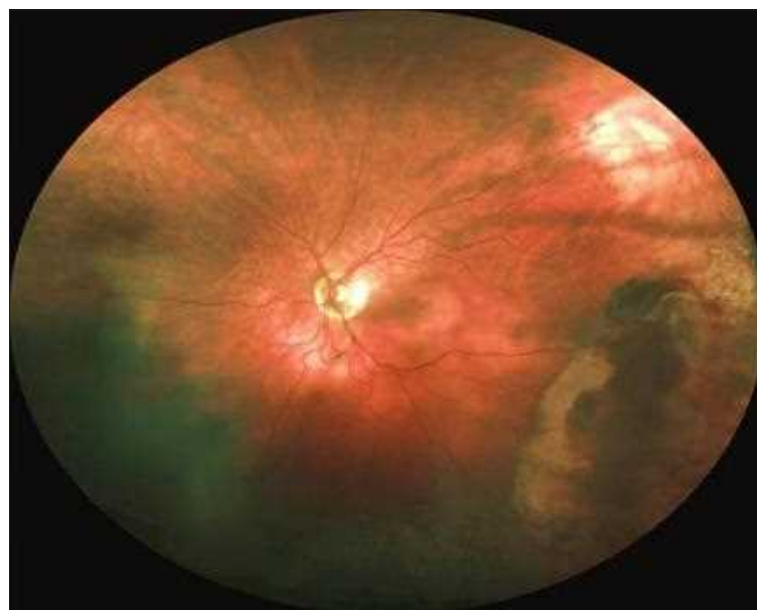
of black RPE pigment with surrounding chorioretinal atrophy. Because of its dark color, such a lesion is occasionally mistaken for a choroidal melanoma. There is usually no subretinal fluid associated with the lesion. B-scan ocular US confirms the presence of moderately hyperreflective soft tissue corresponding to the fundus lesion.

### SPONTANEOUS SUBRETINAL HEMATOMAS

Subretinal hematomas are masses composed of extravasated blood accumulated between the sensory retina and RPE or between the RPE and choroid.<sup>20</sup> The hematoma appears as a dark red to almost black subretinal mass that is usually bordered by a thin marginal zone of bright red subretinal blood. Because of its dark color and thickness, such a hematoma is frequently mistaken for a choroidal melanoma. The most common source of the blood is a choroidal neovascular membrane–associated age-related macular degeneration<sup>21</sup> (Fig. 8.3.14) or peripheral exudative-hemorrhagic chorioretinopathy (Fig. 8.3.15).<sup>22,23</sup> Choroidal neovascularization that is polypoidal in character is particularly likely to give rise to subretinal hematomas.<sup>22</sup> Chorioretinal atrophy is frequently evident adjacent to the hematoma in affected eyes, and fibrous organization of prior subretinal blood is frequently present as well. In most patients, the underlying disorder is evident bilaterally, but its clinical manifestations may be markedly asymmetrical. An alternative source of the blood that closely simulates



**Fig. 8.3.14** Massive Subretinal Hematoma Associated With Age-Related Macular Degeneration.



**Fig. 8.3.15** Massive Peripheral Subretinal Hematoma Associated With Peripheral Exudative-Hemorrhagic Chorioretinopathy.

choroidal melanoma is a retinal arterial macroaneurysm that has ruptured (Fig. 8.3.16).<sup>24,25</sup> Blood from this retinal vascular lesion generally extends not only into the subretinal space under the macroaneurysm but also into the retina and overlying vitreous. The preretinal blood frequently obscures the macroaneurysm. When the macroaneurysm is visible, it is frequently misinterpreted as a focal eruption of a choroidal melanoma through Bruch's membrane. Fluorescein angiography frequently reveals focal hyperfluorescence corresponding to the macroaneurysm that helps to identify the source of the bleeding.

### LOCALIZED SUPRACHOROIDAL HEMATOMA

Localized suprachoroidal hematomas (sometimes referred to as limited hemorrhagic choroidal detachments) are an accumulation of blood between the outer layers of the choroid and the overlying sclera.<sup>26</sup> This type of hematoma generally appears as a golden brown subretinal mass (Fig. 8.3.17) that is commonly misidentified as a choroidal melanoma. Unlike a subretinal hematoma, the localized suprachoroidal hematoma shows no marginal zone of thin bright red subretinal blood. The surface of the

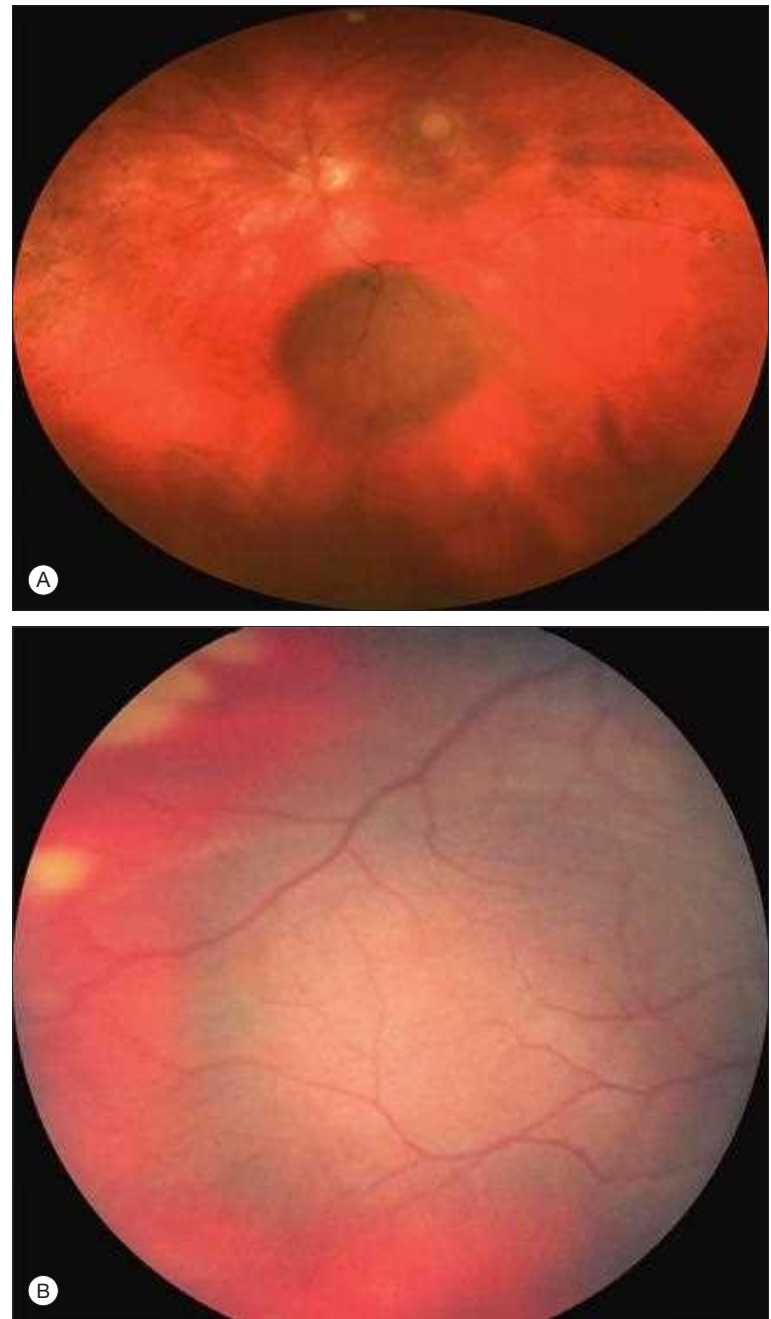


**Fig. 8.3.16 Subretinal Hematoma and Intraretinal Bleeding from Ruptured Macroaneurysm of Retinal Artery.** (A) Relatively fresh lesion with bright red blood except for the subretinal hematoma under the macroaneurysm. (B) Older lesion with dark gray to off-white subretinal blood deep to macroaneurysm and dark red intraretinal blood around macroaneurysm.

mass is generally smooth and bland, and the color of the mass is generally uniform. If the hematoma has been present for several days already, a series of choroidal folds is frequently present overlying the mass. Such folds are not evident over choroidal melanomas. On fluorescein angiography, the mass shows mild choroidal hypofluorescence of its marginal zone but exhibits central isofluorescence with surrounding normal choroid. In most cases, hematomas of this type resolve completely without chorioretinal scarring within approximately 6–8 weeks.

### ACQUIRED NONFAMILIAL RETINAL HEMANGIOMATOUS LESION

A proliferation of both glial cells and retinal blood vessels that develops in the fundus periphery in response to chorioretinal ischemia or inflammation is known by a variety of names, including acquired nonfamilial retinal hemangiomatous lesion, retinal vasoproliferative tumor, and peripheral



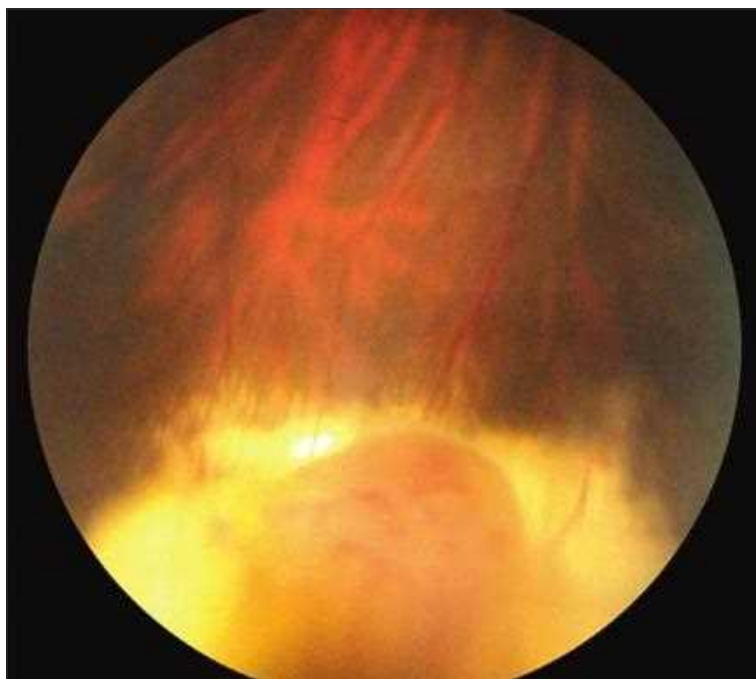
**Fig. 8.3.17 Localized Suprachoroidal Hematoma.** (A) Wide-field image showing dark color of the hematoma. (B) Suprachoroidal hematoma exhibiting choroidal folds on its surface.

exudative hemangiomatous chorioretinal gliovascular tumor.<sup>27,28</sup> This lesion appears as an off-white peripheral chorioretinal tumor having an irregular network of retinal blood vessels on its inner surface (Fig. 8.3.18). Unlike a retinal capillary hemangioma, this tumor does not exhibit any dilated tortuous afferent or efferent retinal blood vessels. However, an exudative intraretinal and subretinal response is frequently associated with the tumor. Most lesions of this type develop in the oral zone of the fundus inferotemporally in middle-aged to older individuals. However, a substantial percentage of these lesions are more posterior in the fundus and associated with an underlying disorder such as pars planitis or retinitis pigmentosa (Fig. 8.3.19).<sup>27</sup> Although tumors of this type are not darkly pigmented, they are frequently misdiagnosed as choroidal melanomas that have erupted through Bruch's membrane in the fundus periphery.

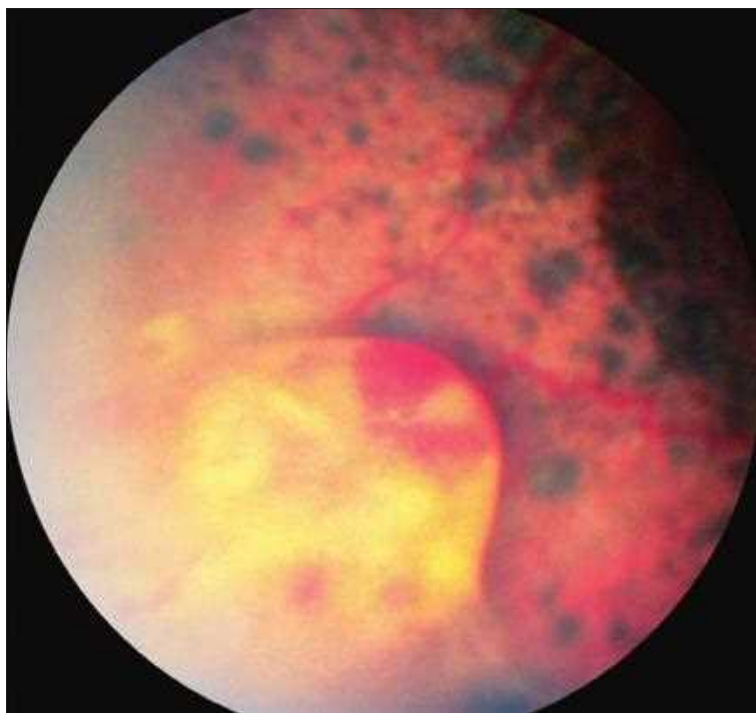
### NODULAR POSTERIOR SCLERITIS

Nodular posterior scleritis is a nonmicrobial inflammatory disorder that affects a localized portion of the posterior sclera.<sup>29–31</sup> The eye is usually uncomfortable (achy and tender) and intensely erythematous (Fig. 8.3.20A). The lesion appears as a nodular or ridge-like posterior subretinal mass that is usually golden-brown to pale in color (Fig. 8.3.20B–C). These masses are frequently misdiagnosed as amelanotic choroidal or ciliochoroidal





**Fig. 8.3.18** Typical Idiopathic Peripheral Acquired Nonfamilial Retinal Hemangiomatous Lesion (Vasoproliferative Tumor). Note the off-white color of the tumor, presence of abnormal retinal blood vessels on the surface of the lesion, and associated subretinal exudates.



**Fig. 8.3.19** Secondary Acquired Nonfamilial Retinal Hemangiomatous Lesion Associated With Retinitis Pigmentosa.

melanomas. Marginal choroidal folds concentric to the mass are evident in many cases. A secondary serous retinal detachment is frequently associated with the lesion. The condition can usually be distinguished from choroidal melanoma by ocular B-scan ultrasonography, which confirms moderately sonoreflective fusiform thickening of the involved posterior sclera and the presence of a retrobulbar sonolucent cleft of inflammatory fluid (Fig. 8.3.20D) rather than the low internal sonoreflectivity typical of choroidal melanoma. If recognized and treated promptly by systemic corticosteroids, the mass generally shrinks abruptly and occasionally resolves completely. In contrast, if the inflammation becomes chronic before the condition is recognized or is not treated aggressively enough, the thickened sclera frequently becomes densely fibrotic and fails to shrink in response to any therapy.

## BILATERAL DIFFUSE UVEAL MELANOCYTIC PROLIFERATION ASSOCIATED WITH SYSTEMIC CARCINOMA

Bilateral diffuse uveal melanocytic proliferation associated with systemic carcinoma (BDUMPASC, frequently referred to by the abridged acronym BDUMP) is a paraneoplastic proliferation of uveal melanocytes stimulated in some way by an underlying systemic carcinoma (which may be overt or occult).<sup>32-34</sup> This uveal melanocytic proliferation commonly occurs in association with geographical or reticular clumping of orange pigment in the fundus and rapid development of an opalescent cataract bilaterally in phakic eyes. The uveal melanocytic stimulation sometimes results in development of multiple discrete melanotic uveal tumors in both eyes that can be mistaken for primary or metastatic uveal melanomas (Fig. 8.3.21A,B). In other cases, the choroid becomes thickened diffusely without any prominent multifocal or diffuse melanotic pigmentation. Such cases are more likely to be mistaken for diffuse uveal lymphoma than for primary posterior uveal melanoma. A secondary serous retinal detachment may develop in some cases (Fig. 8.3.22). The stimulatory substance and the reason certain individuals with systemic carcinoma develop this disorder have yet to be discovered. Identification and effective treatment of the underlying carcinoma can slow progression of the disorder in some patients, while plasmapheresis seems to stabilize the ocular lesions in some patients.<sup>35</sup> However, systemic corticosteroid therapy and whole-eye external beam radiation therapy appear to have limited if any value.

## VORTEX VEIN VARICOSITY

A varix (varicosity) of a choroidal vortex vein ampulla is a choroidal vascular channel that becomes distended when the patient looks in certain directions of gaze.<sup>36,37</sup> Presumably this is due to compression of the ophthalmic vein exiting the sclera in the corresponding quadrant by the belly or tendon of one of the vertical extraocular muscles. The fundus mass attributable to this localized venous distension appears as a smooth dark red tumor just posterior to the ocular equator in one of the oblique quadrants (usually superonasal or inferonasal) when the patient looks in the direction of gaze that results in ophthalmic vein compression (Fig. 8.3.23A–B). The dark color of the “mass” frequently leads to the mistaken diagnosis of choroidal melanoma. However, unlike a choroidal melanoma, the lesion flattens instantly when the patient changes direction of gaze and the extraocular venous compression is no longer present. The mass can be demonstrated by B-scan ultrasonography when the patient looks in the appropriate direction of gaze.

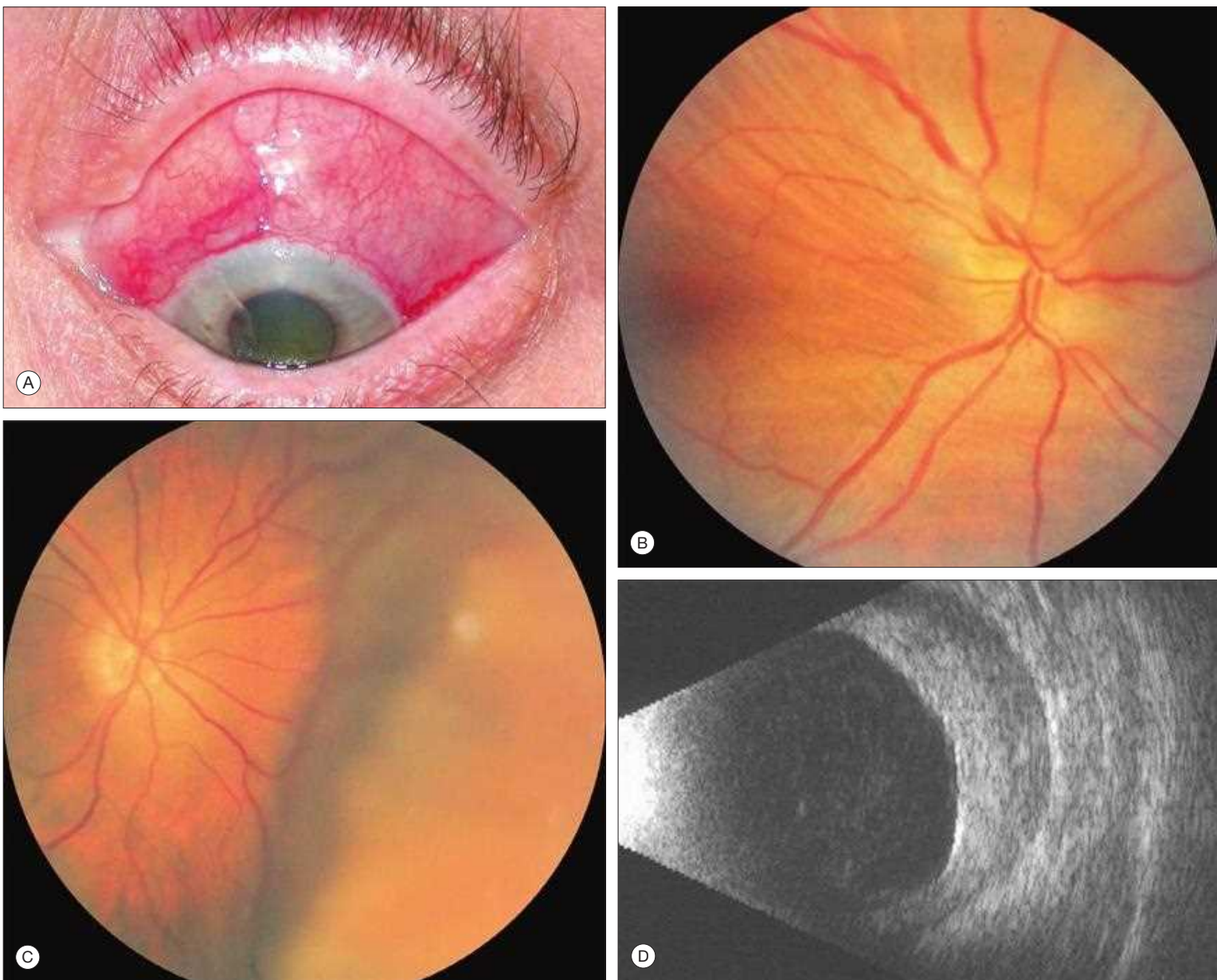
## ORBITAL TUMOR INDENTING EYE WALL

An orbital tumor not adherent to the globe occasionally indents the eye wall focally in such a way that an examiner perceives a localized fundus mass that may be interpreted as a choroidal melanoma or metastatic choroidal tumor.<sup>38</sup> Unlike a true choroidal malignant neoplasm, however, the position of the mass with regard to the optic disc and fovea appears to change as the patient changes his or her direction of gaze (Fig. 8.3.24A–B). Ocular ultrasonography or orbital imaging by computed tomography (CT) or magnetic resonance (MR) discloses the presence and size of the underlying orbital tumor.

## SCLEROCHOROIDAL CALCIFICATION

Sclerochoroidal calcification is a degenerative lesion that develops in the posterior sclera and underlying choroid of both eyes (sometimes very asymmetrically) in some elderly individuals who seem to be healthy systemically and in somewhat younger individuals who have abnormalities of calcium and phosphate metabolism (e.g., hyperparathyroidism).<sup>39</sup> The typical lesion appears as an ill-defined to nummular elevated pale fundus lesion (Fig. 8.3.25). A single lesion may be evident, but several lesions may be located along arcs extending from above and below the optic disc toward the fundus midline temporally just outside the superotemporal and inferotemporal retinal vascular arcades (Fig. 8.3.26A–B). Especially in this latter situation of multiple bilateral pale fundus lesions, this condition is frequently misdiagnosed ophthalmoscopically as metastatic cancer to the choroid. The retina is attached over and around the lesions. B-scan ocular ultrasonography shows dense hyperreflectivity of the lesions with shadowing of the orbital tissues behind them. CT scans of the orbit show the individual lesions to be bone dense. If there is any question about the





**Fig. 8.3.20 Nodular Posterior Scleritis.** (A) External image showing intense reddish discoloration of the sclera. (B) Fundus image showing chorioretinal folds and partial inward tilt of optic disc by ill-defined subretinal mass superonasally. (C) Ridge-like fundus mass attributed to nodular posterior scleritis. (D) B-scan ultrasonographic image showing diffuse posterior scleral thickening.

patient's calcium–phosphorus metabolism, serum levels of calcium and phosphorus should be checked as a baseline study.

### ENDOGENOUS MICROBIAL SUBRETINAL ABSCESS

Some patients with microbial sepsis develop endogenous microbial subretinal abscesses.<sup>40–45</sup> These lesions are white to yellow subretinal masses, commonly associated with prominent vitreous cells (Fig. 8.3.27), and can be mistaken for primary vitreoretinal lymphoma. Such lesions are more common in immunosuppressed individuals than in fully immunocompetent ones and often develop in individuals with chronic underlying diseases such as AIDS, cystic fibrosis, or hairy cell leukemia. The subretinal mass can expand relentlessly and destroy the eye or remain relatively localized depending on the patient's immune status. Transvitreal fine-needle aspiration biopsy or vitrector biopsy may be required to establish the microbiological diagnosis and direct antibiotic therapy.

### ATYPICAL RETINAL PIGMENT EPITHELIAL DETACHMENT

The typical RPE detachment is a localized blister-like accumulation of serous or exudative fluid between the RPE and Bruch's membrane. It

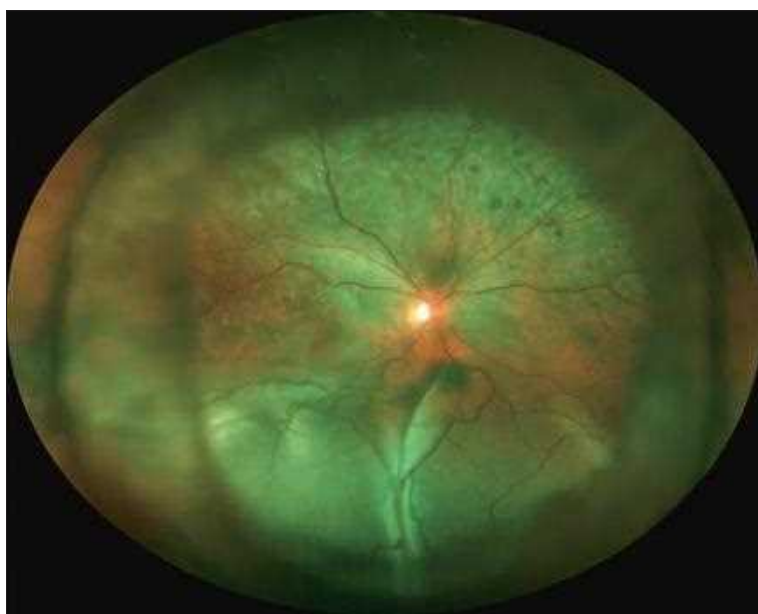
generally measures between about 1 and 3 disc diameters in basal size, but is usually no more than 1–1.5 mm in maximal height. The lesion has a smoothly biconvex cross-sectional shape and well-defined margins. Its most common location is in the macula. It typically occurs secondary to choroidal neovascularization in age-related macular degeneration<sup>46</sup> or as a manifestation of choroidal inflammation such as in Harada's disease.<sup>47</sup> On fluorescein angiography, the blister fills slowly but exhibits well-defined margins by the recirculation phase of the study. Atypical RPE detachments differ from typical ones in being substantially larger than the typical lesion<sup>46</sup> (Fig. 8.3.28) [in which case they frequently simulate either amelanotic choroidal melanoma or a metastatic choroidal tumor], hemorrhagic and therefore dark in color<sup>48</sup> (Fig. 8.3.29) [in which case they can simulate a melanotic choroidal melanoma], or multifocal<sup>49</sup> (Fig. 8.3.30) [in which case they can simulate metastatic choroidal tumors or primary intraocular lymphoma]. In spite of their atypical features, such RPE detachments retain features of their typical counterparts and therefore can usually be distinguished from malignant neoplastic lesions.

### BULLOUS CENTRAL SEROUS CHORIORETINOPATHY

Typical central serous chorioretinopathy (CSC) is a fundus disorder characterized by a central blister of serous subretinal fluid that occurs unilaterally or bilaterally in young to middle-aged men. On fluorescein angiography,

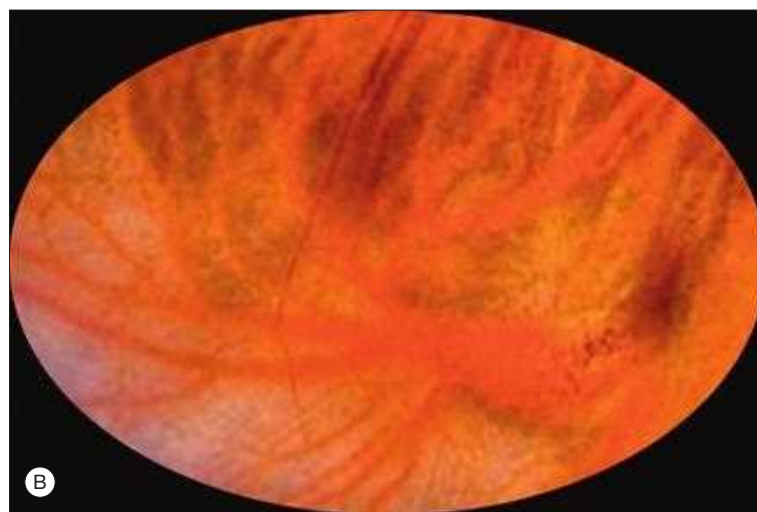
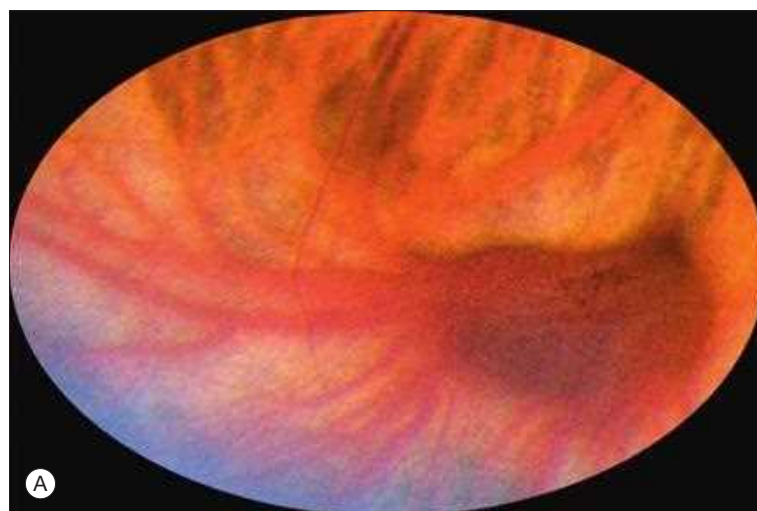


**Fig. 8.3.21 Paraneoplastic Bilateral Diffuse Uveal Melanocytic Proliferation (BDUMP) Associated With Systemic Cancer.** (A) Right eye fundus. (B) Left eye fundus.



**Fig. 8.3.22 Paraneoplastic Diffuse Uveal Melanocytic Proliferation Associated With Secondary Partial Serous Retinal Detachment.**

the blister characteristically fills slowly from a focal hyperfluorescent site at the RPE level, with fluorescein ascending within the subretinal fluid to appear in an umbrella pattern. The margins of the blister are usually somewhat indistinct on fundus biomicroscopy but appear more distinct in late fluorescein angiography images. Bullous central serous chorioretinopathy is an uncommon subtype of CSC that is associated with multiple turbid RPE detachments, giving rise to overlying and surrounding accumulations of serous subretinal fluid that can become bullous and shifting in character (Fig. 8.3.31A).<sup>50-53</sup> On fluorescein angiography, the turbid RPE detachments exhibit early nonfluorescence (due to blockage of choroidal fluorescence) but gradually increasing hyperfluorescence as the study continues (Fig. 8.3.31B). This condition is usually bilateral, but may be markedly asymmetrical in the two eyes. The turbid RPE detachments associated with this condition can simulate metastatic choroidal tumors quite closely. However, patients with this condition do not have any non-ophthalmic primary cancer capable of metastasizing.

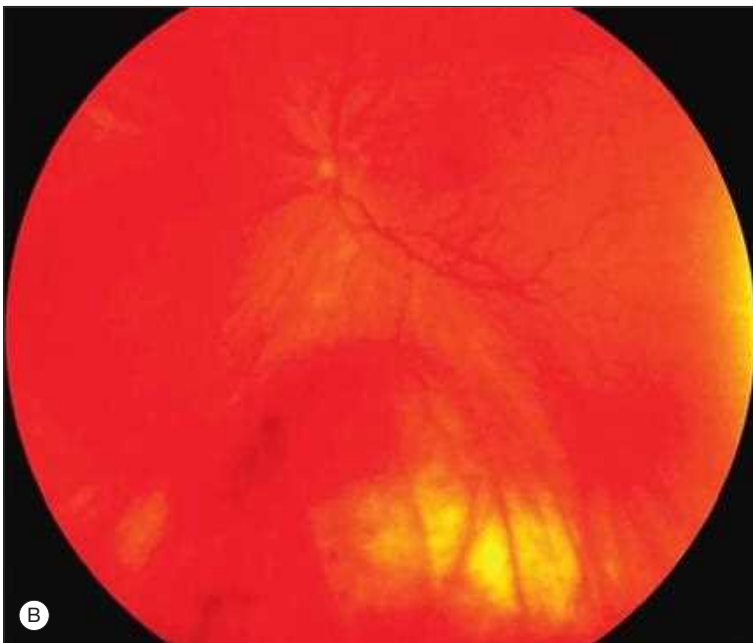
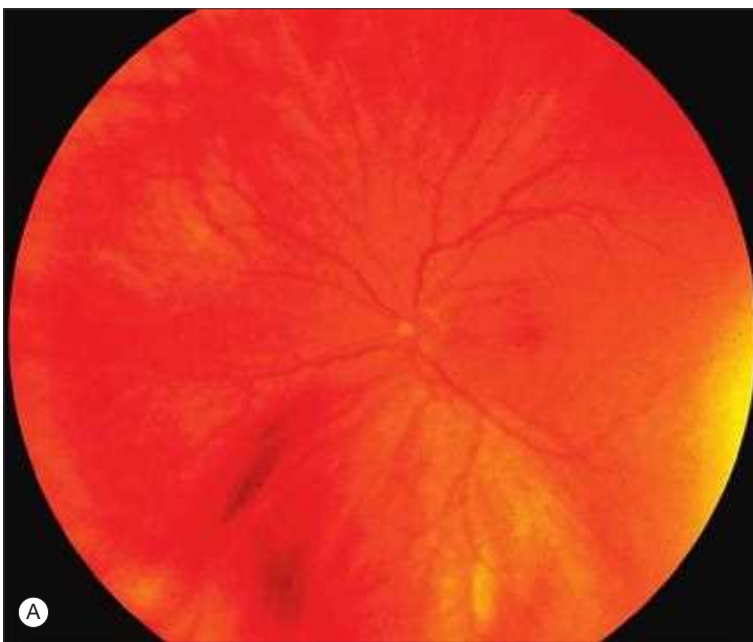


**Fig. 8.3.23 Varicosity of Vortex Vein Ampulla.** (A) Fundus image showing vortex vein ampulla when it is distended. (B) Fundus image showing same vortex vein ampulla when it is collapsed.

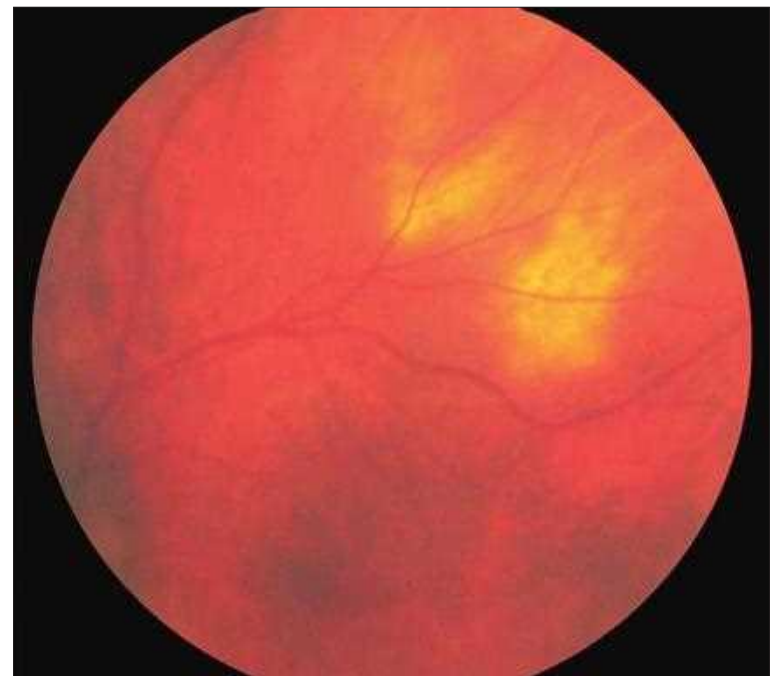


### CILIOCHOROIDAL EFFUSION AND IDIOPATHIC UVEAL EFFUSION SYNDROME

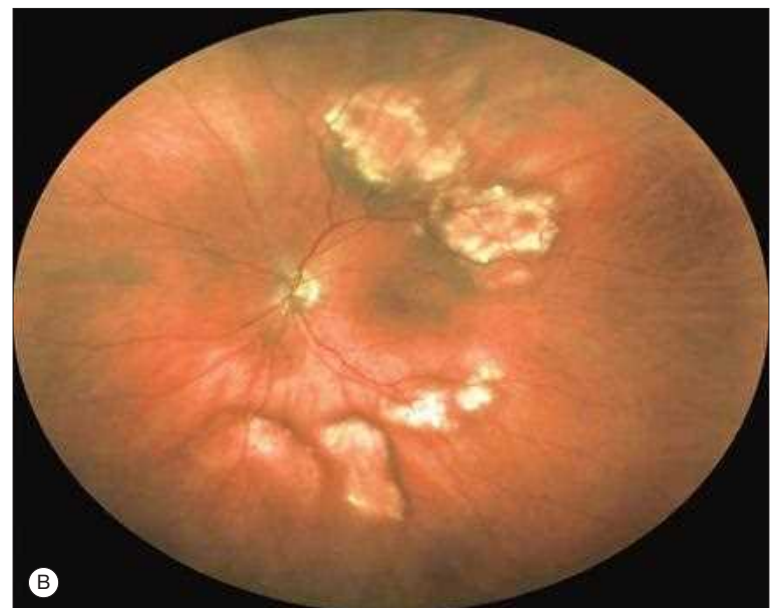
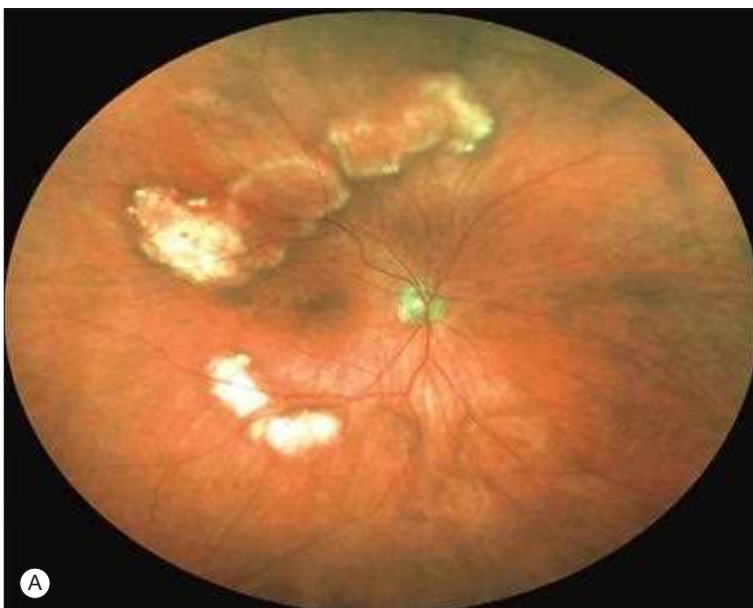
Ciliochoroidal effusion (frequently referred to as choroidal detachment) is an accumulation of serous subretinal fluid between the uvea and sclera in the ciliary body and peripheral choroidal regions.<sup>54</sup> The accumulated serous fluid usually extends circumferentially around the eye, but may be evident ophthalmoscopically only in regions where it is accentuated (Fig. 8.3.32). Masses of this type are commonly misdiagnosed as amelanotic ciliochoroidal melanoma or metastatic carcinoma to the peripheral uvea. The anterior chamber angle is generally narrowed due to anterior rotation of the detached ciliary body, and intraocular pressure may be elevated (due to secondary angle closure) or low (due to reduced production of aqueous from the ciliary body). The process is frequently unilateral but can be bilateral. If the suprachoroidal fluid is bullous, several prominent lobules bounded by the vortex vein ampullae may be evident on ophthalmoscopy (Fig. 8.3.33). Secondary serous retinal detachment with shifting subretinal fluid is frequently associated with more prominent cases. B-scan ocular ultrasonography shows anechoic suprachoroidal fluid within lobules of bullous serous ciliochoroidal effusion, and UBM confirms ciliary body detachment by supraciliary serous fluid. Ocular transillumination does not show any discrete ciliary body shadow.



**Fig. 8.3.24 Orbital Tumor Indenting Eye Wall.** (A) Fundus image with patient looking up. (B) Fundus image with patient looking down.



**Fig. 8.3.25 Individual Smudgy Fundus Lesion of Idiopathic Sclerochoroidal Calcification.**



**Fig. 8.3.26 Well-Defined Bilateral Multifocal Fundus Lesions of Sclerochoroidal Calcification.** (A) Right eye. (B) Left eye.



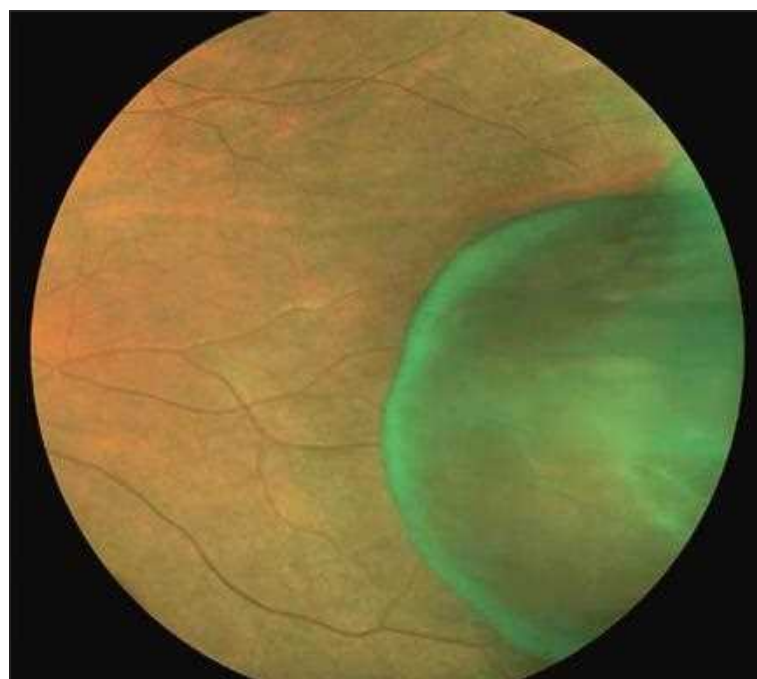


**Fig. 8.3.27** Microbial Subretinal Abscess Due to *Pseudomonas Aeruginosa* in a Patient With Cystic Fibrosis.

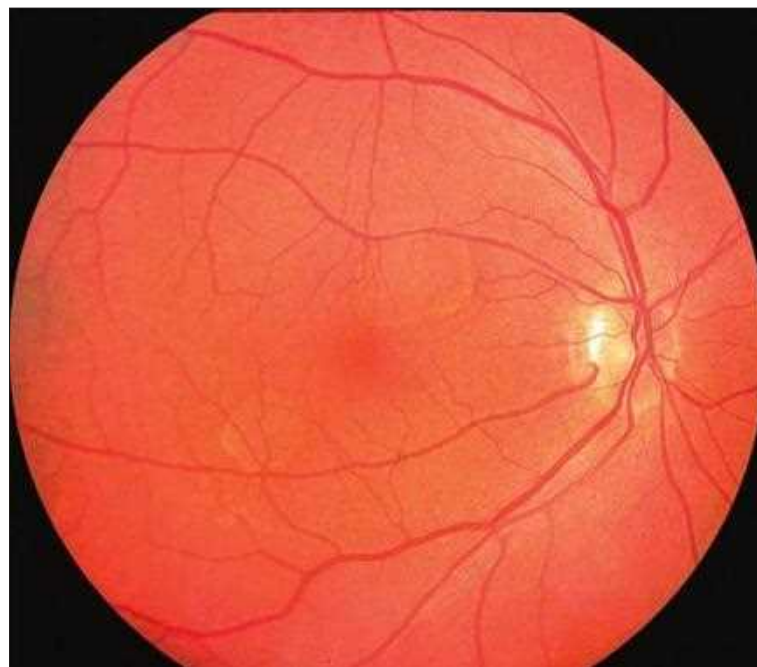


**Fig. 8.3.28** Large Retinal Pigment Epithelial Detachment With Turbid Fluid and Well-Defined Margins.

A particular subtype of serous ciliochoroidal effusion occurs in some middle-aged to older adult men, most of whom are hyperopic and have eyeballs of slightly smaller than average size. This disorder, known as idiopathic uveal effusion syndrome,<sup>55-57</sup> appears to be due to slightly thicker and denser anterior sclera than normal. The condition tends to affect both eyes but is frequently very asymmetrical at initial presentation. The ciliochoroidal effusion in this disorder tends to be chronic and associated with bullous serous subretinal fluid (Fig. 8.3.34A–B). The subretinal fluid generally shifts vigorously with changes in the patient's eye-head position. Because of the shifting subretinal fluid, which is frequently quite turbid, an underlying metastatic carcinoma to the posterior uvea or a diffuse posterior uveal melanoma may be suspected. As a consequence of the serous retinal detachment, the affected eye tends to develop extensive disruption of the RPE with multifocal RPE clumping (Fig. 8.3.34C), especially in the inferior hemisphere of the fundus. Ocular axial length measurement typically confirm a slightly smaller than average eyeball size, and ultrasound biometry frequently shows slightly thicker than average sclera in the ciliary body region. This condition usually responds favorably to excision of relatively thick lamellar scleral rectangles behind the level of the insertions of the rectus muscles to the equatorial region of the eye in each quadrant.<sup>56</sup>



**Fig. 8.3.29** Hemorrhagic Retinal Pigment Epithelial Detachment. Note Dark Color of This Lesion Compared to Fig. 8.3.28.

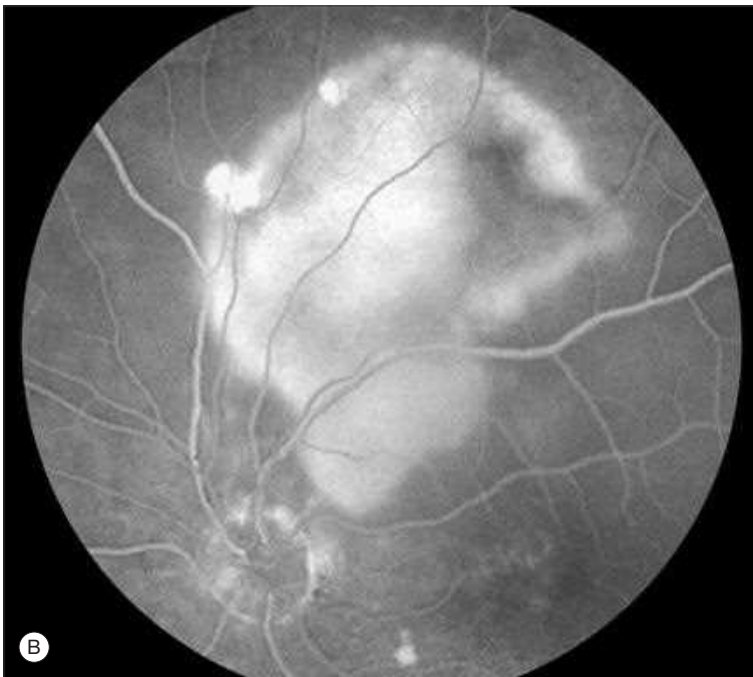
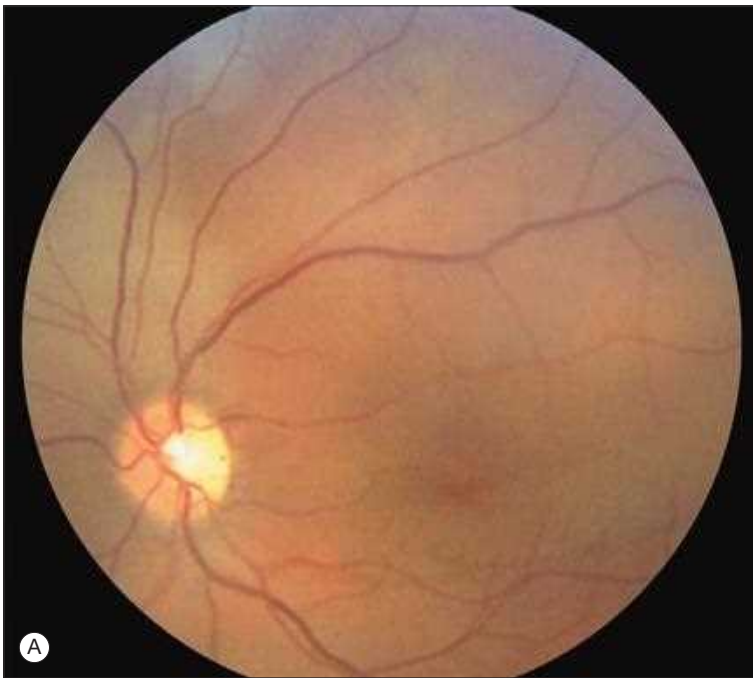


**Fig. 8.3.30** Multifocal Retinal Pigment Epithelial Detachments.

## MULTIFOCAL BEST VITELLIFORM RETINAL DYSTROPHY AND VITELLIFORM PARANEOPLASTIC RETINOPATHY

Best vitelliform retinal dystrophy is an autosomal dominant disorder characterized in its typical form by development of a central macular lesion resembling an egg yolk.<sup>58</sup> The macular lesion appears to be an accumulation of lipofuscin on Bruch's membrane that elevates and causes secondary degeneration of the RPE and outer segments of the sensory retina. The macular lesions generally become apparent by the second half of the first decade of life. The disorder has been linked to mutations in the *VMD2* (hBEST1) gene. Atypical forms include cases with late onset of the macular lesion<sup>59</sup> and ones with multiple extramacular vitelliform lesions<sup>60</sup> (Fig. 8.3.35). In this latter situation, the pale color of the individual lesions, the multiplicity of lesions, and the bilaterality of the process frequently lead to the mistaken initial diagnosis of metastatic carcinoma to the choroid.

Vitelliform paraneoplastic retinopathy is an extremely uncommon fundus disorder characterized by abrupt development of multiple discrete

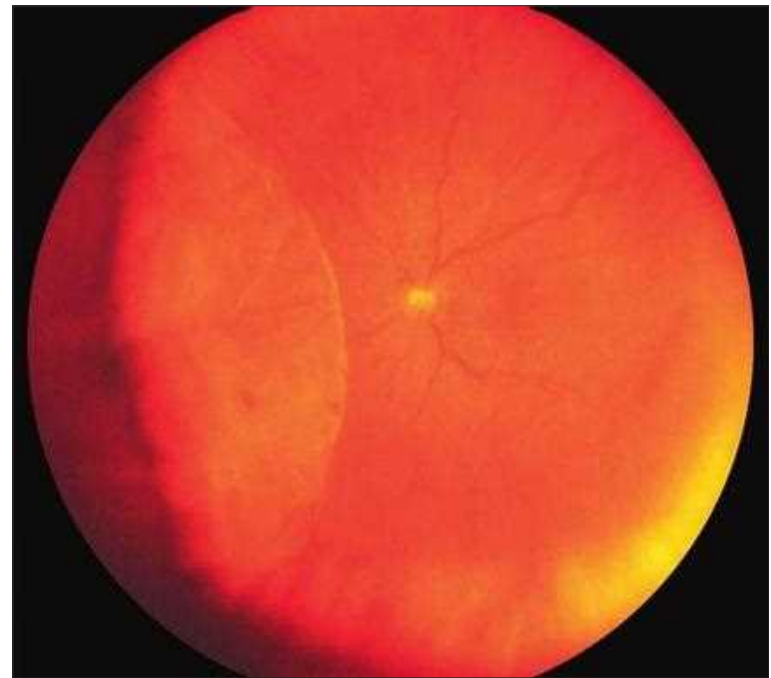


**Fig. 8.3.31 Bullous Central Serous Chorioretinopathy.** (A) Color image showing smudgy subretinal lesion superior to optic disc and secondary serous retinal detachment. (B) Fluorescein angiography frame highlighting subretinal fluid in this case.

orange subretinal lesions scattered about the posterior fundus in a patient with an underlying systemic cancer.<sup>61</sup> The individual lesions resemble the lesions of multifocal Best disease but tend to be of variable sizes and slightly more irregular shape than those of classic Best disease (Fig. 8.3.36). Patients commonly report flickering lights and progressive blurring or dimming of vision in both eyes. The fundus lesions of this disorder are likely to be misdiagnosed as metastatic tumors to the choroid, at least initially.

### MASSIVE GLIOSIS OF RETINA

A benign non-neoplastic tumor composed principally of proliferated retinal glial cells occurs in some eyes in response to prior retinal inflammation or injury. These tumors are generally off-white in color and irregular in contour. When such a proliferation gives rise to a three-dimensional tumor, it is referred to as **massive gliosis of the retina**<sup>62</sup> (Fig. 8.3.37). If the lesion is relatively small (e.g.,  $\leq 5$  mm in largest linear dimension), it is commonly referred to as *focal retinal gliosis*.<sup>63</sup> In contrast, if the lesion involves an extended portion of the fundus, it is commonly referred to as



**Fig. 8.3.32 Choroidal Detachment (Ciliochoroidal Effusion) Having a Solitary Accentuated Lobule.**

*diffuse retinal gliosis*.<sup>63</sup> Lesions of these types can be misdiagnosed as retinoblastoma if they are identified in children and as amelanotic choroidal melanomas if detected in adults.<sup>64</sup>

### INFLAMMATORY CHORIORETINAL GRANULOMA

Inflammatory chorioretinal granulomas appear as golden to yellow choroidal or outer retinal nodules with overlying vitreous cells in the acute phase and clumping of RPE pigment on its surface or around its margin in the chronic phase (Fig. 8.3.38).<sup>65–69</sup> These lesions can develop in individuals of any age. In most cases, such lesions are unilateral and unifocal, but bilateral multifocal lesions occur in some patients. Such a lesion can simulate a metastasis to the choroid by a nonophthalmic primary cancer or an infiltrate of primary intraocular lymphoma quite closely. Biopsy of the lesion by a method such as fine-needle aspiration biopsy may be necessary to rule out these malignant neoplasms.

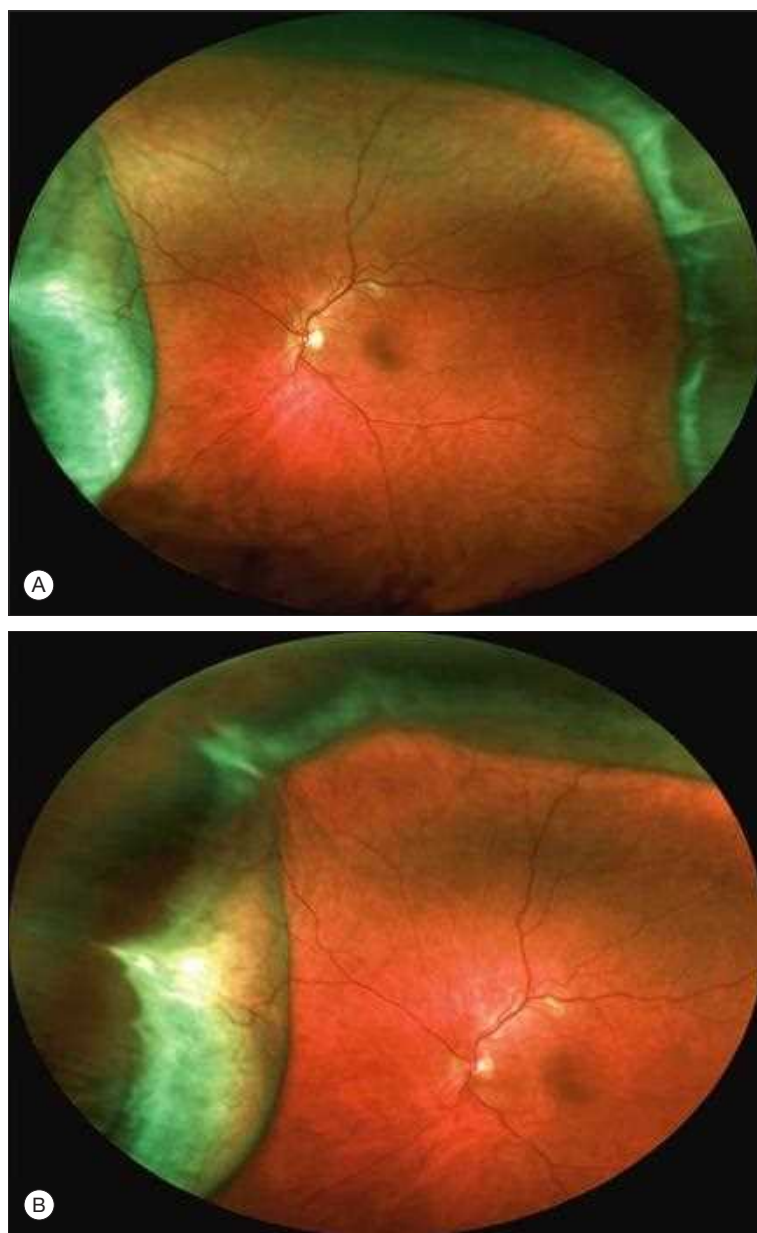
### HARADA'S DISEASE

Harada's disease is an inflammatory chorioretinal disorder that is generally believed to be an autoimmune condition.<sup>70,71</sup> It is characterized in its acute phase by vitreous cells and frequently by development of multiple foci of serous retinal detachment due to turbid subretinal fluid (Fig. 8.3.39A,B). The disorder is commonly associated with a variety of acquired cutaneous abnormalities (e.g., vitiligo, poliosis) and various neurological abnormalities (e.g., Vogt-Koyanagi-Harada disease). The majority of cases are bilateral and seen in individuals between the ages of 20 and 50 years. Harada's disease is much more common in women and people of Asian, Middle Eastern, or Native American descent. When multifocal serous retinal detachment and vitreous cells are prominent features, Harada's disease can be misdiagnosed as primary vitreoretinal lymphoma.<sup>72</sup> When multifocal serous retinal detachment is evident but vitreous cells are not, the condition can be mistaken for a nonophthalmic primary malignant neoplasm metastatic to the choroid.

### IDIOPATHIC UVEITIS IN THE ELDERLY

Idiopathic posterior uveitis is characterized by diffuse accumulation of intravitreal cells as an inflammatory response to unknown antigens. Most cases respond to systemic corticosteroid therapy or various immunomodulatory drugs. When idiopathic posterior uveitis develops in a patient over the age of 50 years, the condition is frequently suspected to be primary vitreoretinal lymphoma.





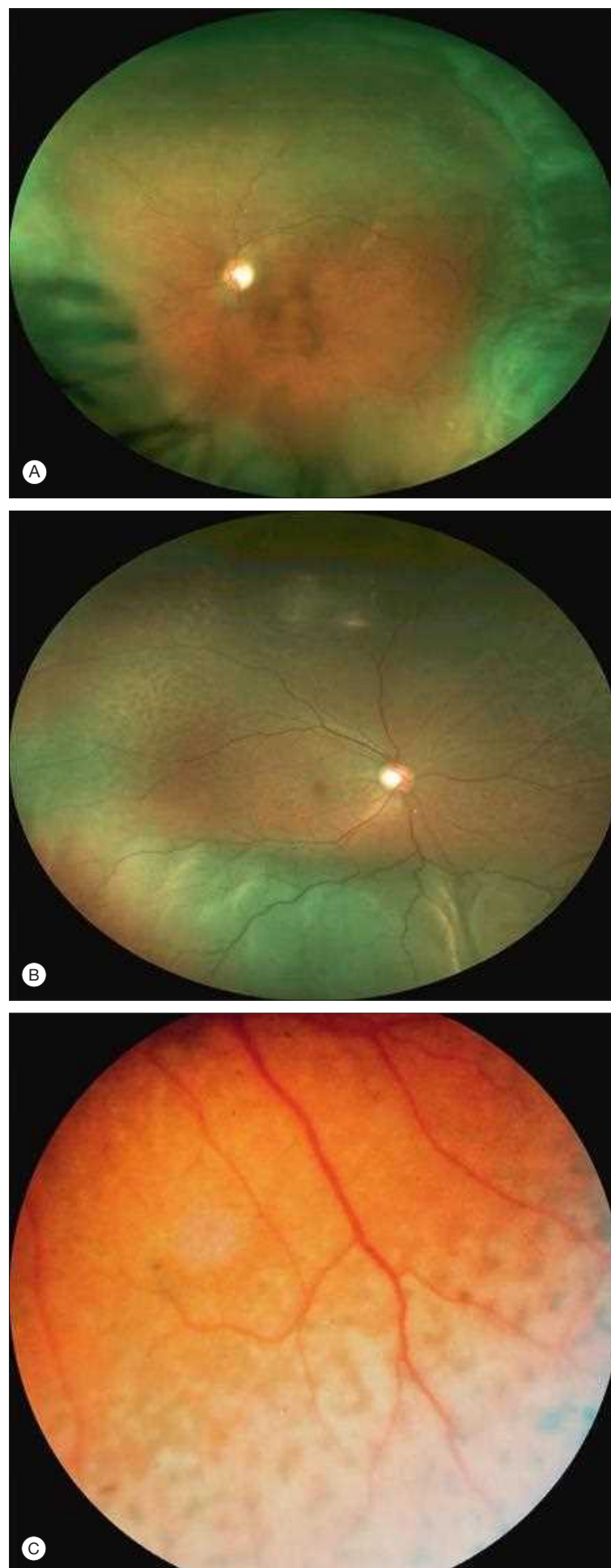
**Fig. 8.3.33 Annular (Circumferential) Choroidal Detachment (Ciliochoroidal Effusion).** (A) Fundus image centered on macula of left eye showing a peripheral ridge-like fundus elevation nasally, temporally and superiorly. (B) Fundus image centered just superonasal from optic disc showing the ora serrata on the crest of the ciliochoroidal ridge nasally, superonasally and superiorly.

### VITILIGINOUS (BIRDSHOT) CHOROIDITIS

Vitiliginous choroiditis, sometimes referred to as birdshot chorioretinopathy, is an inflammatory chorioretinal disorder of unknown cause that tends to affect older individuals (the same age group commonly affected by primary vitreoretinal lymphoma) preferentially.<sup>73,74</sup> This disease is characterized by development of multiple small round depigmented chorioretinal foci, most commonly in the inferior midzone of the fundus in both eyes, in association with the accumulation of pale vitreous cells (Fig. 8.3.40A–B). This disorder is strongly associated with HLA-A29 positivity and is frequently suspected of being primary vitreoretinal lymphoma.

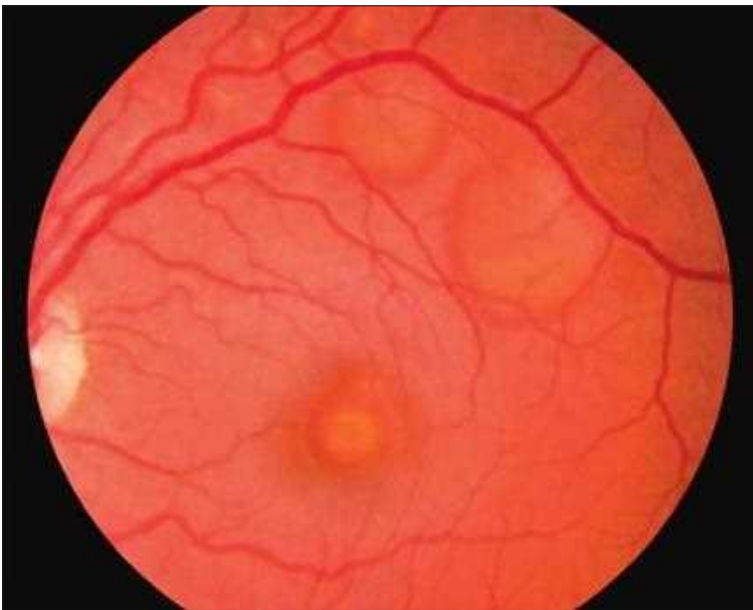
### ENDOGENOUS ENDOPHTHALMITIS

Various microbes (e.g., bacteria, fungi, parasites) that enter the bloodstream from a nonophthalmic site of infection can give rise to endogenous (hematogenously disseminated) endophthalmitis in one or both eyes.<sup>44,75</sup> The onset of the condition tends to be abrupt and relentlessly progressive over a very short time. The condition is most frequently encountered in older debilitated persons and those whose systemic immunity is impaired (e.g., patients with HIV infection). When multifocal choroidal or subretinal



**Fig. 8.3.34 Uveal Effusion Syndrome.** (A) Wide-angle image showing peripheral choroidal detachment. (B) Wide-angle image showing secondary serous retinal detachment inferiorly. (C) Localized fundus image showing characteristic clumping of retinal pigment epithelium in this disorder.



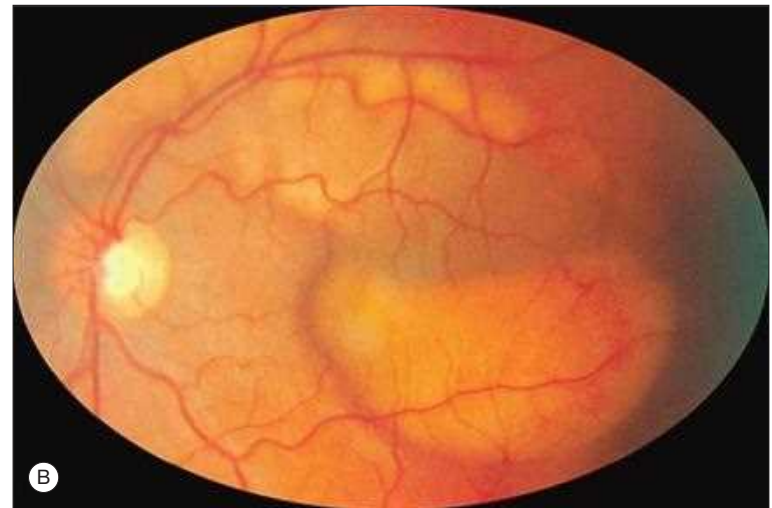
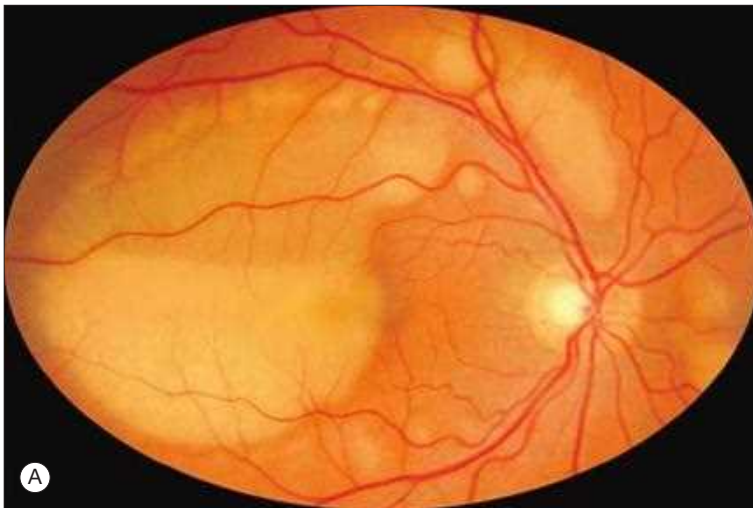


**Fig. 8.3.35 Multifocal Best Vitelliform Retinal Dystrophy in Left Eye.** The image shows a small central macular vitelliform lesion and two slightly larger vitelliform lesions superior and superotemporal to the fovea.

infiltrates are prominent features, the condition can be mistaken for a non-ophthalmic primary malignant neoplasm metastatic to the choroid. When vitreous cells and retinal infiltrates are prominent features, this condition can simulate primary vitreoretinal lymphoma.

### NON-NEOPLASTIC INTRAOCULAR LESIONS AND DISORDERS SIMULATING INTRAOCULAR RETINOBLASTOMA

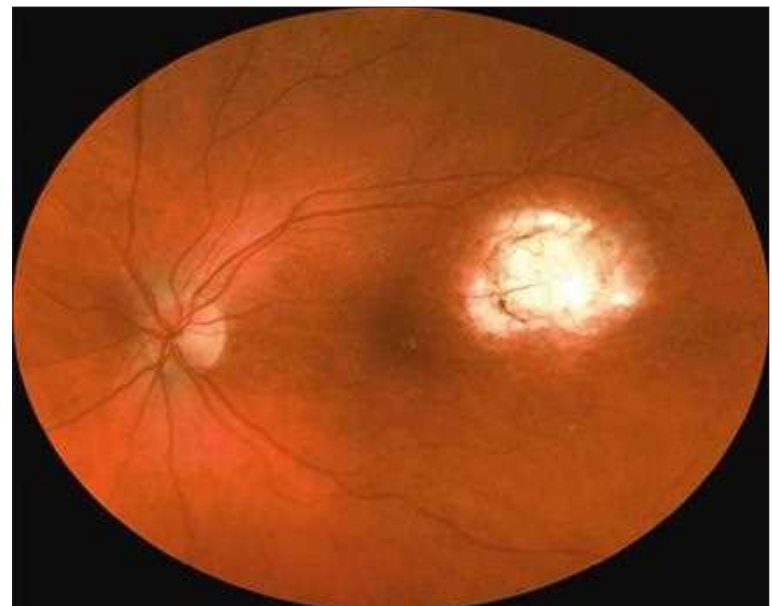
The differential diagnosis of retinoblastoma includes a number of non-neoplastic lesions and disorders that are not usually represented in lists of pseudo-malignant neoplasms of the uvea. These lesions and disorders affect infants and young children in the typical age range for initial diagnosis of retinoblastoma. Most cases of retinoblastoma are diagnosed correctly by experienced ocular tumor specialists, but certain forms of retinoblastoma (e.g., diffuse infiltrating retinoblastoma, anterior retinoblastoma, advanced endophytic retinoblastoma with prominent vitreous seeding, or advanced exophytic retinoblastoma associated with a total bullous retinal detachment) can pose diagnostic challenges even to experienced examiners. In the following paragraphs, several non-neoplastic lesions and disorders that can simulate different clinical presentations of retinoblastoma are discussed.



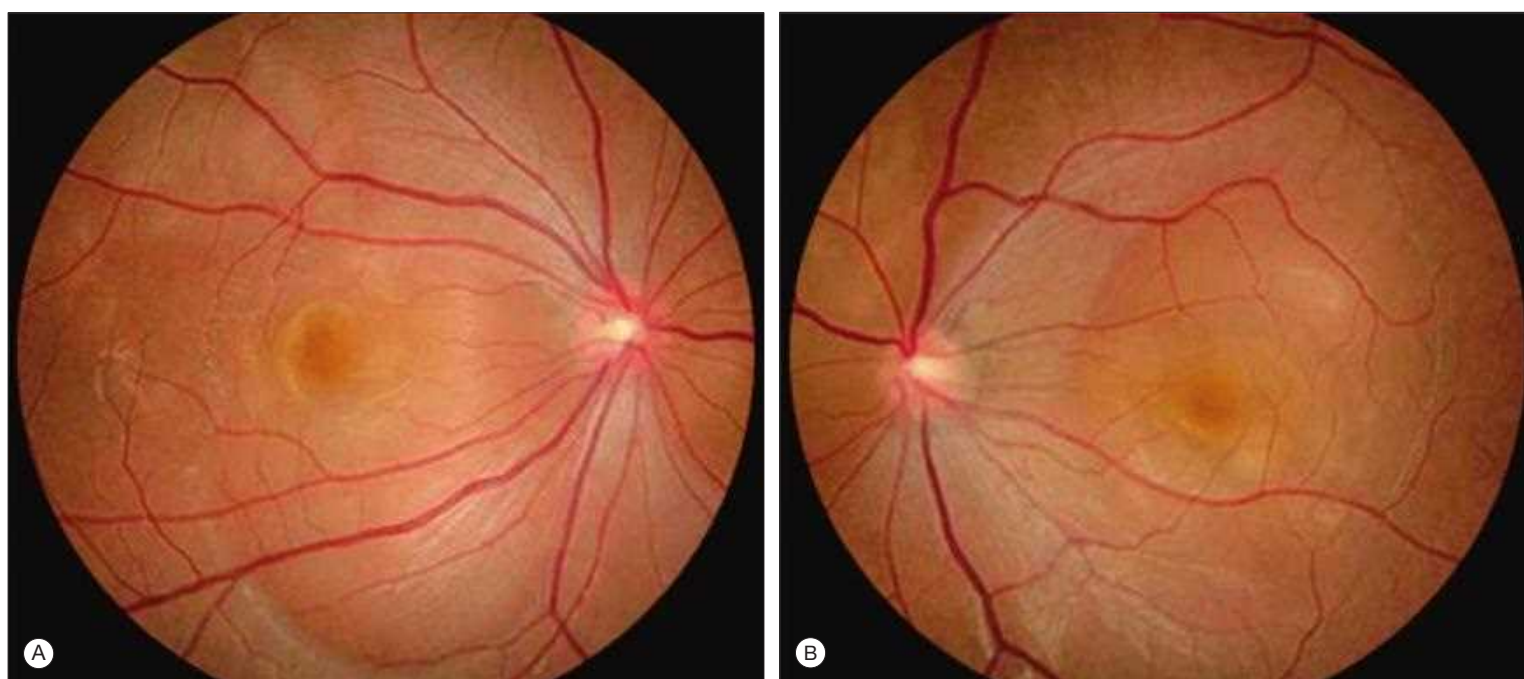
**Fig. 8.3.36 Paraneoplastic Vitelliform Chorioretinopathy.** (A) Right eye fundus. (B) Left eye fundus.



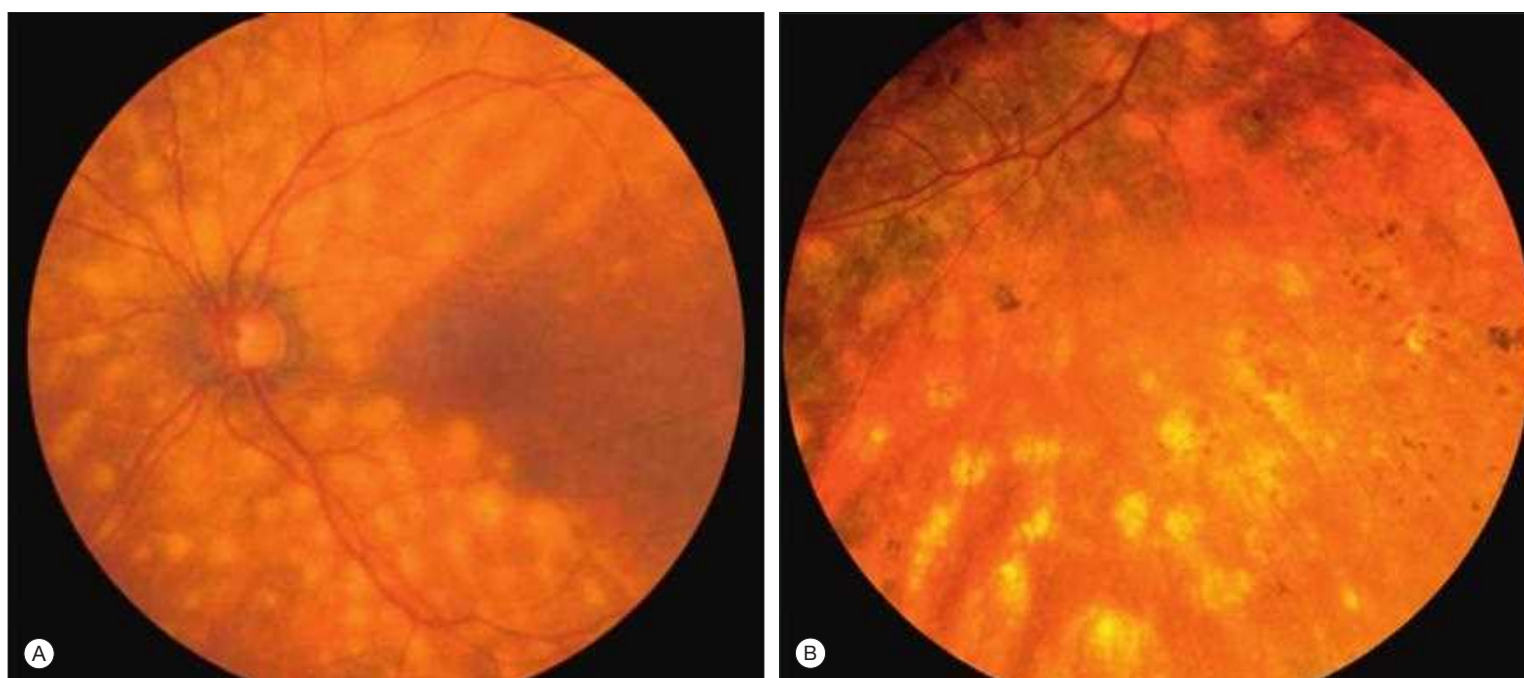
**Fig. 8.3.37 Massive Gliosis of Retina.**



**Fig. 8.3.38 Inflammatory Choroidal Granuloma.**



**Fig. 8.3.39 Harada's Disease With Bilateral Turbid Serous Retinal Detachment Posteriorly.** (A) Right eye fundus. (B) Left eye fundus.



**Fig. 8.3.40 Vitiliginous Chorioretinopathy.** (A) Posterior fundus appearance. (B) Inferior fundus appearance.

### NON-NEOPLASTIC LESIONS AND DISORDERS SIMULATING INTRARETINAL RETINOBLASTOMA

The typical intraretinal retinoblastoma appears as a translucent to opaque white retinal tumor nodule fed and drained by prominently dilated and tortuous retinal blood vessels. Tumors more than about 3 mm in diameter frequently exhibit foci of intralesional calcification. Retinal astrocytoma (isolated or associated with tuberous sclerosis) is the neoplastic lesion most frequently mistaken for intraretinal retinoblastoma. The following non-neoplastic lesions and disorders can also simulate discrete intraretinal tumors of retinoblastoma.

#### VITREORETINAL TOXOCARA GRANULOMA

Occasional individuals develop an inflammatory vitreoretinal granuloma as a manifestation of endogenous ocular toxocariasis.<sup>76,77</sup> The white vitreo-retinal lesion, typically found in young children, is characteristically located at the optic disc or in the fundus periphery (Fig. 8.3.41A–B). The

lesion is generally associated with prominent vitreoretinal membranes and inflammatory cells in the vitreous. The mass does not exhibit intralesional calcification or any dilated–tortuous associated retinal blood vessels.

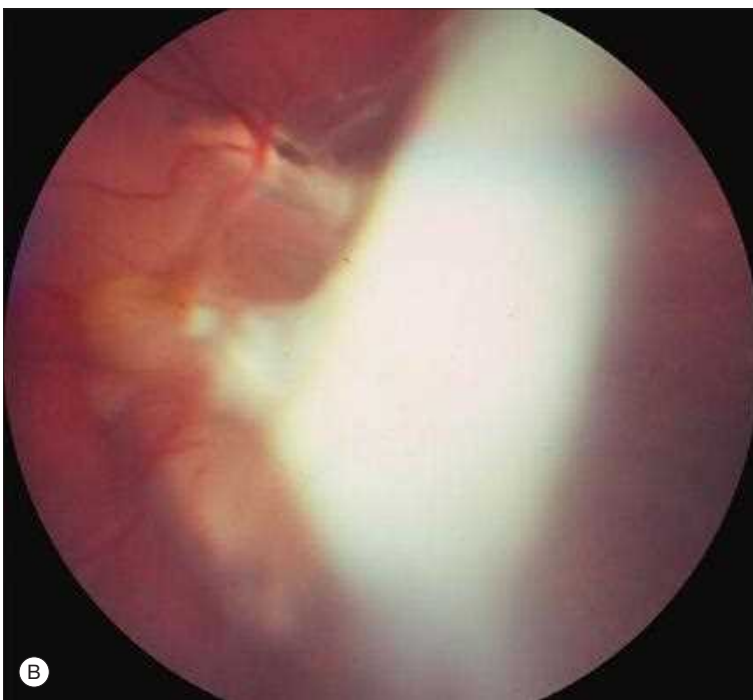
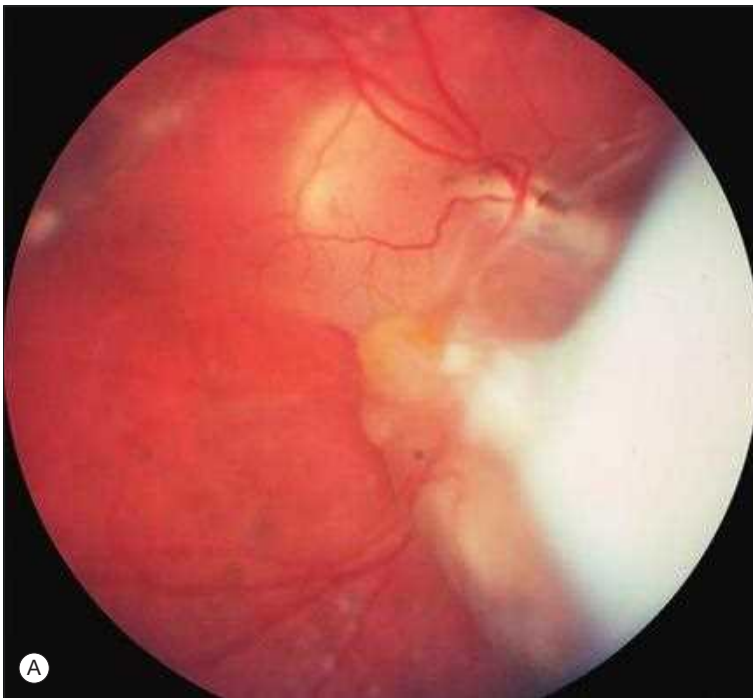
#### EXTENSIVE MYELINATION OF RETINAL NERVE FIBER LAYER

In normal ocular development, the nerve fibers in the nerve fiber layer of the retina are not myelinated. However, occasional eyes that are otherwise normal develop focal or patchy myelination of the retinal nerve fiber layer as a developmental anomaly.<sup>78,79</sup> In rare instances, the myelination becomes so extensive that it involves a substantial portion of the posterior retina (Fig. 8.3.42).

#### CHORIORETINAL COLOBOMA

A chorioretinal coloboma is a congenital anomaly of the choroid and retina in which the developing optic cup does not fuse completely and a developmental defect of the retina and choroid becomes evident.<sup>80,81</sup> The typical





**Fig. 8.3.41 Toxocara Vitreoretinal Granuloma in Right Eye.** (A) Color fundus photo centered just temporal to optic disc (hidden by vitreoretinal and subretinal fibrosis) showing elevated white mass just nasal to disc. (B) Color image of same lesion centered on the elevated white preretinal mass.

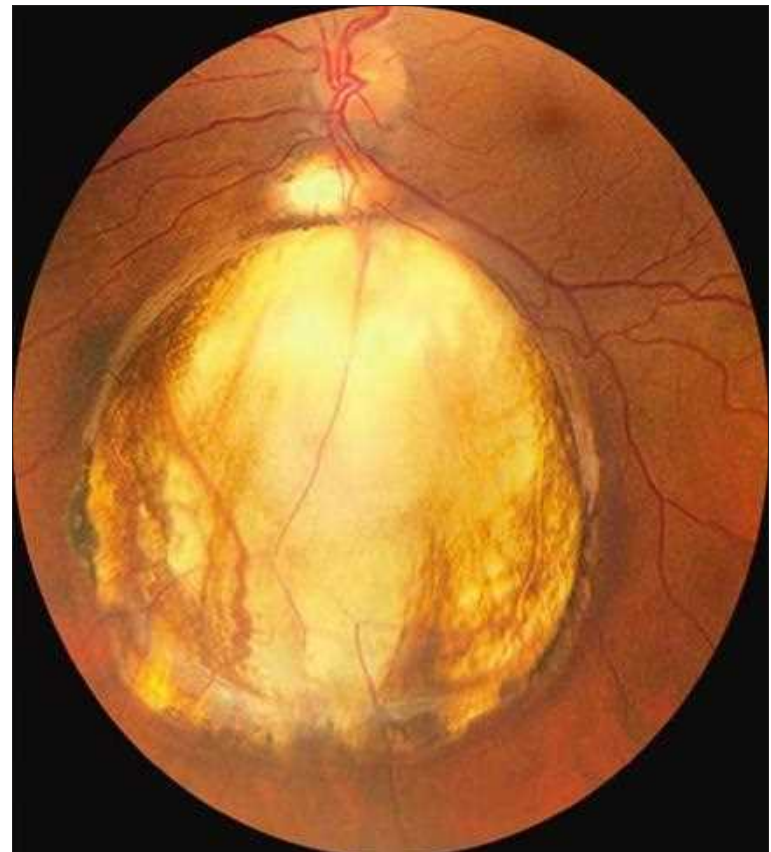
lesion appears as a well-defined absence of choroid and RPE and maldevelopment of the associated sensory retina in the inferior to inferonasal quadrant of the fundus (Fig. 8.3.43). The spectrum of chorioretinal coloboma is broad, ranging from limited areas of fundus involvement between the optic disc and fundus periphery, involvement of the optic disc and inferior juxtapapillary fundus only, to extended involvement of the inferior fundus that also encompasses the optic disc. Unilateral and bilateral cases have been identified.<sup>82</sup>

### TOXOPLASMIC RETINITIS

Congenital ocular toxoplasmosis frequently gives rise to a fundus lesion resembling a congenital chorioretinal coloboma.<sup>83,84</sup> Unlike the classic fundus coloboma, this lesion is usually located in the macula, is associated with prominent clumping of black RPE pigment along its margins, and is frequently bilateral (Fig. 8.3.44). Due to the white appearance of the central portion of the lesion and its detection in infants and young children, it can



**Fig. 8.3.42 Extensive Myelination of Retinal Nerve Fiber Layer.**

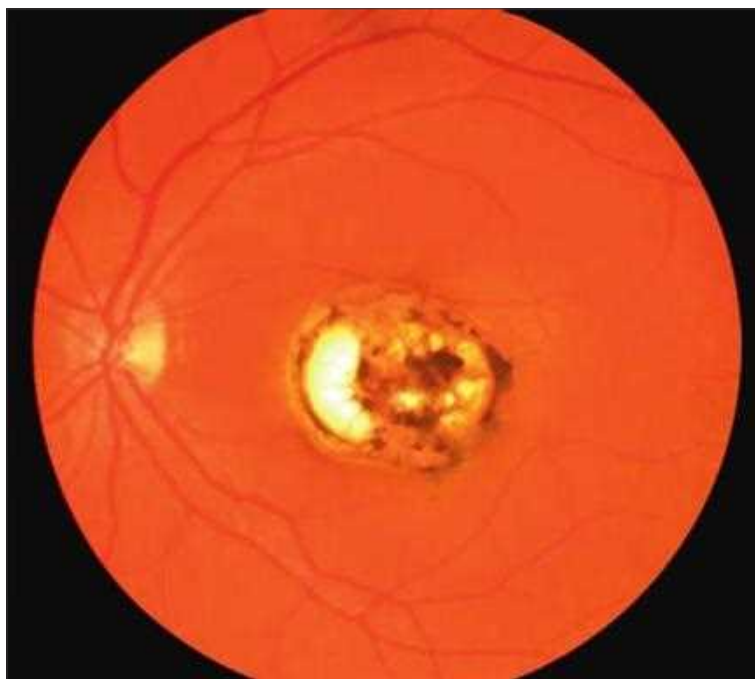


**Fig. 8.3.43 Chorioretinal Coloboma.**

be mistaken for retinoblastoma. However, the flat nature of the lesion and absence of any associated feeder and drainer retinal blood vessels generally allows for appropriate diagnosis of this lesion.

Acquired retinal toxoplasmosis in its typical form appears as a fuzzy white focus of active retinitis with overlying vitreous inflammatory cells.<sup>83,84</sup> If the lesion is a reactivation of a prior lesion, black RPE hyperplasia is typically evident adjacent to the lesion. Atypical multifocal toxoplasmic retinal lesions are encountered occasionally as acquired foci of retinitis in immunosuppressed individuals (Fig. 8.3.45A–B).<sup>45</sup> If the underlying condition responsible for the immunosuppression is leukemia, the multifocal retinal lesions of acquired toxoplasmic retinitis can be mistaken for leukemic retinal infiltrates.





**Fig. 8.3.44** Macular Lesion of Congenital Ocular Toxoplasmosis.

### FOCAL RETINAL GLIOSIS

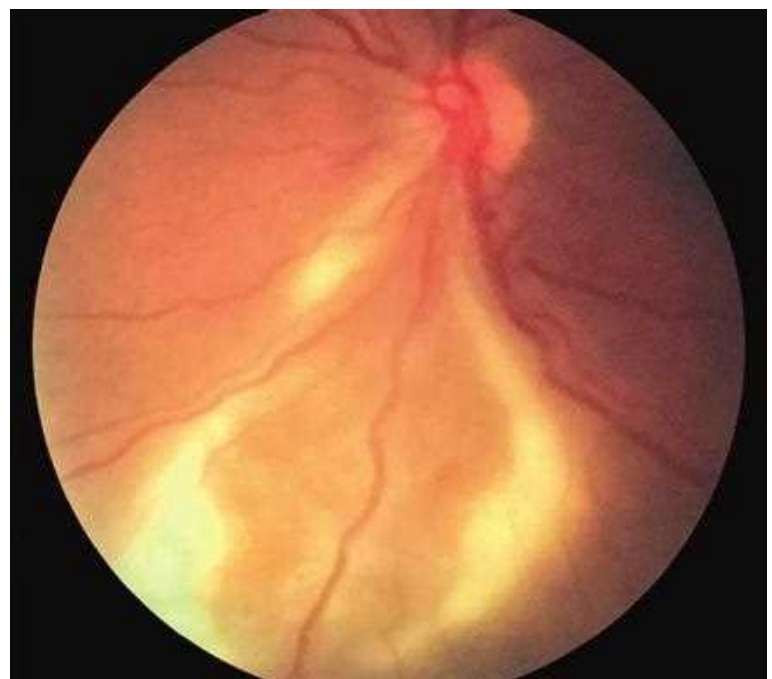
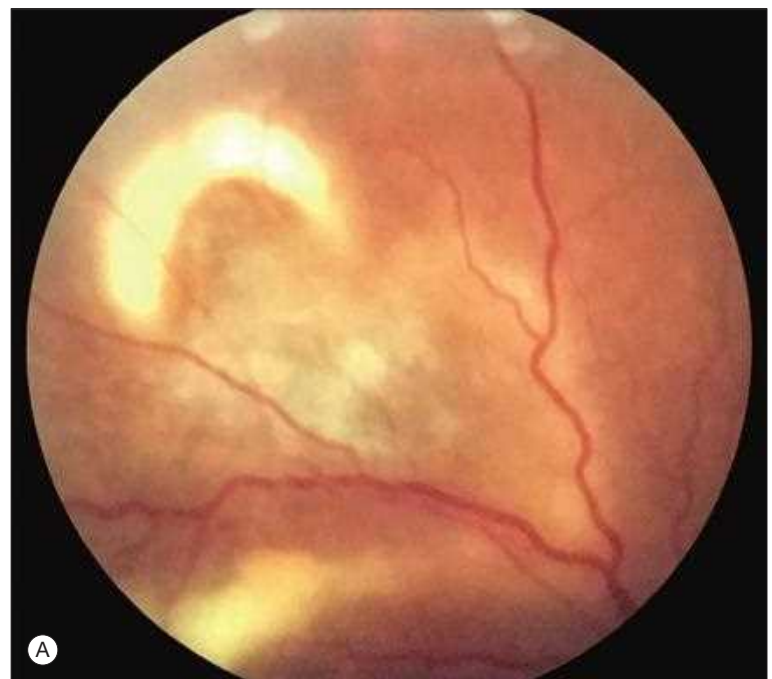
As mentioned earlier (see Massive Retinal Gliosis), occasional focal lesions of this type appear as localized off-white retinal lesions that can be mistaken for viable intraretinal retinoblastoma or spontaneously arrested retinoblastoma (retinoma).<sup>63</sup> In most cases, there is a history of prior ocular injury or severe intraocular inflammation that led to development of the retinal lesion.

### LESIONS AND DISORDERS SIMULATING EXOPHYTIC RETINOBLASTOMA

Retinoblastoma is classified as exophytic if the intraretinal tumor expands preferentially from the outer aspect of the sensory retina and causes a surrounding nonrhegmatogenous retinal detachment. In these cases the tumor frequently sheds viable tumor cells into the subretinal fluid (subretinal tumor seeds). If the serous retinal detachment becomes bullous and the subretinal fluid becomes turbid, the tumor responsible for the retinal detachment may not be obvious on ophthalmoscopy. In most cases, the exophytic tumor can be detected unequivocally by ocular ultrasonography, CT scanning, or MR imaging. However, the following lesions and disorders are frequently mistaken for advanced intraocular retinoblastoma associated with a bullous retinal detachment.

### ADVANCED COATS' DISEASE

Coats' disease is an eponym applied to advanced cases of idiopathic retinal telangiectasis.<sup>85</sup> In this disorder, peripheral and sometime midzonal retinal blood vessels (which may be predominantly capillaries, venules, arterioles, or a combination) develop multiple focal fusiform or saccular expansions as a limited developmental disorder, which is almost always limited to one eye. The cause of this disorder is unknown, but it is much more common in males than in females. The abnormally dilated (ectatic) retinal blood vessels lack the tight intercellular junctions and supporting pericytes and thus lack the normal blood–retina barrier capability. These vessels can leak a protein- and lipid-containing exudative fluid that accumulates in the adjacent retina and underlying the retina. If the abnormal blood vessels are limited in extent in the fundus, the amount of accumulated exudative fluid tends to remain localized. These cases tend to be asymptomatic and are detected later in life (usually during the teenage years). In contrast, if the abnormal blood vessels involve more than one clock hour of the fundus, they frequently lead to an exudative retinal detachment of the portion of the retina containing the ectatic blood vessels and accumulation of intraretinal and subretinal exudates in the central macula (exaggerated macular exudative response) (Fig. 8.3.46). When the abnormal retinal



**Fig. 8.3.45** Acquired Multifocal Toxoplasmic Retinitis in Patient With Prior Leukemia in Remission Following Chemotherapy and Bone Marrow Transplantation. (A) Right eye fundus. (B) Left eye fundus.

blood vessels involve more than 6 clock hours of the fundus, the exudative retinal detachment frequently becomes total and bullous (Fig. 8.3.47A–B). These cases are likely to become apparent within the first 2–3 years of life. While limited forms of idiopathic retinal telangiectasis are generally easy to diagnose, advanced idiopathic retinal telangiectasis (Coats' disease) simulates exophytic retinoblastoma quite closely.<sup>86,87</sup> Ocular ultrasonography, CT scanning, and MR imaging all confirm the total retinal detachment in such cases but fail to show any solid underlying retinal tumor that is present in retinoblastoma.

### PERSISTENT HYPERPLASTIC PRIMARY VITREOUS (PERSISTENT FETAL VASCULATURE)

Persistent hyperplastic primary vitreous (PHPV), also referred to in recent years as persistent fetal vasculature (PFV), is a developmental disorder of the eye characterized by failure of regression of the embryological intravitreal and perilental vasculature, proliferation of fibroblasts associated with that vasculature, and ultimately impairment of normal ocular growth.<sup>88,89</sup> The condition is usually monocular. In its complete form, it is



**Fig. 8.3.46 Exaggerated Macular Exudative Lesion of Coats' Disease Simulating Intraretinal Retinoblastoma.**

characterized clinically by a smaller eye on the affected side (Fig. 8.3.48A), a dense retrolenticular fibrovascular mass that pulls the ciliary processes centripetally (Fig. 8.3.48B), and a fibrovascular stalk extending from the retrolenticular fibrovascular mass to the optic disc that is usually evident on B-scan ocular ultrasonography. The retina is frequently malformed, the anterior chamber is shallower than normal, and iris blood vessels are frequently noted to extend across the pupillary margin into the perilenticular fibrovascular mass (Fig. 8.3.48B). A progressive secondary cataract usually develops. This condition is frequently misdiagnosed initially as advanced exophytic retinoblastoma.<sup>90</sup>

### CONGENITAL RETINAL DYSPLASIA

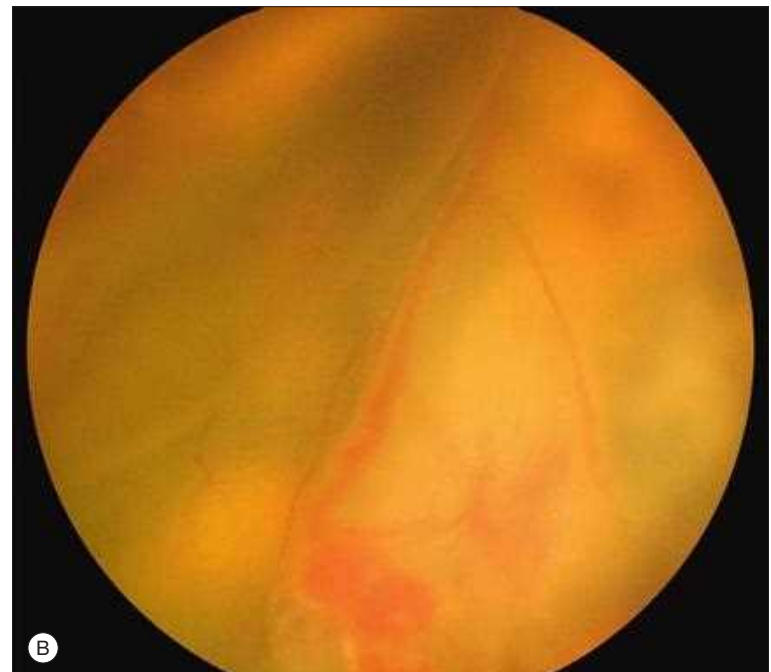
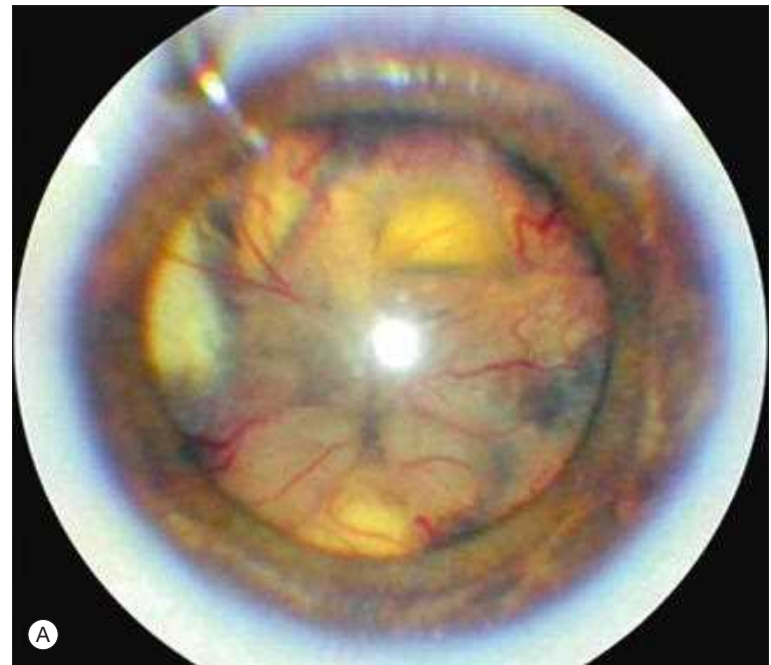
Congenital retinal dysplasia is an anomalous maldevelopment of the retina in which the developing retina becomes totally detached and balled up behind the developing lens.<sup>91</sup> The condition appears as a dense white retrolenticular mass that precludes any view of the fundus in a newborn infant (Fig. 8.3.49). The condition is frequently unilateral but can be bilateral in individuals with Norrie's disease. The location of the mass behind the lens rather than more posteriorly in the eye and the lack of intratumoral calcification help to make the diagnosis. In some cases, biopsy of the retrolenticular mass is performed to rule out retinoblastoma pathologically.

### ADVANCED RETINOPATHY OF PREMATUREITY (RETROLENTAL FIBROPLASIA)

Retinopathy of prematurity (ROP) is a developmental disorder of the retinal vasculature that occurs in infants born prematurely, prior to full vascular development of the retina.<sup>92</sup> The condition is virtually always bilateral but can be substantially asymmetrical. The spectrum of this disorder is extremely broad, ranging from congenital avascularity of the peripheral retina with a well-defined vascular-avascular interface to total fibrotic retinal detachment that simulates advanced intraocular retinoblastoma (Fig. 8.3.50).<sup>93</sup> This advanced form of ROP is commonly known as retrolental fibroplasia (RLF). While this condition was once quite common, it is relatively infrequent today except in regions of the world with limited access to regular screening and treatment.

### ADVANCED FAMILIAL EXUDATIVE VITREORETINOPATHY (FEV)

Familial exudative vitreoretinopathy is a hereditary vitreoretinal disorder that closely resembles ROP but occurs bilaterally in infants and children who were born full-term.<sup>94</sup> The condition is usually transmitted as



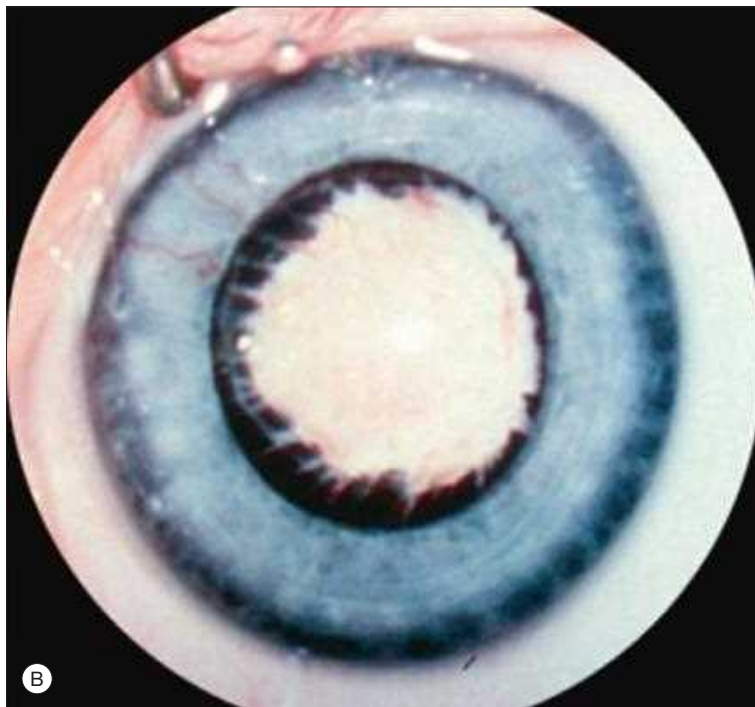
**Fig. 8.3.47 Advanced Coats' Disease.** (A) Total bullous retinal detachment behind lens. (B) Visible telangiectatic retinal blood vessels within the detached retina.

an autosomal dominant condition. Mutations of several genes, mostly on chromosome 11, have been linked with this disorder. In its advanced form, one or both eyes develop a total retinal detachment that resembles retrolental fibroplasia and can be misdiagnosed as exophytic retinoblastoma.

### ADVANCED INCONTINENTIA PIGMENTI RETINOPATHY

Incontinentia pigmenti is an X-linked dominant developmental retinal disorder that also resembles ROP.<sup>95</sup> The disorder is attributable to a mutation of the *NEMO IKBKG* gene (chromosomal locus Xq28). The condition is almost always fatal to affected males, so almost all clinically affected infants are female. In addition to the eye abnormalities, affected individuals develop a characteristic blistering of the skin (evident from birth to about 3–4 months of age) that resolves followed by development of widespread dermal melanotic pigmentation (usually evident after about 6 months of age) that gives the condition its name (Fig. 8.3.51). In its advanced form, one or both eyes develop a total retinal detachment that resembles retrolental fibroplasia.

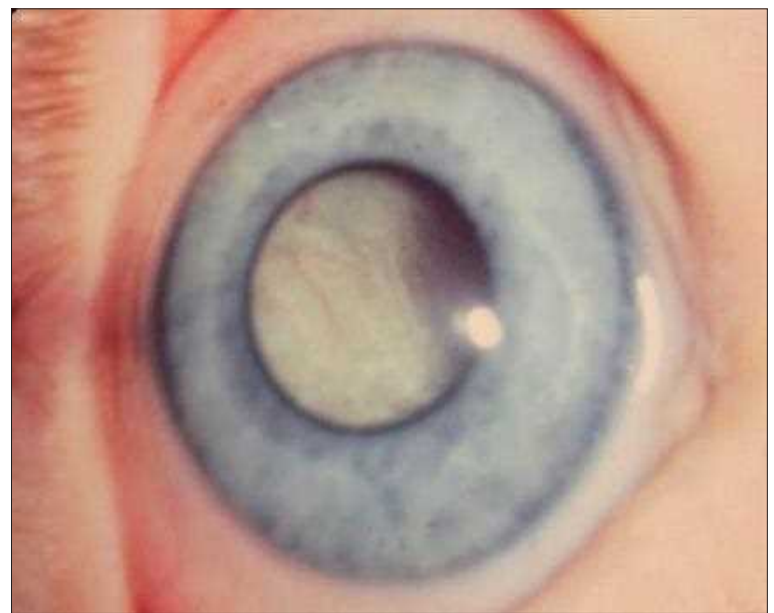




**Fig. 8.3.48 Persistent Hyperplastic Primary Vitreous (Persistent Fetal Vasculature).** (A) External view showing small cornea and leukocoria of affected esotropic right eye. (B) Anterior segment image of affected eye showing dense retrolenticular membrane, ciliary processes pulled centrally into the fibrovascular mass, and iris blood vessels extending across pupil into retrolenticular mass.



**Fig. 8.3.49 Congenital Retinal Dysplasia.**



**Fig. 8.3.50 Advanced Retinopathy of Prematurity (Retrolental Fibroplasia).**



**Fig. 8.3.51 Skin Lesions Characteristic of Incontinentia Pigmenti.**

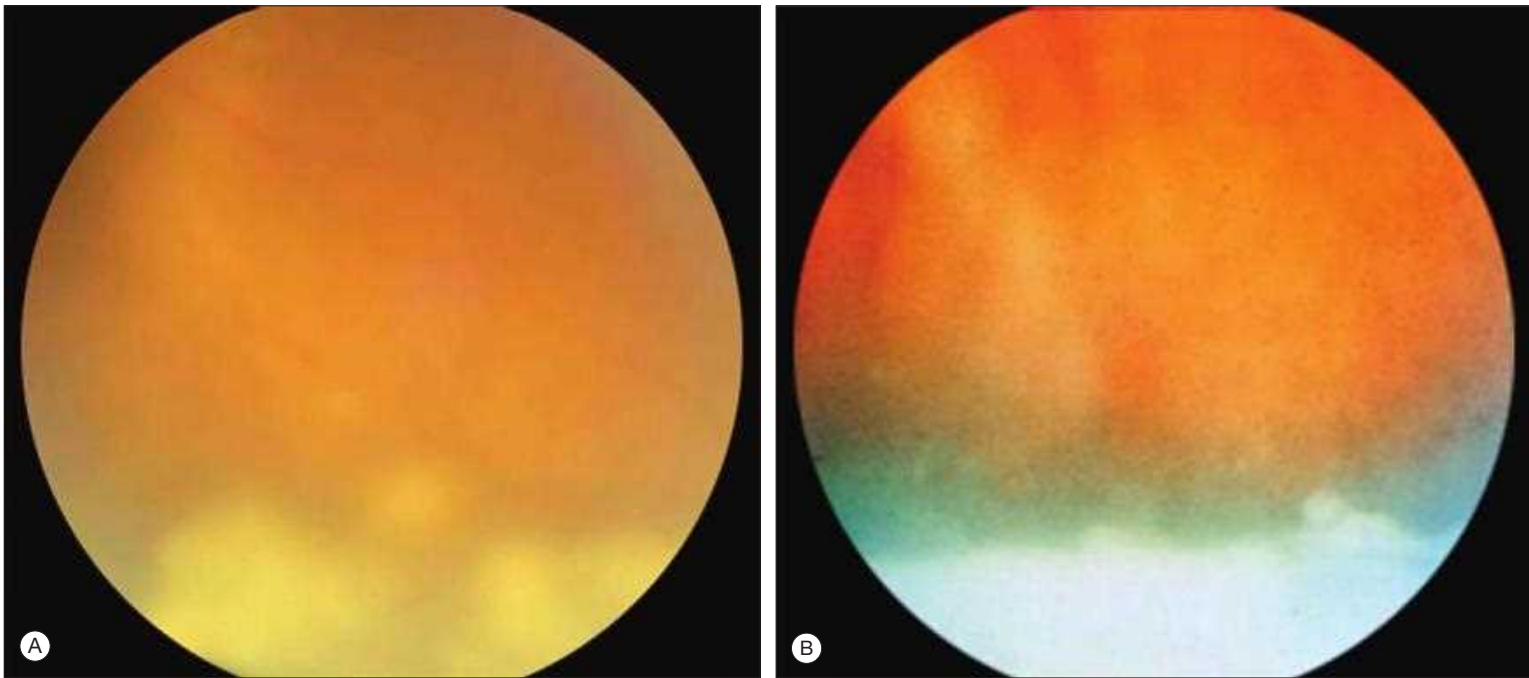
## LESIONS AND DISORDERS SIMULATING ENDOPHYTIC RETINOBLASTOMA

Retinoblastoma is classified as endophytic if the intraretinal tumor expands preferentially from the inner aspect of the sensory retina, becomes matted on the inner surface of the retina, and sheds viable tumor cells into the vitreous (vitreous seeds). If the vitreous seeds are particularly dense, the underlying retinal tumor may not be obvious on ophthalmoscopy. In most cases, the endophytic tumor can be detected unequivocally by ocular ultrasonography, CT scanning, or MR imaging. However, the following lesions and disorders can be mistaken for advanced endophytic retinoblastoma.

### PARS PLANITIS (INTERMEDIATE UVEITIS)

Pars planitis (intermediate uveitis) is an intraocular inflammatory disorder of unknown cause characterized by diffuse vitreous cells most prominently in the peripheral vitreous (Fig. 8.3.52A), and “snowbank” infiltrates that develop on the pars plana and peripheral retina in the oral zone. These occur most commonly inferiorly in both eyes (Fig. 8.3.52B).<sup>96</sup> Most affected eyes develop chronic cystoid macular edema. Advanced cases can simulate endophytic retinoblastoma with extensive vitreous seeding or diffuse infiltrating retinoblastoma.<sup>97</sup>





**Fig. 8.3.52 Pars Planitis (Intermediate Uveitis).** (A) Snowball opacities in vitreous. (B) Inferior peripheral snowbank of pars planitis.

### ENDOGENOUS ENDOPHTHALMITIS SIMULATING ENDOPHYTIC RETINOBLASTOMA

Acquired systemic infection of immunocompetent young children by parasites such as *Toxocara canis*,<sup>76,77</sup> *Toxoplasma gondii*,<sup>45,83</sup> and other organisms<sup>98</sup> occasionally leads to hematogenously disseminated (endogenous) intraocular infection that stimulates a pronounced intraocular inflammatory response. The disorder can be unilateral or bilateral. It is characterized by a dense accumulation of intravitreal inflammatory cells and frequently leads to generalized retinal deterioration. In children with congenital or acquired immunodeficiency, various microbes that are usually of limited virulence can give rise to a similar clinical picture that can also resemble endophytic retinoblastoma.

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# Phakomatoses

James J. Augsburger, Zélia M. Corrêa

8.4

**Definition:** Group of multisystem syndromes that have characteristic ophthalmic manifestations:

- Neurofibromatosis type 1 (von Recklinghausen's disease) and type 2 (central neurofibromatosis).
- Tuberous sclerosis.
- von Hippel–Lindau syndrome.
- Sturge–Weber syndrome.
- Wyburn–Mason syndrome.

## Key Features

- Inherited in an autosomal dominant fashion (neurofibromatosis, tuberous sclerosis, and von Hippel–Lindau) or sporadic and nonheritable (Sturge–Weber syndrome and Wyburn–Mason syndrome).
- Multisystem disorders associated with characteristic intraocular lesions (uveal or retinal) and central nervous lesions that in some cases may be life threatening.
- Underlying genetic defects, when present, are not treatable but in instances ocular disease or complications are treatable.

## INTRODUCTION

The phakomatoses are a group of complex multisystem disorders linked, at least in a historical sense, by various attributes of the component lesions, the organs involved, and the pattern of clinical inheritance observed in some cases. Although the term phakomatoses was coined by van der Hoeve in 1923 in a paper concerned with the similarities between von Recklinghausen's neurofibromatosis (NF) and Bourneville's tuberous sclerosis (TS), this term has never been defined satisfactorily. Absolute inclusion criteria were not presented by van der Hoeve,<sup>1</sup> and a consensus about such criteria has not been reached in the years since. Some authors define the phakomatoses as neurocutaneous syndromes characterized by autosomal dominant inheritance.<sup>2</sup> Others define them as neurocutaneous syndromes associated with ocular lesions regardless of their inheritance pattern.<sup>2,3</sup> Still others define them as syndromes characterized by the presence or development of multiorgan hamartomas.<sup>4</sup> Ophthalmologists commonly regard the phakomatoses as neuro-oculo-cutaneous syndromes that have prominent or characteristic ocular manifestations.

For the purposes of this chapter, the authors of this chapter define the phakomatoses as a group of independent clinical syndromes characterized by multiple tumors or tumor-like lesions, some of which are or can become malignant and arise in disparate organs of the body, including the eye in a substantial proportion of patients. Three syndromes are consistently classified as phakomatoses by most authors and also meet our definitional criteria: neurofibromatosis (NF), tuberous sclerosis (TS), and von Hippel–Lindau syndrome (VHL). Two other syndromes are classified as phakomatoses by many authors but do not conform precisely to our definition: Sturge–Weber syndrome (SWS) and Wyburn–Mason syndrome (WMS). These five syndromes are reviewed briefly in this chapter. Other syndromes that are occasionally grouped with the phakomatoses by some authors (e.g., Louis–Bar syndrome [ataxia telangiectasia], Weskamp–Cotlier syndrome [retinal-neuro-cutaneous cavernous hemangioma syndrome], PTEN [phosphatase and TENsin homolog gene] hamartoma-tumor syndrome, and PHACE [posterior fossa malformations, hemangioma, arterial anomalies, cardiac defects, and eye anomalies] syndrome) are not reviewed in this chapter.

## NEUROFIBROMATOSIS

The syndrome of neurofibromatosis (NF) consists of three distinct genetic diseases with considerable phenotypic overlap.<sup>5</sup> All are characterized by neuroectodermal tumors that arise within multiple organs and autosomal dominant inheritance. The three forms of NF are termed NF-1, NF-2, and schwannomatosis.

## EPIDEMIOLOGY AND PATHOGENESIS

Neurofibromatosis is the most common phakomatosis, having a frequency of approximately one case per 2000–3000 persons in the general population.<sup>5</sup> NF-1 is by far the more common of the two types, affecting approximately one person per 2500–3000 in the general population. In contrast, NF-2 affects no more than one person per 40 000–50 000 persons. Schwannomatosis is the least common of these disorders, affecting no more than one person per 60 000–70 000 persons. Men and women appear to be affected with equal frequency, and there is no racial predilection for any of the types of the disease. Many features of these syndromes do not appear until late childhood or early adulthood. The severity of the syndrome varies markedly from patient to patient. Many patients who have limited forms of NF are probably not identified.

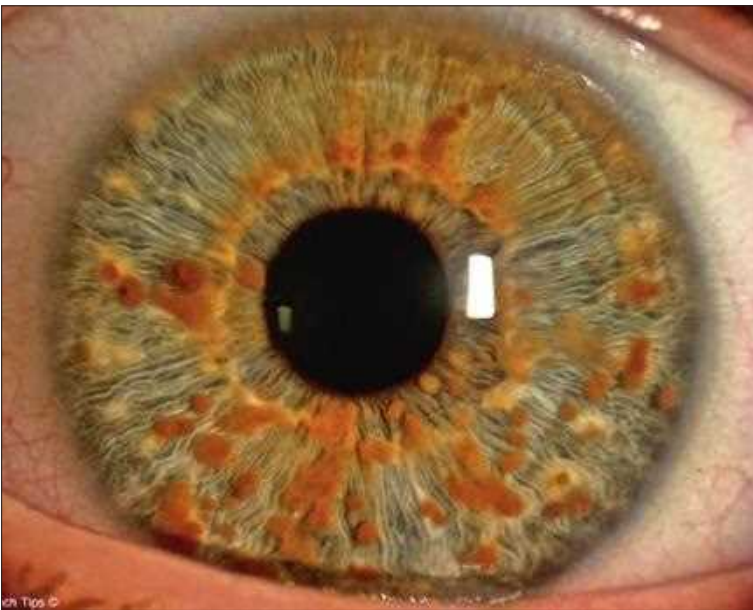
The gene for NF-1 has been localized to chromosome 17q11.2,<sup>6</sup> that for NF-2 has been localized to chromosome 22q12.2,<sup>7</sup> and that for schwannomatosis has been linked to an alternative region of chromosome 22 encompassing the *SMARCB1* and *LZTR1* genes (chromosome 22q11.21–11.23).<sup>8</sup>

## EXTRAOPHTHALMIC MANIFESTATIONS

Neurofibromatosis type 1 (peripheral NF, von Recklinghausen's disease) is characterized by cutaneous café-au-lait spots (Fig. 8.4.1), axillary and inguinal freckling, Lisch nodules of the iris (Fig. 8.4.2), several types of cutaneous neurofibromas, optic nerve gliomas (Fig. 8.4.3), and neurofibromas or other solid neoplasms of the central nervous system (CNS).<sup>5,9,10</sup> The café-au-lait spots (see Fig. 8.4.1) in this syndrome tend to be multiple. Many are larger than 0.5 cm in diameter in childhood and enlarge to 1.5 cm in diameter by the postpubertal years. Six or more café-au-lait spots larger than 1.5 cm in diameter in postpubertal individuals are generally



**Fig. 8.4.1** Prominent Café-Au-Lait Spot of Skin in a Patient With Neurofibromatosis Type 1.



**Fig. 8.4.2 Lisch Nodules of Iris in Neurofibromatosis Type 1.** Similar Multiple Iris Nodules Were Evident in the Fellow Eye.



**Fig. 8.4.3 Optic Nerve Glioma Causing Proptosis in Girl With Neurofibromatosis Type 1.** (A) Clinical photo showing proptosis and slight downward displacement of the left eye. (B) Reconstructed sagittal magnetic resonance imaging of left orbit showing optic nerve tumor causing proptosis.

considered diagnostic of NF-1. Axillary freckling and inguinal freckling are present in 90%–95% of affected individuals. Subcutaneous neurofibromas in NF-1 tend to arise multifocally and can be either pedunculated nodules or diffuse plexiform lesions. CNS neurofibromas can cause hemiparesis, hemiatrophy, and seizures in some affected individuals. Because of bone abnormalities related to the syndrome, some individuals develop severe scoliosis. About one half of all patients affected by NF-1 have some sort of learning disability, but most are of normal intelligence. In older patients, systemic hypertension appears to be more frequent than it is in the general



**Fig. 8.4.4 Magnetic Resonance Image Showing Bilateral Acoustic Neuromas in a Patient With Neurofibromatosis Type 2.**

population. Comprehensive clinical criteria for diagnosis of NF-1<sup>10</sup> and recommendations for genetic testing of individuals suspected of having this disorder<sup>5</sup> have been published and should be consulted by clinicians desiring such information.

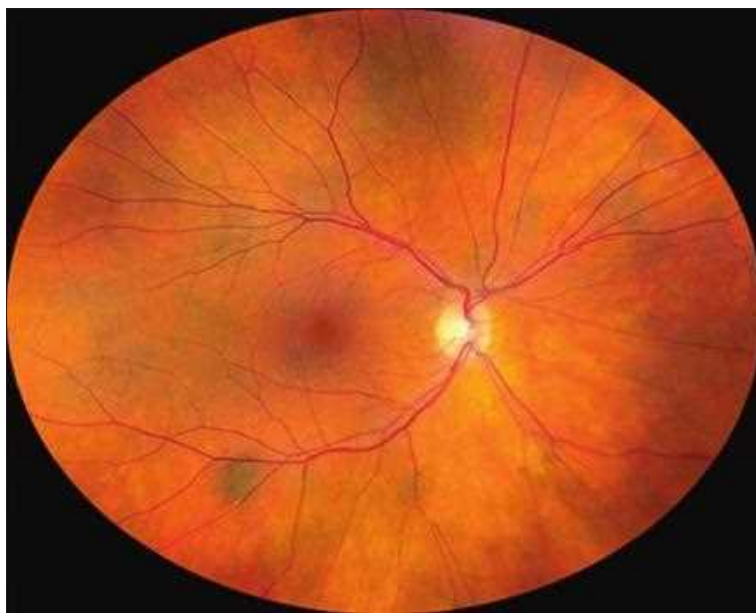
Neurofibromatosis type 2 (central NF) is typified by bilateral vestibular schwannomas (acoustic neuromas) (Fig. 8.4.4) and widely scattered neurofibromas, meningiomas, gliomas, and schwannomas.<sup>5,11,12</sup> The most consistent extraophthalmic problem suffered by patients affected by NF-2 is sensorineural deafness caused by the vestibular schwannomas. Comprehensive clinical criteria for diagnosis of NF-2<sup>11,12</sup> and recommendations for genetic testing of individuals suspected of having this disorder<sup>5</sup> have been published and should be consulted by clinicians desiring such information.

Schwannomatosis is also characterized by scattered schwannomas but not ones involving the vestibular nerve.<sup>5,13</sup> Comprehensive clinical criteria for diagnosis of schwannomatosis<sup>13</sup> and recommendations for genetic testing of individuals suspected of having this disorder<sup>5</sup> have been published and should be consulted by clinicians desiring such information.

## OCULAR MANIFESTATIONS

Ophthalmological findings in NF-1 include Lisch nodules of the iris (see Fig. 8.4.2), subcutaneous pedunculated and plexiform neurofibromas of the eyelids, optic nerve gliomas (see Fig. 8.4.3), multifocal choroidal freckles or nevi (Fig. 8.4.5), and occasionally retinal tumors indistinguishable from the retinal astrocytomas found in tuberous sclerosis.<sup>14,15</sup> Lisch nodules have been described as melanocytic hamartomas of the iris stroma. These lesions appear as tan to light brown nodules that stud the iris surface (see Fig. 8.4.2). They are rarely present at birth but tend to develop by the second to third decade of life in over 95% of persons who have NF-1.<sup>16</sup> Histopathologically, Lisch nodules consist of closely packed dendritic or spindle-shaped melanocytes within the anterior layers of iris stroma. Because these cells are normal uveal melanocytes and not nevus cells, these lesions are not true nevi. Neurofibromas of the eyelids can be either nodular or plexiform in nature. They tend to develop early in life and can enlarge progressively. Gliomas of the optic nerve develop in 10%–15% of affected patients.<sup>17</sup> They can occur unilaterally or bilaterally





**Fig. 8.4.5 Multiple Melanocytic Choroidal Freckles in the Fundus of a Patient With Neurofibromatosis Type 1.** The fellow eye contained a similar number of discrete choroidal freckles.

and frequently involve the optic chiasm. Optic nerve gliomas in the orbit (see Fig. 8.4.3) can cause progressive proptosis and optic atrophy and frequently result in unilateral or bilateral blindness. Those that arise within the brain and involve the chiasm can cause bilateral visual loss as well as intracranial mass effects. Some patients affected by NF-1 have pulsating exophthalmos caused by anomalous development of the sphenoid bone. Congenital and infantile glaucomas appear to be common in patients who have this syndrome. Some affected patients develop multifocal choroidal melanocytic freckles or nevi bilaterally (see Fig. 8.4.5). Individuals with NF-1 appear to have an increased cumulative lifetime risk for development of a uveal melanoma.<sup>18</sup>

Ophthalmological findings in NF-2 are relatively uncommon.<sup>3,9,10,14</sup> Lisch nodules of the iris, eyelid neurofibromas, and optic nerve gliomas occur occasionally but are not generally present. The most consistent ocular findings in patients who have NF-2 are combined hamartomas of the retina<sup>19</sup> (described and illustrated in Chapter 8.2) and juvenile posterior subcapsular or cortical lens opacities. To date, no recurring eye abnormalities have been associated with schwannomatosis.

## SYSTEMIC MANIFESTATIONS

Detailed recommendations for systemic evaluation of patients who have suspected NF-1 or NF-2 have been published.<sup>5,9-12</sup> For patients who have suspected NF-1, the basic diagnostic evaluation should consist of a complete history and comprehensive physical examination, including an ophthalmic examination. Ancillary studies such as computed tomography (CT) and magnetic resonance imaging (MRI) should be performed in NF-1 if the history or findings revealed by physical examination suggest that they might be helpful. For patients who have suspected NF-2, the basic diagnostic evaluation should consist of a complete history and physical examination, including an ophthalmic examination and high-resolution MRI or CT imaging of the brain and spinal cord. The imaging studies should address the presence or absence of vestibular schwannomas. Other studies in suspected NF-2 are obtained as indicated by the findings detected during the basic evaluation.

## TREATMENT

Treatment of optic nerve gliomas in NF is covered in Chapter 12.10, and treatment of neurofibromas of the eyelids is covered in Chapter 12.7. Treatment of the intracranial lesions of NF-1 and NF-2 is beyond the scope of this book.

## COURSE AND OUTCOMES

Life expectancy is reduced substantially in patients who have NF-1 or NF-2.<sup>5,9-11</sup> The principal causes of early death in persons who have NF-1



**Fig. 8.4.6 Ash Leaf Spots of the Skin in a Patient With Tuberous Sclerosis.**

are complications of systemic hypertension, cancer, and expansive growth of benign intracranial neoplasms. Several types of cancer, including neurofibrosarcoma, other sarcomas, leukemias, and lymphomas, occur with increased frequency in patients who have NF-1. In patients with NF-2, the main cause of early death is expansion of a CNS neoplasm. Unilateral or bilateral blindness occurs in some individuals affected by NF-1 or NF-2, usually because of glioma of the optic nerves or chiasm (especially in NF-1) but occasionally because of expansile intracranial growth of a vestibular schwannoma or an apoplectic episode (NF-2).

## TUBEROUS SCLEROSIS

Tuberous sclerosis (TS) is a multiorgan tumor syndrome that is characterized by multifocal bilateral retinal astrocytic hamartomas, astrocytic tumors of the CNS, several unusual cutaneous lesions, mental retardation, seizures, and a variety of cysts and tumors of other organs.<sup>20</sup> The clinical spectrum is extremely broad and ranges from minimal to marked in affected individuals. Many persons who have limited forms of the disease are probably not recognized as having TS.

## EPIDEMIOLOGY AND PATHOGENESIS

The prevalence of TS in the general population has been estimated to be approximately one case per 10,000 persons.<sup>20</sup> About one third of cases are familial and two thirds are sporadic. No recognized racial predilection exists, and the sexes are affected equally. Signs and symptoms of TS usually begin by the time the patient is 6 years of age.

TS genes have been identified on loci on the long arm of chromosome 9 (9q32-34), on the long arm of chromosome 11, on the short arm of chromosome 16 (16p13), and on the long arm of chromosome 12 (12q22-24).<sup>21</sup> Of these loci, the 9q32-34 locus has been the most consistent, being associated with between one third and one half of all familial cases.

## EXTRAOPHTHALMIC MANIFESTATIONS

The characteristic extraophthalmic clinical features of TS are congenital and acquired skin lesions, benign CNS astrocytomas, and a variety of cysts and tumors that occur in organs such as the kidney, heart, and lungs.<sup>20,22</sup> The cutaneous lesions characteristically associated with TS include ash leaf spots, adenoma sebaceum, shagreen patches, and subungual and periungual fibromas. Ash leaf spots (Fig. 8.4.6) are congenital white or hypomelanotic skin macules ranging in size from about 1 mm to several centimeters in diameter and having a configuration that resembles an ash leaf. These lesions usually show up prominently when the skin is viewed under ultraviolet light. Adenoma sebaceum (Fig. 8.4.7) is an unusual facial dermatological eruption characterized by pinhead to pea-sized yellowish to reddish brown papules distributed in a butterfly fashion over the nose, cheeks, and nasolabial folds in teenagers to young adults. Histopathologically, the





**Fig. 8.4.7 Adenoma Sebaceum of Face in a Patient With Tuberous Sclerosis.**



**Fig. 8.4.8 Computed Tomography Scan of Brain Showing Paraventricular and Intracerebral Astrocytomas in a Patient With Tuberous Sclerosis.**

individual skin lesions are angiofibromas. The shagreen patch is a thickened patch of skin with the texture of pigskin or sharkskin that is usually located on the lower back. Subungual and periungual fibromas are benign fibrous tumors that develop under and at the sides of the nail beds in some patients. The CNS tumors that occur in TS are generally low-grade astrocytomas. These CNS lesions can become calcified and detectable on skull radiographs, but they are revealed much more effectively by CT or MRI (Fig. 8.4.8).<sup>20</sup> Complications associated with such lesions include mental deficiency and seizures, both of which can range from mild to severe. Many individuals who have TS have normal intellectual abilities. The most common visceral tumor that occurs in TS appears to be the angiomyolipoma of the kidney. Probably the most distinctive visceral tumor in TS is the benign cardiac rhabdomyoma. In some patients who have TS, an unusual lung disease (pulmonary lymphangioleiomyomatosis) develops.

In addition, benign cysts develop multifocally in various visceral organs, including the kidneys, liver, and lungs, in many patients who have TS.

## OCULAR MANIFESTATIONS

The typical ophthalmological feature of TS is the retinal astrocytoma (astrocytic hamartoma).<sup>23</sup> Lesions of this type are described in detail and illustrated in Chapter 8.2. Approximately one half of all patients affected by TS develop at least one retinal astrocytoma in one eye. In individuals who have TS and develop retinal astrocytomas, multiple lesions in both eyes occur in 40%–50% of cases. Malignant transformation of retinal astrocytomas occurs in TS but is rare.

## SYSTEMIC EVALUATION

Systemic evaluation of individuals for whom TS is suspected should include fundus examination, dermatological evaluation to identify characteristic skin lesions, CT or MRI of the CNS, and CT or MRI of the abdominal viscera.<sup>20,22</sup> Examination of family members to look for a familial pattern is also appropriate. Genetic testing usually is performed in suspicious cases to confirm the presence of one or more of the gene mutations associated with this disorder.<sup>21</sup>

## TREATMENT

Treatment of affected individuals with TS has changed from symptomatic management of the various lesions associated with the disorder to medical therapy of affected individuals using a variety of mTOR inhibitors to suppress development of the CNS and systemic tumors or prevent their progression.<sup>24</sup> Periodic physical examination and imaging of the CNS and abdominal–thoracic viscera by CT or MRI are appropriate to identify and monitor potentially treatable problems such as cardiac rhabdomyomas, cysts and tumors of the kidney, and enlarging CNS astrocytomas.

## COURSE AND OUTCOME

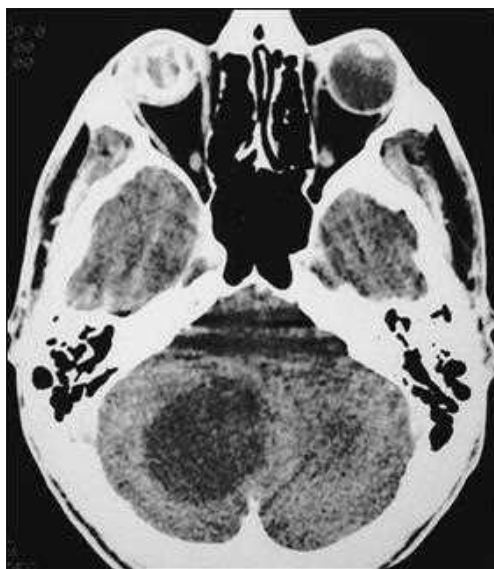
Historically, life expectancy of individuals who have TS has been reduced substantially compared with that expected in the normal population.<sup>20</sup> The most common cause of early death in this syndrome is renal failure secondary to angiomyolipomas, cysts, or both.<sup>25</sup> The second most common cause of death is obstructive hydrocephalus or other CNS problems caused by enlargement of one or more of the CNS astrocytomas. Other important but less frequent causes of death are cardiac conduction defects and heart failure from cardiac rhabdomyoma and chronic pulmonary insufficiency associated with lymphangioleiomyomatosis of the lung. In patients who have profound mental retardation and severe seizures, death occurs occasionally as a result of status epilepticus or pneumonia.

## VON HIPPEL–LINDAU SYNDROME

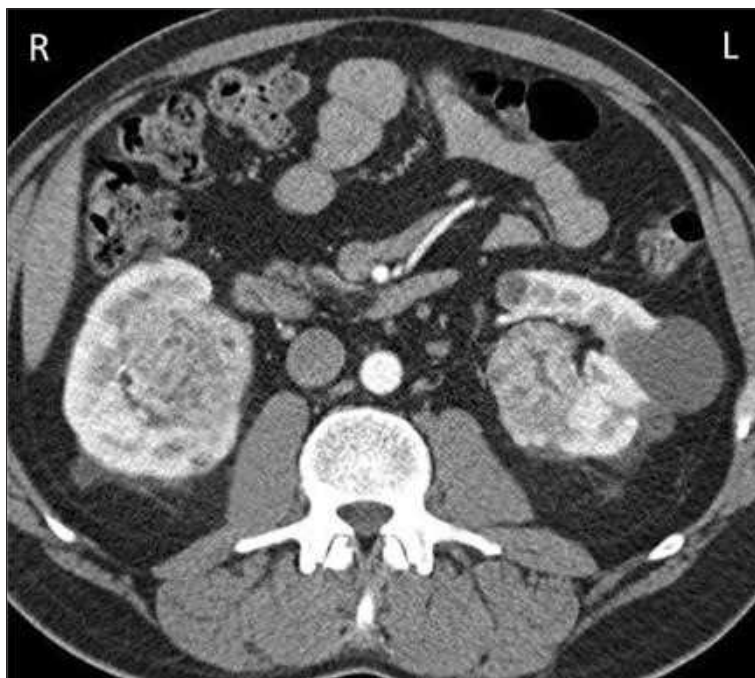
The von Hippel–Lindau syndrome (VHL) is a multiorgan disorder characterized by retinal capillary hemangiomas, CNS hemangioblastomas, various solid and cystic visceral hamartomas and hamartias, and malignant neoplasms, including renal cell carcinomas and pheochromocytomas.<sup>26–29</sup> The full-fledged syndrome commonly runs in families that have a clear autosomal dominant inheritance pattern. Affected individuals are at substantial risk of early death, usually because of their intracranial hemangiomatous lesion or renal cell carcinoma.

## EPIDEMIOLOGY AND PATHOGENESIS

VHL is a rare disorder, having a cumulative lifetime incidence of approximately 1 in 30 000–40 000 persons.<sup>30</sup> In patients who have full-fledged VHL, one or more clinically identifiable manifestations of the disease are usually present by or before the third decade of life. The median age at detection of the first clinical features of VHL is 20–25 years.<sup>26–29</sup> Capillary hemangiomas of the retina (described and illustrated in Chapter 8.2) are usually the earliest detected manifestation of VHL (probably because they are easiest to detect at a small size), whereas CNS hemangioblastomas typically appear slightly later and renal cell carcinomas substantially later in life. However, the timing of clinical emergence of the various lesions in individual patients who have VHL varies greatly. The cumulative probability of developing retinal capillary hemangiomas and CNS hemangioblastomas in a patient who has VHL is more than 80%, and the probability of



**Fig. 8.4.9** Computed Tomography Scan of Head Showing Cystic Cerebellar Hemangioblastoma in von Hippel-Lindau Syndrome. Note cerebellar tumor and increased intraocular density ipsilaterally (related to advanced retinal capillary hemangiomatosis causing phthisis bulbi).



**Fig. 8.4.10** Computed Tomography Scan of Abdomen of a Patient With von Hippel-Lindau Syndrome Showing Bilateral Renal Cell Carcinoma.

developing renal cell carcinoma is more than 60%. VHL affects both sexes equally and occurs in all racial groups.

As mentioned earlier, VHL is inherited as an autosomal dominant disorder in affected families. Molecular biological studies have localized the VHL gene to chromosome 3p25-26.<sup>29,31</sup>

## EXTRAOPHTHALMIC MANIFESTATIONS

Important extraocular features of VHL include hemangioblastomas (capillary hemangiomas) of the brain (Fig. 8.4.9) and spinal cord, renal cell carcinoma (Fig. 8.4.10), pheochromocytoma, several other less common solid neoplasms and related lesions, and cystic lesions of various visceral organs.<sup>26-29</sup> The typical CNS lesions of VHL are solid and cystic cerebellar hemangioblastomas (see Fig. 8.4.9), which occur in about 40% of affected individuals by the age of 30 years and in about 70% of them by the age of 60 years. The component cells in these tumors appear benign by histopathological criteria. Similar vascular lesions also occur in the medulla and spinal cord in 10%–15% of patients who have VHL.

Renal cell carcinoma is an acquired malignant neoplasm of the kidney that occurs in about 5% of VHL patients by the age of 30 years but in more than 40% by the age of 60 years. The renal cell carcinomas that occur in VHL (see Fig. 8.4.10) are bilateral in approximately 75% of cases. This tumor can metastasize, so it must be recognized early and treated aggressively if a fatal outcome is to be avoided. Other visceral neoplasms that

develop in some patients who have VHL include pheochromocytoma, islet cell carcinoma of the pancreas, and cyst-adenomas of the pancreas and epididymis. Also, those affected by VHL have a strong tendency to develop multifocal cysts in the kidneys, pancreas, and ovaries. Unlike NF and TS, VHL does not have dermatological lesions as part of the syndrome.

## OCULAR MANIFESTATIONS

The characteristic ocular lesion of VHL is the retinal capillary hemangioma,<sup>26-29</sup> which is described in detail and illustrated in Chapter 8.2. Approximately 50%–60% of patients who have VHL develop retinal capillary hemangiomatosis during their lifetimes, and about one half of these individuals have multiple retinal capillary hemangiomas in both eyes.

## SYSTEMIC EVALUATION

As a result of the frequency and severity of the various multiorgan lesions in VHL, a comprehensive baseline evaluation and periodic re-examination and ancillary testing of patients suspected of having the disease is appropriate.<sup>26-29</sup> The baseline evaluation should include genetic testing of a peripheral blood specimen to identify or rule out the presence of a deletion or mutation of the VHL gene (located on chromosome 3p25-26). The baseline systemic evaluation should include MRI of the CNS and abdomen to identify or rule out identifiable tumors and fundus examination to identify or rule out retinal capillary hemangiomas. The frequency and intensity of follow-up evaluations are dependent on the absence versus presence and extent of the abnormalities evident on the baseline evaluation and the age of the patient at the time of that evaluation.<sup>30</sup> Management of VHL must be multidisciplinary and address the specific lesions that occur in each individual patient.

## TREATMENT

Signs and symptoms of VHL and the necessity for treatment depend on the nature of the lesions that are present, the location and size of these lesions, and the symptoms that result from these lesions.<sup>30</sup> Treatment of retinal capillary hemangiomas is covered in Chapter 8.2. Treatment of the CNS and visceral lesions of this disease is generally surgical and beyond the scope of this book.

## COURSE AND OUTCOMES

Progression of retinal capillary hemangiomas in VHL is highly variable, but tumor enlargement, intraretinal and intravitreal bleeding, exudation, gliosis, and retinal detachment may develop. These complications can result in profound visual loss or even phthisis bulbi of one or both eyes. Fortunately, ophthalmic treatment is usually able to preserve good vision in at least one eye. If the associated renal tumors and intracranial vascular tumors are not detected at an early stage or are not controlled by aggressive intervention, they commonly prove fatal to the affected individuals.<sup>26-29</sup> Consequently, the life expectancy of patients who have VHL is reduced considerably compared with that of unaffected persons in the general population. The median age at death in patients who have VHL is 45–50 years in most series.

## STURGE-WEBER SYNDROME

Sturge-Weber syndrome (SWS) is a dermato-oculo-neural syndrome characterized by cutaneous facial nevus flammeus in the distribution of the branches of the trigeminal nerve, ipsilateral diffuse cavernous hemangioma of the choroid, and ipsilateral meningeal hemangiomatosis.<sup>32</sup> The lesions in the eye, skin, and brain are always present at birth (i.e., they are birthmarks or congenital anomalies rather than acquired neoplasms such as those that occur in the three syndromes already covered in this chapter).

## EPIDEMIOLOGY AND PATHOGENESIS

The frequency of the complete SWS and its formes frustes is approximately one case per 50,000 persons.<sup>32</sup> Men and women appear to be affected equally. No recognized racial predilection occurs. The vast majority of patients affected by SWS have sporadic nonfamilial disease. Only a few familial clusters of the syndrome have been reported, and most of these have not exhibited the clear-cut autosomal dominant inheritance pattern that typifies NF, TS, and VHL.



## EXTRAOPHTHALMIC MANIFESTATIONS

The classical cutaneous feature of SWS is the facial nevus flammeus (Fig. 8.4.11), a flat to moderately thick zone of dilated telangiectatic cutaneous capillaries lined by a single layer of endothelial cells in the dermis. The lesion is usually unilateral and most frequently involves the regions of the face innervated by the first, occasionally the first and second, and rarely all three branches of the trigeminal nerve. The ipsilateral nasal and buccal mucosa is involved in some patients, and localized hypertrophy of the involved tissues may be present. The characteristic CNS manifestation of SWS is ipsilateral leptomeningeal hemangiomas, which causes atrophy of the cortical parenchyma of the brain, seizures, and frequently mental retardation. The CNS lesions are present at birth and are detectable by MRI or CT (Fig. 8.4.12).<sup>33</sup> These lesions tend to be progressive throughout life.<sup>34</sup> In many patients, the affected meninges become irregularly calcified during life, in which case the CNS vascular lesion can be detected on routine skull radiographs.

## OCULAR MANIFESTATIONS

The classical ocular manifestation of SWS is the diffuse choroidal hemangioma.<sup>32,35</sup> This lesion is a generalized thickening of the choroid by mature blood vessels of various sizes. It is almost always present at birth but frequently becomes accentuated during the first two decades of life. Because the diffuse choroidal hemangioma gives the entire posterior choroid a saturated red color (Fig. 8.4.13A), it is frequently not evident on routine ophthalmoscopy, but comparing the affected fundus to the contralateral fundus (see Fig. 8.4.13) usually reveals a much more saturated red color

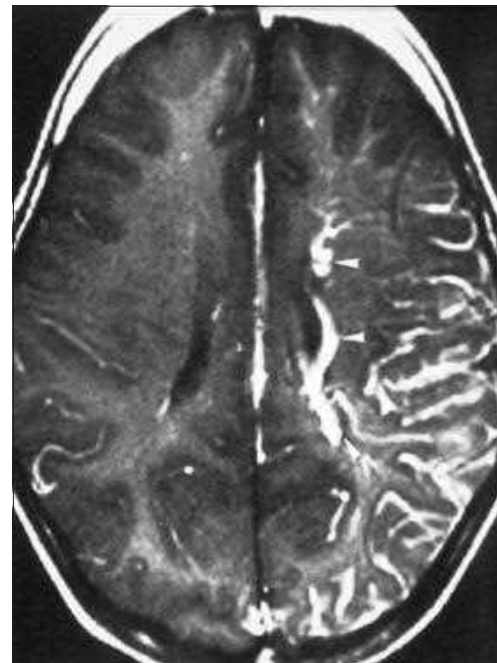
on the affected side, absence of any distinctly visible large caliber choroidal blood vessels on the side of the hemangioma, and deep ipsilateral cupping of the optic disc (which is frequently due to the abnormal thickness of the circumpapillary choroid but may also be due to secondary glaucomatous cupping). The generalized choroidal thickening caused by a diffuse choroidal hemangioma is better appreciated by B-scan ocular ultrasonography (Fig. 8.4.14) than by ophthalmoscopy. Other ocular abnormalities that are found in some patients who have SWS include telangiectasia of the conjunctiva and episclera (Fig. 8.4.15) and ipsilateral congenital, infantile, or juvenile glaucoma. Many eyes affected by diffuse choroidal hemangioma develop a secondary serous retinal detachment that can cause profound visual loss if not recognized and treated appropriately.

## SYSTEMIC EVALUATION

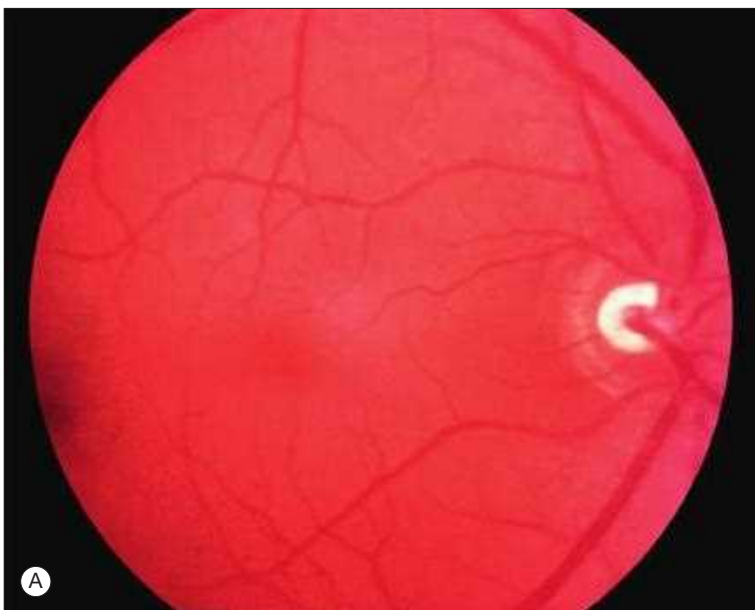
Because patients affected by SWS do not have any recognized propensity to develop benign or malignant neoplasms, they do not require periodic systemic or CNS screening tests for such lesions. However, patients who have SWS and develop seizures or progressive mental deterioration probably need periodic neurological evaluation and intermittent evaluation by CT or MRI of the brain to rule out treatable lesions or disorders.<sup>32,33</sup> Regular ophthalmological evaluations are appropriate in all patients who have



**Fig. 8.4.11 Facial Nevus Flammeus in a Patient With Sturge-Weber Syndrome.**

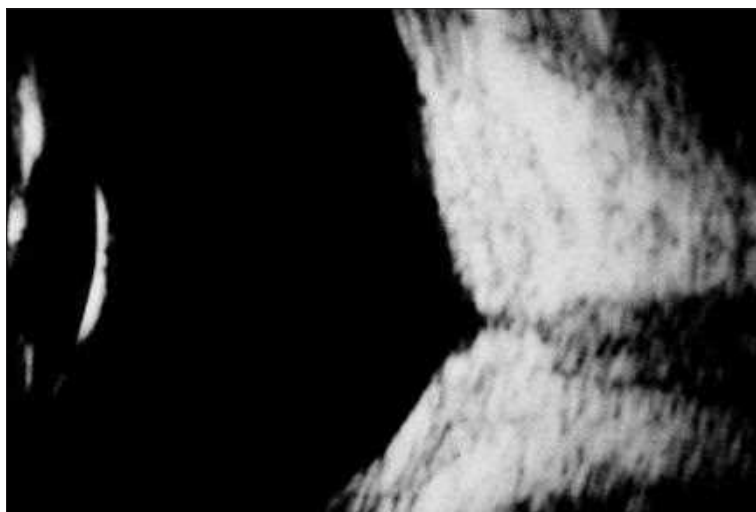


**Fig. 8.4.12 Computed Tomography Scan of Brain in a Patient With Left-Sided Facial Nevus Flammeus and Ipsilateral Diffuse Choroidal Hemangioma.** Note the extensive leptomeningeal hemangioma involving the left side of the brain.



**Fig. 8.4.13 Comparative Fundus Appearance in the Two Eyes of a Patient With Diffuse Choroidal Hemangioma on the Right.** (A) Affected right eye fundus showing saturated red choroid diffusely and deep optic disc cup secondary to circumpapillary choroidal thickening. (B) Unaffected left eye fundus showing visible large caliber choroidal blood vessels and physiological optic disc cupping.





**Fig. 8.4.14** Axial B-Scan Ultrasound Image of an Eye With Diffuse Choroidal Hemangioma Showing Generalized, Moderately Sonoreflective Thickening of the Posterior Choroid and Deep Focal Posterior Pit Corresponding to Optic Disc.



**Fig. 8.4.15** Episcleral Telangiectasis Ipsilateral to Facial Nevus Flammeus and Diffuse Choroidal Hemangioma in a Patient With Sturge-Weber Syndrome. This is the same patient shown in Fig. 8.4.11.

suspected or confirmed SWS to screen for treatable ocular complications such as glaucoma and serous nonrhegmatogenous retinal detachment.<sup>35</sup>

## TREATMENT

Treatment of patients who have SWS is generally symptomatic and directed toward complications caused by the vascular lesions of the brain and eyes.<sup>32</sup> Seizures are treated medically unless that therapy proves unsuccessful. Intractable seizures and progressive mental deterioration are sometimes treated surgically by techniques such as subtotal hemispherectomy.<sup>36</sup> The facial nevus flammeus can be treated by dermatological laser therapy. This treatment frequently results in marked regression of the vascular birthmark and substantial cosmetic improvement. Treatment of the ophthalmic lesions and complications of SWS include medical and surgical treatments for glaucoma and photodynamic therapy or low-dose external beam or plaque radiotherapy for nonrhegmatogenous retinal detachment secondary to the hemangioma.<sup>35</sup> Unfortunately, the visual prognosis for affected eyes is usually quite poor.<sup>37</sup>

## COURSE AND OUTCOME

The life expectancy of patients who have SWS appears to be reduced substantially compared with that of persons in the general population.<sup>32,34</sup> However, most early deaths occur in individuals who have profound mental retardation and intractable seizures and not in those who have a limited form of the disease, normal intellectual ability, and no seizures. The visual outcome of eyes affected by diffuse choroidal hemangioma depends on the thickness of the hemangioma (especially in the macula), the presence, extent and duration of secondary nonrhegmatogenous retinal detachment prior to its detection, the response of the hemangioma and the retinal detachment to photodynamic therapy or radiation therapy, and the presence and severity of secondary glaucoma in the affected eye.<sup>37</sup>



**Fig. 8.4.16** Moderately Complex Arteriovenous Malformation of Posterior Retina Superotemporally in a Patient With Wyburn-Mason Syndrome.



**Fig. 8.4.17** Complex Arteriovenous Malformation of Retina in a Patient With Wyburn-Mason Syndrome.

## WYBURN-MASON SYNDROME

Wyburn-Mason syndrome (WMS) is characterized by arteriovenous malformations (AVMs) of the retina (Figs. 8.4.16 and 8.4.17) and ipsilateral CNS (Fig. 8.4.18).<sup>38,39</sup> Because the abnormal lesions are not distinct tumors but rather anomalous arteriovenous communications and because this disorder is not associated with any characteristic skin lesions, this syndrome is not a true phakomatosis by the definition used herein. Most patients who have WMS have unilateral, nonfamilial disease.

## EPIDEMIOLOGY AND PATHOGENESIS

This syndrome is very uncommon. The retinal and intracranial AVMs of WMS are congenital. However, they are usually incompletely developed at



**Fig. 8.4.18** Computed Tomography Scan of Head Showing Prominent Arteriovenous Malformations of Brain, Orbit, and Facial Soft Tissues on the Right in a Patient With Wyburn–Mason Syndrome.

birth but progress during growth and aging.<sup>40</sup> Consequently, the vascular malformations in the retina and CNS are often undetected until the second through fourth decades of life. The more extensive the congenital vascular lesions, the earlier the presentation in most patients.<sup>38,39</sup> Men and women appear to be affected equally. No racial predilection occurs. No hereditary pattern has been identified.

## EXTRAOPHTHALMIC MANIFESTATIONS

In patients with WMS, complex AVMs occur in the orbit, the periorbital soft tissues and bones, and the midbrain ipsilateral to the retinal AVM.<sup>33,34</sup> When they are prominent, they can frequently be demonstrated by CT scanning or MR imaging (see Fig. 8.4.18), but when they are small, arteriography may be needed to image them. Not all patients who have a retinal AVM have or develop extraretinal AVMs, and only those who have both retinal and CNS AVMs should be considered to have WMS. In general, the more complex the retinal vascular anomalies, the higher the likelihood of associated CNS AVMs.<sup>38</sup>

## OCULAR MANIFESTATIONS

The classical ophthalmic abnormality of WMS is the AVM of the retina (see Figs. 8.4.16 and 8.4.17).<sup>38,39</sup> The characteristic finding is the presence of one or more retinal arterioles that enter the retina at the optic disc,

extend a variable distance away from the disc, and connect to a draining vein without any interposed capillary bed. The efferent and afferent limbs of the malformation tend to be dilated and tortuous, and the severity of dilation and tortuosity of these vessels is proportional to their respective calibers. The transit of blood through the arteriovenous loops is very fast, a feature that can be demonstrated with clarity by fluorescein angiography. In some eyes with complex arteriovenous malformations of the retina, one or more of the loops may occlude spontaneously due to kinking of the involved blood vessels.<sup>41</sup> Such an occlusion may result in ischemic or hemorrhagic retinopathy and profound vision loss in the affected eye.

## SYSTEMIC EVALUATION

Baseline assessment of patients who have a complex retinal AVM should probably include MRI and possibly magnetic resonance angiography of the ipsilateral orbit and brain.<sup>42</sup> Such investigation is probably not indicated in patients who have small, limited retinal AVMs unless they have neurological symptoms. Currently, no consensus exists about what constitutes appropriate follow-up of affected patients.

## TREATMENT

No effective treatment is currently available for retinal AVMs. Complex, symptomatic intracranial AVMs can sometimes be managed effectively by intracranial resection, arterial ligation, arterial embolization, stereotactic radiosurgery, or charged particle beam irradiation.<sup>43,44</sup>

## COURSE AND OUTCOMES

Life expectancy is reduced in patients who have WMS because of early deaths attributable to spontaneous bleeding from the intracranial AVMs<sup>38,39</sup> and strokes related to their treatment.<sup>43</sup> In addition, the affected eye is sometimes blinded as a result of spontaneous occlusion of the retinal AVM.<sup>41</sup>

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# Principles of Imaging in Neuro-Ophthalmology

Swaraj Bose

## 9.1

**Definition:** Computed tomography (CT), magnetic resonance imaging (MRI), MR and CT angiography (MRA, CTA), conventional catheter angiography, and functional imaging including positron emission tomography (PET), functional MRI (fMRI), and ultrasonography (US) are important in the neuro-ophthalmic evaluation of the anatomical, pathological, vascular, and functional status of the eye, orbit, visual pathways, brain, and ocular motor system.

### Key Features

- Recent advances in neuroimaging have revolutionized patient management in neuro-ophthalmology.
- CT scans use ionizing radiation but are advantageous in detection of acute intracranial hemorrhages and bony lesions.
- MRI uses different pulse sequences to identify the anatomy and pathology of the visual system and its disorders.
- Defines and differentiates central nervous system vascular pathologies using MRA, MR venogram, CTA, CT venogram, and catheter angiography.
- Functional studies including PET, single-photon emission computed tomography (SPECT), and fMRI identify changes in the metabolic and perfusion states of the brain.
- Neuroimaging results should be interpreted in association with history and clinical findings.

## INTRODUCTION

### Ophthalmologist's Role in Neuroimaging

Although neuroimaging is an integral part of the diagnostic criteria and/or prognostic data in neuro-ophthalmological diseases, ancillary testing should be used in conjunction with, not as a substitute for a thorough clinical evaluation. For example, a positive MRI finding of a plaque lesion is both diagnostic and prognostic for patients with demyelinating optic neuritis,<sup>1,2</sup> whereas presence of a single plaque without any clinical signs would not necessarily prove to be demyelinating in origin. The optic neuritis treatment trial (ONTT study) concluded that the 10-year risk of multiple sclerosis following an initial episode of acute optic neuritis was significantly higher if there was a single brain MRI lesion. Also, a negative neuroimaging is one of the criteria for making a diagnosis of pseudotumor cerebri or idiopathic intracranial hypertension.<sup>3</sup> Furthermore, live three-dimensional localization of orbital and intracranial tumors have improved the results of surgery, whereas PET and fMRI have improved our understanding of the functional basis of pathology.

## COMPUTED TOMOGRAPHY

### Principles

The scanning assembly in computed tomography consists of an X-ray detector on one side of the patient, rigidly connected to a collimated source of X-rays on the other side. The X-ray tube and the detector move around the patient as a single unit and cross-sectional images can be acquired at different tissue levels such as near the top of the skull or at the skull base. The computer then reconstructs the image from data points that are

TABLE 9.1.1 CT Versus MRI of Orbit

CT	MRI
Coronal and axial views	Multipplanar imaging including sagittal views
Excellent for bone and bony lesions, sinuses	Excellent soft tissue delineation
Useful in assessing retro-orbital mass in proptosis	Fat suppression with contrast essential for assessment
Calcification seen well	Retro-orbital fat is bright and contrasts with low signal of surrounding bone
Indications: orbital inflammation, trauma, tumor, thyroid ophthalmopathy, disc drusen, foreign body	Orbital tumor, optic nerve glioma, orbital apex, and parasellar lesions

CT, Computed tomography; MRI, magnetic resonance imaging.

assigned a numerical value based on the attenuation of the X-ray beams and represented as pixels. This attenuation coefficient (in Hounsfield units [H]); it ranges from -1000 H for air, to +1000 H for dense bone) provides a numerical matrix that helps the computer reconstruct the image. To display the values of each data point in a meaningful way on photographic film, gray scales are chosen in which each contrast change represents a range of attenuation coefficients.

### Clinical Applications

CT scans are most useful in the detection of orbital disorders (thyroid, trauma, infection, and tumor, sinus, and lacrimal diseases), acute intracranial bleeds, bony abnormalities, and fractures of the orbit and skull.<sup>4</sup> The advantages include rapid image acquisition, relatively low cost, wide availability, and excellent spatial resolution;. Newer generation helical and spiral CT scanners employ thinner sections, less volume averaging, faster scan times, decreased motion artifact, reduced radiation exposure, and new reconstruction algorithms that enable multiplanar reformations. The disadvantages of CT are patient exposure to radiation, lack of sagittal imaging, potential intravenous contrast reactions, and dental and bony artifacts (Table 9.1.1).

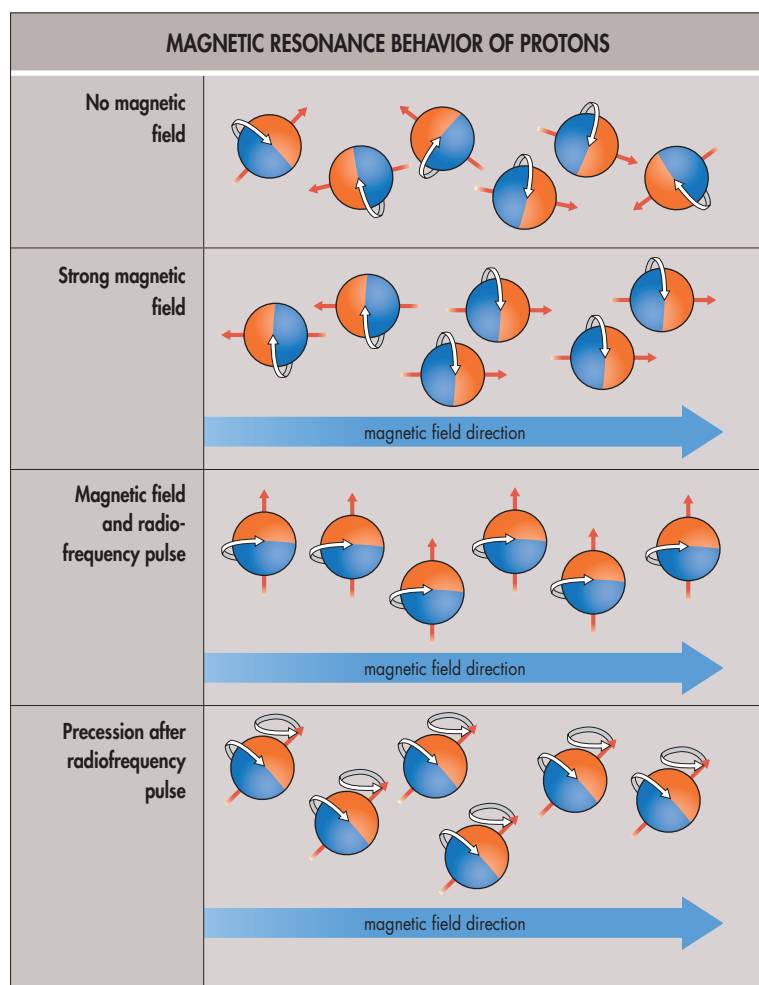
### Safety

CT scans do produce ionizing radiation; the national recommended dosages are below 150 milliGray (mGy) per scan. The adjunctive intravenous injection of iodinated contrast provides enhancement in cranial CT to areas of increased vascularity and to areas of blood-brain barrier breakdown, through which seepage of iodinated contrast occurs. Although the contrast is used to detect intracranial extension of orbital tumors and evaluation of chiasmal and parachiasmal lesions, use of these agents must be weighed against their risks, including allergic reactions, nephrotoxicity, and anaphylactic shock, which can be life threatening.

## MAGNETIC RESONANCE IMAGING

### Principles

MRI is based on the principle of nuclear magnetic resonance, in which the nuclei of certain atoms become aligned or polarized when placed in a strong magnetic field, and the subsequent information from magnetic field gradients can be translated into position-dependent image maps.



**Fig. 9.1.1 Magnetic Resonance Behavior of Protons.** In the absence of an external magnetic field, the spin orientation of free protons is random. In a strong magnetic field, the free protons become aligned with their magnetic axis parallel (or, less often, antiparallel) to the magnetic field. Exposure to a brief radiofrequency pulse at the Larmor frequency changes the alignment of the free protons' spin axes. After the radiofrequency pulse, the free protons twirl like tops around the lines of force of the magnetic field with a motion called precession.

When body tissue is placed in a strong magnetic field, the magnetic axes of a small percentage of randomly oriented, mobile hydrogen atoms (protons distributed in the body water) align parallel (and some antiparallel) to the magnetic field (Fig. 9.1.1). The precession frequency is dependent on the strength of the external magnetic field. Thus, the stronger the magnetic field (higher Tesla), the higher the precession frequency. During this state, there are more protons aligned parallel to the external field, resulting in a net magnetic moment aligned with or longitudinal to the external magnetic field (see Fig. 9.1.1, second from top). An exposure to a brief radiofrequency (RF) pulse at the same frequency as the precessing protons causes resonance or transfer of energy to the protons. This results in more protons being antiparallel and thus neutralizing more protons in the opposite direction. The consequence is a decrease in the longitudinal magnetization. The RF pulse can also cause the protons to precess in phase or be synchronous, resulting in a new magnetic vector called the *transversal magnetization*. Computer analysis is used to encode spatial localization and an image is created.<sup>5</sup>

## Imaging Parameters

### T1 and T2

When the RF pulse is switched off, the longitudinal magnetization increases and the transversal magnetization dissipates. The longitudinal relaxation is described by the time constant T1, the longitudinal or spin-lattice relaxation time. The transversal relaxation is described by the time constant T2, the transversal or spin-spin relaxation time. T1 depends on tissue composition, structure, and surroundings and is an expression of the time it takes for the energy imparted by the RF pulse to be transferred to the lattice of atoms that surround the nuclei. T1-weighted images are good for delineating anatomy, as fluid appears dark ("black" vitreous, looks

**TABLE 9.1.2 T1 and T2 Signal Characteristics of Common Tissues and Materials**

	T1 Signal	T2 Signal
Air	Dark	Dark
Bone		
Dense calcification		
High protein	Bright	Dark
Paramagnetic substances (e.g., gadolinium, melanin)		
Fat	Bright	Dark (bright on fast spin echo)
Water	Dark	Bright
Edema		
Vitreous		
Cerebrospinal fluid		
Very viscous protein	Dark	Dark
Fibrosis		
Dura mater		
Ligaments		
Muscle	Light gray	Dark gray
Nerve		
Gray matter	Dark gray	Light gray
White matter	Light gray	Gray

**TABLE 9.1.3 Image Contrast as a Function of the Repetition and Echo Times**

	Short Repetition Time, 300–800 ms	Long Repetition Time, 2000–3000 ms
Short echo time, 10–40 ms	T1-weighted scan	Intermediate scan (proton-density scan)
Long echo time, 60–120 ms	Poor signal-to-noise ratio	T2-weighted scan

like high-definition CT scan) and fat appears bright. Contrast-enhanced images are done with T1 weighting. T2-weighted images are best to discern pathology; fluid is bright ("white" vitreous). The T1 and T2 signal characteristics are summarized in Table 9.1.2.

### TR and TE

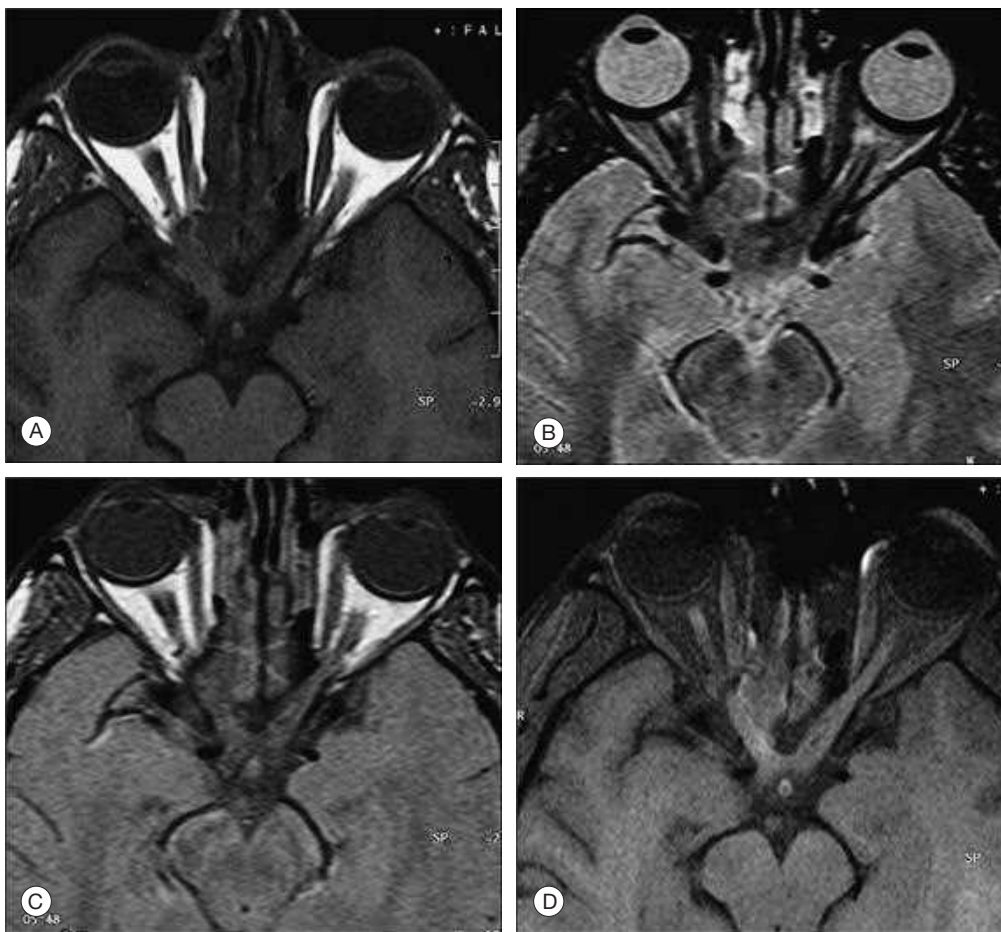
Extrinsic parameters may be altered to capitalize on various intrinsic tissue parameters; they include time between RF pulses or repetition time (TR), and the time between the RF pulse and the signal measurement, or the echo time (TE). Alteration of TR and TE creates images that depend more on either the T1 or the T2 characteristics of the tissues (Table 9.1.3). T1-weighted images are created by using relatively short TE and TR, whereas T2-weighted images require a relatively long TE and TR. Images that have a mixture of the T1 and T2 tissue characteristics also may be created by using a long TR and short TE (proton-density image, Fig. 9.1.2).

## Special Sequences and Techniques in the Production of an Image

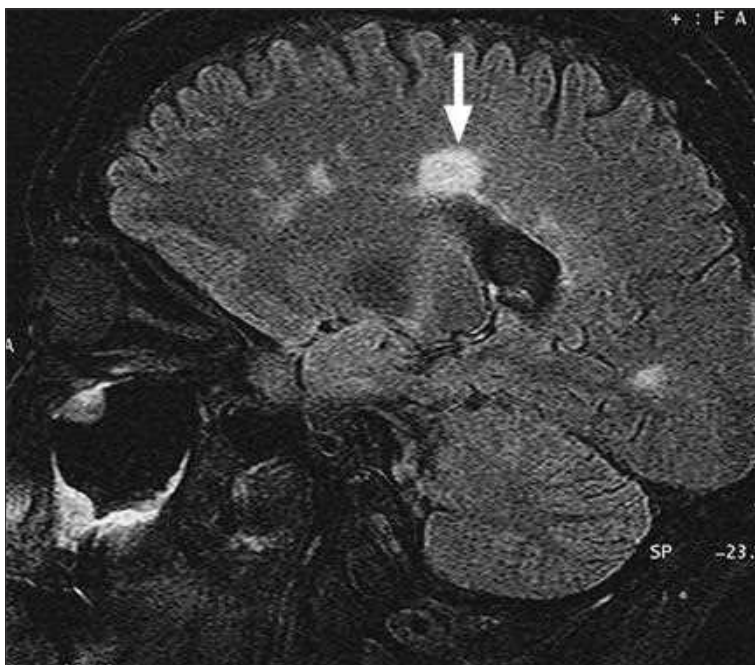
### Spin Echo, Gradient-Echo, Fluid-Attenuated Inversion Recovery, and Fat Suppression

Fast spin echo (SE) techniques reduce motion artifact but are inferior to SE in the detection of hemorrhage or small lesions that have weak signal strengths. Gradient echo (GRE) protocols have a shorter TR (which allows faster imaging), a high signal-to-noise ratio (which allows thinner slices), and provide flow-related enhancement (which can be used to form images for MRA). Fluid-attenuated inversion recovery (FLAIR) techniques diminish the signal from protons of particular substances that are relaxed only partially to a perpendicular orientation to the main magnetic field, such as fat in short time interval inversion recovery and in spectral presaturation inversion recovery sequences or cerebrospinal fluid (CSF). They also help to reveal demyelination plaques in the central nervous system, which often are not visible on routine MRI (Fig. 9.1.3).<sup>6</sup>

Fat suppression is a technique that deletes the fat and utilizes two techniques: (1) STIR—short time inversion recovery, and (2) CHESS—chemical-shift-selective fat suppression, also called fat-sat, which is very useful when combined with intravenous contrast. This allows small orbital lesions, the pituitary, and around the skull base (which has fat in the bone marrow) to be visualized but also may introduce artifacts, particularly in the lower aspects of the orbit.<sup>7</sup>



**Fig. 9.1.2 Comparison of Image Contrast.** (A) T1-weighted image. (B) T2-weighted image. (C) Proton-density image. (D) Fat suppression reducing the normal bright signal of orbital fat in T1-weighted images and improving contrast between fat, optic nerve, and extraocular muscles. (Courtesy Dr. Ramon Figueroa.)



**Fig. 9.1.3 Fluid-Attenuated Inversion Recovery (FLAIR).** FLAIR sequences help reveal demyelination in the central nervous system that often is not visible on routine magnetic resonance imaging (arrow). (Courtesy Dr. Ramon Figueroa.)

### Diffusion-Weighted Imaging

By measuring the phenomenon of slow water diffusion in tissues (which generally increases in pathological states), diffusion-weighted images (DWI) help in the evaluation of cytotoxic edema, demyelinating plaques, inflammation, tumors, and early brain infarction and in defining internal tissue architecture.<sup>8</sup>

### Contrast Enhancement

Gadolinium is the most commonly used MRI contrast material. It is natively a toxic metal ion, but when chelated with diethylenetriamine

pentaacetic acid (DTPA), its toxicity is reduced but its paramagnetic properties are retained and its biodistribution characteristics mimic those of iodinated contrast media used in CT scans. The chelate remains extracellular, does not cross the intact blood–brain barrier, and is excreted renally. In pathological states, the chelate tends to move from the intravascular to the extracellular space and thereby highlights pathological processes.

Because it shortens the T1 relaxation time, gadolinium typically is used for T1-weighted imaging, in which it provides a bright signal. For orbital studies, T1-weighting techniques are combined with a fat suppression technique to enhance lesions so that they may be differentiated from the otherwise bright orbital fat signal (see Fig. 9.1.3).<sup>9,10</sup> Gadolinium-DTPA is usually used in the form of its dimeglumine salt at a dose of 0.1 mmol/kg. Gadolinium has an excellent safety record, relative contraindication is hemolytic or sickle cell anemia, and rare serious reactions are hives, bronchospasm, and asthmatic attack. Other side effects include headache, hypotension, or a transient rise in serum iron or bilirubin levels. However, development of nephrogenic systemic fibrosis among patients with severe renal insufficiency following exposure to gadolinium is approximately 4% and mortality can reach 31%. The mechanism is unclear, but this technique should not be used in patients with renal insufficiency or if the calculated glomerular filtration rate is less than 60 mL/minute/1.73 m<sup>2</sup>.<sup>11</sup>

### Surface and Head Coils

The placement of receiver coil antennae close to the tissues to be scanned may provide much stronger signal acquisition and thus allow thinner sections, better resolution, and shorter scan times that provide high-resolution visualization of the globe, orbital apex, optic nerve, and chiasm.

### Magnetization Transfer Imaging

Magnetic transfer imaging capitalizes on the effect large proteins have on the transfer of energy between bound and unbound water protons. The benefits of magnetization transfer are greatest in tissues that have high macromolecular concentrations (e.g., brain, muscle) rather than those that have low macromolecular concentrations (e.g., fat). Magnetic transfer contrast sequences improve the detection of brain lesions such as cerebral metastases, and the best differentiation of demyelinating plaques from edematous lesions is effected with magnetization transfer techniques combined with gadolinium enhancement.<sup>12</sup>





**Fig. 9.1.4 Magnetic Resonance Angiography of the Circle of Willis.** (Courtesy Dr. Ramon Figueroa.)

## Safety

Physical injury may occur in the presence of implanted ferromagnetic bodies because these could be transformed into projectiles due to the strong magnetic fields used in MRI. Ferromagnetic, metallic, intraocular, intraorbital, or intracranial foreign bodies; cochlear implants; intracranial aneurysm clips; cardiac pacemakers; and defibrillators are contraindications for MRI.<sup>13</sup> Most neurosurgical clips are not ferromagnetic, and those placed in other locations (e.g., episcleral tantalum clips used in retinal detachment surgery and for proton beam irradiation) are not a contraindication. When unsure, CT scans may be carried out to screen for such objects.

## ANGIOGRAPHY

### Magnetic Resonance Angiography

#### Principles

MRA utilizes three basic techniques: time of flight (TOF) MRA, phase-contrast (PC) angiography, and gadolinium-enhanced MRA (GDx-MRA). These approaches share two basic steps: acquisition of flow-sensitive image of vessels with suppression of stationary background to enhance vascular anatomy, and production of 2-dimensional images from 3-dimensional volume image data. TOF utilizes a gradient-echo technique that relies on inflow-related signal enhancement of vessels, whereas PCA utilizes a similar technique to detect velocity-induced phase shifts that distinguish flowing blood from stationary tissues. A newer hybrid technique, multiple overlapping thin slab acquisitions, combines the advantages of 2-dimensional and 3-dimensional modes for TOF acquisitions because it limits signal drop-off yet retains high resolution.<sup>14</sup> MRA is not a simple display of vascular anatomy. Instead, it extrapolates physiological data obtained from flow characteristics of protons to demonstrate anatomy. Thus the diameter of the blood vessels sometimes may appear smaller when using MRA than with conventional or CT angiography.

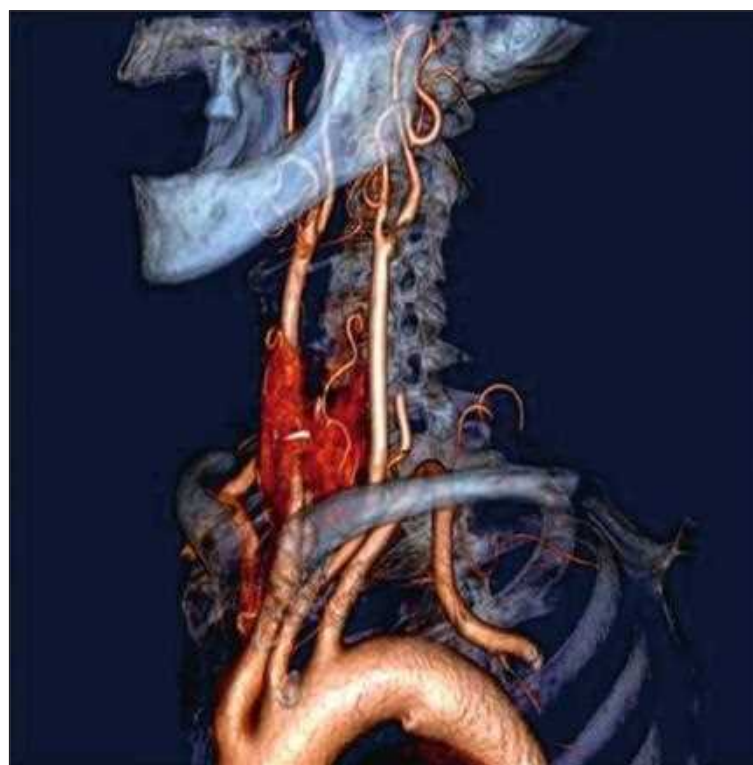
#### Clinical Applications of MRA

These include evaluation of the extracranial (carotid stenosis, plaques, and dissections in the evaluation of transient visual loss) and the intracranial circulations (aneurysms, arteriovenous malformations, occlusive disease, and carotid fistulas). MRA is an excellent noninvasive technique for detecting asymptomatic aneurysms measuring greater than 5 mm (Fig. 9.1.4). Limitations of MRA include poor detection of aneurysms less than 5 mm in diameter, false-positive results in tightly wound vessel loops, and a tendency to over-interpret vessel stenosis.

### Computed Tomographic Angiography

#### Principles

CTA utilizes an intravenous bolus injection of iodinated contrast followed by high-speed spiral CT scan with computer-generated 3-dimensional images of medium-sized and large-sized arteries. The advantages of CTA over standard MRA are the rapidity of examination and images of the true lumen (rather than flow within a vessel) and the ability to be performed in patients with claustrophobia, pacemakers, and older aneurysm clips<sup>15</sup> (Fig. 9.1.5).



**Fig. 9.1.5 CT Angiogram of the Carotids.** Note the simultaneous demonstration of the surrounding bony landmarks.

#### Clinical Applications

Detection of aneurysms as small as 1.7 mm, superior imaging of the neck of the aneurysm, better delineation of surgical anatomy, characterization of mural thrombi, detection of vasospasm, arterial stenosis, and carotid-cavernous fistulas, and provision of rotating 3-dimensional images are the major clinical uses.<sup>16</sup> Limitations include difficult detection and delineation of cavernous sinus and posterior inferior cerebellar artery aneurysms, feeding vessels for dural carotid-cavernous fistulas, and risks arising from radiation exposure and contrast agents.

#### CTA Versus MRA

In the management of patients with intracranial aneurysms—and especially for the evaluation of patients with painful partial third nerve palsy to rule out posterior communicating artery (PCOM) aneurysms—the commonly asked question is: Which imaging is superior, CTA or MRA? Sometimes the easy answer is that it depends on the local institutional expertise and the neuroradiologist reading the films, but clinical data have shown that contrast-enhanced 3Tesla MRA was comparable in image quality to time of flight MRA (TOF-MRA) and CTA.<sup>17</sup> However, other reports have shown that a 7-mm PCOM aneurysm was missed by brain MRI and MRA but detected by CTA.<sup>18</sup> Also, CTA was found to be a better procedure for traumatic aneurysms with skull base fractures.<sup>19</sup>

### Conventional Angiography

#### Principles

Conventional percutaneous cerebral angiography (usually via the femoral artery) remains the gold standard for accurate detection and localization of small intracranial aneurysms with or without subarachnoid hemorrhage. Interventional neuroimaging involves the introduction of coaxial systems of extremely flexible microcatheters, balloons, coils, and other devices in the cerebral vascular system for therapeutic purposes; it is used commonly for aneurysms, arteriovenous malformations and carotid-cavernous and dural fistulas using GDCs (Guglielmi detachable coils, Target Therapeutics, Fremont, CA)<sup>20</sup> (Fig. 9.1.6). Digital subtraction angiography (DSA) is a technique that reduces artifacts by subtracting densities created by the overlying bony skull and uses smaller amounts of dye. The contrast dye outlines the column of flowing blood within the injected vessel and demonstrates stenosis, aneurysms, vascular malformations, flow dynamics, and vessel wall irregularities such as dissections or vasculitis. Morbidity (~2.5%) is primarily related to ischemia from emboli or vasospasm, dye-related reactions, or complications at the arterial puncture site (e.g., hematoma).



**Fig. 9.1.6** Conventional Catheter Angiography Demonstrating a Posterior Communicating Artery Aneurysm.

## Ultrasonography

### Principles

Ultrasonographic technology is based on the reflection of ultrasound waves (5–20 MHz) at acoustic interfaces and is used in neuro-ophthalmology for the evaluation of orbital pathology such as mass lesions, inflammatory-congestive processes (see Chapter 9.23), and foreign bodies. B-Scan US provides a useful, inexpensive, rapid, and easily tolerated method to distinguish solid from cystic orbital lesions, to show an enlarged superior ophthalmic vein and extraocular muscles, and to distinguish and demonstrate an optic nerve head drusen from true dilatation of the optic nerve sheath in papilledema.<sup>21</sup> Also, transcranial Doppler imaging can be used to assess patency and location of the temporal artery for patients being evaluated for temporal arteritis.<sup>22</sup>

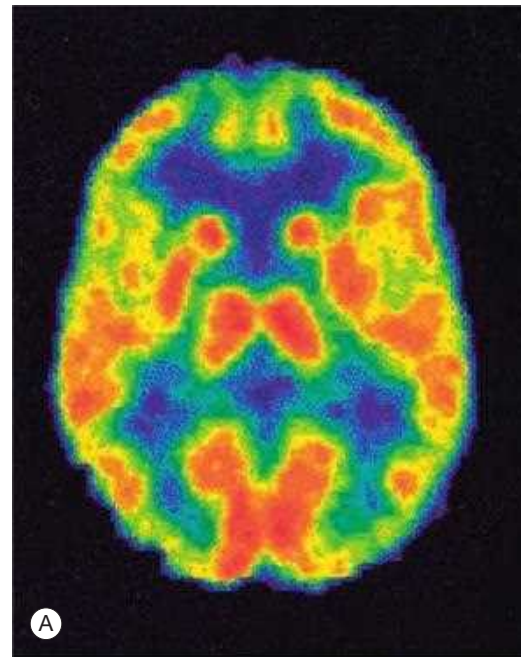
## FUNCTIONAL IMAGING

### Positron Emission Technology and Single-Photon Emission Computed Tomography

#### Principles

PET and SPECT are performed with systemically administered isotopes (such as 18F-fluoro-2-deoxyglucose [FDG], 13N ammonia [13NH<sub>3</sub>], fluoride-18 [18F]) that emit protons. They are used to image biological processes that measure regional cerebral blood flow and glucose consumption and thus, indirectly, tissue metabolism.<sup>23</sup> These techniques trace the transport and phosphorylation of glucose, and the glucose-linked positron emits two photons that strike detectors placed around the head. The greater the rate of glucose metabolism of the tissue, the more photons are emitted. Glucose metabolism provides about 95% of the adenosine triphosphate required for brain function. FDG is taken rapidly into the intracellular compartment, but it cannot diffuse from the brain because its metabolism stops following its phosphorylation to deoxyglucose-6-phosphate. Therefore, FDG remains trapped intracellularly and thus is an excellent agent to use for cerebral metabolism imaging. Tomographic images are obtained in a manner similar to those for MRI or CT scanning. Cerebral blood flow, oxygen utilization, and glucose utilization may be measured. PET scanning is used mainly for evaluation of ischemia/stroke, tumors, migraine, blepharospasm, cortical visual loss, and mapping of the visual cortex, among others.<sup>24</sup> The shortcoming of PET is its relatively poor resolution of 57 mm, cost, and limited availability because of the requirement for close proximity to a cyclotron to produce the radioisotopes.

In SPECT, isotopes such as iodine-123 iodoamphetamine or technetium-99 are incorporated into biologically active compounds, and CT plots their distribution. The information provided by SPECT is similar to that of PET, but SPECT does not require the use of isotopes produced in a cyclotron. However, resolution is even poorer with SPECT. The future of these technologies is very bright, and with the recent advent of micro-PET, higher resolution receptor and genetic imaging will provide greater understanding of the workings and abnormalities of the human brain (Fig. 9.1.7).



**Fig. 9.1.7** (A) PET images in a subject demonstrated metabolic increases (red) and decreases (blue) in the brain. (B) Functional magnetic resonance imaging (fMRI) obtained with a 3Tesla magnet demonstrating the images generated following a visual task.

### Clinical Applications

Current applications of functional imaging include detection of hypermetabolic states associated with tumor, differentiation of tumor from areas of radiation necrosis, localization of seizure foci, detection of ischemic regions, evaluation of biochemical changes associated with cognitive and psychiatric abnormalities and their response to pharmaceutical intervention, and drug localization in the brain.<sup>25</sup>

## Magnetic Resonance Spectroscopy

### Principles

Magnetic resonance spectroscopy (MRS) is used for diagnostic biochemistry in vivo and is based on the same principle previously used in analytical chemistry to obtain MR spectra. MRS studies of cerebral ischemia are confined solely to proton (1H) and phosphorus-31 (31P) because of their intrinsically higher sensitivity compared with other nuclear species. Neurospectroscopy (proton MRS, which has higher sensitivity than 31P MRS), uses a small voxel size (1 cm<sup>3</sup>) and enables the detection of compounds such as N-acetylaspartate, creatine, choline, lactate, and inositols (Fig. 9.1.8). Each metabolite has a “signature” that, when added to the other major metabolites, results in a complex spectrum of overlapping peaks.<sup>26</sup> Pathologies documented by MRS include brain tumor, stroke, focal cerebral lesions, multiple sclerosis, and intracranial hemorrhage. An acutely ischemic brain produces lactate by anaerobic metabolism during the first

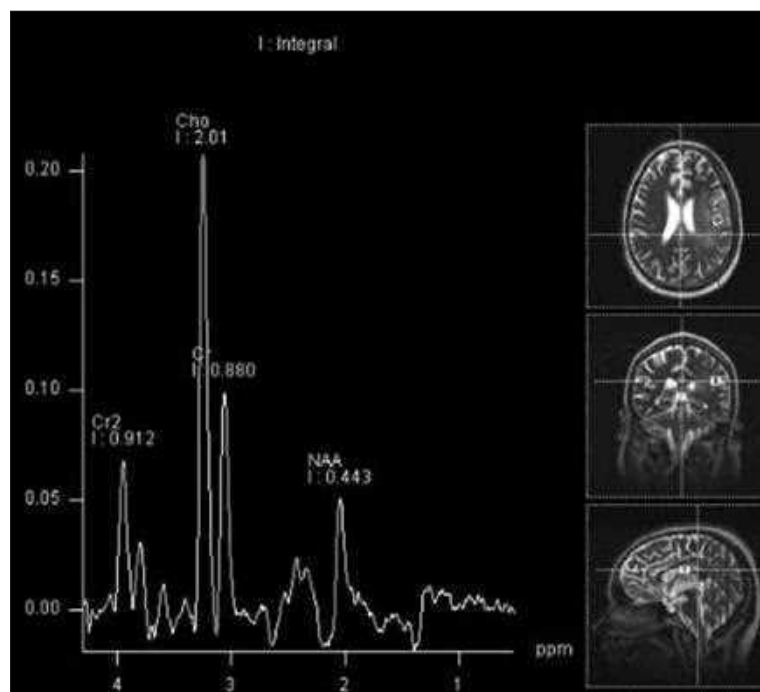


23 days after injury, which can be detected by MRS. With the advent of MRS and using multi-MR modalities (MRI, MRA, perfusion MR), it is now possible to evaluate extensively not only regions of cerebral injury but also regions at risk of infarction.<sup>27</sup>

## Functional Magnetic Resonance Imaging

### Principles

fMRI is a less invasive technology for mapping cerebral cortical activation in response to performing specific cognitive, sensory, or motor tasks. The basis for most fMRI is measurement of increases in blood oxygenation level during the performance of specific tasks (BOLD: blood oxygen level dependent).<sup>28</sup> This method utilizes the change in magnetic susceptibility of hemoglobin as it changes from oxyhemoglobin (diamagnetic, reduces magnetic field into which it is placed) to deoxyhemoglobin (paramagnetic, increases magnetic field), which results in T2 shortening. The advantage of this technique is that no injection is required. fMRI is evolving rapidly into a useful experimental and clinical tool for functional cortical mapping, psychophysical tests, brain tumor mapping, and understanding the basis of higher visual functioning.<sup>29</sup>



**Fig. 9.1.8** MR Spectroscopy in a Patient With a Malignant Lesion in the Brain With Corresponding Alteration of the Chemicals. (Courtesy Dr. Anton Hasso.)

## IMAGING STRATEGIES IN NEURO-OPHTHALMOLOGY

Choosing the correct imaging modality should be based on the differential diagnosis, nature of suspected lesion, patient characteristics, and the available modalities. To obtain the most meaningful neuroimaging results, communication with the neuroradiologist is vital and should include providing adequate history, type of scan, sequence, contrast material, scan thickness, and area of interest. The ordering physicians should explain the procedure, risks, and contraindications to the patient directly.

MRI is usually more valuable than a CT scan in detecting the anatomy and pathology of the lesion and narrowing down the differential diagnosis. However, a CT scan is useful for the evaluation of orbital pathology (tumor, trauma, and thyroid) and in patients with acute intracranial bleeding. Orbital fat provides an excellent contrast with other components on CT and MRI for more precise anatomical localization. Orbital scans require negative angulations that are parallel to the orbital floor, whereas head scans require positive angulations. Gadolinium-enhanced, fat suppression MRI generally best demonstrates pathology of the optic nerve, which includes tumors (such as glioma, meningioma, and hemangioma), radiation damage, demyelinating disease, and inflammatory damage (such as sarcoidosis). We should consider MRA, CTA, and DSA if we suspect a large vessel disease. Optic neuritis studies have found MRI changes to be of diagnostic and predictive value<sup>30</sup> (Table 9.1.4). Papilledema can be evaluated using B-scan US to look for a dilated optic nerve sheath and confirm by a decrease in the diameter of the sheath with abduction (or adduction) of the eye by 30°. MRI of the brain in papilledema may show slit ventricles, and an MR venogram (MRV, a different sequence for veins) may reveal a venous thrombosis. Optic nerve drusen, often calcified, may be seen with B-scan US, CT, MRI, or autofluorescence (for guidelines, see Table 9.1.5).

Combining an understanding of neuro-ophthalmological anatomy with proper imaging techniques provides a powerful method for detecting

**TABLE 9.1.4** Features of CT Versus MRI

CT	MRI
Better for bony lesions	Better for soft tissue delineation
Sensitive to acute hemorrhage	Insensitive
Chronic hemorrhage may be subtle	Well seen
60% acute strokes visualized	80% acute strokes visualized
Posterior fossa degraded by artifact	Well visualized
Poor resolution of demyelinating lesions	Demyelinating lesions well seen at all stages
Metal artifacts (skull plates, clips)	Ferromagnetic artifacts
Axial and coronal images	Axial, coronal, sagittal, and angled images
Iodinated contrast agent	Paramagnetic contrast agent
Risk: ionizing radiation	Risk: magnetic field

CT, Computed tomography; MRI, magnetic resonance imaging.

**TABLE 9.1.5** General Guidelines for the Choice of Neuroimaging Techniques in Neuro-Ophthalmology

Anatomical Location	Clinical Condition	Neuroimaging Technique(s)
Orbit	Tumors Thyroid ophthalmopathy, trauma, hemorrhage, foreign body Optic nerve tumor, orbital apex tumor	US (solid vs. cystic), CT (noncontrast) MRI (soft tissue, fat suppression) Noncontrast CT (preferred imaging) Gd-enhanced, fat-suppressed MRI
Cavernous sinus, chiasm, parasellar region	Tumor Aneurysm (e.g., third nerve palsy) Aneurysm with bleeding	High-resolution contrast CT (fine cuts), MRI Gd-enhanced MRI, MRA, catheter angiography Noncontrast CT scan
Retrochiasmal area and posterior fossa	Aneurysm or AV malformation with bleeding	Noncontrast CT scan
Brain	Intracerebral hemorrhage 1. Acute (intracellular Fe <sup>2+</sup> /methHb) 2. Subacute (extracellular Fe <sup>3+</sup> /methHb) 3. Chronic (methHb/hemosiderin) Papilledema Multiple sclerosis	CT density MRI-T1 MRI-T2 Bright Isodense Hypodense Isodense Hyperdense Hyperdense Dark Hyperdense Hyperdense "B" scan US (optic sheath dilatation) Gd-enhanced MRI, MR venogram Gd-enhanced MRI, T2, FLAIR sequence
Carotids and vertebrals	Stenosis, dissection, plaques, evaluation of amaurosis	Carotid Doppler (US), MRA, CT angiography, catheter angiography
Globe	Optic disc drusen Tumor, trauma, calcification	"B" scan US, noncontrast CT Noncontrast CT

AV, Arteriovenous; CT, computed tomography; Fe<sup>2+</sup>, ferrous iron; Fe<sup>2+</sup>/methHb, iron-methemoglobin; Fe<sup>3+</sup>, ferric iron; FLAIR, fluid-attenuated inversion recovery; Gd, gadolinium; MR, magnetic resonance; MRA, magnetic resonance angiography; MRI, magnetic resonance imaging; US, ultrasonography.





**Fig. 9.1.9 MRI “Section” of the Optic Nerve Seen Using a 12Tesla Ultrahigh Resolution MRI Scan.** The arrows point to the location of the lamina cribrosa.

lesions involving the afferent and efferent visual pathways and for monitoring the effect of neurological therapies.<sup>31</sup> In contrast, the diagnostic yield of neuroimaging patients with a normal examination and isolated, unilateral eye/facial pain referred to a neuro-ophthalmologist is low.<sup>32</sup> Modern advances in speed and resolution will continue to impress, as can be seen in the 12T MRI picture of the postmortem human optic nerve that resembles a histopathological section (Fig. 9.1.9).<sup>33</sup>

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# Optical Coherence Tomography in Neuro-Ophthalmology

## 9.2

Piero Barboni, Nicole Balducci, Giacomo Savini, Michelle Y. Wang

**Definition:** Optical coherence tomography is an ancillary test that documents the morphology of the optic disc and quantifies the nerve fiber layer, macular ganglion cells, and other retinal layers.

### Key Features

- Noninvasive, noncontact, reproducible, and quantitative.
- Defines and differentiates specific forms of optic neuropathy.
- Documents changes in retinal nerve fiber layer (RNFL) and macular ganglion cell layer (GCL) thickness over time.
- Helps to correlate structural RNFL and macular GCL changes with visual function.
- Optical coherence tomography angiography (OCTA) is a new tool that visualizes the microvascular network of optic nerve head, peripapillary and retina.

### INTRODUCTION

Optical coherence tomography (OCT) is a noninvasive, noncontact, imaging technology that provides high-quality in vivo resolution of the retina and the optic nerve head. It has been widely used in neuro-ophthalmology for several purposes, including defining and differentiating specific forms of optic neuropathy, quantifying changes in RNFL and macular GCL thickness over time, and correlating structural changes with visual function. OCT analysis of the RNFL and GCL thickness is a useful biomarker for disease diagnosis and management.<sup>1</sup> For a more comprehensive explanation of the use of OCT in central nervous system diseases, please refer to a recent publication.<sup>2</sup>

### OCT INTERPRETATION

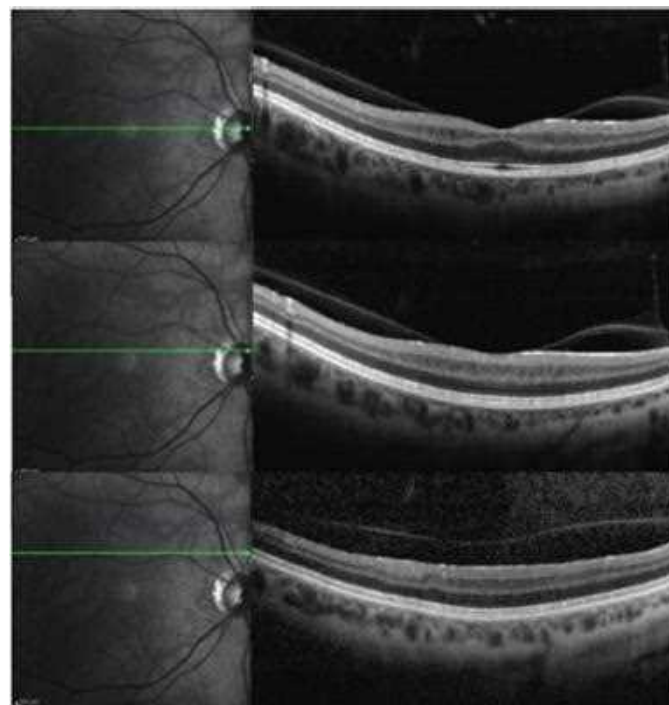
In neuro-ophthalmology, two main structural measures of optic nerve function are provided by OCT: peripapillary RNFL and macular GCL thickness. The combined results of RNFL and GCL thickness aid both diagnosis and monitoring of the optic nerve diseases.

#### Peripapillary Retinal Nerve Fiber Layer

The RNFL thickness is usually measured via a circular scan 3.4 mm from the center of the optic disc, as this distance reduces inter-individual variability related to the location of the vessels and the shape of the optic disc.<sup>3-4</sup> OCT software provides data on average and sectorial RNFL thickness in micrometers, analyzed by quadrants, clock hours, or finer sectors. Early, and even subtle, RNFL changes are often detectable by the deviation map (where RNFL thickness is compared to normal age-matched population)<sup>5</sup> and by the thickness map (which reports absolute thickness values not based on the normative database comparison).<sup>6</sup> Some OCT devices also provide information on the sizes of optic disc, neuroretinal rim, and optic cup.

#### Macular Ganglion Cells Layer

The macular GCL layer is thickest in the macula,<sup>7</sup> accounting for 30% of the entire macular thickness. Its thickness is not influenced by inter-individual variability of optic disc shape or by the presence of large retinal vessels and glial elements. In some cases, GCL thickness is reduced before RNFL



**Fig. 9.2.1 Microcystic Inner Nuclear Layer Abnormalities.** Case of a 45-year-old man affected by dominant optic atrophy, where microcysts in the nuclear layer are well detectable at the level of vitreo-retinal adhesion (*top and middle figures*). Note that the microcysts disappear where the vitreo-retinal adhesion is not seen (*bottom figure*).

thinning, and its measurement is particularly useful for recognizing axonal loss during optic disc edema, where RNFL swelling can mask retinal nerve fiber loss.<sup>8-10</sup>

Most OCT devices provide analyses of the macular GCL, providing data on average, minimum, maximum, and sectorial macular GCL thickness. Deviation and thickness maps are also available in some devices.

#### Microcystic Inner Nuclear Layer Abnormalities

Microcystic macular edema (MME) is present in 5%–25% of patients with optic neuropathy. It is characterized by the presence of microcystic changes in the inner nuclear layer, which may cause reduction in visual acuity. MME is easily identified in the perifoveal region with spectral-domain OCT (SD-OCT) (*Fig. 9.2.1*).<sup>11</sup> Typically MME is not identifiable on fundus examination. This finding is nonspecific insofar as it has been associated with various optic neuropathies, such as multiple sclerosis (MS),<sup>12</sup> neuromyelitis optica,<sup>13-14</sup> posterior ischemic optic neuropathy,<sup>15</sup> Leber's hereditary optic neuropathy,<sup>16</sup> and dominant optic atrophy.<sup>17</sup>

Various hypotheses have been postulated, including retrograde trans-synaptic degeneration in the visual pathways,<sup>18,19</sup> vitreo-macular traction,<sup>20,21</sup> Muller cells dysfunction,<sup>11</sup> and inflammation.<sup>12</sup>

### PAPILLEDEMA

Papilledema occurs when increased perineural pressure produces axoplasmic flow stasis, causing swelling of the optic nerve fibers at the level of





**Fig. 9.2.2** In the same patient shown in Fig. 9.2.1, a vertical scan through the optic nerve shows a lazy V pattern of the subretinal space inferior to the optic nerve.

the optic disc. A number of studies have evaluated optic disc edema using OCT. Swelling of the peripapillary RNFL is the most relevant finding.<sup>22</sup> Since errors in defining the outer border of the RNFL may occur in the most advanced cases due to a decreased signal-to-noise ratio, analysis of the whole peripapillary retinal thickness has been proposed as a potential alternative method to quantify edema of the optic nerve.<sup>23</sup> A subretinal hyporeflective space can also be visualized around the optic nerve head (ONH) in cases of disc edema. Cross-sectional images of the ONH reveal that such a space has a “lazy V” pattern (thickest near the ONH and tapering away from the ONH, Fig. 9.2.2). This characteristic pattern helps to differentiate disc edema from optic disc drusen, in which a “lumpy-bumpy” internal contour is seen.<sup>24</sup> Recent analyses of the subsurface architecture of the ONH have found that in the case of high intracranial pressure, the peripapillary retinal pigment epithelium is flexed toward the vitreous as a result of increased intracranial pressure, which influences the architecture of the neural canal opening.<sup>25</sup> OCT is therefore helpful in detecting and characterizing disc edema, but it alone cannot differentiate generalized disc edema from more specific papilledema.

A study performed on children with craniosynostosis and hydrocephalus showed that quantitative measures of the peripapillary retinal structure by OCT correlated with intracranial pressure.<sup>26</sup> The analysis of macular GCL thickness can detect fiber loss when the optic disc is still swollen, which can help differentiate axonal loss from resolution of RNFL swelling in cases of improving papilledema.<sup>8</sup>

### Nonarteritic Ischemic Optic Neuropathy

OCT is useful in both the edematous and atrophic stages of nonarteritic ischemic optic neuropathy (NAION). In the early stages, optic disc edema—principally caused by increased water content within axons and in the interstitial tissue—is the major clinical sign. OCT studies show that the peripapillary RNFL is thickened and a hyporeflective subretinal space can be detected around the ONH (see Fig. 9.2.2).<sup>22</sup> Later, when optic disc atrophy develops, the RNFL becomes thinner, even in the sectors corresponding to the relatively unaffected hemifield of the visual field.<sup>27</sup>

Different patterns of RNFL involvement can be observed, depending on the clinical features of NAION. In patients with visual field (VF) defects confined to the inferior hemifield, OCT shows thinning in the superior, nasal, and temporal RNFL quadrants. In patients with diffuse VF loss, thinning is seen in all RNFL quadrants. In patients with a central VF defect, the RNFL thinning is limited to the superior and temporal quadrants.<sup>28</sup> OCT has also been used to evaluate the characteristics of the ONH in patients with NAION. Ophthalmoscopic findings of crowded disc (e.g., lower cup-to-disc ratio) have been confirmed by OCT.<sup>29</sup> The peripapillary retinal pigment epithelium is not flexed toward the vitreous, as usually seen in papilledema.<sup>4</sup>

The analysis of macular GCL thickness can detect fiber loss when the optic disc is still swollen.<sup>9</sup> A significantly greater vertical hemispheric difference in GCL thickness was found in NAION but not in optic neuritis. Recognizing the pattern of altitudinal ganglion cell loss can help in distinguishing the two diseases.<sup>30</sup> There is a strong correlation between the pattern of GCL loss and the location of the VF defect.<sup>9</sup>

## COMPRESSIVE OPTIC NEUROPATHY

Posterior compression of the optic nerve can produce optic disc edema indistinguishable from papilledema on both clinical examination and OCT testing. Therefore the determination of true papilledema caused by increased intracranial pressure can only be confirmed by lumbar puncture.

In cases of optic nerve tumors or orbital compression, such as Graves' orbitopathy, OCT can be important in recognizing early optic nerve damage and in estimating visual prognosis after treatment. A study conducted in patients with compressive optic neuropathy due to anterior pathway meningioma showed that patients with normal pretreatment RNFL and shorter duration of symptoms are more likely to improve posttreatment.<sup>31</sup> Significant temporal RNFL thinning was detected in patients with chronic dysthyroid optic neuropathy compared to patients with acute dysthyroid optic neuropathy and healthy controls. Moreover, thicker inferior peripapillary RNFL thickness was associated with a better visual outcome.<sup>32</sup> OCT can help differentiate compressive optic neuropathy from glaucomatous optic neuropathy. Recently, a large study found that compressive optic neuropathy is associated with significantly thinner nasal and temporal sectors and thinner cup volume compared with glaucomatous optic neuropathy.<sup>33</sup>

OCT can evaluate the pattern of retinal ganglion cell loss in patients with chiasmal compression. This unique but often subtle pattern of nerve fiber loss is characterized by predominant atrophy of the temporal and nasal fibers of the optic nerve, defined as band atrophy (Fig. 9.2.3). Numerous studies demonstrate that OCT can identify band atrophy caused by chiasmal compression.<sup>34,35</sup> Analysis by OCT shows a diffuse reduction of fiber thickness with preferential involvement of the temporal and nasal sectors (crossing optic nerve fibers), suggesting that the compressive lesion may also affect noncrossing fibers.<sup>36</sup> Comparisons of structure-function in chiasmal compression reveal a good correlation between RNFL and macular thickness and visual field sensitivity, but not between RNFL thickness and pattern electroretinograms.<sup>36–38</sup> Other studies suggest a strong correlation between RNFL and GCL thickness and visual outcome after chiasmal decompression, confirming the prognostic value of OCT.<sup>39,40</sup> Pre- and post-chiasmal decompression OCT analyses have shown a reduction in RNFL and macular GCL thickness in the first 3 months after surgery and an increase in thickness for both measurements in the following 6 months. These results suggest that after surgical chiasmal decompression, progression of the retrograde degeneration is expected in the first 3 months, followed by compensatory changes after 6 months.<sup>41</sup>

### Transsynaptic Retrograde Degeneration in Homonymous Hemianopia

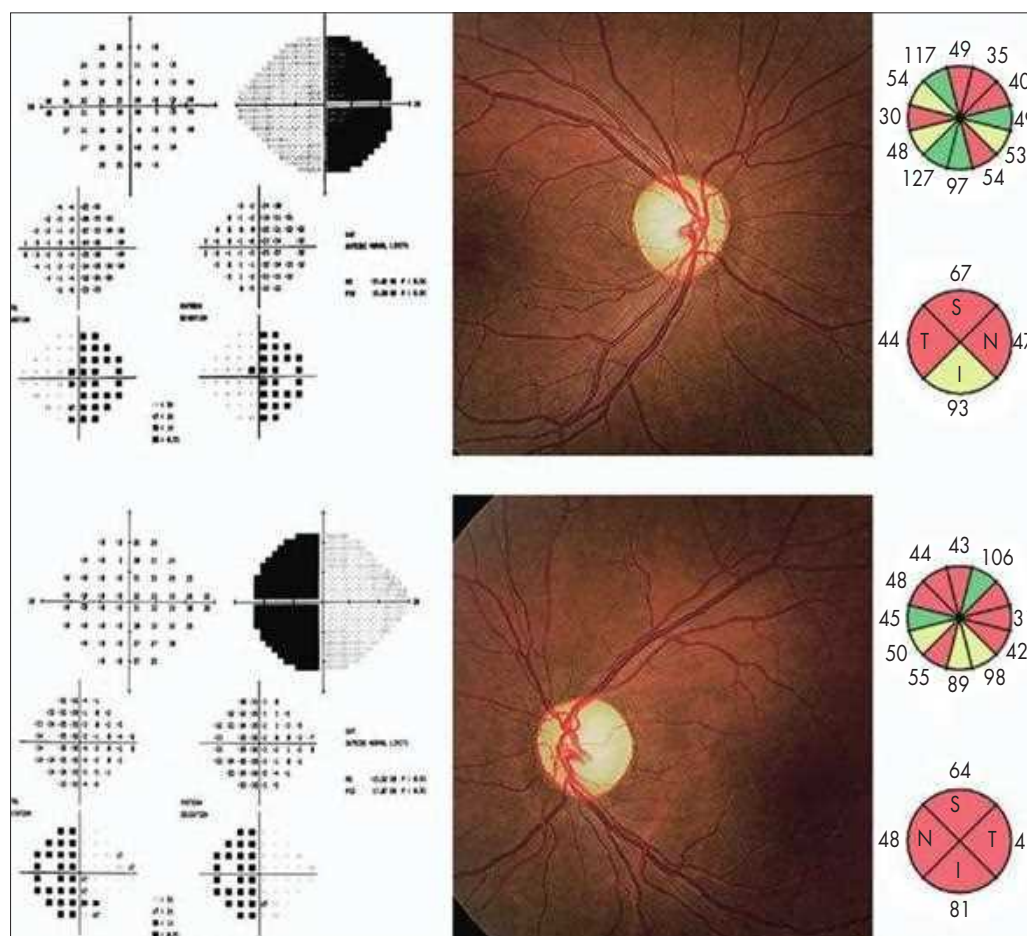
In a study of patients affected by occipital infarction, RNFL thickness reduction was detected as early as 3.6 months after onset.<sup>42</sup> RNFL thinning was found in the superior, inferior, and nasal quadrants in the contralateral eyes and in the superior, inferior, and temporal quadrants in the ipsilateral eyes.

In retrogeniculate lesions, GCL thinning was detected, and the correlation was stronger between visual field defect and GCL thickness than peripapillary RNFL thickness.<sup>43</sup> This correlation is evident also in smaller defects, such as quadrantanopia.<sup>44</sup> In the macula, the topographic distribution of the bodies of the retinal ganglion cells is organized to correspond to VF.

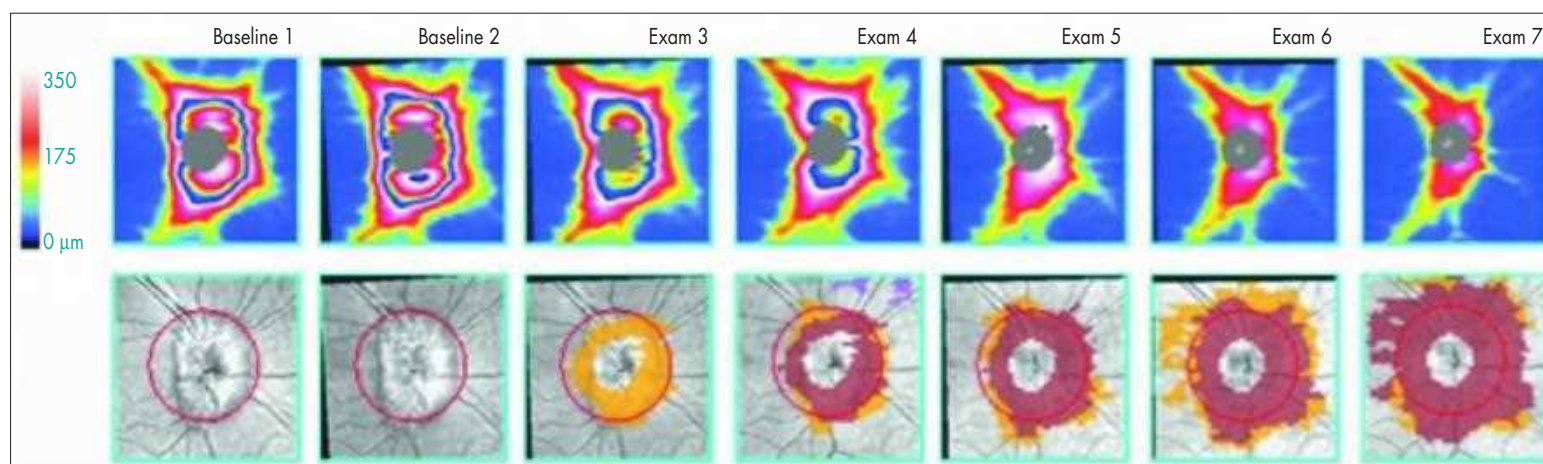
## MULTIPLE SCLEROSIS

Since the first quantitative OCT study of RNFL thickness in MS was published in 1999,<sup>45</sup> there has been rapidly growing interest in various applications of OCT in the diagnosis and management of patients with multiple sclerosis associated optic neuritis (MSON) and multiple sclerosis without optic neuritis (MSNON). OCT has emerged as a potential metric for axonal loss in patients with MS.

In the acute phase of optic neuritis, the peripapillary RNFL thickens as a result of edema, and a hyporeflective space develops in the subretinal space.<sup>22,46</sup> The increase in RNFL thickness resolves in about 1.5 months.<sup>47</sup> Once the acute phase has resolved, the OCT-measured RNFL values are reduced in comparison to normal values (Fig. 9.2.4).<sup>45–50</sup> The earliest evidence of RNFL thinning that can be seen on OCT occurs about 2 months after optic neuritis in the temporal sector, with most RNFL loss occurring within 3–6 months of the ON event. The thickness stabilizes 7–12 months after the onset of optic neuritis.<sup>48,49</sup> Peripapillary RNFL



**Fig. 9.2.3** Visual Field (Left), Optic Nerve Photograph (Middle), and Stratus OCT Results (Right) of a Patient With Band Atrophy of the Optic Nerve. Visual field shows complete temporal hemianopia in agreement with the RNFL loss in the temporal and nasal portions of the optic nerve with relative preservation of the superior and inferior quadrants. (From Monteiro ML, Moura FC, Medeiros FA. Diagnostic ability of optical coherence tomography with a normative database to detect band atrophy of the optic nerve. *Am J Ophthalmol* 2007;143:896–9.)



**Fig. 9.2.4** Optic Nerve Head Analysis in Multiple Sclerosis Shows the Progressive Thinning of Fibers Swelling With Final Diffuse Atrophy.

thinning has also been reported in asymptomatic patients, thus suggesting subclinical axonal damage in the anterior visual pathway in patients with MS-non-ON.<sup>45,51</sup>

A recent study conducted on 879 patients affected by MS showed that patients with peripapillary RNFL less than or equal to 87/88 μm had double the risk of the disability worsening at any time between the first and the third year of follow-up (hazard ratio 2.06). The hazard ratio increased to 3.81 three to five years later.<sup>52</sup>

Longitudinal studies reveal that in some cases, progressive peripapillary RNFL thinning occurs as a function of time and is associated eventually with clinically significant visual loss—with or without a previous history of ON and even in patients with clinically benign MS.<sup>53</sup>

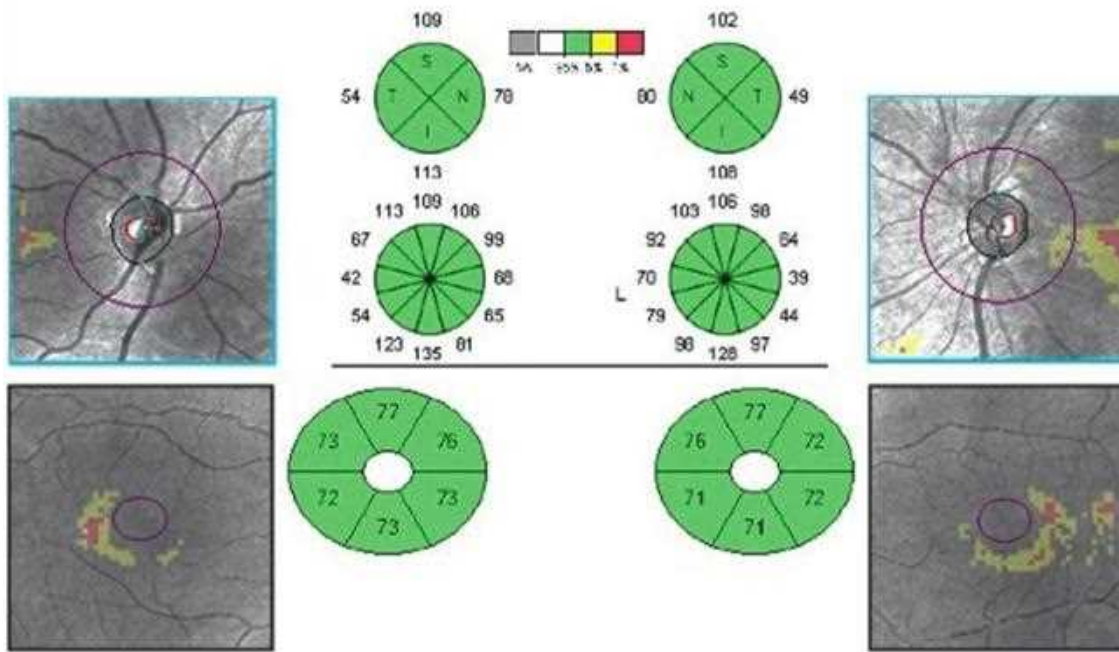
Earlier studies with time-domain OCT showed that ganglion cell loss leads to reduced macular volume in eyes with previous MSON and that macular volume reduction is associated with peripapillary RNFL thinning.<sup>47</sup> Subsequently, SD-OCT studies confirm that eyes of patients with MSON have a thinner macula because of the reduced thickness of the macular RNFL, ganglion cell layer (GCL), and inner plexiform layer (IPL).

Recently, a thinning of all the retinal layers (except for the internal limiting membrane) was reported in patients with MS. Greater effects were

observed in the inner retinal layers (nerve fiber, ganglion cells, inner plexiform, and inner nuclear layers) of eyes with previous optic neuritis ( $P < 0.05$ ).<sup>54</sup> Thinning of the macular RNFL (but not of the GCL and IPL) can also be detected in patients with MS-non-ON patients.<sup>50</sup> The temporal and spatial associations between axonal injury and ganglion cell loss have yet to be determined, although retrograde degeneration of the RNFL has been implicated as the most important mechanism leading to macular damage. In a subset of patients with MS, however, primary disproportionate thinning of the macular inner and outer nuclear layers has been reported in the presence of normal peripapillary RNFL thickness. These patients may present with MS-related macular pathology as a primary process independent of optic nerve pathology.<sup>55</sup> Recently, some studies demonstrated that GCL thickness has better sensitivity than peripapillary RNFL thickness for detecting changes in patients with MS.<sup>56,57</sup> Logistic regression analysis demonstrated that GCL thickness is a potential predictor of axonal damage in MS.<sup>54</sup>

Reduction of peripapillary, macular RNFL, GCL, and IPL thickness is associated with (1) loss of visual function, (2) function disability as measured by the Expanded Disability Status Scale (EDSS), and (3) vision-specific quality of life in MS patients.<sup>50,54,58</sup>





**Fig. 9.2.5 Optical Coherence Tomography in Parkinson's Disease.** Case of a 74-year-old woman affected by mild Parkinson's disease. Note the selective loss of the peripapillary retinal nerve fiber and macular ganglion cells at the level of the papillomacular bundle, detectable only with the deviation maps and not with the sectorial maps.

## OCT and Brain Atrophy

OCT has been regarded as a potential surrogate marker for brain atrophy. A good correlation between average RNFL thickness and lesion volumes in the brain has been found in patients with MS-non-ON, where RNFL thinning may reflect the degenerative process in the brain. The same correlation was not detected in patients with MSON, where axonal loss following ON occurs independently of brain atrophy.<sup>59</sup>

## Neuromyelitis Optica

Neuromyelitis optica (NMO) is a distinct entity from MS, with the highest incidences in Asia.<sup>60</sup> OCT demonstrates a significant reduction of RNFL thickness in patients with NMO compared to healthy controls.<sup>61</sup> The RNFL thickness reduction is well correlated to the visual field damage and the EDSS score. There is also a weak correlation between OCT findings and both visual acuity and visual potential latencies.<sup>61</sup> After a single episode of optic neuritis, the mean RNFL thickness has been found to be lower in patients with NMO than in those with MS, even after adjusting for visual acuity outcome (56.7 vs. 66.6  $\mu\text{m}$ ,  $P = 0.01$ ).<sup>62</sup> When the peripapillary quadrants are compared, the superior and inferior quadrants are thinner in patients with NMO. Moreover, some authors have reported that after a single episode of optic neuritis the mean RNFL thinning was 31  $\mu\text{m}$  in NMO but only 10  $\mu\text{m}$  in MS.<sup>63</sup>

A single subsequent episode of optic neuritis can cause a mean RNFL reduction of 10  $\mu\text{m}$  in NMO but no significant reduction in MS. Moreover, macular volume analysis has shown lower values in NMO compared with MS (5.83 vs. 6.38  $\text{mm}^3$ ,  $P = 0.001$ ). In unilateral cases, the difference between affected and nonaffected eyes has been reported to be greater than 15  $\mu\text{m}$  in 75% of patients with NMO and in 25% of patients with MS. Thus RNFL thinning could be considered a marker of the disease.

The presence of microcystic macular edema at the level of inner nuclear layer is identified in 20%–26% of patients affected by NMO and is correlated with severe disease.<sup>13,64</sup>

## NEURODEGENERATIVE DISEASES

### PARKINSON'S DISEASE

Parkinson's disease (PD) is a common, age-dependent, neurodegenerative disorder characterized by loss of dopaminergic neurons in the substantia nigra. The typical clinical picture of PD includes the presence of motor symptoms, such as bradykinesia, tremor, and rigidity. Nonmotor manifestations, including visual system impairment, are increasingly recognized in PD.<sup>65</sup> The human retina contains dopaminergic amacrine cells, and

retinal dopamine content and metabolites are substantially lowered in patients with PD,<sup>66</sup> so it is not surprising to observe retinal involvement in PD patients.

However, many published studies used OCT to investigate the PD macula have shown contradictory results, probably due to different areas of scanned retina or different algorithms used to quantify thinning.<sup>1</sup> Most studies, however, have at least confirmed one of the first published findings—that the inner retinal layer (including the RNFL, the GCL, and the IPL) is thinner in the macular region of patients with PD compared to healthy subjects, resulting in changes in the slope of the foveal pit.<sup>67,68</sup>

A recent segmentation study revealed that the INL of the macular area is more affected by disease duration.<sup>69</sup> GCL thickness is inversely correlated with disease duration and disease severity.

The analysis of peripapillary RNFL thickness showed a reduction in average RNFL thickness and a significant thinning of the nerve fibers entering the temporal quadrant of the optic disc.<sup>70,71</sup>

The eye contralateral to the more affected body side is more affected than the ipsilateral eye, suggesting an asymmetry of the neurodegenerative process that involves both the substantia nigra and the ipsilateral eye.

The pattern of axonal loss is similar to that typically seen in Leber's hereditary optic neuropathy (LHON) and dominant optic atrophy (DOA), where the temporal fibers belonging to the papillomacular bundle are characteristically susceptible (Fig. 9.2.5).<sup>72</sup> Both diseases are associated with a mitochondrial respiratory chain complex I defect, which is also recognized as a key feature in the pathogenesis of sporadic and genetic forms of PD. This common underlying mechanism explains the similar pattern seen in patients with PD and those with LHON and DOA.

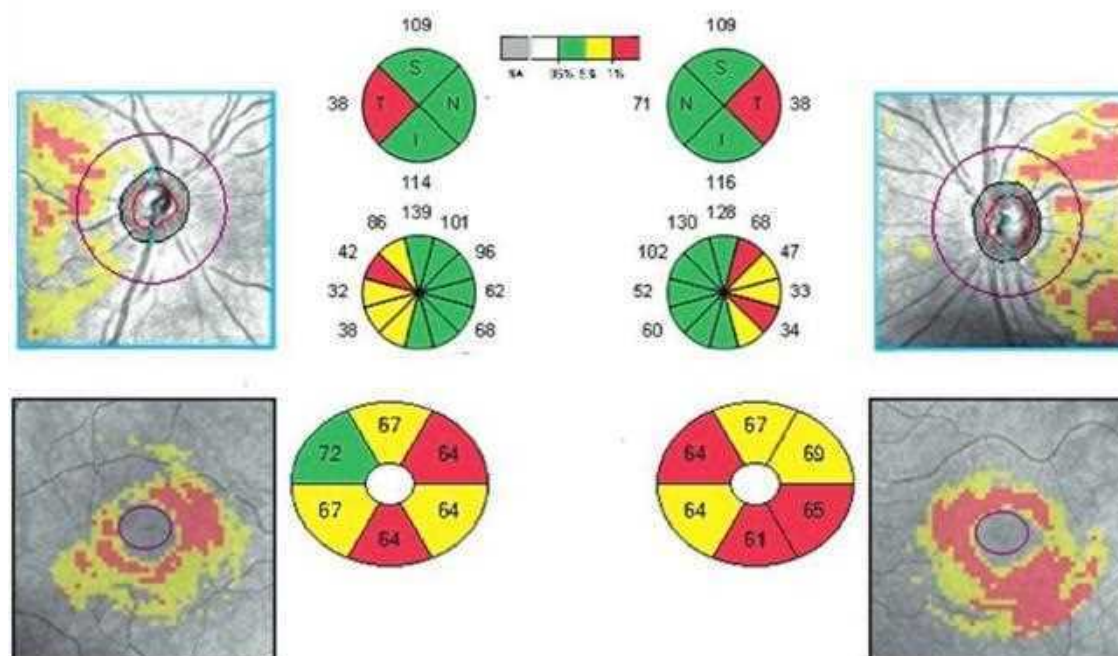
A recent meta-analysis containing a total of 644 eyes of PD patients and 604 eyes of healthy controls reported significant peripapillary RNFL thinning in all the quadrants in PD patients.<sup>73</sup>

The role of a specific PD neuropathology in the retina is controversial, and clear evidence of alpha-synuclein deposition is still missing. The most consistent link hypothesized between subclinical optic nerve involvement in PD and the major mitochondrial optic neuropathies in LHON and DOA is based on complex I dysfunction and altered mitochondrial dynamics.<sup>72</sup>

### ALZHEIMER'S DISEASE

Alzheimer's disease (AD) was first noted to produce optic neuropathy in the late 1980s.<sup>74–76</sup> Subsequent studies with time-domain OCT have shown a significant thinning of the peripapillary RNFL in patients with AD and mild cognitive impairment (MCI), thus confirming previous histopathological investigations (Fig. 9.2.6).<sup>77–79</sup> A recent meta-analysis<sup>80</sup> including 380 patients with AD—68 with MCI and 293 healthy controls—showed a significant mean RNFL thinning in subjects with MCI (weighted mean differences in  $\mu\text{m}$ , WMD = −13.39) and in subjects with AD (WMD = −15.95)





**Fig. 9.2.6 Optical Coherence Tomography in Alzheimer's Disease.** Diffuse macular ganglion cells and temporal, superotemporal, and inferotemporal peripapillary retinal nerve fiber layer reduction in a 73-year-old man affected by Alzheimer's disease.

compared to healthy controls. The meta-analysis showed that significant RNFL thinning is detectable in all quadrants ( $P < 0.0001$ ) in AD patients, and the reduction is more pronounced in the superior quadrant (WMD =  $-24.0$ ) followed by the inferior (WMD =  $-20.8$ ), the nasal (WMD =  $-14.7$ ), and the temporal (WMD =  $-10.7$ ) quadrants. In subjects with MCI, a significant reduction in RNFL was observed in the inferior (WMD =  $-20.22$ ,  $P = 0.0001$ ), nasal (WMD =  $-7.4$ ,  $P = 0.0001$ ), and temporal (WMD =  $-6.88$ ,  $P = 0.01$ ) quadrants, with the exception of the superior quadrant (WMD =  $-19.45$ ,  $P = 0.06$ ).

Macular volume, as measured by OCT, also seems to be reduced in comparison to healthy subjects with the reduction being associated with the severity of cognitive impairment.<sup>79</sup> However, in a calculated linear discriminant function, the combination of the peripapillary RNFL parameters seems to show the highest diagnostic accuracy in AD compared to macular thickness measurements.<sup>81</sup>

A mouse model of AD showed accumulation of beta-amyloid in the inner retinal layers and dendritic atrophy of the retinal ganglion cells.<sup>82</sup> GCL and inner plexiform layer (IPL) thinning was detected in AD patients and found to be more sensitive than RNFL thinning to distinguish AD patients from controls (see Fig. 9.2.6).<sup>83</sup> GCL and IPL thinning was associated with AD duration and severity.<sup>84</sup>

## FRIEDREICH'S ATAXIA AND OTHER RARE NEUROLOGICAL SYNDROMES

Friedreich's ataxia has been long regarded as mitochondrial hereditary ataxia with cerebellar and motor disorders. However, Friedreich's ataxia patients can also develop optic neuropathy characterized by reduced RNFL thickness. The diffuse and progressive fiber loss does not initially result in any perimetric damage, which occurs only in later stages.<sup>42</sup> Ganglion cell loss is uniformly scattered over the entire ganglion cell pool without the typical selectivity shown by other mitochondrial optic neuropathies, where the papillomacular bundle is preferentially affected. Furthermore, in addition to loss in the anterior visual pathway, degeneration is also found in the optic radiations.<sup>85</sup>

OCT studies have also been published in other rare neurological syndromes, such as spinocerebellar ataxia, Wolfram syndrome, autosomal recessive spastic ataxia of Charlevoix-Saguenay, cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), hereditary spastic paraplegia due to SPG7 mutations, DNA (cytosine-5)-methyltransferase 1 (DNMT1), and Jansky-Bielschowsky disease. For a more comprehensive review, please refer to a recent monography.<sup>2</sup>

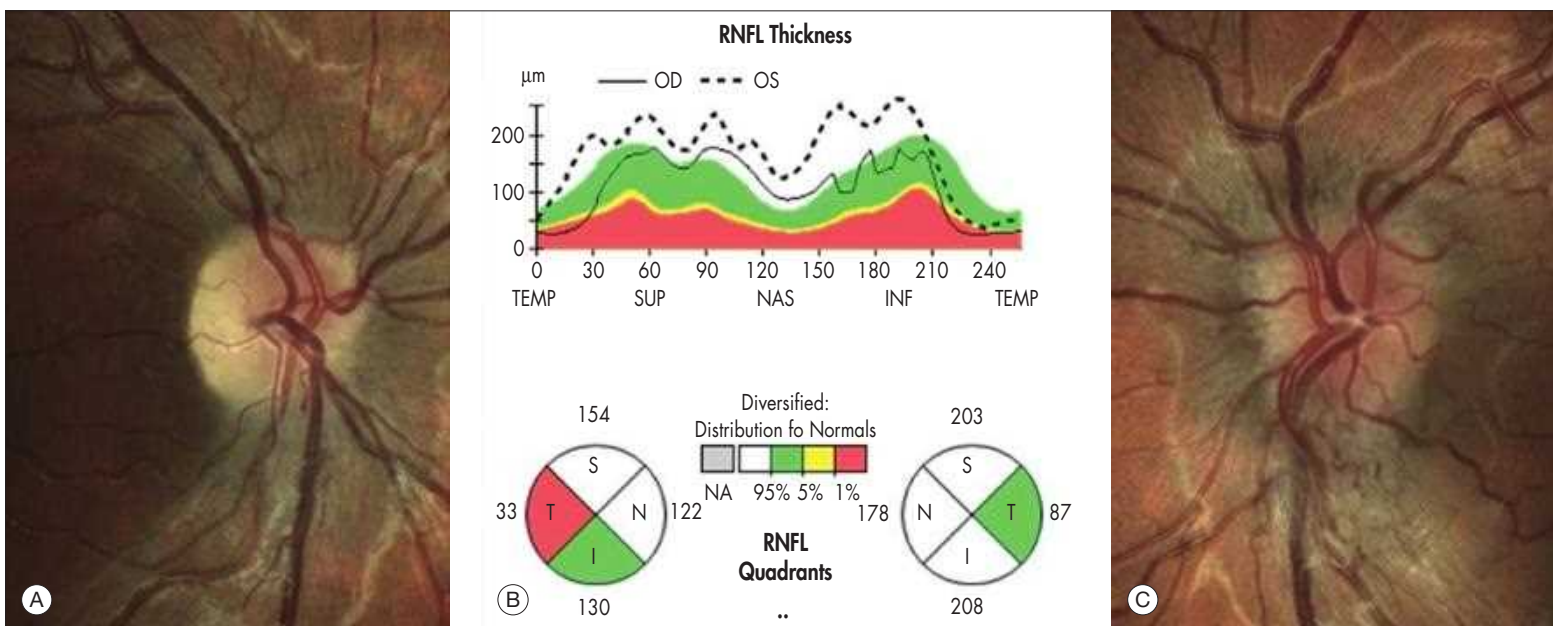
## HEREDITARY OPTIC NEUROPATHIES

### LEBER'S HEREDITARY OPTIC NEUROPATHY

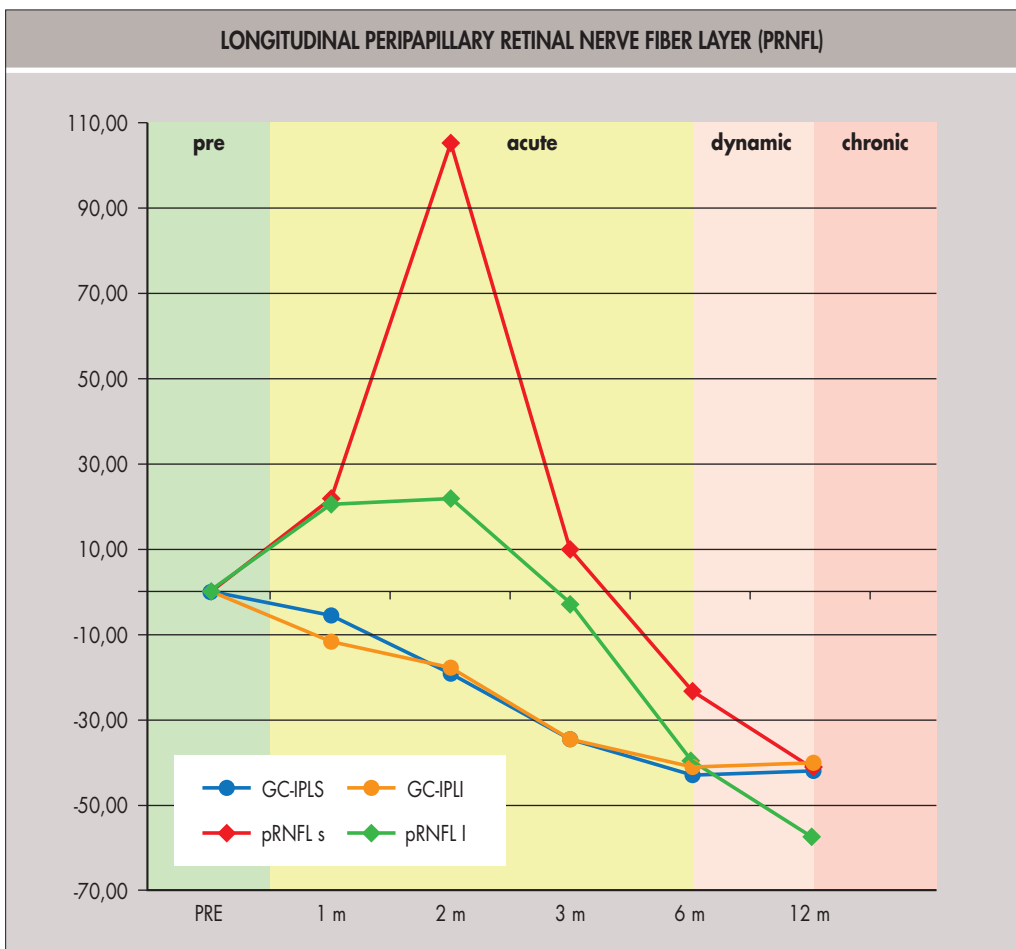
LHON is a maternally inherited cause of blindness usually manifested in young adults that is caused by one of several mutations in the mitochondrial genome.<sup>86</sup> OCT has been used to study changes in RNFL thickness in both unaffected carriers and patients affected with LHON. In unaffected carriers, compared to the control group, a significant increase in thickness was observed in the temporal quadrant along with a smaller increase in the inferior quadrant.<sup>87</sup> In the acute phase, and more precisely within 6 months after onset of the visual defect, RNFL analysis shows thickening in the superior and inferior quadrants, whereas the temporal quadrant shows no significant differences compared to the controls (Fig. 9.2.7).<sup>88</sup>

Finally, once optic atrophy has set in, all quadrants of the optic disc show a thinning of the fibers (see Fig. 9.2.7).<sup>88</sup> The lack of any thickening of the papillomacular bundle in the acute phase has been interpreted as initial atrophy of the fibers in this sector following the edematous phase. A study conducted on patients before, during, and after the acute phase identified the temporal sequence of RNFL during the early acute phase (Fig. 9.2.8).<sup>89</sup> In the transition from the presymptomatic phase to the acute phase, the temporal fibers begin to thicken then start thinning at the beginning of the symptomatic phase. This finding confirms the preferential involvement of the small fibers of the papillomacular bundle. A simultaneous thickening takes place in the inferior sectors for the first 3 months, after which the fibers begin to thin (Fig. 9.2.9). This finding is in line with the larger temporal and inferior thickening observed in asymptomatic subjects. The superior and nasal sectors are involved in a subsequent stage and show thickening after 3 months, when the other sectors are already in the atrophic phase. The acute phase of LHON has proven to be a more dynamic and progressive phase than was previously envisaged, being characterized by a series of events lasting at least 3 months.<sup>89</sup>

OCT analysis of the RNFL in childhood LHON shows that in acute forms there is diffuse fiber atrophy affecting all quadrants.<sup>90</sup> This finding holds for all acutely affected eyes in both bilateral and unilateral forms. In this case, the childhood forms do not differ from adult-onset ones. Slowly progressive forms show a significant fiber reduction in the temporal quadrant, which extends, albeit insignificantly, to the inferior quadrant, with relative preservation of fibers in the other sectors. Finally, in eyes with a subclinical course of disease, the situation in terms of fiber loss is comparable to that of slowly progressive forms, with preferential involvement of the temporal quadrant and, to a lesser extent, of the inferior quadrant.<sup>90</sup> In these two atypical forms, the ophthalmoscopic picture and pattern of



**Fig. 9.2.7 Fundus Appearance and Retinal Nerve Fiber Layer Analysis in Acute Asymmetric Leber's Hereditary Optic Neuropathy Patient.** Right eye (A–B) shows inferotemporal thinning of fibers and swelling of the supero-nasal quadrants. Left eye (B–C) shows an initial thinning of temporal fibers with swelling the other quadrants.



**Fig. 9.2.8 Longitudinal Peripapillary Retinal Nerve Fiber Layer (pRNFL) and Macular Ganglion Cells-Inner Plexiform Layer (GC-IPL) Changes in Acute Leber's Hereditary Optic Neuropathy.** Thickness variation is expressed as percentage of reduction with respect to the presymptomatic examination. Note the different natural history of pRNFL, which shows early thickening and late thinning in comparison to the early GC-IPL thinning. (Modified from Balducci N, Savini G, Cascavilla ML, et al. Macular nerve fibre and ganglion cell layer changes in acute Leber's hereditary optic neuropathy. *Br J Ophthalmol* 2016;100:1232–7.)

fiber loss, though clinically reminiscent of DOA, are more typical of LHON since the damage remains limited to the papillomacular bundle without extending to other fibers, as occurs in late DOA.

Analysis of the optic disc reveals that optic nerve size varies significantly according to clinical form. Patients with acute onset show a significantly smaller disc than healthy subjects or subjects with a slowly progressive course.<sup>90</sup>

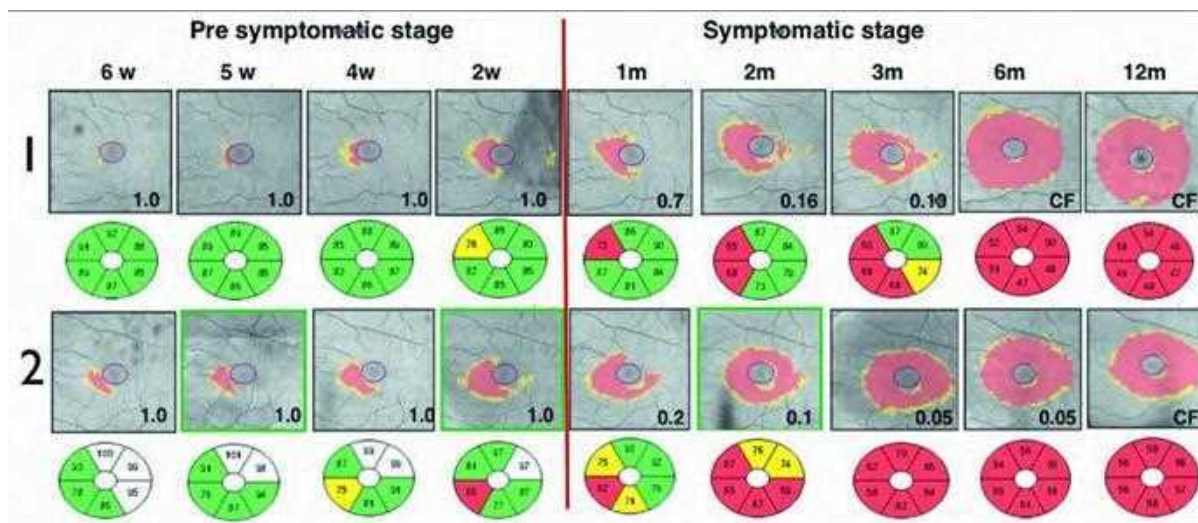
A small optic disc with a small cup-to-disc ratio, defined as a “disc at risk,” has been viewed historically as a predisposing factor for NAION. With respect to LHON, a large optic disc represents a favorable prognostic factor in terms of both protecting against the development of the disease and improving the visual prognosis in affected patients. In both diseases, onset is an acute event that could be linked to the mechanical phenomenon

of fiber crowding in the ONH.<sup>91</sup> In slowly progressive forms of LHON and DOA, as discussed later, the clinical course is associated with a slow process of axonal degeneration, which does not imply a mechanical crowding phenomenon.

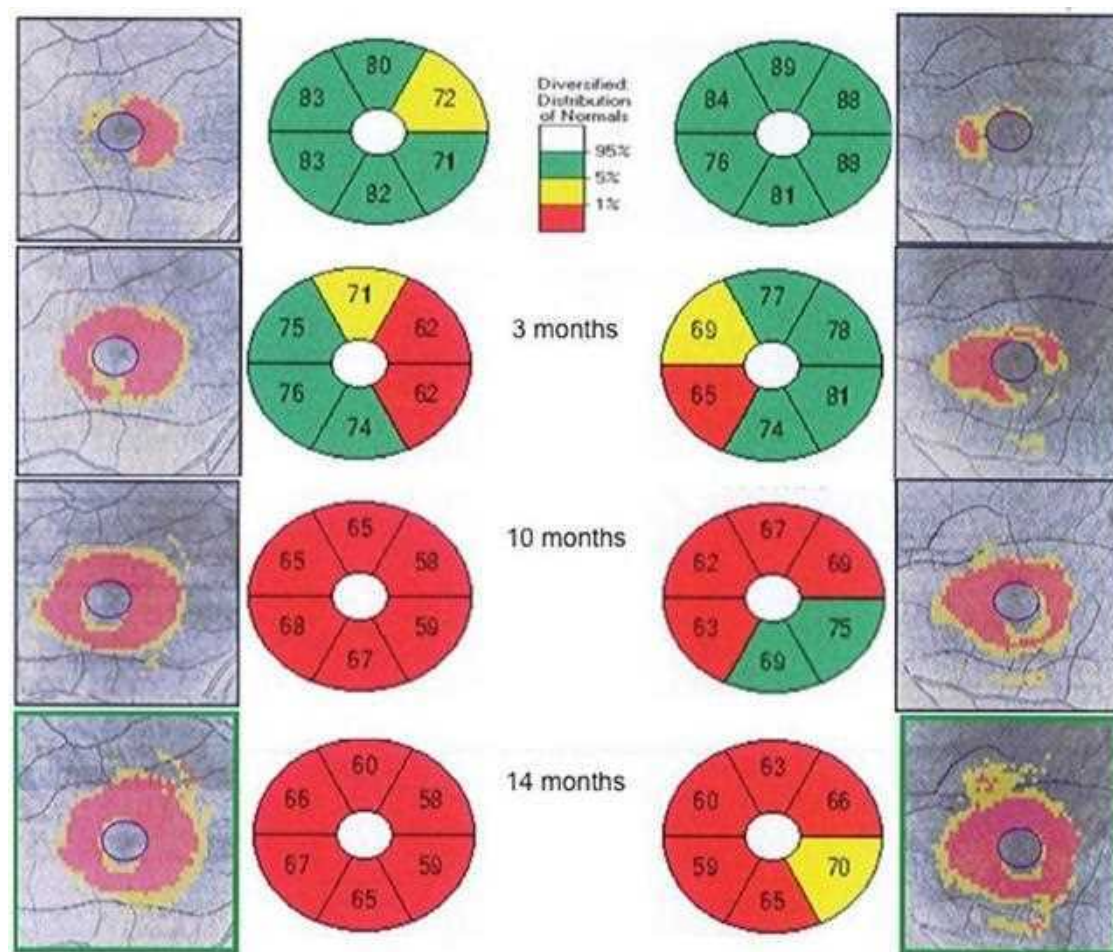
Macular thickness in LHON is reduced before RNFL thinning, and this reduction follows a particular sequence: within 3 months after LHON onset, macular thickness was reduced compared to healthy controls in the superior, nasal, inferior, and temporal quadrants of the inner ring and in the nasal quadrant of the outer ring. Then, within 3–6 months the temporal quadrant of the outer ring also became thinner. Finally, 6 months after visual loss, macular thickness was reduced in all the quadrants.<sup>92</sup>

The macular thickness reduction is due to GCL reduction, which is detectable before RNFL thinning.<sup>93</sup> Specifically, analysis of GCL 6 weeks





**Fig. 9.2.9** Longitudinal Deviation and Sectorial Map Changes of Two Patients Affected by Leber's Hereditary Optic Neuropathy Followed From the Pre-symptomatic to the Chronic Stage. Note the similar early nasal thinning detected in the deviation map during the presymptomatic stage and its progression in a centrifugal and spiral pattern resembling the anatomic distribution of the papillomacular bundle fibers (*m*: months after onset of visual loss; *w*: weeks before onset of visual loss). (From Balducci N, Savini G, Cascavilla ML, et al. Macular nerve fibre and ganglion cell layer changes in acute Leber's hereditary optic neuropathy. *Br J Ophthalmol* 2016;100:1232–7.)



**Fig. 9.2.10** Progressive Ganglion Cell Layer (GCL) Thinning in Toxic Optic Neuropathy. A 40-year-old man with a history of smoking and alcohol consumption was placed on antiretroviral drugs for HIV and tetracycline for syphilis. The initial thinning in GCL was at the level of papillomacular bundle, which worsened over time. The patient recovered vision after stopping the toxins and receiving antioxidant therapy.

before onset of visual loss shows thinning of the inner ring of the nasal sectors, detectable with the deviation map. This defect progressively extends to the inner ring of the inferior sector and enlarges to the outer ring of the nasal sectors over a period of 1 month.<sup>10</sup> Notably, GCL loss may represent the first sign of LHON conversion from the unaffected carrier stage to the acute stage. Later, the defect enlarges, reflecting the anatomical course of papillomacular fibers and a diffuse GCL thinning is detectable 6 months after visual loss (see Fig. 9.2.9).

## DOMINANT OPTIC ATROPHY

A hereditary degenerative optic neuropathy similar to LHON is dominant optic atrophy. The latter is due to a mutation in the nuclear genome and has a clinical picture more insidious than that of LHON.<sup>86</sup> OCT analysis of the retinal peripapillary nerve fiber layer reveals diffuse fiber atrophy affecting all quadrants (Fig. 9.2.10).<sup>94,95</sup> In patients with DOA, RNFL thinning is more evident in the temporal and inferior quadrants, with the reduction (compared to the control group) of 49.7% (eye with better vision) and

52.4% (eye with worse vision). The thickness reduction, though present, is smaller in the superior quadrant (28.4%–31.4%) and nasal quadrant (26.3%–28.3%).<sup>95</sup> This pattern of RNFL atrophy is generally comparable to the pattern observed in LHON, confirming the vulnerability of the small fibers of the papillomacular bundle as a pathognomonic sign of mitochondrial optic neuropathies (Fig. 9.2.11).

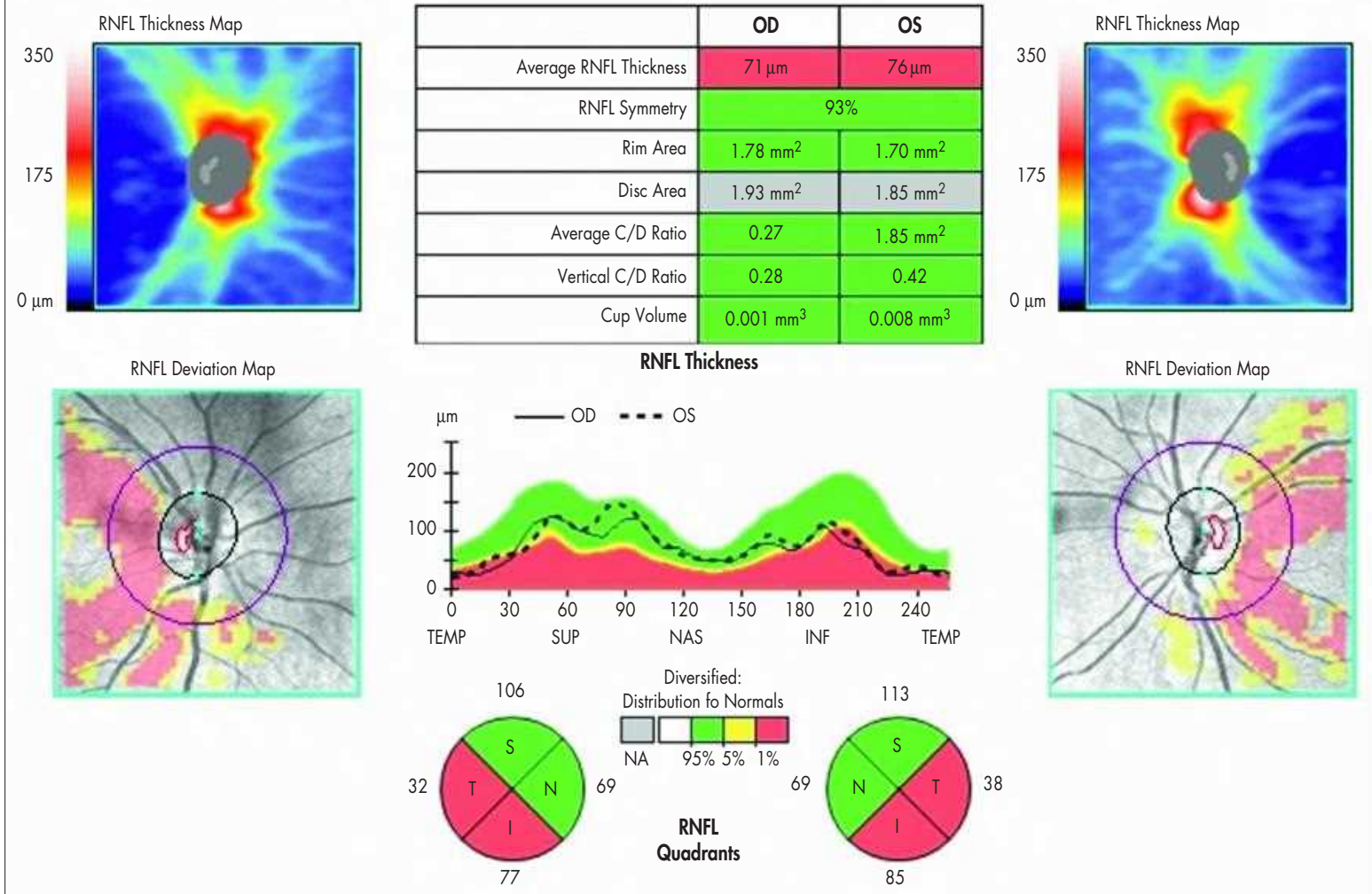
The progressive fiber loss in affected patients is similar to that normally occurring with age. In fact, in patients with DOA, the average decrease in fibers is 0.19 microns per year, comparable to the loss observed in different control groups: 0.16–0.25–0.22.<sup>94,95</sup> This result is correlated with the anatomical conformation of the optic nerve.<sup>95</sup>

Optic disc size is an important parameter in DOA. In DOA patients, the disc area is significantly smaller when compared with that of healthy controls.<sup>96</sup> In patients who are OPA1 mutation carriers, the disc area and vertical and horizontal disc diameters are significantly smaller than those of healthy controls (Fig. 9.2.12). By stratifying these results according to OPA1 mutation, it is possible to identify different degrees of optic disc size, where the mutations range from those associated with a normal optic



## ONH and RNFL OU Analysis: Optic Disc Cube 200×200

OD ● OS ●



**Fig. 9.2.11 Optical Coherence Tomography (OCT) Analysis in Dominant Optic Atrophy (DOA) Patient.** Both eyes show inferotemporal thinning of fibers.

disc size to those associated with much smaller sizes and more severe clinical features of DOA (see Fig. 9.2.12). The proposed hypothesis is that OPA1 expression regulates apoptosis, thereby playing an important role in the embryonic development of the eye and contributing to the determination of optic disc size and conformation. Ultimately, optic nerve size may be important in the phenotypic expression of the disease, the quantity of fibers present at birth, and the determination of the age of onset, progression, severity, and penetrance of DOA.<sup>96</sup>

Optic disc size is thus an important parameter in DOA, one that requires a careful differential diagnosis to distinguish DOA from optic nerve hypoplasia. DOA in isolated form is not associated with developmental abnormalities of the central nervous system.

Retinal thickness is reduced in DOA when compared to healthy controls.<sup>97</sup> The retinal thinning is due to RNFL and GCL reduction, whereas the other retinal layers do not differ from controls.

In DOA, the thinning of GCL is the earliest pathological event and is diffusely reduced in all macular sectors.<sup>97,98</sup> Genotype/phenotype correlation was demonstrated—based on specific OPA1 mutation, different grades of GCL thinning correlated with visual loss.<sup>98</sup> Different GCL thickness also declined with age.<sup>99</sup>

## Nutritional and Toxic Optic Neuropathies

Nutritional and optic neuropathies are characterized by dyschromatopsia and by painless, progressive, symmetric, and bilateral visual loss due primarily to selective damage to the papillomacular bundle. Malnutrition associated with alcohol abuse may be the most common cause of nutritional optic neuropathy. Common drugs causing toxic neuropathies are ethambutol, chloramphenicol, linezolid, erythromycin, streptomycin, antiretroviral, amiodarone, infliximab, quinine, dapsone, pheniprazine, suramin, and isoniazid.<sup>100</sup>

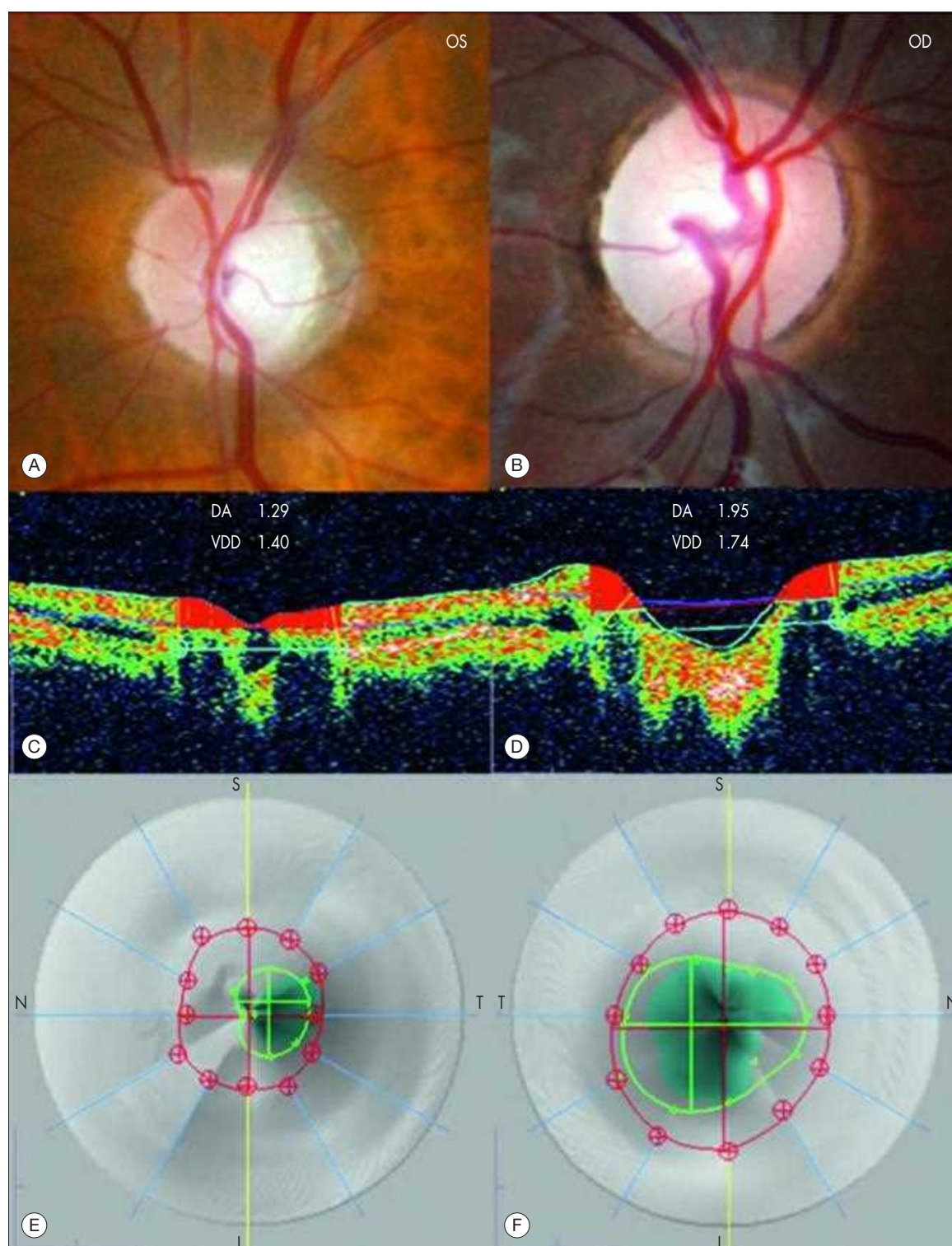
In early stages, mitochondria accumulate within retinal ganglion cells, which leads to RNFL thickening detectable by OCT.<sup>101</sup> If toxic drugs are not discontinued, peripapillary RNFL thinning in the inferotemporal sector and GCL thinning in the nasal sectors (corresponding to the papillomacular bundle) can occur (see Fig. 9.2.10). Finally, diffuse RNFL and GCL thinning results in the late stages. OCT is very helpful for early diagnosis to remove the toxic drugs or to treat malnutrition.

## Optical Coherence Tomography Angiography

In recent years, a new promising OCT detection system has been introduced—optical coherence tomography angiography (OCTA). The OCTA is a functional extension of OCT that images ocular vessels by detecting motion contrast between consecutive scans. Different devices are available for this purpose using different methods to detect the image (speckle or intensity decorrelation, phase variance, etc.). OCTA can show separately the microvasculature in various vascular networks including the optic nerve head, the superficial retina capillaries, the deep retina capillaries, and choriocapillaries (Fig. 9.2.13). Moreover, some OCTA devices can quantify optic nerve head and peripapillary perfusion.<sup>102</sup> The continuous updating of the software makes the measurements more accurate and reliable.

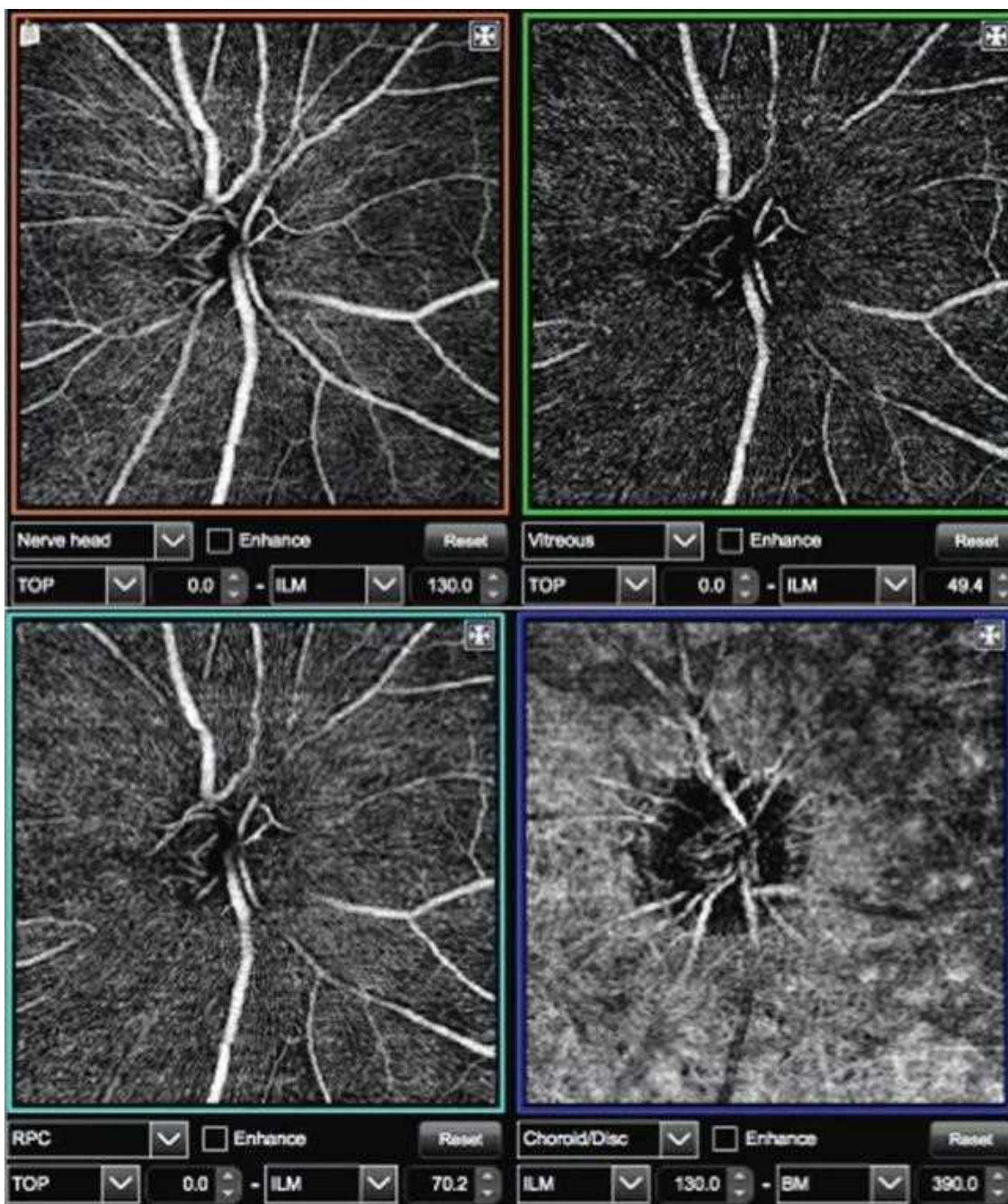
With use of OCTA, a reduction of optic nerve head perfusion has been detected in DOA<sup>104</sup> and in patients affected by MS with a history of optic neuritis, but not in patients affected by MS without a history of optic neuritis.<sup>103</sup>

A study conducted in chronic NAION shows reduction of vessel density in the peripapillary retina and within the optic disc. Moreover, the severity of visual field defect and peripapillary RNFL thinning was significantly associated with the peripapillary vessel density reduction but not with vessel density within the optic disc.<sup>105</sup> OCTA studies in the next few years are expected to lead to new understanding in the pathophysiology of different optic nerve diseases.



**Fig. 9.2.12** Fundus Pictures and Optical Coherence Tomography (OCT) Analysis of Dominant Optic Atrophy (DOA) Patients With a Small Optic Disc (A,C,E) and DOA Patient With Normal Optic Disc Size (B,D,F). (From Barboni P, Carbonelli M, Savini G, et al. OPA1 mutations associated with dominant optic atrophy influence optic nerve head size. *Ophthalmology* 2010;117:1547–53.)





**Fig. 9.2.13** Visualization of the Optic Nerve Head and of the Peripapillary Retina by Optical Coherence Tomography Angiography (OCTA) in a Normal 40-Year-Old Man. Note the different segmentation and the different vascular visualization of the four layers: nerve head, vitreous, radial peripapillary capillaries (RPC), and choriocapillary.

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# Anatomy and Physiology

Alfredo A. Sadun

## 9.3

**Definition:** The optic nerve, being a portion of the central nervous system, is really a tract and not a (peripheral) nerve. The 1.2 million axons that emanate from the retinal ganglion cells carry the name optic nerve until they partially decussate at the optic chiasm.

### Key Features

- The optic nerve consists of four portions: intraocular (the optic disc), intraorbital, intracanalicular, and intracranial.
- Myelination starts posterior to the lamina cribrosa.
- The intraorbital optic nerve has redundant length by at least 8 mm for protection during eye movement.
- The intracranial optic nerves join at the optic chiasm, which also makes them susceptible to compression by lesions in the cavernous sinus.
- Blood supply to the optic nerve head is derived from the circle of Zinn–Haller, which receives blood from choroidal vessels, short posterior ciliary arteries, and pial arterial network.

### HISTORICAL REVIEW

Aristotle described optic nerves as joining at the optic chiasm, so-called because it resembles the Greek letter  $\chi$  (chi). In about AD 150, Galen of Pergamon gave a more detailed description of the optic nerves as sensory in nature but incorrectly as hollow and continuous with the ventricular system. Little progress in the understanding of the visual pathways occurred between Galen and Gratiolet, 1700 years later. Using soft

orangewood sticks for blunt dissection, Gratiolet was able to follow the retinofugal projection to the pretectum as well as to confirm the main pathway to the lateral geniculate nucleus.<sup>1</sup>

### GENERAL ANATOMY

The optic nerve carries about 1.2 million axons that derive from the retinal ganglion cells and project to the eight primary visual nuclei (Fig. 9.3.1).<sup>2–4</sup> However, only the anterior part of this heavily myelinated tract is termed the optic nerve. The optic chiasm consists of the partial decussation; the optic tract is the posterior continuation of the same fiber tract to its termination.

The optic nerve is about 50 mm long and extends from the eye to the optic chiasm. It is often described as consisting of four portions (Fig. 9.3.2):

- Intraocular portion (the optic disc, 1 mm in anterior–posterior length).
- Intraorbital portion (about 25 mm long).
- Intracanalicular portion within the optic canal (about 9 mm long).
- Intracranial portion (about 16 mm long).

Three anatomical zones occur within the 1-mm long intraocular optic nerve (optic disc): anteriorly, the retinal or prelaminar zone; centrally, the choroidal or laminar zone; posteriorly, the scleral or retrolaminar zone.

Each zone contains different structures and elements of neuroectoderm and mesoderm.<sup>5,6</sup>

### CONSTITUENT ELEMENTS

#### Axons

Retinal ganglion cell axons course toward the optic nerve head as unmyelinated, retinal nerve fibers and later as myelinated optic nerve fibers. A

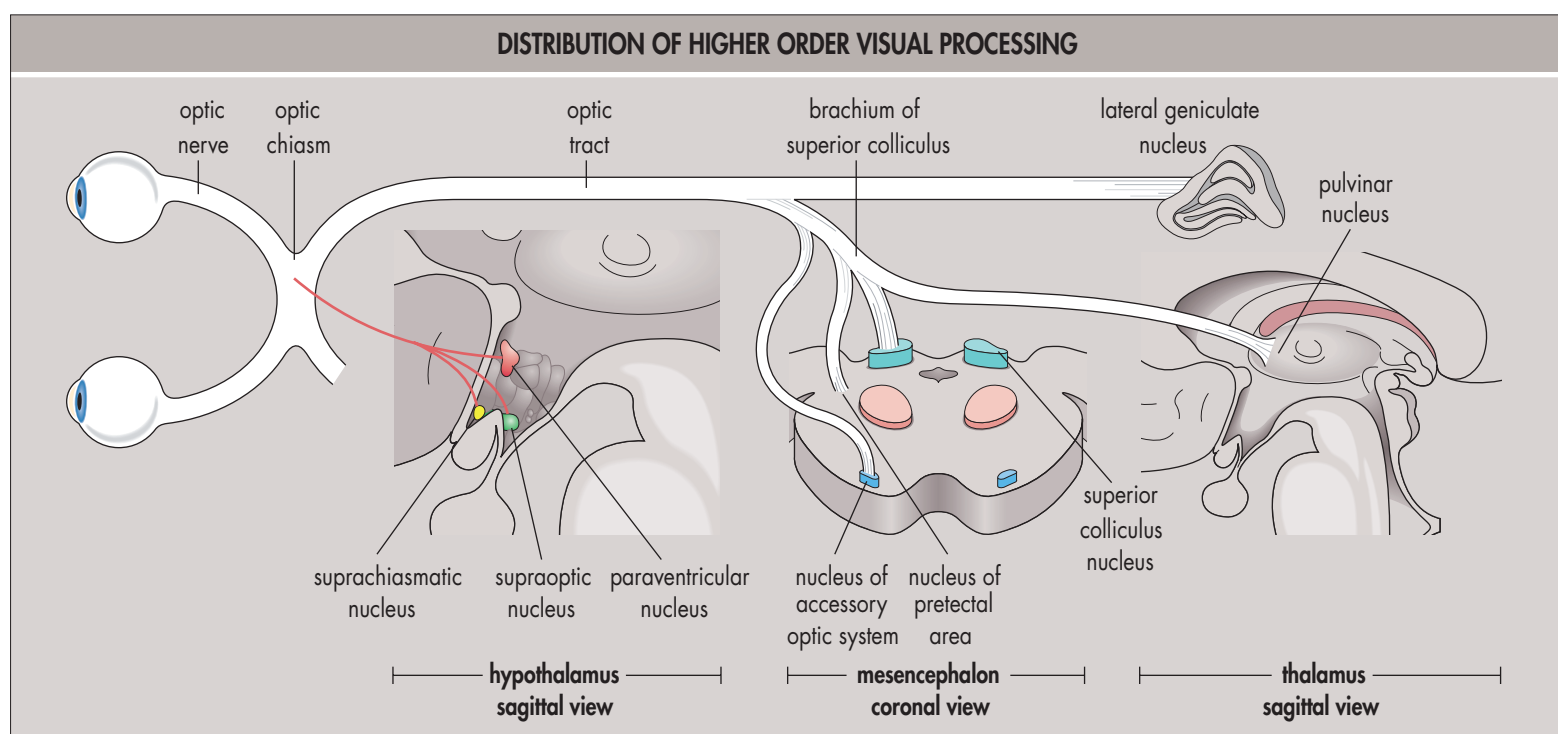
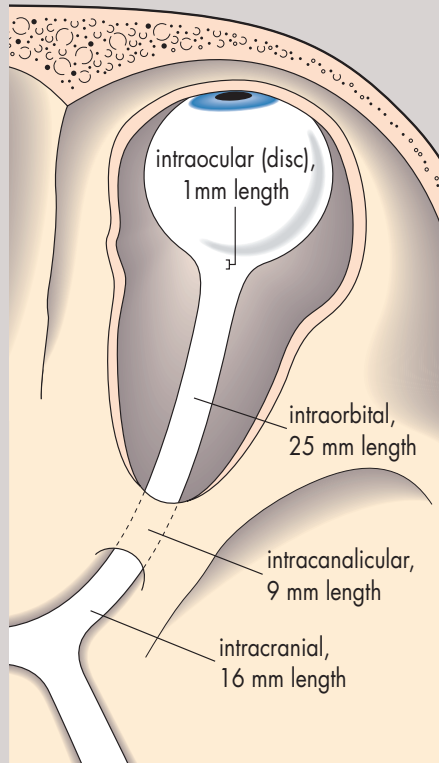


Fig. 9.3.1 Retinal Projections to the Eight Primary Nuclei, Showing Distribution of Higher Order Visual Processing.



## THE FOUR PORTIONS OF THE OPTIC NERVE



**Fig. 9.3.2 The Four Portions of the Optic Nerve.** The lengths are given.

topographical separation of fibers begins in the retina, continues in the optic nerve, and then becomes less precise near the optic chiasm.

The axons represent the anatomical substrate of the neural connection. Their membrane cable properties permit a regenerative signal to be transferred from the retina to the primary visual nuclei. This signal travels fastest in the axons of largest caliber and in those with the most myelin. Conduction velocities in large, myelinated fibers (about 20 m/second) are much faster than the velocities in small, unmyelinated fibers (about 1 m/second) in the retina.<sup>7</sup>

This optic nerve-mediated signal is coded spatially (the axons are retinotopically distributed in the brain) and probably temporally (axonal firing frequency carries information).

In addition to the neural signals, axons permit the transfer of intracellular chemicals and organelles such as mitochondria from the neuron soma to the distal terminal and vice versa. Orthograde (proceeds from eye to brain) axoplasmic transport has a slow component that progresses at 0.5–3.0 mm/day and a rapid component that moves at 200–1000 mm/day.<sup>8,9</sup> Retrograde (brain to eye) axonal transport also occurs at an intermediate rate.

Most of the retinal ganglion cells are relatively small, concentrated in the macula, and contribute axons of small caliber that project to the parvocellular layers of the dorsal lateral geniculate nucleus (the so-called P cell system). P cells have color-opponent physiology and are thought to subserve high-contrast, high-spatial-frequency resolution. In contradistinction, M cells are larger cells that contain large, fast-conducting axons and make up about 5%–10% of the retinal ganglion cells. The M cells may be involved primarily with noncolor information of high-temporal and low-spatial frequency.<sup>10</sup>

Melanopsin retinal ganglion cells (mRGCs) belong to a newly discovered class of photoreceptor RGCs that subserve the autonomic functions including pupils and circadian rhythms.<sup>11,12</sup> mRGCs are intrinsically photoreceptive but also part of the retinal circuitry for nonimage-forming functions.<sup>11</sup> They may be selectively sensitive or robust to different retinal and optic nerve diseases.<sup>12</sup>

## Glia

Oligodendrocytes are specialized glia that provide membranes for axonal myelination. Myelination begins centrally during development and stops

at the lamina cribrosa of the optic disc at birth. However, oligodendrocytes may extend anomalously anterior to the lamina to myelinate the peripapillary retinal nerve fiber layer (optic disc medullation) in about 1% of the general population. Microglia and macrophages are cells that derive from the immune system and can move readily into the central nervous system from the vascular beds. The apoptosis of retinal ganglion cells, which occurs during development and in various diseases, is probably modulated by these glial cells. Astrocytes have extensive neurofibrillary processes that spread among the nerve fibers. These specialized glial cells line the borders between axons and other tissues and form part of the blood–brain barrier. When axons are lost because of optic atrophy, astrocytes move and proliferate to fill the empty spaces.

## FOUR PORTIONS OF THE OPTIC NERVE

### Optic Disc

The optic nerve head is 1 mm deep in the anteroposterior direction and 1.5 mm (horizontally) by 1.8 mm (vertically) in diameter at the level of the retina.<sup>13</sup> The retinal ganglion axons make an orthogonal turn from the nerve fiber layer and pass through one of 200–300 holes that perforate the lamina cribrosa, the collagenous support of the optic disc.<sup>6</sup> These axons must pass from an area of higher tissue pressure (intraocular compartment) to a zone of lower pressure (retrobulbar space). The arterial supply shifts from the central retinal artery to branches of the ophthalmic artery. The axons become myelinated immediately posterior to the lamina cribrosa.

### Intraorbital Optic Nerve

This portion of the nerve (25 mm) exceeds the anteroposterior distance from the globe to the optic foramen by at least 8 mm. This redundancy of the sinuous optic nerve protects it and the eye during eye movements.

The optic nerve diameter increases from 3 mm just behind the globe to about 4 mm at the orbital apex.<sup>14</sup> Most of their increased caliber is due to connected tissue. Throughout its orbital course, the nerve is surrounded by dura, arachnoid, and pia mater (Fig. 9.3.3). The subarachnoid space is continuous with the intracranial subarachnoid space and carries cerebrospinal fluid.

The optic nerve substance consists of 400–600 fascicles, each of which contains about 2000 fibers. The fascicles are separated by connective tissue septa through which run the smaller blood vessels. The axons are heavily myelinated (Fig. 9.3.4) by oligodendrocytes.

### Intracanalicular Optic Nerve

The optic nerve's intracanalicular portion begins as it enters the optic canal through an opening in the lesser wing of the sphenoid bone at the apex of the orbit known as the optic foramen (see Fig. 9.3.2). The orbital canal opening is elliptic, with its widest diameter oriented vertically. The intracranial opening of the optic canal is also elliptic but with the horizontal width greater than the height.<sup>15</sup> The medial canal wall is the thinnest and most likely to fracture. Small lesions that arise within the optic canal may compress and significantly damage the optic nerve.

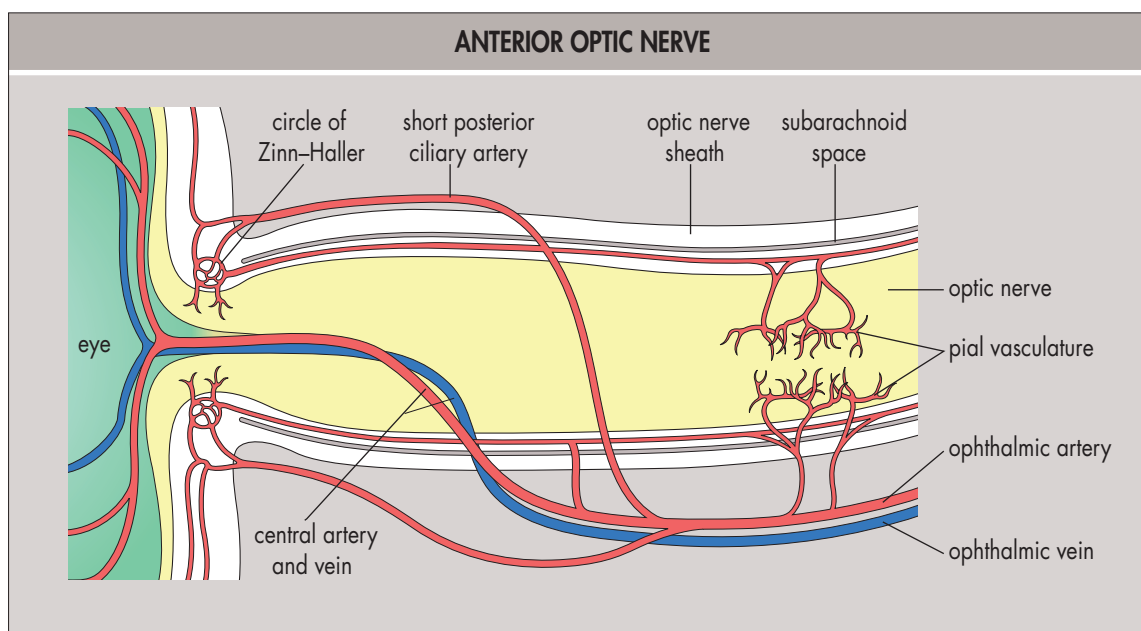
### Intracranial Optic Nerve

Once past the hard fold of dura above the intracranial opening of the canal, the intracranial optic nerve runs for 12–16 mm to reach the optic chiasm. The intracranial optic nerve is now about 4.5 mm in average diameter.

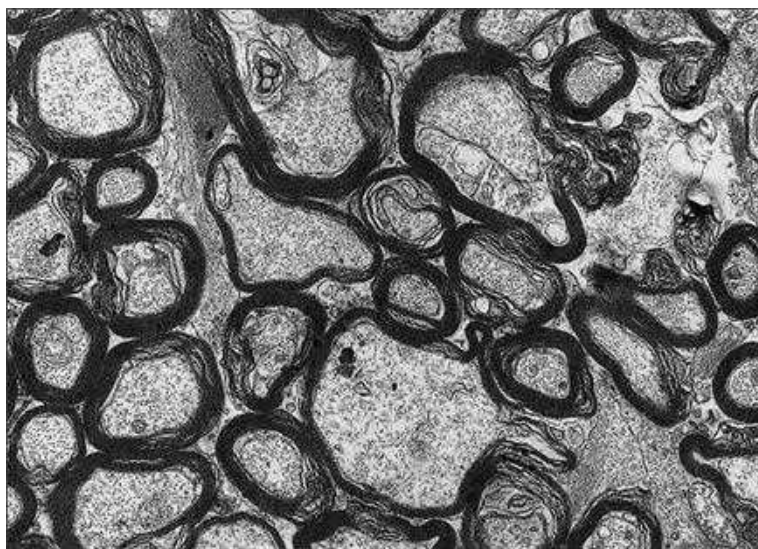
Above each nerve lie the gyri recti of the frontal lobes of the brain. On the lateral side of the optic nerve may lie the internal carotid artery. The ophthalmic artery arises from the carotid and lies to the lateral side and below the nerve within its dural sheath. The proximity of the cavernous sinus makes it possible for tumors to produce cranial nerve palsies in combination with an optic neuropathy.

## CIRCULATION OF THE OPTIC NERVE

The ophthalmic artery derives from the top of the internal carotid artery siphon where it joins up with and occupies an inferior position to the nerve in the optic canal. In the canal and orbit, the artery gives off several branches that feed the pial circulation. At 8–12 mm behind the globe, the ophthalmic artery passes through the nerve sheath and into the nerve, where it runs up to the optic disc; here it is renamed as the central retinal



**Fig. 9.3.3 Anterior Optic Nerve.** The sheath and the vascular supply to the intraocular and intraorbital portions are shown.



**Fig. 9.3.4 Axons in the Retrobulbar Optic Nerve.** This is an ultrastructural high-magnification view approximately 5 mm behind the globe. Note the heavily myelinated axons of various sizes. The smaller axons are 0.6–0.9  $\mu\text{m}$  in diameter and are probably of retinal ganglion cells of the P cell system. The larger axons are 1–2  $\mu\text{m}$  in diameter and may be part of the M cell system.

artery (see Fig. 9.3.3); this artery does not contribute directly to the circulation of the optic nerve head. Instead, blood flow to the optic nerve head derives from the circle of Zinn-Haller, which receives three major sources of blood<sup>16,17</sup>:

- Choroidal vessels.
- Four or five short posterior ciliary arteries.
- Small contribution from the pial arterial network.

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# Differentiation of Optic Nerve From Macular Retinal Disease

## 9.4

Alfredo A. Sadun, Vivek R. Patel

**Definition:** Optic nerve disease involves injury to the retinal ganglion cells and the axons that constitute the optic nerve, whereas macular disease involves injury to the retina in the foveal and parafoveal areas.

### Key Features

- Optic nerve lesions generally produce an afferent pupillary defect and a severe dyschromatopsia.
- Macular lesions cause variable loss of central acuity and metamorphopsia.
- Brightness sense is reduced in optic nerve disease and augmented in macular disease.

### Diagnostic Features

- Optical coherence tomography (OCT) and multifocal electroretinography testing can reveal macular disease.
- Contrast sensitivity and visual evoked response testing may disclose optic nerve disease.

## INTRODUCTION

Optic neuropathies and maculopathies often have overlapping presentations. For example, optic neuritis and central serous retinopathy may both present in a young adult as acute, painless, monocular visual loss. The relative absence of fundus findings in patients with acute visual loss may make the correct diagnosis problematic. Impairment of vision secondary to optic nerve dysfunction may be an indication of intracranial pathology, often requiring neurosurgical intervention. Conversely, maculopathies may respond to local treatments<sup>1</sup> such as laser photocoagulation, photodynamic therapy, corticosteroids, or antivascular endothelial growth factor (antiVEGF) agents or surgery. These differences in management strategies underscore the need to make an early and accurate distinction between an optic neuropathy and a maculopathy.

Optic neuritis and nonarteritic anterior ischemic optic neuropathy are the most common forms of optic neuropathies in younger and older adults, respectively. Macular disease may localize to the inner or outer retina, and the most common form of macular disease is age-related macular degeneration.

## OCULAR FEATURES

Loss of visual acuity due to optic nerve disease is usually perceived as a sense of generalized dimness, patchy dark spots, or black curtains across the visual field.<sup>2</sup> Optic neuropathies may also produce a darkening or desaturation of colors and objects, which may appear to have reduced contrast to the point of becoming indistinguishable. Pain may be associated with certain optic neuropathies but is a distinctly unusual finding in maculopathies.

Patients who have maculopathies complain of metamorphopsia in the central visual field.<sup>3</sup> Micropsia is more common than macropsia. Patients may also experience slight photophobia (increased brightness sense) or glare, in contrast to the dimness perceived by optic neuropathy patients.

## DIAGNOSIS AND ANCILLARY TESTING

### History

Determining the tempo of disease is central to reaching an accurate diagnosis. Optic neuritis usually develops over hours to days, stabilizes, and then shows improvement in the ensuing weeks. Anterior ischemic optic neuropathy causes a sudden loss of vision usually with minimal progression or resolution thereafter.<sup>2</sup> Maculopathies, on the other hand, may be acute or insidious in onset.

### Physical Examination

Although quite variable, visual acuity is generally more severely affected in macular diseases than in diseases of the optic nerve. Measurement of the afferent pupillary response,<sup>4</sup> color vision, and brightness sense testing<sup>5</sup> are three tests that are particularly sensitive to impairments of the optic nerve and may be affected to an extent that is out of proportion to the observed reduction in visual acuity. Brightness sense may be estimated subjectively when the patient is asked which eye sees a light brighter or quantified using neutral density filters or spectacles composed of two pairs of cross-polarizing filters.<sup>5</sup>

Fundus examination may disclose optic disc swelling, but optic disc elevation itself does not produce significant impairment of visual function.<sup>6</sup> Optic atrophy is generally first visualized about 1 month after acute injury to the nerve. Optic neuropathies may produce diffuse dropout or segmental losses in the nerve fiber layer (NFL). Sectoral disc edema with flame-shaped hemorrhages (anterior ischemic optic neuropathy), lumps and bumps (optic disc drusen), pathological cupping (glaucoma), sectoral optic atrophy, and secondary optic atrophy are patterns of optic disc changes that indicate different types of optic nerve damage.

Serous neurosensory retinal or retinal pigment epithelium (RPE) detachments, retinal vascular abnormalities, and exudates may all be seen by direct or indirect ophthalmoscopy or by stereomicroscopy. The indications and clinical utility of optical coherence tomography (OCT) (see Chapter 9.2) is rapidly increasing, allowing precise anatomical localization and characterization of posterior pole pathologies. In addition, simultaneous imaging of the retinal NFL can help determine the presence or absence of concurrent optic nerve fiber atrophy.

### Ancillary Testing

Optic neuropathies may cause a variety of visual field defects, some of which are fairly specific to the underlying disease. For example, toxic or nutritional deficiency optic neuropathies usually cause centrocecal field defects, whereas diseases of the optic nerve head often produce arcuate or altitudinal field defects. The visual field defect of a maculopathy is almost invariably a central scotoma with a zone of metamorphopsia that surrounds it. Tangent visual field testing remains a very effective way of assessing the central 20° of visual field and makes the identification of a small central scotoma easily. Amsler chart testing provides a very sensitive assessment of the central 10° of visual field<sup>7</sup> and documents the presence or absence of metamorphopsia, a strong indicator of macular disease. Threshold Amsler chart testing is a method in which the Amsler grid is made very sensitive.<sup>8</sup> In this approach, the patient wears specialized glasses with cross-polarizers in front of both oculars, which are turned to reduce the patient's perception so that the Amsler chart is barely discerned or views a computer screen with variable contrast.<sup>9</sup>

In macular disease, a delay usually occurs in the recovery of visual pigments that are bleached by a bright light. Conversely, bright light has no effect on optic nerve conduction. Fundus fluorescein angiography and autofluorescence are very useful for the characterization of retinal diseases.

The visual evoked response is not very helpful in distinguishing optic nerve dysfunction from a variety of other diseases, which include refractive error, maculopathy, or even feigned visual loss.<sup>10</sup> Nevertheless, the test can be useful when a bilateral disease of the optic nerves exists or when documentation is desired for medicolegal purposes.

Another test that is used to discriminate between the two diseases is contrast sensitivity testing, which can be done at different spatial frequencies.<sup>11</sup> Patients who have optic neuropathies may have deficiencies in the middle to high spatial frequencies, whereas patients who have maculopathies usually have deficiencies only in the highest spatial frequencies.

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# Congenital Optic Disc Anomalies

Michael C. Brodsky

## 9.5

**Definition:** Unusual configurations of the optic disc(s) present since birth.

### Key Feature

- Small, pale, or unusually shaped optic discs may reflect mere curiosities or significant anomalies associated with visual defects.

### Associated Feature

- Abnormalities of the surrounding retina (e.g., in morning glory syndrome), anterior segment (e.g., iris coloboma), face, or brain may occasionally be seen.

## INTRODUCTION

The principles outlined here apply to the evaluation and management of children who have congenital optic disc anomalies.<sup>1</sup>

### Age Association

Children who have bilateral optic disc anomalies generally present in infancy with poor vision and nystagmus; those who have unilateral optic disc anomalies generally present during the preschool years with sensory esotropia.

### Central Nervous System Malformations

Central nervous system malformations are common in patients who have malformed optic discs. Small discs are associated with a variety of malformations that involve the cerebral hemispheres, pituitary infundibulum, and midline intracranial structures (e.g., septum pellucidum, corpus callosum).

Optic discs of the morning glory configuration are associated with the transsphenoidal form of basal encephalocele, whereas optic discs with a colobomatous configuration are associated with systemic anomalies in a variety of coloboma syndromes.

## OPTIC NERVE HYPOPLASIA

Optic nerve hypoplasia is a congenital anomaly that represents a major cause of impaired vision in children.<sup>1</sup> Histologically, it is characterized by a subnormal number of optic nerve axons with normal mesodermal elements and glial supporting tissue.<sup>2</sup> The ophthalmoscopic appearance is that of a small, gray, or pale optic nerve head, which is often surrounded by a yellowish mottled peripapillary halo, flanked on either side by a ring of pigment (double-ring sign)<sup>2</sup> (Fig. 9.5.1). Visual acuity may range from 20/20 to no light perception.<sup>2</sup> Because visual acuity depends only on the degree of papillomacular nerve fiber bundle hypoplasia, it does not necessarily correlate with the overall size of the disc.<sup>1</sup>

The term septo-optic dysplasia (de Morsier syndrome) describes the constellation of optic nerve hypoplasia, absence of the septum pellucidum, and partial or complete agenesis of the corpus callosum.<sup>2</sup> MRI of the brain in optic nerve hypoplasia frequently shows coexistent cerebral hemispheric abnormalities (most often schizencephaly) and absence of the pituitary infundibulum with or without posterior pituitary ectopia.<sup>3</sup>

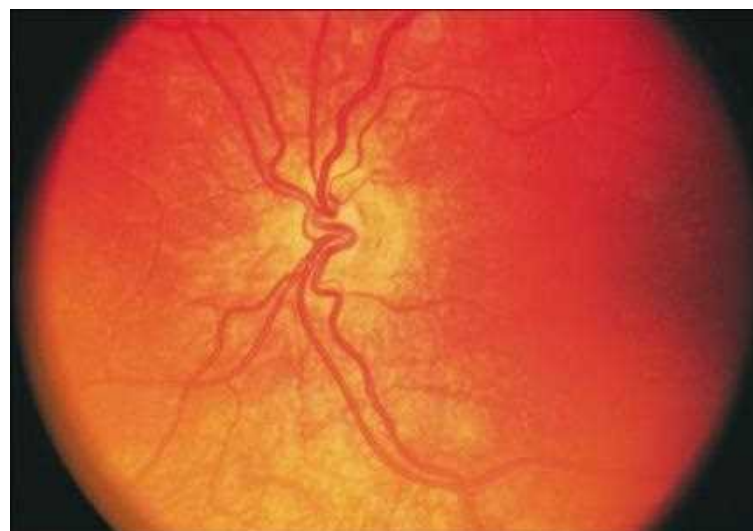


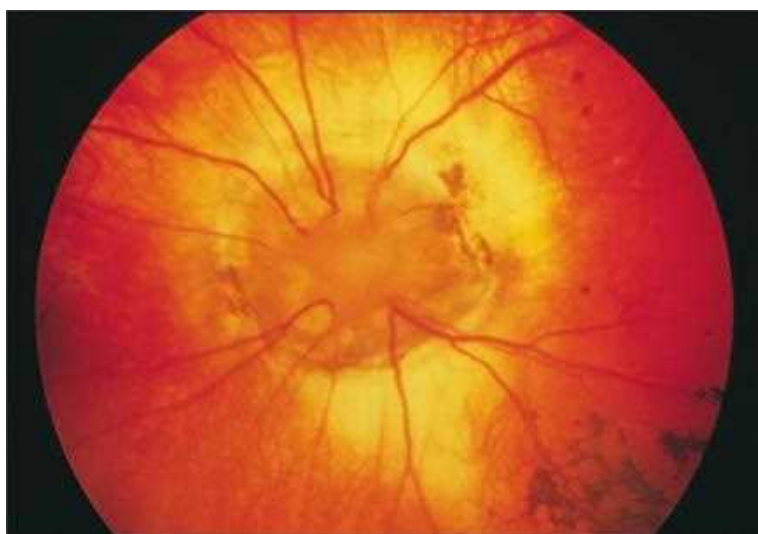
Fig. 9.5.1 Optic Nerve Hypoplasia (Note Double-Ring Sign).

The association of septo-optic dysplasia with pituitary hormone deficiencies warrants endocrinological evaluation in children who have both optic nerve hypoplasia and absence of the pituitary infundibulum on MRI. Growth hormone deficiency is most common, followed by deficiency of thyroid-stimulating hormone, corticotrophic hormone, and vasopressin. In infants who have septo-optic dysplasia, a history of neonatal jaundice suggests hypothyroidism and neonatal hypoglycemia indicates corticotropin deficiency. Children who have corticotropin deficiency are at risk of sudden death from hypoglycemia and shock during intercurrent illness; parents should be instructed to administer injectable parenteral corticosteroids at the onset of febrile illness.<sup>4</sup>

## MORNING GLORY DISC ANOMALY

The morning glory disc anomaly is a congenital excavation of the posterior globe that involves the optic disc.<sup>5</sup> In morning glory anomaly, the optic disc is enlarged, orange or pink in color, and either excavated or situated within a funnel-shaped area of excavation (Fig. 9.5.2).<sup>5</sup> A variably elevated annular zone surrounds the disc with irregular areas of pigmentation and depigmentation. A white tuft of glial tissue overlies the center of the disc. The retinal blood vessels appear increased in number, arise from the periphery of the disc, run an abnormally straight course over the peripapillary retina, and tend to branch at acute angles. It is often difficult to distinguish arteries from veins. The macula may be incorporated into the excavated defect (macular capture).<sup>5</sup> Although mistakenly referred to as a variant of optic disc coloboma, the morning glory disc anomaly is truly a distinct anomaly, as evidenced by its sporadic occurrence, its lack of association with iris or retinal colobomas, and its systemic associations.<sup>5</sup>

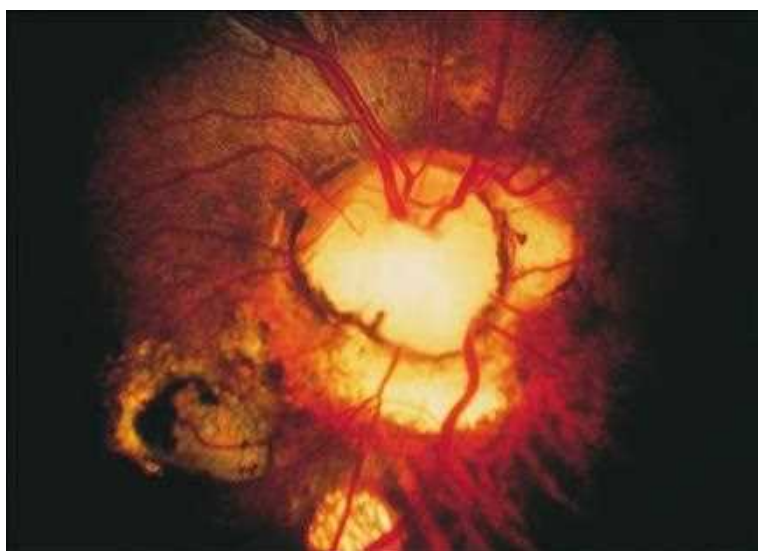
The morning glory disc anomaly is associated with transsphenoidal encephalocele<sup>1</sup> and with hypoplasia of the ipsilateral intracranial vasculature (which can be visualized by magnetic resonance angiography).<sup>5,6</sup> Children who have this occult basal encephalocele have characteristic facies, which consist of mild hypertelorism with a depressed nasal bridge, a midline notch in the upper lip, and sometimes a midline cleft in the soft palate. Respiratory symptoms of transsphenoidal encephalocele in infancy may include rhinorrhea, nasal obstruction, mouth breathing, or snoring. Most affected children have no overt intellectual or neurological deficits,



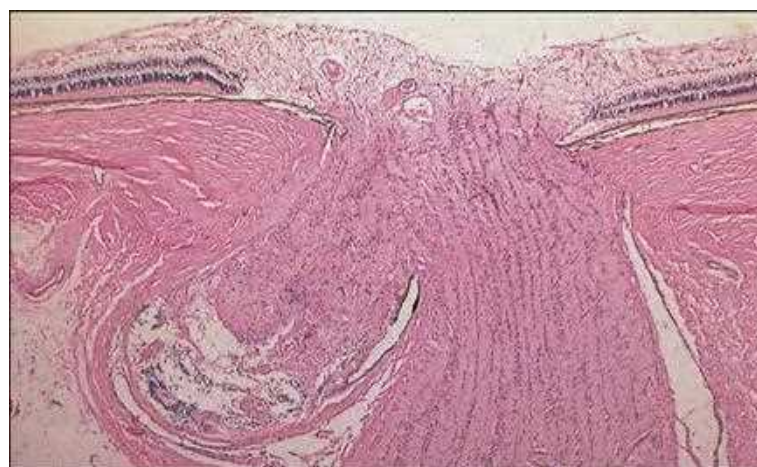
**Fig. 9.5.2 Morning Glory Disc Anomaly.**



**Fig. 9.5.4 Optic Pit.**



**Fig. 9.5.3 Optic Disc Coloboma.**



**Fig. 9.5.5 Optic Pit.** Herniation of retinal tissue through an enlarged scleral opening along one side of the optic nerve. (Courtesy Dr. JB Crawford, from Irvine AR, Crawford JB, Sullivan JH. The pathogenesis of retinal detachment with morning glory disc and optic pit. *Retina*. 1986;6:146–50.)

but panhypopituitarism is common. Patients who have morning glory discs are also at risk of acquired visual loss. Nonrhegmatogenous retinal detachments develop in approximately one-third of eyes with morning glory discs and usually involve the peripapillary retina.<sup>5</sup>

## OPTIC DISC COLOBOMA

In optic disc coloboma, the disc appears enlarged and incorporates a sharply demarcated, glistening white, bowl-shaped excavation (Fig. 9.5.3).<sup>7</sup> The inferior rim of the disc is thinner than the superior rim, which reflects the position of the embryonic fissure relative to the primitive epithelial papilla. The excavation may extend inferiorly to involve the adjacent choroid and retina, in which case microphthalmia is frequently present. In some instances, the entire disc is excavated, but the colobomatous nature of the defect can still be appreciated ophthalmoscopically because the excavation is deeper inferiorly. The excavation is contained within the colobomatous optic disc, as opposed to the morning glory disc anomaly, in which the disc falls within the excavation.<sup>7</sup> Visual acuity may be minimally or severely affected, depending upon the extent of the lesion. Although the optic disc area appears enlarged, optic disc coloboma is actually an inferior segmental form of optic nerve hypoplasia, because the only remaining neural tissue lies superiorly in a C-shaped or moon-shaped crescent (see Fig. 9.5.3).

Optic disc coloboma may arise sporadically or be inherited in an autosomal dominant fashion and may be accompanied by iris or retinochoroidal colobomas in the same or fellow eye. Often it is associated with systemic anomalies in a number of genetic syndromes (e.g., CHARGE [coloboma of the eye, heart anomaly, choanal atresia, retardation, and genital and ear anomalies] association, Walker-Warburg syndrome, Goltz focal dermal

hypoplasia, Goldenhar's syndrome, linear nevus sebaceous syndrome) but rarely is it associated with transsphenoidal encephalocele.<sup>1</sup>

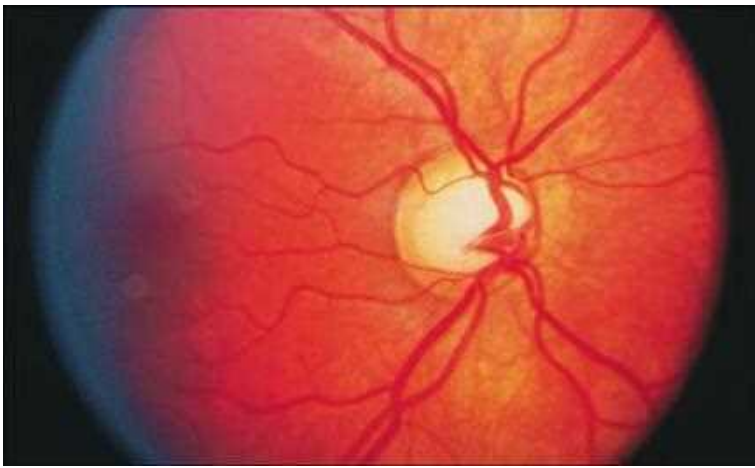
## OPTIC PIT

An optic pit appears as round or oval, gray, white, or yellowish crater-like depression in the optic disc (Fig. 9.5.4).<sup>7</sup> Optic pits commonly involve the temporal optic disc but may be situated in any sector.<sup>8</sup> Temporal optic pits are often associated with adjacent peripapillary retinal pigment epithelium changes.<sup>8</sup> In unilateral cases, the involved disc is slightly larger than the normal disc.<sup>8</sup>

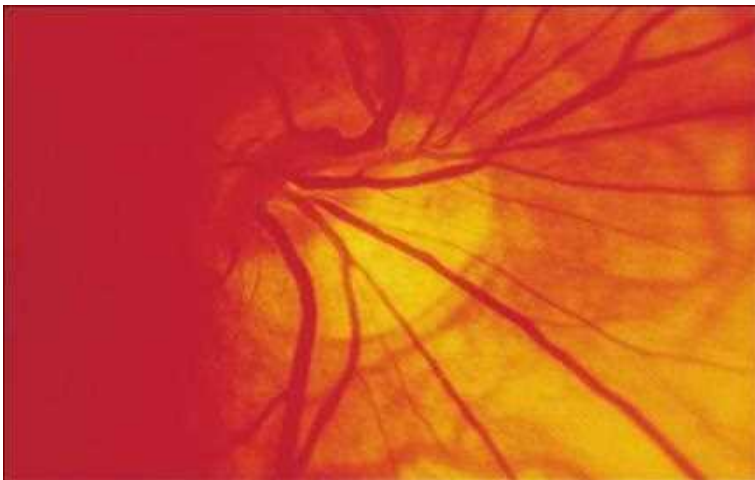
Visual field defects are variable and often correlate poorly with the location of the pit; the most common defect appears to be a paracentral arcuate scotoma connected to an enlarged blind spot. Acquired depressions in the optic disc that are indistinguishable from optic pits have been documented in eyes with normal-tension glaucoma.<sup>1</sup> Histologically, an optic pit is a herniation of rudimentary neuroectodermal tissue into a pocket-like depression within the nerve substance<sup>8</sup> (Fig. 9.5.5). Its pathogenesis is unknown.

Optic pits are not associated with brain malformations, and their discovery does not warrant neuroimaging. Approximately 45% of eyes with optic pits develop macular retinoschisis and/or serous retinal detachments.<sup>6</sup> Some serous retinal detachments associated with optic pits resolve spontaneously, but the visual prognosis remains poor.<sup>8</sup> The subretinal fluid most likely originates from the vitreous cavity and/or the subarachnoid space that surrounds the optic nerve. Lincoff et al.<sup>9</sup> demonstrated that fluid from the optic pit initially produces an inner layer retinal separation (retinoschisis) that overlies the posterior pole. An outer layer macular hole subsequently develops through which this intraretinal fluid communicates with the subretinal space to form a sensory macular detachment





**Fig. 9.5.6 Megalopapilla.**



**Fig. 9.5.7 Congenital Tilted Right Optic Disc.** Note the inferonasal retinochoroidal depigmentation. (Left optic disc is the mirror image.)

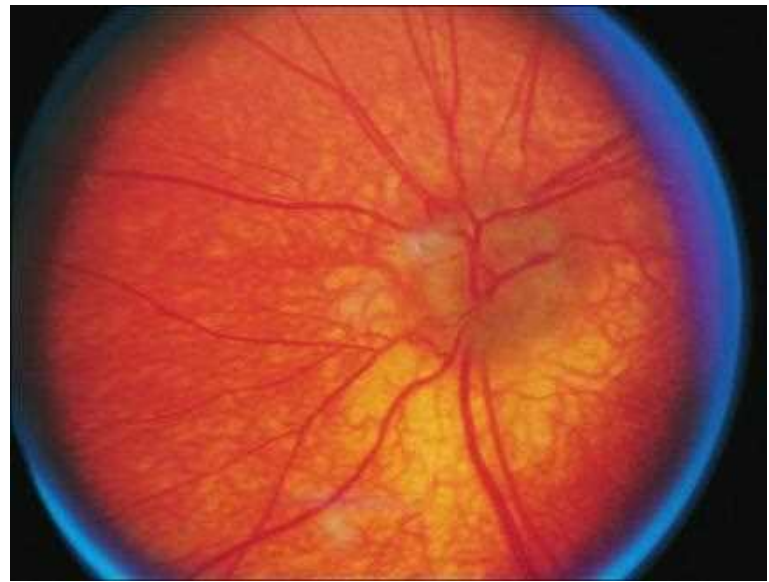
that gradually enlarges.<sup>9</sup> The recent finding that vitrectomy with induction of posterior vitreous detachment without gas tamponade or laser photocoagulation allows resolution of optic disc pit maculopathy suggests that primary vitreous traction is the trigger for the schisis cavity and that the perivascular space around the pit allows for the passage of fluid into the retina.<sup>10</sup>

## MEGALOPAPILLA

Megalopapilla is a generic term that connotes an abnormally large optic disc that lacks the inferior excavation of optic disc coloboma or the numerous anomalous features of the morning glory disc anomaly.<sup>1</sup> This condition is usually bilateral and often associated with a large cup-to-disc ratio. Patients who have megalopapilla are often suspected to have glaucoma. Unlike the situation in glaucoma, however, the optic cup is usually round or horizontally oval with no vertical notch or encroachment (Fig. 9.5.6). Visual acuity is generally normal in megalopapilla but may be mildly decreased in some cases. Visual fields are usually normal except for an enlarged blind spot, which enables the examiner to rule out low-tension glaucoma or a compressive lesion. Megalopapilla is only rarely associated with brain anomalies, and neuroimaging is not warranted unless midline facial anomalies are present.

## CONGENITAL TILTED DISC SYNDROME

Tilted disc syndrome is a nonhereditary bilateral condition in which the superotemporal optic disc is elevated and the inferonasal disc is displaced posteriorly, which results in an optic disc of oval appearance with its long axis obliquely orientated (Fig. 9.5.7).<sup>11</sup> This configuration is accompanied by situs inversus of the retinal vessels, congenital inferonasal conus, thinning of the inferonasal retinal pigment epithelium and choroid, and myopic astigmatism. These features presumably result from a generalized



**Fig. 9.5.8 Congenital Optic Disc Pigmentation.**

ectasia of the inferonasal fundus that involves the corresponding sector of the optic disc.

Familiarity with this condition is important, because affected patients may present with the suggestion of bitemporal hemianopias, which involve primarily the superotemporal quadrants. However, when observed carefully these field defects do not respect the vertical meridian (as do chiasmal lesions). Furthermore, large and small isopters are fairly normal, but medium-sized isopters are constricted selectively because of the ectasia of the midperipheral fundus. Repeated visual field tests after correcting for the myopic refractive error often eliminate the field defect, which confirms its refractive nature. In some cases, retinal sensitivity is decreased in the area of the ectasia, which causes the defect to persist despite refractive correction. Rare cases of the tilted disc syndrome have been documented in patients who have congenital suprasellar tumors; neuroimaging is therefore warranted when the associated bitemporal hemianopia respects the vertical meridian.<sup>11</sup>

## CONGENITAL OPTIC DISC PIGMENTATION

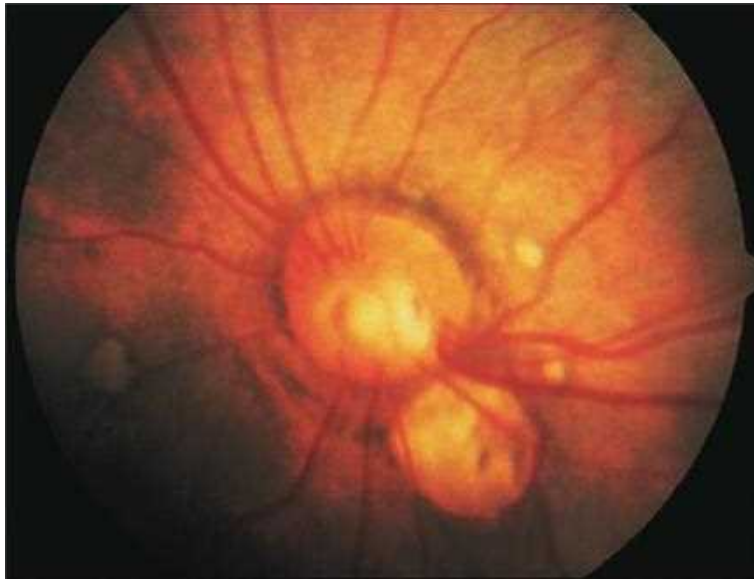
Congenital optic disc pigmentation is a condition in which melanin anterior to or within the lamina cribrosa imparts a gray appearance to the disc (Fig. 9.5.8). True congenital optic disc pigmentation is extremely rare. Congenital optic pigmentation is compatible with good visual acuity but may be associated with coexistent optic disc anomalies that decrease vision.<sup>12</sup>

Most cases of gray optic discs are not caused by congenital optic disc pigmentation.<sup>12</sup> For reasons that are understood poorly, optic discs of infants who have delayed visual maturation or albinism—and those of some normal neonates—have a diffuse gray tint when viewed ophthalmoscopically. In these disorders, the gray tint disappears within the first year of life without visible pigment migration.

## AICARDI SYNDROME

The major features of Aicardi syndrome are infantile spasms, agenesis of the corpus callosum, modified hypsarrhythmia on electroencephalography, and a characteristic optic disc appearance that consists of multiple depigmented chorioretinal lacunae clustered around the disc (Fig. 9.5.9).<sup>13</sup> Associated systemic anomalies include vertebral malformations (e.g., fused vertebrae, scoliosis, spina bifida) and costal malformations (e.g., absent ribs, fused or bifurcated ribs).<sup>13</sup> Severe mental retardation is almost invariable. The intriguing association between choroid plexus papilloma and Aicardi syndrome has been documented in numerous patients.<sup>1</sup> In addition to agenesis of the corpus callosum, neuroimaging abnormalities in Aicardi syndrome include cortical migration anomalies (pachygyria, polymicrogyria, cortical heterotopia) and central nervous system malformations (cerebral hemispheric asymmetry, Dandy-Walker syndrome, colpocephaly, midline arachnoid cysts).<sup>1</sup> The inheritance pattern of Aicardi syndrome is attributed to an X-linked mutational event that is lethal in males.<sup>1</sup>





**Fig. 9.5.9** Aicardi Syndrome.

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# Papilledema and Raised Intracranial Pressure

Alfredo A. Sadun, Michelle Y. Wang

## 9.6

**Definition:** Optic disc edema, usually bilateral, which results from increased intracranial pressure.

### Key Features

- Blurring of the optic disc margins.
- Anterior extension of the nerve head.
- Venous congestion of arcuate and peripapillary vessels.
- Hyperemia of the optic nerve head.

### Associated Features

- Gross elevation of the optic nerve head.
- Engorged and dusky veins.
- Peripapillary splinter hemorrhages.
- Occasionally choroidal folds and retinal striae.

## INTRODUCTION

About 1.2 million axons converge at the optic disc to form the optic nerve. The optic nerve follows a 50-mm course as it extends from the back of the eye, travels through the orbit, passes through the optic canal, runs intracranially, and partially decussates to form the optic chiasm. Each axon must maintain active axonal transport in both the orthograde (eye to brain) and retrograde directions. The subarachnoid space of the brain is continuous with the optic nerve sheath. A wide variety of insults may lead to dysfunction or compression of the optic nerve, potentially resulting in a partial arrest of axoplasmic transport, manifested as optic disc edema. If the compression is caused by raised intracranial pressure, the condition is termed papilledema, thus carrying neurological and neurosurgical connotations. If the cause of the disc edema is not increased intracranial pressure, the term optic disc edema should be used. Long-standing or severe papilledema, in addition to reflecting intracranial pathology, also may result in bilateral optic nerve dysfunction.

## EPIDEMIOLOGY AND PATHOGENESIS

Patients may suffer from many of the features of intracranial tumors in the absence of any mass lesion. Tumors of the posterior fossa may cause obstruction of cerebrospinal fluid (CSF) flow between the ventricles, but most cases of increased intracranial pressure in adults arise from large hemispheric masses that produce a mass effect.

Pseudotumor cerebri (PTC), also termed idiopathic intracranial hypertension (IIH), requires that neuroimaging prove negative for mass lesions and obstruction of the ventricular system and that a lumbar puncture reveals a high opening pressure with normal fluid composition.

Among young adults, papilledema is more likely to be caused by IIH than real tumor. IIH may initially present only with headache, which tends to be worst when recumbent. There is usually an absence of any neurological signs other than visual loss. Most patients are obese young women of childbearing age, leading to a suggestion that female sex hormones and endocrine abnormalities play an important role in this disorder. IIH may be seen in association with certain drugs such as tetracycline, oral contraceptive pills, growth hormone, vitamin A, or corticosteroids (or more commonly, corticosteroid withdrawal).

One well-understood association is intracranial venous thrombosis, which may be due to trauma, otitis media with mastoiditis, connective tissue disease, or hypercoagulable states. Chronic respiratory insufficiency, renal syndrome, iron deficiency anemia, and obstructive sleep apnea also have been associated with IIH.<sup>1</sup> When there is an identifying etiology, the condition is considered as secondary intracranial hypertension. Like glaucoma, increased intracranial pressure can be consequent to an increased production of fluid or to a decrease in outflow facility. Many investigators feel that most causes of IIH involve increased resistance to CSF drainage. Obstruction of the ventricular system or shunt failure may lead to a very rapid rise in intracranial pressure and fulminant papilledema.<sup>2</sup>

The principal pathophysiology of optic disc swelling is blockage of axoplasmic transport. Mechanical and vascular causes can combine to produce a blockage of optic nerve axoplasmic flow. Such blockage at the level of the lamina choroidalis and lamina scleralis occurs when optic disc edema is produced experimentally through increased intracranial pressure, ocular hypotony, or increased intraocular pressure. Optic disc edema also may be produced by an event that increases venous pressure at or near the lamina cribrosa,<sup>3,4,5</sup> such as occurs secondary to intrinsic tumors or extrinsic orbital masses or by abnormalities in blood flow such as central retinal vein occlusion (CRVO).

## OCULAR MANIFESTATIONS

It is useful to characterize the changes in the optic nerve head that occur in papilledema as being mechanical or vascular in nature.

The five mechanical clinical signs of optic disc edema are:

- Blurring of the optic disc margins.
- Filling in of the optic disc cup.
- Anterior extension of the nerve head (3 diopters = 1 mm of elevation).
- Edema of the nerve fiber layer.
- Retinal or choroidal folds or both.

The five vascular clinical signs of optic disc edema are:

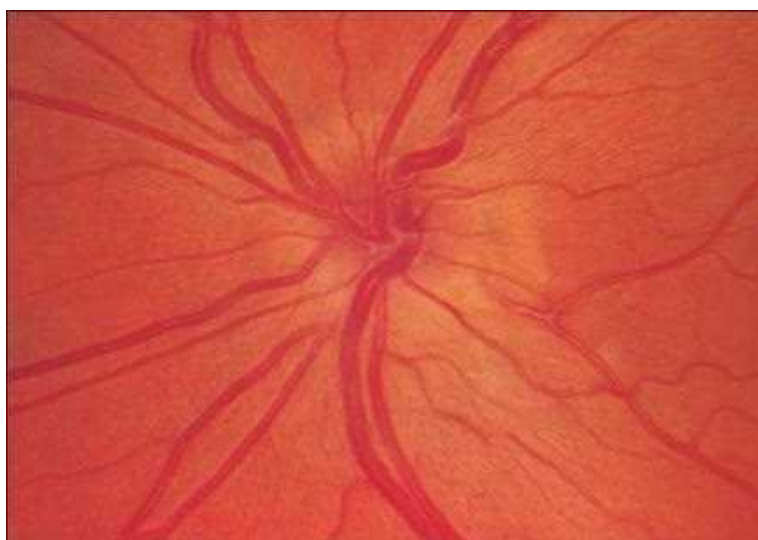
- Venous congestion of arcuate and peripapillary vessels.
- Papillary and retinal peripapillary hemorrhages.
- Nerve fiber layer infarcts (cotton-wool spots).
- Hyperemia of the optic nerve head.
- Hard exudates of the optic disc.

In addition, elements of optic disc swelling can be used to help characterize the papilledema as early, fully developed, chronic, or late. Disc hyperemia, disc swelling, blurring of the disc margins, and blurring of the nerve fiber layer are found in early papilledema (Fig. 9.6.1). In fully developed papilledema, gross elevation of the optic nerve head and engorged and dusky veins appear, peripapillary splinter hemorrhages and sometimes choroidal folds arise, and retina striae are seen (Fig. 9.6.2). In chronic papilledema, fewer hemorrhages occur, the optic disc cup is obliterated completely, less disc hyperemia is seen, and hard exudates occur within the nerve head (Fig. 9.6.3). In late disc edema, secondary optic atrophy occurs, disc swelling subsides, retinal arterioles are narrowed or sheathed, and the optic disc appears dirty gray and blurred, secondary to gliosis (Fig. 9.6.4).

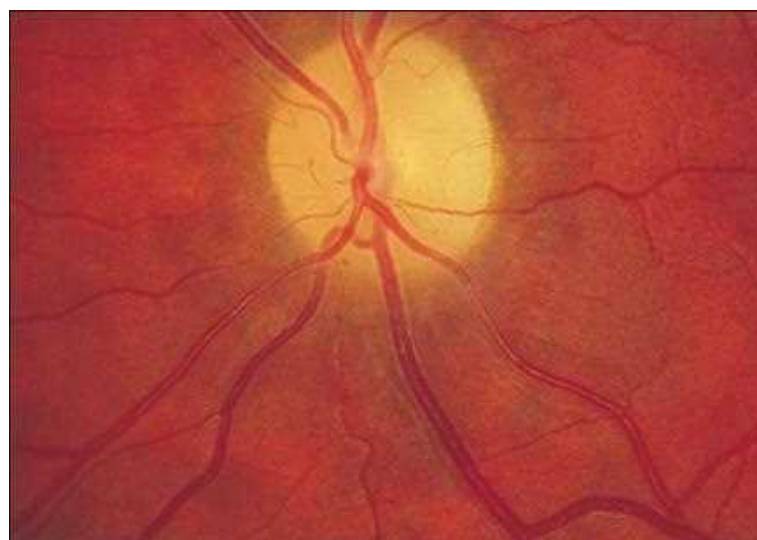
The Modified Frisén Scale was designed to help further quantitate papilledema<sup>6</sup>:

Grade 1 papilledema is characterized by a C-shaped halo with a temporal gap.

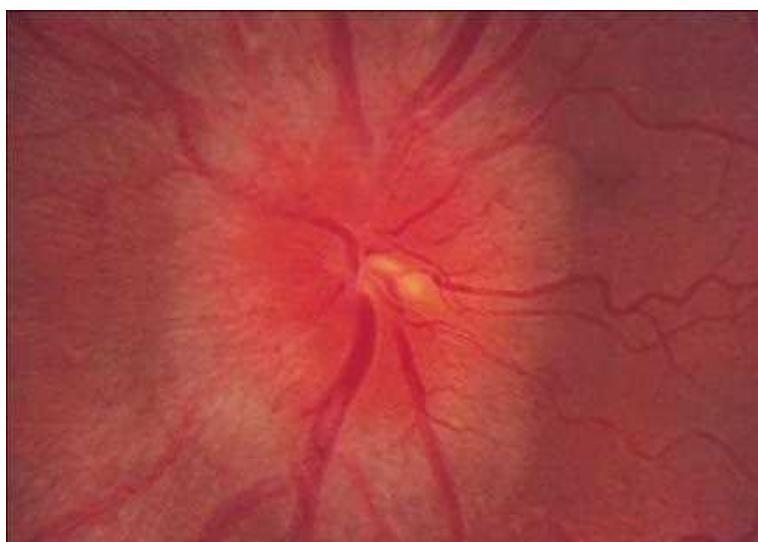




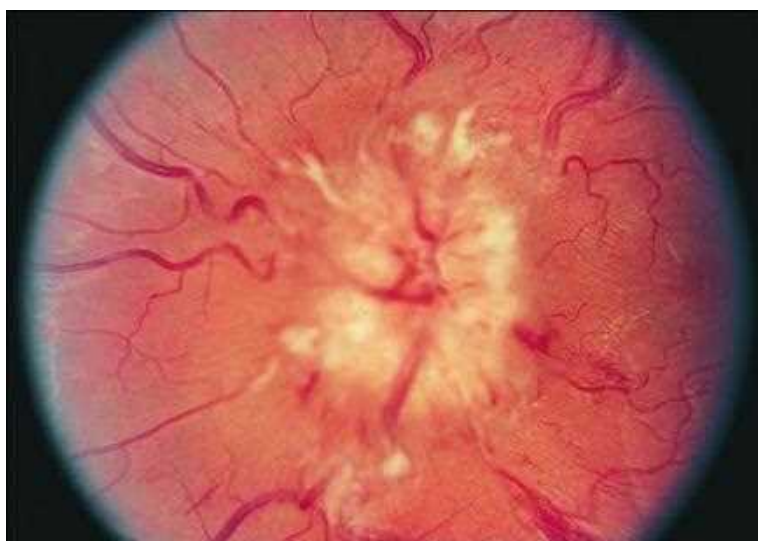
**Fig. 9.6.1 Early Papilledema.** The optic disc of an 18-year-old man 2 weeks after he had complained of diplopia arising from sixth cranial nerve palsies caused by increased intracranial pressure. Note the evidence of only mild edema.



**Fig. 9.6.4 Secondary Optic Atrophy From Chronic Papilledema.** The same 27-year-old obese female patient 5 months later. Note the secondary optic atrophy has developed fully. The disc margins appear hazy or "dirty."



**Fig. 9.6.2 Developed Papilledema.** The optic disc of a 36-year-old woman who suffered headache and blurred vision for 2 months. Fully developed disc edema present—note the engorged veins and peripapillary hemorrhages.



**Fig. 9.6.3 Chronic Papilledema.** Severe and chronic disc edema in a 27-year-old, very obese woman who has pseudotumor cerebri. Note that the disc cup is obliterated and hard exudates are present.

Grade 2 papilledema is characterized by circumferential halo.

Grade 3 papilledema is characterized by obscuration of one or more major blood vessels leaving the disc.

Grade 4 papilledema is characterized by obscuration of major vessels on the disc.

Grade 5 papilledema is characterized by obscuration of all vessels on and leaving the disc.

The most common symptoms as reported by the Idiopathic Intracranial Hypertension Study Group are headache, followed by, in decreasing frequency, transient visual obscuration, back pain, pulsatile tinnitus, and visual loss.<sup>7</sup>

The headache of increased intracranial pressure usually is quite distinctive. When elevated intracranial pressure is marked, the headache is particularly severe or associated with nausea and vomiting or a sense of pressure around the ears. Further symptoms of more advanced elevated intracranial pressure include worsening of the headache in a recumbent position and in the early morning, with improvement during the day. More specific complaints are the transient obscurations of vision, usually described as monocular or binocular blackouts, which last 3 to 4 seconds and most often occur as the patient arises from the recumbent position to sitting or standing.<sup>8</sup> Papilledema may produce visual blurring because of enlargement of the blind spot or retinal edema; this blurring usually is reversible. However, further injury to the optic nerve may be associated with secondary optic atrophy and be permanent, which results in symptoms such as constricted visual fields and later poor color vision and poor visual acuity. Diplopia usually arises from nonlocalizing sixth cranial nerve palsies, and it often resolves after the increased intracranial pressure has been controlled. The headache of raised intracranial pressure should be carefully distinguished from secondary headaches in IIH. Friedman and Rausch reported that the majority of IIH patients may suffer from chronic tension-type, migraine, or cluster headaches long after intracranial pressure has normalized.<sup>9</sup>

## DIAGNOSIS AND TESTING

Suspicion for papilledema is provided by the history. Careful fundus examination is mandatory. The optic nerve head is assessed for each of the 10 signs of disc edema described earlier and the papilledema characterized also as early, developed, late, or chronic. To determine whether the disc edema is, in fact, papilledema, neuroimaging is followed by a lumbar puncture with manometry. Automated visual fields such as Humphrey (HVF) are most important in assessing visual status. This is key to quantifying changes and monitoring response to treatment. HVF is as critical in the management of IIH as for the management of glaucoma.

In IIH, the most common visual field loss is arcuate defect with an enlarged blind spot. Optical coherence tomography (OCT) may be a helpful tool to quantitate the extent of papilledema, especially for lower grades (see Chapter 9.2). The diagnostic criteria were first introduced by

Dandy in 1937, which were later modified in 1985<sup>10</sup>: IIH patients must exhibit signs and symptoms of elevated intracranial pressure (confirmed by opening pressure measurement) without localizing neurological signs, abnormal CSF composition, or structural abnormalities on neuroimaging.

## DIFFERENTIAL DIAGNOSIS

The differential diagnosis of papilledema is disc edema without increased intracranial pressure and pseudopapilledema. The latter rubric includes all abnormalities of the optic disc that can mimic optic disc edema. The most common of such disc anomalies are optic disc drusen, which, especially when deeply buried, may give the disc a lumpy, elevated appearance. Other causes of optic disc edema without increased intracranial pressure need to be considered—compressive optic neuropathies, papillitis, anterior ischemic optic neuropathy, CRVO, juvenile diabetic papillopathy, and optic disc vasculitis.

### Compressive Optic Neuropathies

Compressive optic neuropathies that may produce disc edema often are due to lesions located in the anterior orbit. Neoplasms of the optic nerve itself (gliomas) or of its sheaths (meningiomas) or masses from the orbital tissues or paranasal sinuses may impinge on the anterior optic nerve and result in disc edema. Inflammatory and infiltrative lesions also may manifest as masses. Distal malignancies may involve the optic nerve and its sheaths by metastasis.

### Papillitis

Papillitis often has a component of disc edema and may follow a prodromal viral illness. The inflammation may extend beyond the confines of the optic disc as a neuroretinitis. Cells are found in the vitreous humor; retinal exudates may form a macular star or a half-star figure. Both papillitis and neuroretinitis are seen often in young, healthy adults.

### Anterior Ischemic Optic Neuropathy

Anterior ischemic optic neuropathy usually presents as disc edema with peripapillary hemorrhages. An acute loss of vision is noted, and the visual field deficit may take on an altitudinal shape. Anterior ischemic optic neuropathy is found most often in patients age 50 to 75 years who have hypertension, diabetes, hyperlipidemia, or obstructive sleep apnea.<sup>11</sup>

### Central Retinal Vein Occlusion

CRVO may result in congestion in the optic nerve heads. However, the retinal hemorrhages and venous tortuosity in all four quadrants found in CRVO usually make the differentiation easy. Generally, CRVO occurs in middle-aged or older individuals who have hypertension or, less often, hyperviscosity syndrome. CRVO is typically unilateral.

### Diabetic Papillopathy

Diabetic papillopathy may present with unilateral or bilateral disc edema. Visual loss is usually minimal. The fundus examination often reveals dilated telangiectatic vessels over the discs, which disappear when the disc edema resolves spontaneously 4 to 8 weeks later.

### Optic Disc Vasculitis

Optic disc vasculitis (papillophlebitis), or posterior segment uveitis, also may result in optic disc edema. Papillophlebitis, optic disc vasculitis, benign retinal vasculitis, and “the big blind spot syndrome” may be considered variations on this theme. These conditions often develop in young, healthy adults who have only minimal visual impairment. The optic disc edema usually occurs in association with engorged retinal veins. If a cilioretinal artery is present, it may be obstructed. This condition is rarely bilateral.

### Other Causes

Other causes of disc edema include advanced Graves’ disease, malignant hypertension, and hypotony. Malignant processes such as carcinoma,

lymphoma, or leukemia as well as uremia<sup>12</sup> and sarcoid granuloma also may cause swelling of the optic disc. Nutritional optic neuropathies such as in tropical epidemics and toxic optic neuropathies often caused by drugs such as ethambutol may rarely result in mild disc edema.<sup>13</sup> Orbital or cranial trauma, radiation, and burns also may cause swelling of the optic discs.

## SYSTEMIC ASSOCIATIONS

In addition to papilledema and the potential for visual loss, increased intracranial pressure can cause other signs and symptoms. However, the most serious and irreversible problems associated with increased intracranial pressure per se are visual, hence the ophthalmologist is a critical member of the clinical team for such patients. Palsies of the sixth cranial nerve, hearing loss, and facial nerve palsies also are found, in decreasing order of frequency, in patients who have increased intracranial pressure. However, these cranial nerve palsies are likely to be self-limiting after reduction of the pressure.

## PATHOLOGY

The histopathology of acute optic disc edema reveals axoplasmic stasis, edema, and vascular congestion (Fig. 9.6.5). Peripapillary hemorrhages are seen primarily in the retinal nerve fiber layer, but they may overlie the optic disc. The increase in tissue mass fills the physiological cup and causes the optic nerve head to protrude anteriorly. The small blood vessels are engorged and tortuous. Vacuoles of extracellular fluid accumulate in and anterior to the retinal lamina cribrosa, and the subarachnoid space is enlarged with stretching of the subarachnoid strands.

The neural retina is displaced away from the optic disc, and the outer layer of the retina may be buckled (retinal folds). The rods and cones are displaced away obliquely from their anchor near Bruch’s membrane. A shallow retinal detachment in the peripapillary area probably accounts for most of the enlarged blind spot.

Engorgement of axons in the laminar portion of the optic nerve is demonstrated by electron microscopy. The swollen axons are filled with mitochondria primarily anterior to the choroidal lamina cribrosa. The mitochondria and the fascicles of microtubules are in disarray. Importantly, the extracellular accumulation is minimal compared with the intracellular and intra-axonal accumulation.<sup>14</sup>

## TREATMENT

The treatment of papilledema associated with visual loss depends in large part on the cause, symptoms, signs, and progression of the problem. Attempts must be made to address the pathophysiology, but a few comments on the general concepts are provided. Treating the cause of high intracranial pressure and lowering the pressure should occur in parallel.

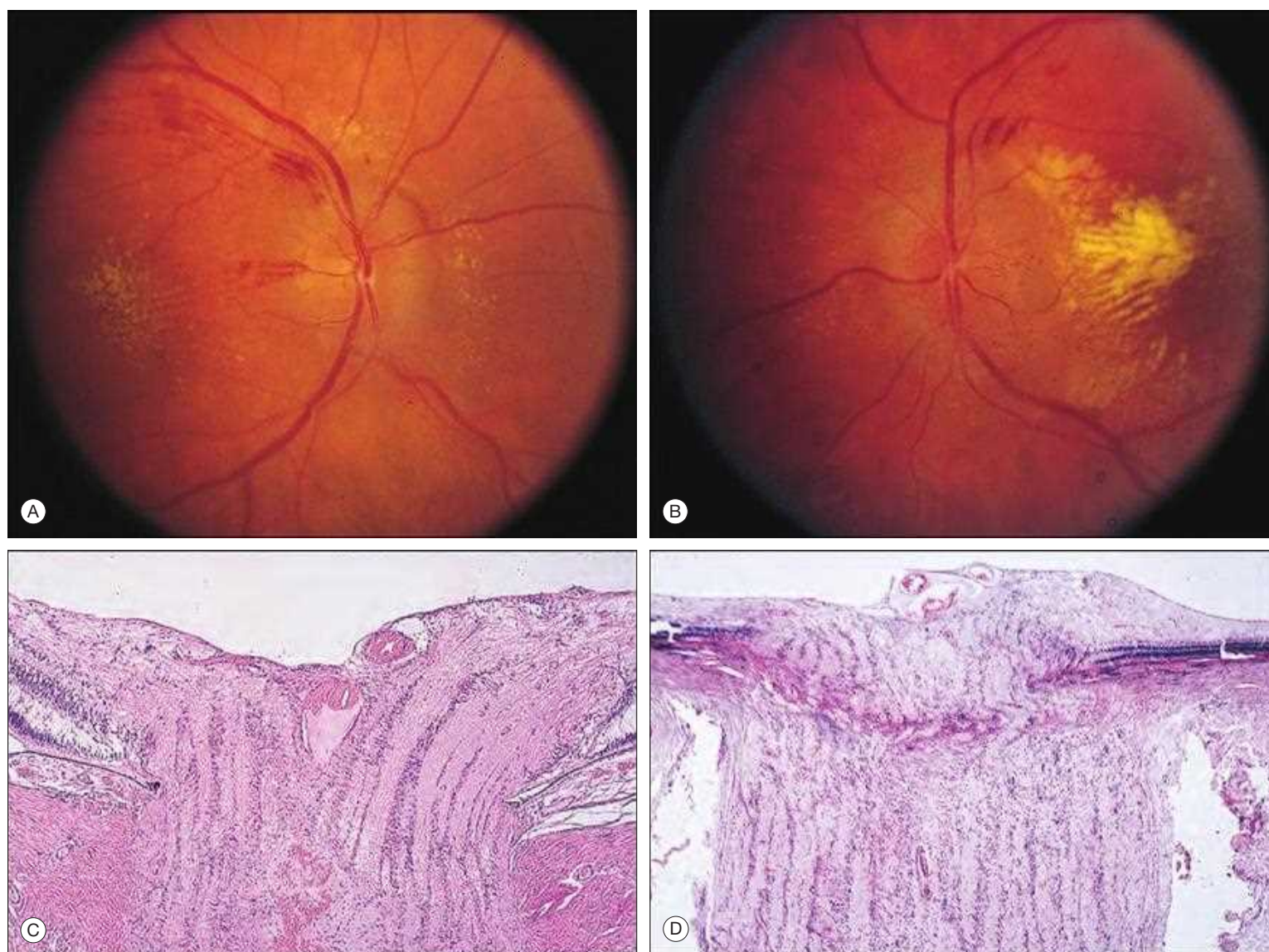
Medical treatment usually consists of diuretics, especially carbonic anhydrase inhibitors such as acetazolamide and, in cases of IIH, weight reduction.<sup>15</sup> Serial lumbar punctures can at least buy time. If medical treatment is not sufficient, surgical approaches such as optic nerve sheath decompression<sup>16,17</sup> or a ventriculo- or lumboperitoneal shunt<sup>18</sup> may need to be carried out. It is very important to understand that the decision to treat or to alter treatment modality usually is based on the ophthalmologist’s descriptions of the extent of both signs and symptoms and most especially visual loss as measured by visual fields. Hence the ophthalmologist is a crucial member of the clinical team that makes management decisions.

## COURSE AND OUTCOME

The prognosis for papilledema is largely dependent on the cause. Most patients who have metastatic brain tumors do very badly; those who have ventricular obstructive disease may be shunted successfully; patients who have IIH usually can be managed well.

Two general points warrant emphasis. The diagnosis of papilledema requires a prompt workup until the most serious pathologies are ruled out. Here, neurological, neurosurgical, or neuroradiological consultations may be required. However, once the problem has been reduced to that of papilledema, the ophthalmologist can best determine how aggressive the course of management needs to be. All too often, permanent visual loss occurs in diseases such as IIH for lack of appropriate and timely ophthalmological involvement.





**Fig. 9.6.5 Optic Disc Edema.** (A–B) Patient has bilateral optic disc edema secondary to grade IV malignant hypertension. Note exudates in nasal macula (B). (C) Histological section shows optic disc edema secondary to ocular hypertension caused by phacolytic glaucoma. (D) Optic disc edema secondary to ocular hypotony caused by a ruptured globe. Optic disc edema can be caused by increased intracranial pressure or increased or decreased intraocular pressure. The main finding in C and D consists of increased mass of anterior optic nerve caused by axonal swelling, optic nerve head tissue edema and vascular congestion, and lateral displacement of photoreceptors from the end of Bruch's membrane, which terminates in a ring at the optic nerve.

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# Inflammatory Optic Neuropathies and Neuroretinitis

## 9.7

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**Definition:** Inflammation of the optic nerve may spare the optic disc (retrobulbar optic neuritis) or may cause optic disc swelling (papillitis). The term optic neuritis is typically reserved for optic nerve inflammation that may be associated with demyelinating disease. Inflammation of the optic disc with adjacent retinal exudation is referred to as neuroretinitis.

## Key Features

- Abrupt and progressive vision loss.
- Dyschromatopsia.
- Afferent pupillary defect in unilateral cases.

## Associated Feature

- Pain, particularly on eye movement.

## INTRODUCTION

Primary inflammation of the optic nerve is referred to as papillitis when the optic disc is swollen and retrobulbar neuritis when the disc appears normal. The most common form of optic nerve inflammation is acute demyelinating optic neuritis. Much of our current knowledge about acute demyelinating optic neuritis derives from the Optic Neuritis Treatment Trial (ONTT). The ONTT was a multicenter trial supported by the National Eye Institute, which assessed the benefit of corticosteroid treatment for optic neuritis and investigated the relationship between optic neuritis and multiple sclerosis (MS).<sup>1-16</sup> Although numerous systemic inflammatory and autoimmune conditions are associated with acute or chronic optic nerve inflammation, this chapter focuses on acute demyelinating optic neuritis.

## EPIDEMIOLOGY AND PATHOGENESIS

The annual incidence of optic neuritis, as estimated in population-based studies, is between 3 and 5 per 100 000 per year,<sup>17</sup> whereas the prevalence is 115 per 100 000.<sup>18</sup> The majority of patients who develop optic neuritis are between the ages of 20 and 50 years. Women are affected more commonly than men. In the ONTT, 77% of the patients were women, 85% were white, and the mean age was  $32 \pm 7$  years. In most cases, the pathogenesis of optic neuritis is inflammatory demyelination, regardless of whether MS is diagnosed clinically.<sup>19-20</sup> It is likely that many cases of monosymptomatic optic neuritis occur as the initial manifestation of MS.<sup>21</sup> A minority of cases are the initial manifestation of neuromyelitis optica, a demyelinating disease now recognized as distinct from MS, particularly with regard to natural history and treatment.

## OCULAR MANIFESTATIONS

Loss of vision in patients with acute demyelinating optic neuritis is usually abrupt and progressive, occurring over several hours to days. Progression for more than one week or failure of recovery to begin within four weeks is possible but should suggest a search for an alternative underlying cause.<sup>22-27</sup> Vision loss is usually monocular, although occasionally both eyes are affected simultaneously, particularly in children and in association with neuromyelitis optica.

Mild pain in or around the eye is present in more than 90% of patients. Such pain may precede or occur concomitantly with visual loss, is usually exacerbated by eye movement, and generally lasts no more than a few days. The presence of pain, particularly on eye movement, is a helpful (although not definitive) clinical feature that differentiates acute demyelinating optic neuritis from nonarteritic anterior ischemic optic neuropathy (NAION).<sup>28</sup>

On examination, optic nerve dysfunction is evident. The severity of visual loss varies from a mild visual field defect to severe loss of central acuity (3% of ONTT participants had no light perception, and in 90% there was at least some loss of central acuity).<sup>3</sup> Severe loss of visual acuity is more common in children.<sup>29</sup> Color vision and contrast sensitivity are impaired in almost all cases, often out of proportion to visual acuity. Visual field loss, which may be diffuse (48%) or focal (i.e., nerve fiber bundle defects, central or cecocentral scotomas, hemianopic defects), is also common in acute optic neuritis.<sup>4</sup> Altitudinal defects (focal visual field loss above or below the horizontal meridian) are less common and should prompt consideration of a diagnosis of AION.<sup>29</sup> Low-contrast letter acuity has recently emerged as a very sensitive test for optic neuropathy.<sup>30</sup> A relative afferent pupillary defect (rAPD) is detected in almost all unilateral cases of optic neuritis. If an rAPD is not present, a pre-existing or coexisting optic neuropathy in the fellow eye must be suspected. In fact, asymptomatic visual dysfunction is fairly common among fellow eyes of patients who have apparent unilateral optic neuritis.<sup>7</sup>

The optic disc appears normal in approximately two-thirds of adults with acute demyelinating optic neuritis (retrobulbar optic neuritis), whereas disc swelling is present in about one-third of adult cases (papillitis) (Fig. 9.7.1). Children with optic neuritis experience optic disc swelling more frequently than do adults.<sup>29</sup> Funduscopic features of optic disc swelling include elevation of the optic nerve head, disc hyperemia, blurring of the disc margins, and edema of the nerve fiber layer.<sup>31</sup> Optic disc hemorrhages were uncommon in the ONTT (6%), and their presence should suggest an alternative diagnosis.

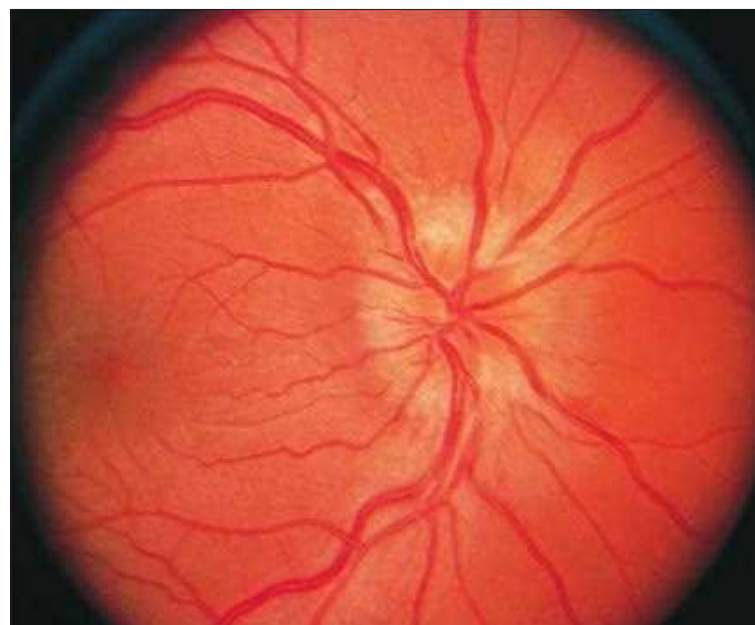


Fig. 9.7.1 Optic Disc Swelling (Papillitis) Associated With Acute Optic Neuritis.

**BOX 9.7.1 Differential Diagnosis of Acute Unilateral Optic Neuropathy****Anterior Ischemic Optic Neuropathy**

Tumor  
 Aneurysm  
 Vasculitis  
 Neuroretinitis  
 Metastatic carcinoma  
 Lymphoreticular disorder  
 Sinusitis  
 Granulomatous inflammation  
 Leber's hereditary optic neuropathy (although always bilateral, this frequently presents initially with visual loss in only one eye)

**DIAGNOSIS AND ANCILLARY TESTING**

The diagnosis of acute demyelinating optic neuritis is based on an appropriate history (typical versus atypical course) and clinical signs and symptoms as described above. Diagnostic tests, including magnetic resonance imaging (MRI), cerebrospinal fluid (CSF) analysis, and serological studies, usually are performed for the following reasons<sup>10–11,16</sup>:

- In atypical cases, to determine if the cause is noninflammatory (such as a compressive lesion), or an inflammatory or infectious process.
- In typical monosymptomatic cases, to determine the prognosis or risk for subsequent development of MS.

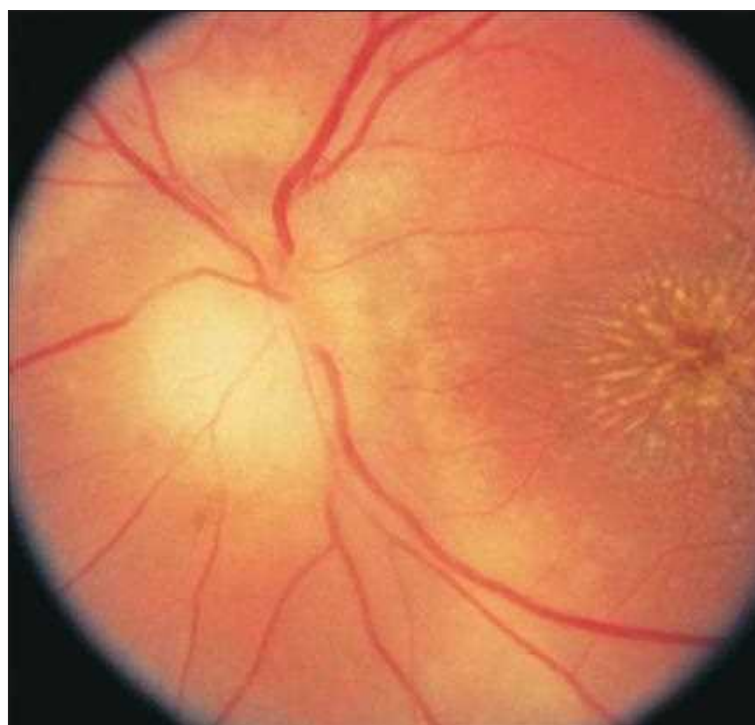
In patients with suspected optic neuritis, MRI of the brain and orbits with fat suppression and gadolinium should be performed, even in typical cases, to confirm the diagnosis and to assess for the presence of other white matter lesions, which may be diagnostic of MS or place the patient in a high-risk category for development of MS.<sup>10–11,16</sup> Optical coherence tomography (OCT) is not altered in the acute phase other than distortion caused by papillitis, although abnormalities developing months after symptom onset may be useful in predicting the subset of optic neuritis patients who will suffer persistent visual dysfunction. A 2006 study of 54 patients documented a poor visual outcome in patients with a retinal nerve fiber layer (RNFL) thickness of less than 75  $\mu\text{m}$  measured with OCT within 3 to 6 months of an initial optic neuritis event.<sup>32</sup>

**DIFFERENTIAL DIAGNOSIS**

The diagnosis of acute visual loss begins with the localization of the involved portion of the visual system. A unilateral optic neuropathy is presumed when no ocular cause for visual loss is apparent and an rAPD is present with or without abnormal appearance of the optic nerve head. The differential diagnosis for acute optic neuropathy is outlined in [Box 9.7.1](#). Because most cases of optic neuritis produce unilateral visual loss, discussion here is limited to unilateral optic neuropathies. When there is acute visual loss and unilateral optic disc swelling, both optic neuritis and AION must be considered. Although the clinical profiles of these disorders overlap, AION is typically painless, occurs in patients over 50 years of age, and may be associated with optic disc hemorrhages. When the optic disc is normal in patients with unilateral optic neuropathy, a compressive lesion must be excluded; this usually is differentiated from acute optic neuritis by a history of progressive visual loss beyond the typical period of 1 to 2 weeks.

Other inflammatory, infectious, and neoplastic disorders may produce infiltration or demyelination—or both—of the optic nerve. These conditions may appear as either acute or progressive visual loss, and include sarcoidosis, systemic lupus erythematosus (SLE), syphilis, postviral syndromes, lymphoma, and leukemia. The treatment of optic neuritis in the setting of such systemic disorders is dictated by guidelines for appropriate treatment of the underlying infectious, inflammatory, or autoimmune disorder itself.<sup>31</sup>

Neuroretinitis, characterized by optic disc edema with macular hard exudates (macular “star”), must be differentiated from acute demyelinating optic neuritis ([Fig. 9.7.2](#)). Macular edema is initially diffuse; hard exudates form within days, frequently in a star-shaped pattern. Deep, whitish lesions may be noted at the level of the retinal pigment epithelium scattered throughout the fundus. Most cases of neuroretinitis are idiopathic, but the diagnosis requires the exclusion of infectious causes such as *Bartonella*



**Fig. 9.7.2 Optic Disc Edema and Macular Star Formation.** Color fundus photograph from a 13-year-old girl who came to medical attention with counting fingers acuity secondary to cat scratch neuroretinitis.

*henselae* (cat scratch disease), *Toxoplasma gondii* (toxoplasmosis), *Treponema pallidum* (syphilis), *Toxocara canis* (toxocariasis), *Borrelia burgdorferi* (Lyme disease), leptospira spp. (leptospirosis), *Mycobacterium tuberculosis* (tuberculosis), *Histoplasma capsulatum* (histoplasmosis), *Rickettsia typhi* (murine typhus), and brucella spp. (brucellosis). Nonspecific viral syndromes and viral etiologies involving Epstein-Barr virus (EBV), herpes simplex virus (HSV), human immunodeficiency virus (HIV), mumps, or hepatitis B or C have also been implicated.<sup>33</sup>

**Viral and Postviral Syndromes**

Parainfectious optic nerve inflammation typically follows the onset of a viral infection by 1–3 weeks, but it also can occur as a postvaccination phenomenon. It is more common in children than adults and likely occurs by an immunological process that produces optic nerve demyelination. Postviral (or parainfectious) optic neuritis may be unilateral but is frequently bilateral. The optic discs may appear normal or swollen; retinal involvement (neuroretinitis) is common when there is optic disc swelling. Associated meningoencephalitis, with MRI changes and CSF pleocytosis, is not unusual. Visual recovery after parainfectious optic neuropathy usually is excellent, even with no treatment. Corticosteroids may or may not hasten recovery, but this treatment is reasonable to consider, particularly in cases of bilateral, severe visual loss.

**Sarcoidosis**

Granulomatous inflammation of the optic nerve is a frequent ocular manifestation of sarcoidosis and may be an initial sign of this disorder. Clinical findings may be similar to those of acute demyelinating optic neuritis. However, the optic disc may have a characteristic lumpy, white appearance, suggestive of granulomatous infiltration. Recovery of vision is rapid in most cases following corticosteroid treatment. In fact, rapid recovery of vision with corticosteroid treatment and subsequent deterioration following taper is atypical for acute demyelinating optic neuritis and should suggest an infiltrative process such as sarcoidosis. Neuroretinitis is an uncommon intraocular finding in sarcoidosis.<sup>34</sup>

**Syphilis**

Syphilitic optic neuritis has become more common since the increase in prevalence of human HIV infection (see later). Optic nerve involvement may be unilateral or bilateral. Vitreous cellular reaction is a feature of



syphilis not seen in acute demyelinating optic neuritis. The diagnosis is established with identification of positive syphilis serological and CSF VDRL (Venereal Disease Research Laboratories) test results. Treatment with aqueous crystalline penicillin G, 18 to 24 million units per day, administered as 3 to 4 million units intravenously every 4 hours (or continuous infusion) for 14 days produces visual recovery in most cases, but recurrences are possible.<sup>35</sup> Secondary syphilis can also manifest as neuroretinitis with variable severity of visual loss.

## Lyme Disease

Although optic neuritis has been reported in patients with positive Lyme serological test (enzyme-linked immunosorbent assay [ELISA] and Western blot) results or other neurological findings suggestive of Lyme disease, definitive evidence of a causal relationship with *B. burgdorferi* infection has not been established in most cases.<sup>36–37</sup> However, patients with neurological or ocular manifestations should, in most cases, receive a 2- to 4-week course of intravenous ceftriaxone or alternative agent, with resolution of related symptoms within weeks.<sup>37–38</sup> Syphilis infection may produce false-positive Lyme disease serological examination results and therefore must also be considered in patients with optic neuropathy or other neurological manifestations.

## Cat Scratch Disease

*Bartonella henselae* is implicated in numerous ophthalmic disease states, including neuroretinitis. Prevalence of neuroretinitis in cat scratch disease (CSD) is documented to be between 1% and 2%. But as was shown in a 2000 retrospective study of patients who develop neuroretinitis, nearly two-thirds show serological evidence of past or present CSD infection (9 out of 14 tested patients, or 64%), suggesting that CSD may be the most common cause of neuroretinitis.<sup>39</sup> Patients with CSD ophthalmopathy show classic ophthalmoscopic signs of neuroretinitis, including diffuse disc edema, nerve fiber layer hemorrhages, cotton-wool spots, multiple discrete lesions in the deep retina, and stellate macular exudates (Fig. 9.7.2). Such patients have diminished visual acuities ranging from 20/25 to counting fingers. APDs, dyschromatopsia, and visual field abnormalities are common. CSD neuroretinitis may be unilateral or bilateral as well as asymptomatic and generally has a benign course with an excellent prognosis for visual recovery to 20/40 or better. A small subset of patients may experience a prolonged febrile illness and remain more severely impaired, with failure to regain baseline visual acuity.

Early therapy with oral doxycycline (for patients older than 8 years) or erythromycin (for younger patients) and rifampin for 4–6 weeks promotes resolution of CSD neuroretinitis and truncates the systemic infection, typically resulting in regression of posterior pole findings and the return of 20/20 visual acuity after 1–4 weeks of therapy. Long-term use of doxycycline or a macrolide may also be useful for preventing recurrences in HIV-positive patients.<sup>40–41</sup>

## Toxoplasmosis

Optic neuropathies are common in patients with *Toxoplasma gondii* infection, the most important protozoan cause of intraocular inflammation in the world, and include retinochoroiditis, papillitis, and neuroretinitis.<sup>42–43</sup> Ocular lesions primarily affect the retina, and the hallmark of the disease is focal necrotizing retinitis, ultimately resulting in characteristic atrophic scars. Active retinal lesions are oval or circular, with a cream-colored retina and surrounding retinal thickening due to necrosis and edema. Common symptoms include black floating spots, blurred vision, ocular pain, and redness, and if the visual axis or macula is involved, severely reduced vision. The disease is bilateral in 40% of cases, almost exclusively in the immunocompromised. It is usually a self-limiting disease in non-AIDS patients, and without treatment, inflammation gradually subsides and the lesions heal in 6–8 weeks.

## Optic Neuropathy in HIV Disease

In immunocompromised patients, particularly those with HIV infection, many infectious diseases may cause optic neuropathy, including tuberculosis, toxoplasmosis, toxocariasis, cytomegalovirus, herpes zoster, Cryptococcus, and other fungi. Primary central nervous system lymphoma infiltrating the optic nerves and chiasm has been reported recently in patients with HIV.<sup>44a</sup> Optic neuropathy may also be from HIV directly or from antivirals used to treat HIV.<sup>44b,c</sup>

## Systemic Lupus Erythematosus and Other Vasculitides

Optic neuropathy may occur in patients with SLE, polyarteritis nodosa, and other systemic vasculitides. Involvement of the optic nerve occurs in about 1% of patients who have SLE. Rarely, the disease manifests with optic neuropathy. The pathogenesis is related to ischemia, which may produce demyelination alone or in combination with axonal necrosis. Clinical manifestations may include those similar to acute optic neuritis (both papillitis and retrobulbar neuritis), acute ischemic optic neuropathy, or chronic progressive visual loss. The diagnosis of SLE as a cause of optic neuropathy is established by identification of systemic symptoms and signs of the disease and by serological testing. Treatment with high-dose corticosteroids is indicated and has been demonstrated to reverse severe visual loss.<sup>45</sup>

The term autoimmune optic neuritis has been suggested for cases of corticosteroid-responsive optic neuropathy with serological evidence of vasculitis (such as antinuclear antibodies, ANA) but no signs of systemic involvement.<sup>46</sup> However, the existence of “autoimmune optic neuritis,” distinct from either SLE or MS, is unproved. Patients with acute demyelinating optic neuritis or MS also may have positive ANA serological test results. Among ONTT participants, the ANA finding was positive at a titer less than 1:320 in 13% and greater than 1:320 in 3%. Only one patient developed a diagnosable connective tissue disease during the first 2 years of follow-up. Visual outcomes for these patients were similar between the placebo and intravenous methylprednisolone groups.

## Neuromyelitis Optica

Neuromyelitis optica (NMO), also known as Devic’s disease, is the association of unilateral or bilateral optic neuritis with longitudinally extensive transverse myelitis lesions and other typical clinical syndromes. It is currently thought of as a distinct entity from MS.<sup>47</sup> Recent work has identified aquaporin-4 antibody (AQP4-IgG) as a serological test that helps to differentiate cases of NMO from typical MS and may help identify monosymptomatic patients who are at risk of developing NMO.<sup>48</sup> Aquaporin-4 is a protein centered around astrocytic foot processes in the blood–brain barrier.<sup>48</sup> The pathology consists of vasculocentric inflammation with deposition of complement that results in necrotic lesions within the optic nerve and spinal cord. Revised NMO spectrum disorder diagnostic criteria were published in 2015 and include criteria for patients with and without detectable levels of AQP4-IgG.<sup>49</sup> Monosymptomatic patients with AQP4-IgG in their serum can be diagnosed with NMO spectrum disorder based on these criteria. The prognosis for functional recovery is worse than multiple sclerosis given the destructive nature of the lesions. It may be monophasic or recurrent. Recurrent disease has a much worse prognosis and higher mortality rate.<sup>50</sup> The treatment mainstay is high-dose corticosteroids and plasmapheresis for acute relapses including optic neuritis. Various immunosuppressive treatments have been used in NMO, including azathioprine (2–3 mg/kg daily), oral prednisone, and mycophenolate mofetil (1 gram twice daily).<sup>47</sup> More recently, rituximab, a monoclonal antibody drug that targets CD20+ cells, has been shown to be effective in NMO.<sup>51</sup>

## Association With Multiple Sclerosis

Although inflammation of the optic nerve occurs in numerous systemic disorders as outlined earlier, acute demyelinating optic neuritis occurs most often in MS (among 50% of patients with MS) and frequently represents the first well-documented manifestation of MS (in 20% of patients with MS).<sup>9–10,21,47</sup> Follow-up of the ONTT cohort to 15 years has continued to demonstrate that brain MRI is the most powerful predictor of subsequent MS risk in monosymptomatic patients.<sup>9–10,16</sup> The presence of one or more white matter lesions was associated with a 72% risk of MS after 15 years, whereas the risk was only 25% if the MRI results were normal (excluding optic nerve enhancement).<sup>9,16,52</sup> Overall, after 15 years of follow-up, the cumulative risk of developing MS after optic neuritis was 50%.<sup>53</sup> The risk with multiple lesions was not significantly higher than it was with a single lesion (58% versus 51%;  $P = 0.22$ , log rank test).<sup>16</sup> Monosymptomatic patients with one or more brain white matter lesions seen with MRI are, therefore, considered to be at high risk of the development of MS following acute demyelinating optic neuritis.

MS diagnostic criteria published in 2010 allow for diagnosis of MS in monosymptomatic patients with both enhancing and nonenhancing lesions on brain MRI.<sup>53</sup> Among patients with normal brain MRI findings

(no white matter lesions) in the ONTT, presence of optic disc swelling, mild visual acuity loss, and male gender were features associated with a reduced risk of MS.<sup>10,16</sup> Painless visual loss, total visual loss (no light perception), and ophthalmoscopic findings of severe disc swelling, hemorrhage of the optic disc or surrounding retina, or retinal exudates were features associated with a 0% risk of MS in these patients.<sup>16</sup> In patients with a normal baseline brain, certain features (severe optic disc swelling, hemorrhages, and exudates) suggest a low risk of developing MS.<sup>16</sup>

As in adults, optic neuritis is predictive of the subsequent risk of MS in children; one longitudinal study found that MS developed in 13% of children within 10 years of the first episode of optic neuritis, and in 19% within 20 years of the first episode.<sup>48</sup> A recent meta-analysis by Waldman and coworkers demonstrated that older age and the presence of brain lesions are the key factors in determining risk of MS. For every 1 year increase in age, the odds of developing MS after a unilateral episode of optic neuritis increase by 25% in children. In this analysis, 29% of children developed MS over the follow-up period of these studies (range of 0.1–31 years).<sup>54</sup> The risk of MS was greater in children with an abnormal MRI at presentation with an odds ratio of 28.<sup>54</sup>

## **PATHOLOGY**

Although the exact underlying cause is unknown, the pathophysiology of acute optic neuritis and MS is that of primary inflammatory demyelination.<sup>19–20</sup> Very little is written about the pathology of “isolated” optic neuritis, and no autopsy data have been reported. The inflammatory response in MS plaques is marked by perivascular cuffing, T cells, and plasma cells. Although MS itself previously was thought to be exclusively a disease of myelin with sparing of nerve axons, neuronal and axonal loss have been demonstrated to occur pathologically.<sup>19</sup>

## **TREATMENT**

One goal of acute therapy for optic neuritis is to improve visual outcome. These are the two major findings of the ONTT with regard to this treatment goal:

- Intravenous methylprednisolone treatment hastens recovery of visual function but does not affect long-term visual outcome; this benefit was greatest in the first 15 days.
- Patients treated with oral prednisone alone (without intravenous methylprednisolone) demonstrated an increased risk of recurrent optic neuritis (30% after 2 years versus 16% for the placebo group and 13% for those receiving intravenous corticosteroids) throughout the follow-up period of 10+ years (44% after 10 years versus 31% for the placebo group and 29% for those receiving intravenous corticosteroids).<sup>8,10,15</sup>

In the acute phase, it is important to recognize patients with possible NMO spectrum disorder based on AQP4-IgG status or history.<sup>49</sup> This is because studies suggest that such patients have a long-term outcome benefit associated with acute therapy with high-dose corticosteroids and therapeutic plasma exchange.<sup>51</sup>

Another goal of optic neuritis treatment is to delay development of clinically definite demyelinating disease. The ONTT demonstrated that monosymptomatic patients in the intravenous methylprednisolone group had a reduced rate of development of MS during the first 2 years of follow-up, but this benefit did not persist beyond 2 years and was seen only in patients with brain MRI scans that indicated a high risk for subsequent MS (originally described as MRI scans with two or more white matter lesions, 10-year follow-up data has confirmed one or more white matter lesions as an equivalent risk).<sup>9–10,16</sup>

Multiple MS therapies have been studied with regard to their ability to reduce cumulative probability of development of clinically definite MS in monosymptomatic patients with brain lesions on initial MRI. The Controlled High-Risk Avonex MS Prevention Study (CHAMPS) demonstrated that treatment with interferon  $\beta$ -1a (Avonex) following acute monosymptomatic demyelinating optic neuritis or other first demyelinating event (including brainstem syndrome or incomplete transverse myelopathy) significantly reduces the 3-year cumulative probability of MS and reduced rates of accumulation of clinically silent lesions on brain MRI.<sup>55</sup> Results were similar in the subgroup of patients in CHAMPS who experienced optic neuritis as their first demyelinating event (192 patients), supporting the initiation of interferon  $\beta$ -1a in optic neuritis patients at high risk for MS by MRI criteria.<sup>57</sup> All patients in CHAMPS (interferon  $\beta$ -1a and placebo groups) also received a 3-day course of intravenous methylprednisolone followed by oral prednisone as per the ONTT protocol. An extension study

(Controlled High-Risk Avonex Multiple Sclerosis Prevention Study in Ongoing Neurological Surveillance, known as CHAMPIONS) confirmed the potential for long-term benefit of interferon  $\beta$ -1a in patients with acute monosymptomatic demyelinating optic neuritis (or other first demyelinating event) and high-risk brain MRI findings.<sup>5</sup> Early interferon therapy following a first demyelinating event is likewise supported by results of a randomized trial of interferon $\beta$ -1a (Rebif) performed in Europe (Early Treatment of Multiple Sclerosis Study, ETOMS).<sup>58</sup>

Results from the Betaferon/Betaseron in Newly Emerging Multiple Sclerosis for Initial Treatment (BENEFIT) trial, involving 487 patients with a first clinical demyelinating event (80 patients with optic neuritis), suggest that 250  $\mu$ g of interferon  $\beta$ -1b (Betaseron) subcutaneously every other day delays the development of multiple sclerosis.<sup>59</sup> Compared with subjects receiving placebo, subjects in the interferon group were less likely to be diagnosed with MS (28% versus 45%) and had significantly fewer lesions on brain MRI than did patients in the placebo group.<sup>60</sup> This effect persisted in the 5-year extension study; early treatment reduced the risk of clinically definite MS by 37%.<sup>61</sup>

Glatiramer acetate (Copaxone) has also been demonstrated to be an effective treatment in the clinically isolated syndrome. The PreCISe study, a randomized, double-blind placebo-controlled trial of 481, demonstrated that Copaxone decreased the risk of conversion to clinically definite MS by 45% compared with placebo.<sup>62</sup> It is important to note that these trials were completed prior to a 2010 revision in MS diagnostic criteria, which allows for MS diagnosis based on a single MRI scan. It is likely that some of the subjects in these trials would have already met these new diagnostic criteria for MS at study entry.<sup>53</sup>

Teriflunomide, an oral therapy for multiple sclerosis, has demonstrated efficacy in reducing onset of clinically definite MS over 2 years in patients with clinically isolated syndrome, including optic neuritis, with two or more T2 lesions on MRI.<sup>63</sup>

## **Other Treatments**

In experimental models of MS, intravenous immunoglobulin G (IVIG) has been shown to promote remyelination of the central nervous system.<sup>64</sup> A small pilot study in 1992 suggested that IVIG treatment may have some benefit in patients with resolved optic neuritis who have significant visual deficits.<sup>65</sup> However, two recent randomized trials of IVIG versus placebo have failed to demonstrate any clinical benefit.<sup>64–66</sup>

## **Management Recommendations**

In patients with a typical clinical course and examination findings for acute monosymptomatic demyelinating optic neuritis (first demyelinating event), MRI of the brain (T2-enhanced and gadolinium-enhanced images) should be performed to determine whether they are at high risk for the development of MS. Characteristic demyelinating lesions in patients at risk of multiple sclerosis are 3 mm or larger in diameter, are ovoid, are located in periventricular areas of the white matter, and radiate toward the ventricular spaces.<sup>47,49–51</sup> Oligoclonal banding of proteins in the cerebrospinal fluid is a useful predictor of the risk of multiple sclerosis among patients with either normal brain MRI or abnormal findings that are not classic for demyelination (e.g., small, punctate lesions that are not periventricular or ovoid).<sup>56</sup> The presence of two or more white matter lesions on MRI (3 mm diameter or larger, at least one lesion periventricular or ovoid) should prompt consideration of one of these treatments<sup>1–16,47,55–62,67</sup>:

- Interferon  $\beta$ -1a (Avonex 30  $\mu$ g intramuscularly once a week).
- Interferon  $\beta$ -1a (Rebif 22  $\mu$ g subcutaneously once a week).
- Betaseron (250  $\mu$ g subcutaneously every other day).
- Glatiramer acetate (Copaxone 20 mg subcutaneously daily).
- Teriflunomide.

In monosymptomatic patients without white matter lesions, with enhancing and nonenhancing white matter lesions that meet criteria for diagnosis of MS and in patients for whom a diagnosis of MS has been previously established, intravenous methylprednisolone treatment (1 g per day, single or divided doses, for 3 days) followed by oral prednisone (1 mg/kg per day for 11 days, then 4-day taper) may be considered on an individual basis to hasten visual recovery, but this has not been demonstrated to improve long-term visual outcome. Effects of corticosteroid treatment and other therapies on the recovery of visual function and on the risk of multiple sclerosis in children have not been established by randomized trials, but intravenous methylprednisolone treatment is generally recommended if visual loss is unilateral and severe or is bilateral.<sup>58</sup>

In monosymptomatic patients with AQP4-IgG in their serum who meet criteria for NMO spectrum disorder or who are judged to be at high risk for NMO spectrum disorder, intravenous methylprednisolone (1 g per day for 5 days) followed by an oral corticosteroid taper should be considered. A second course of high-dose corticosteroids or a course of therapeutic plasma exchange can be considered in patients with progression or poor recovery.<sup>51</sup>

Based on findings from the ONTT, oral prednisone alone (without prior treatment with intravenous methylprednisolone) may increase the risk of recurrent optic neuritis and should be avoided.

A short course of noncorticosteroidal anti-inflammatory agents may be helpful in the occasional case of disabling pain associated with optic neuritis.<sup>31</sup>

## COURSE AND OUTCOME

At least some visual improvement is expected in all patients who have acute demyelinating optic neuritis. Visual improvement usually begins rapidly in patients treated with intravenous methylprednisolone. Even with no treatment, however, most patients start to recover vision within 2–3 weeks of symptom onset. Once recovery begins, most patients achieve near maximal improvement within 1–2 months, although recovery up to 1 year is possible. Severity of the initial visual loss appears to be the only predictor of visual outcome.<sup>2,15</sup>

Despite favorable recovery of vision, frequently to 20/20 or better (as was seen in 74% of patients in 10-year ONTT follow-up),<sup>15</sup> many patients with acute demyelinating optic neuritis continue to experience subtle visual abnormalities that affect their daily function and quality of life. They may report that their vision seems blurred, washed out, or “not right.”<sup>12–13</sup> Persistent abnormalities of visual acuity (15%–30%), contrast sensitivity (63%–100%), color vision (33%–100%), the visual field (62%–100%), stereopsis (89%), light brightness sense (89%–100%), afferent pupillary reaction (55%–92%), optic disc appearance (60%–80%), and the visual-evoked potential (63%–100%) have been demonstrated in such patients. Recurrent episodes of optic neuritis in the initially affected or fellow eye may

occur also. Approximately 35% of placebo-group ONTT participants had a second episode in either eye within the 10-year follow-up period, and risk of recurrence is twofold greater in patients with an MS diagnosis at any time during 10-year follow-up than in patients who do not develop MS (48% versus 24%,  $P < 0.001$ ).<sup>9,15</sup>

During and even beyond the recovery of vision following acute demyelinating optic neuritis, patients frequently experience transient worsening of symptoms with exposure to heat (Uhthoff's symptom).<sup>59</sup> Positive visual phenomena and photopsias are also common and were reported by 30% of ONTT participants.<sup>1,3</sup>

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Ischemic Optic Neuropathy

Anthony C. Arnold, Michelle Y. Wang

9.8

**Definition:** Acute, painless optic neuropathy occurring predominantly in patients over 50 years of age.

Key Features

- Optic disc edema.
- Dimming of vision, dyschromatopsia, afferent pupillary defect, and altitudinal or other optic disc-related visual field loss (in anterior ischemic optic neuropathy).
- No evidence of demyelination.
- Normal optic disc appearance (in posterior ischemic optic neuropathy).
- Pallor (in arteritic anterior ischemic optic neuropathy).

Associated Features

- Peripapillary flame hemorrhages.
- Peripapillary arteriolar narrowing.

ISCHEMIC OPTIC NEUROPATHY

INTRODUCTION

Optic nerve ischemia most frequently occurs at the optic nerve head, where, in susceptible individuals, structural crowding of nerve fibers and the relative reduction of the vascular supply combine to impair perfusion to a critical degree and produce optic disc edema. The most common such syndrome is termed anterior ischemic optic neuropathy (AION).<sup>1</sup> Generally, AION is categorized as either arteritic (associated with temporal arteritis) or nonarteritic (Table 9.8.1). Optic nerve ischemia affects the intraorbital portion of the nerve less frequently, with no visible disc edema, and this has been termed posterior ischemic optic neuropathy.

TABLE 9.8.1 Comparison of Major Features of Arteritic and Nonarteritic Anterior Ischemic Optic Neuropathy (AION)

Feature	Arteritic AION	Nonarteritic AION
Age (mean years)	70	60
Sex ratio	Female > male	Male = female
Associated symptoms	Headache, scalp tenderness, jaw claudication	Mild pain occasionally noted
Visual acuity	Up to 76% <20/200 (6/60)	Up to 61% >20/200 (6/60)
Disc	Pale > hyperemic edema Cup normal	Hyperemic > pale edema Cup small
Mean erythrocyte sedimentation rate (mm/hour)	70	20–40
Fluorescein angiogram	Disc and choroid filling delay	Disc filling delay
Natural history	Improvement rare Fellow eye in up to 95%	Improvement in up to 43% Fellow eye in <30%
Treatment	Corticosteroids	None proved

ANTERIOR ISCHEMIC OPTIC NEUROPATHY

Epidemiology and Pathogenesis

Nonarteritic anterior ischemic optic neuropathy (NAION) is the most common acute optic neuropathy in patients over 50 years of age, with an estimated annual incidence in the United States of 2.3–10.2 per 100 000 population,<sup>2,3</sup> some 6000–8000 new cases each year. Subsequent studies have shown that AION is not so unusual before the age of 50.<sup>4</sup> No gender predisposition exists, but the disease occurs with significantly higher frequency in white than in black or Hispanic populations.<sup>2,5</sup> The incidence of arteritic anterior ischemic optic neuropathy (AAION) is lower.<sup>2</sup>

Arteritic Anterior Ischemic Optic Neuropathy

Ample evidence exists that AAION results from short posterior ciliary artery (SPCA) vasculitis and the resultant optic nerve head infarction. Human autopsy studies of acute AAION demonstrate optic disc edema with ischemic necrosis of the prelaminar, laminar, and retrolaminar portions of the nerve and infiltration of the SPCAs by chronic inflammatory cells. Segments of these vessels in some cases were occluded by inflammatory thickening and thrombus.<sup>6</sup>

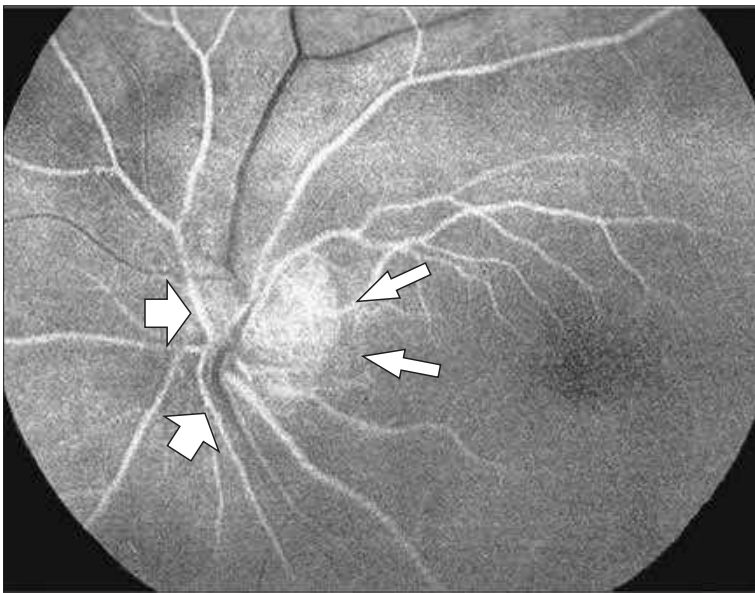
Fluorescein angiographic data support the histopathological evidence of involvement of the SPCAs in AAION.<sup>7</sup> Delayed filling of the optic disc and choroid is a consistent feature; extremely poor or absent filling of the choroid has been depicted as a characteristic of AAION and has been suggested as one useful factor by which to differentiate AAION from NAION. Delayed completion of choroidal fluorescein filling that averages 30–69 seconds has been reported in AAION, compared with a mean of 5–13 seconds in NAION.<sup>8</sup>

Nonarteritic Anterior Ischemic Optic Neuropathy (NAION)

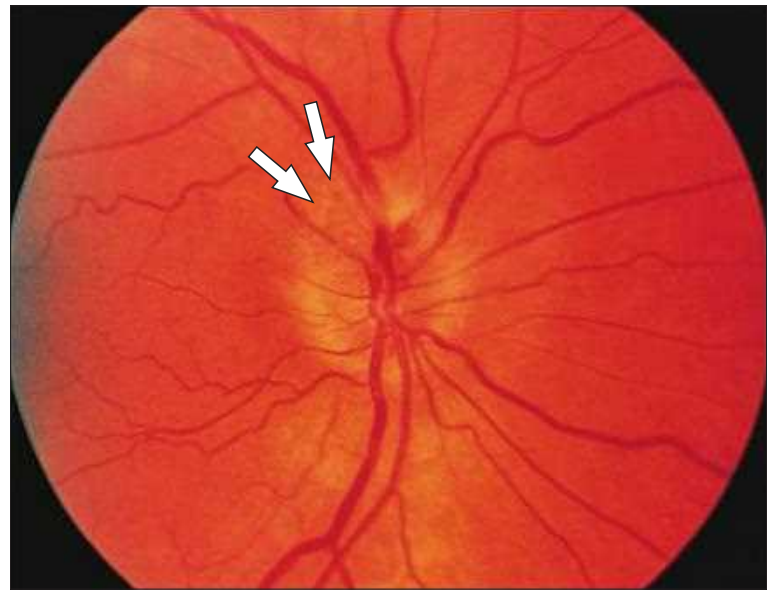
The rapid onset, stable course with generally poor recovery, association with vasculopathic risk factors, and similarity to AAION implies a vascular cause for NAION as well, but the direct evidence remains limited.<sup>9</sup> Several histopathological reports document laminar and retrolaminar infarction, but cases of uncomplicated NAION are rare, and none has confirmed vasculopathy within the SPCAs or their distal branches. The most commonly proposed pathogenic theory states that insufficiency of the optic disc circulation is exacerbated by structural crowding of nerve fibers and supporting structures at the nerve head and eventually reaches a point at which inadequate oxygenation produces ischemia and swelling of the disc. These features may be mild and subclinical (no visual loss), reversible to some degree, or irreversible (infarction). In some cases, a cycle of ischemia, axonal swelling, microvascular compression, and further ischemia may lead to progressive nerve damage. Periodic nocturnal systemic hypotension and that the optic disc is in a watershed zone between distributions of lateral and medial SPCAs may be contributing factors.<sup>10</sup>

Fluorescein angiographic studies in NAION also suggest impaired optic disc perfusion. Detailed quantitative analysis of prelaminar optic disc and peripapillary choroidal filling in NAION confirms delayed disc filling when compared with age-matched controls.<sup>11</sup> Delay in a segment of disc (Fig. 9.8.1) by at least 5 seconds was present in 75.6% of such cases.<sup>12</sup> In contrast, peripapillary choroidal filling was not delayed consistently compared to normal subjects. Significantly delayed optic disc filling is characteristic of ischemia, which is not seen in disc edema from nonischemic causes such as papilledema.<sup>13</sup> Optical coherence tomography angiography, a new diagnostic imaging device, may add additional insights into peripapillary microvasculature and extent of ischemia in NAION.<sup>14</sup>

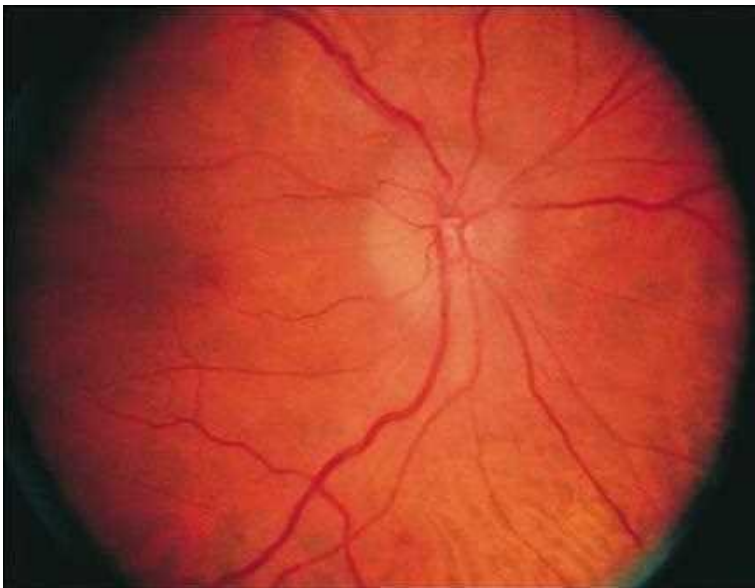




**Fig. 9.8.1** Fluorescein Angiogram, Early Arteriovenous Phase, in Nonarteritic Anterior Ischemic Optic Neuropathy. The temporal portion of the optic disc fills normally (*small arrows*), but the remaining sectors demonstrate markedly delayed filling (*large arrows*) approximately 10 seconds later.



**Fig. 9.8.3** Fundus View, Nonarteritic Anterior Ischemic Optic Neuropathy. The hyperemic disc edema is more prominent superiorly. Focal surface telangiectasia of disc vessels is seen superotemporally (*arrows*).



**Fig. 9.8.2** Fundus View, Anterior Ischemic Optic Neuropathy. The optic disc demonstrates pale, diffuse edema.

## Ocular Manifestations

AION presents with rapid onset of painless, unilateral visual loss manifested by decreased visual acuity, visual field, or both. The level of visual acuity impairment varies widely, from minimal loss to no light perception, and the visual field loss may conform to any pattern of deficit related to the optic disc. An altitudinal field defect is most common, but generalized depression, broad arcuate scotomas, and cecocentral defects also are seen. A relative afferent pupillary defect is present with monocular optic neuropathy. The optic disc is edematous at onset, and edema occasionally precedes visual loss by weeks to months.<sup>15</sup> Although pallid edema has been described as the hallmark of AAION (Fig. 9.8.2), it is common to see hyperemic swelling (Fig. 9.8.3), particularly in the nonarteritic form. The disc most often is swollen diffusely, but a segment of more prominent involvement may be present (see Fig. 9.8.3), and either focal or diffuse surface telangiectasia is not unusual and may be quite pronounced. Commonly, flame hemorrhages are located adjacent to the disc, and the peripapillary retinal arterioles frequently are narrowed.

### Arteritic Anterior Ischemic Optic Neuropathy

In 5%–10% of cases, AION may occur as a manifestation of the vasculitis associated with temporal arteritis. Patients with the arteritic form note other symptoms of the disease—headache, jaw claudication, and temporal

artery or scalp tenderness are those aligned most frequently with a final diagnosis of temporal arteritis. Malaise, anorexia, weight loss, fever, proximal joint arthralgia, and myalgia also are noted commonly, but the disease rarely manifests with visual loss in the absence of overt systemic symptoms, so-called occult temporal arteritis.

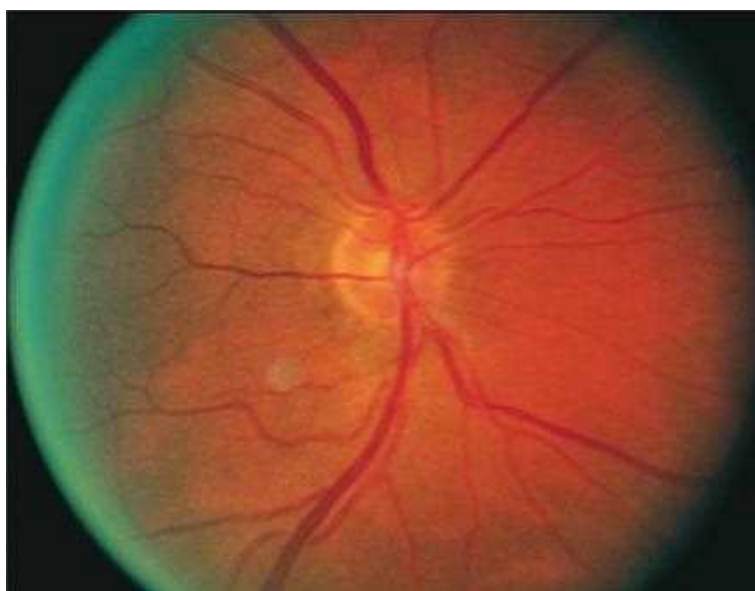
Typically, AAION develops in patients over 50 years—with a mean age of 70 years—with severe visual loss (visual acuity <20/200 [6/60] in the majority). However, this mean is misleading, reflecting the ascertainment bias of fewer individuals who survive to the oldest ages. In fact, AAION probably increases in frequency with every decade. A recent study showed that AAION is the most common cause of vision loss in patients with giant cell arteritis.<sup>16</sup> Among those with permanent vision loss, the average age was 82 years as compared to 76 years in the remaining group. AAION may be preceded by transient visual loss similar to that of carotid artery disease; this finding is extremely unusual in the nonarteritic form and, when present, is highly suggestive of arteritis.<sup>17</sup> Pallor of the optic disc, which may be severe, chalky white, is associated with AAION. Choroidal ischemia may be associated with the optic neuropathy and produces peripapillary pallor and edema deep to the retina. The disc of the fellow eye is of normal diameter in AAION.<sup>18</sup>

### Nonarteritic Anterior Ischemic Optic Neuropathy

In 90%–95% of cases, AION is unrelated to temporal arteritis. The nonarteritic form of the disease occurs in a somewhat younger age group (mean age of 60 years) and usually is associated with less severe visual loss. Frequently, visual impairment is reported on awakening, possibly related to nocturnal systemic hypotension. The initial course of visual loss usually is static (with little or no fluctuation of visual level after the initial loss) but may be progressive (with either episodic or visual loss that declines steadily over weeks). The progressive form has been reported in up to 37% of NAION cases.<sup>19</sup> Usually, no associated systemic symptoms occur, although periorbital pain is occasionally described. Fellow eye involvement is estimated to occur in 12%–19% by 5 years after onset.<sup>20</sup> Recurrent episodes of visual loss that result from NAION in the same eye are very unusual.

The optic disc edema in NAION may be diffuse or segmental, hyperemic or pale, but pallor occurs less frequently than it does in AAION. A focal region of more severe swelling is often seen and typically displays an altitudinal distribution, but it does not correlate consistently with the sector of visual field loss.<sup>11</sup> Diffuse or focal telangiectasia (see Fig. 9.8.3) of the edematous disc may be present, occasionally prominent enough to resemble a vascular mass or neovascularization. This finding may represent microvascular shunting from ischemic to nonischemic regions of the optic nerve head, so-called luxury perfusion. The optic disc in the contralateral eye typically is small in diameter and demonstrates a small or absent physiological cup.<sup>18</sup> The disc appearance in such fellow eyes (Fig. 9.8.4) has been described as the disc-at-risk, with postulated structural crowding of the axons at the level of the cribriform plate, associated mild disc elevation, and disc margin blurring without overt edema.





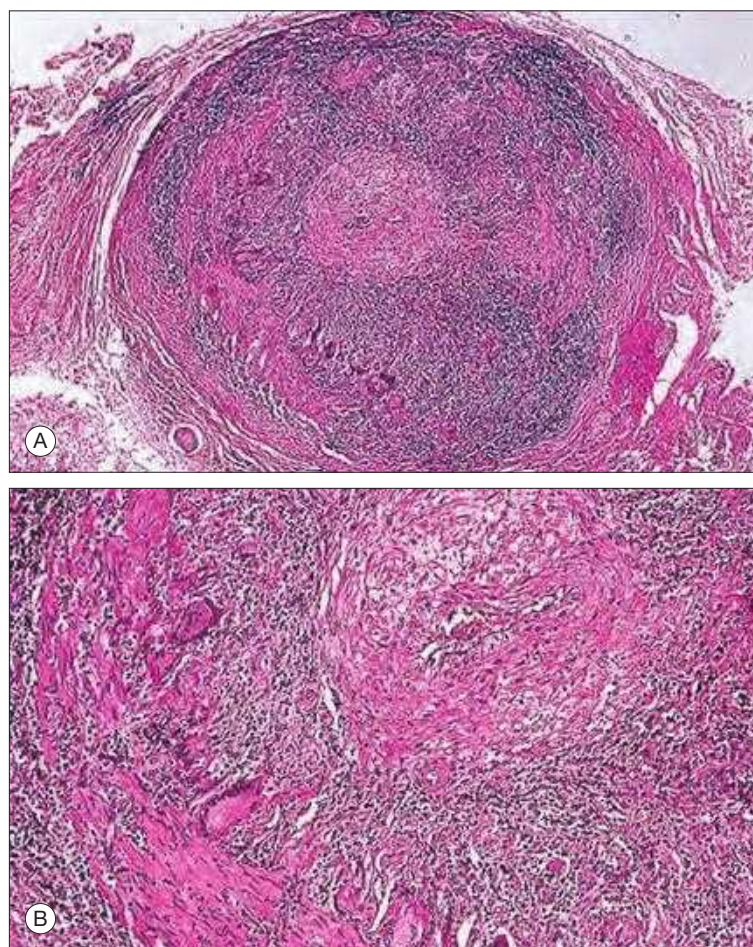
**Fig. 9.8.4 Fellow Eye in Nonarteritic Anterior Ischemic Optic Neuropathy.** The optic disc is small in diameter, with absent physiological cup and slight blurring of the nasal margin.

## Diagnosis and Ancillary Testing

The most important early step in the management of AION is the differentiation of the arteritic from the nonarteritic form of the disease. Measurement of the inflammatory markers remains the standard of care. Active temporal arteritis usually is associated with an elevation of erythrocyte sedimentation rate (ESR) to 70–120 mm/hour, and this finding suggests the arteritic form; in most cases, it should prompt immediate corticosteroid therapy and confirmatory temporal artery biopsy (see later). The test carries a significant rate of both false positives and false negatives, however, with normal measurements found in an estimated 16% of biopsy-proved cases.<sup>21</sup> Conversely, abnormally high readings occur normally with increasing age and with other diseases, most commonly occult malignancy, other inflammatory disease, and diabetes. Measurement of serum C-reactive protein (CRP), another acute phase plasma protein, may aid in diagnosis. Hayreh et al.<sup>22</sup> reported 97% specificity for temporal arteritis in cases of AION in which both ESR greater than 47 mm/hour and CRP greater than 2.45 mg/dL were found. However, elevated platelet count may have the strongest association with positive temporal artery biopsy when compared to CRP and ESR.<sup>23</sup> When two or more inflammatory markers were elevated, the association was highest. Several proinflammatory cytokines have been identified in AAION. Of those, interleukin-6 (IL-6) gained much more interest as it also plays an important role in acute-phase response induction. Plasma IL-6 has also been suggested as a biological marker of AAION disease activity.<sup>24</sup>

Confirmation of the diagnosis of temporal arteritis by superficial temporal artery biopsy is often recommended in cases of AION in which a clinical suspicion of arteritis exists based on age, associated systemic symptoms, severity of visual loss, and elevated ESR and CRP levels. Positive biopsy findings, such as intimal thickening, internal limiting lamina fragmentation, and chronic inflammatory infiltrate with giant cells, provide support for long-term systemic corticosteroid therapy (Fig. 9.8.5). A negative biopsy result, however, does not rule out arteritis. Both discontinuous arterial involvement (“skip lesions”) and solely contralateral temporal artery inflammation may result in false-negative results. A 3%–5% false-negative error rate has been reported.<sup>25</sup>

As previously mentioned, fluorescein angiography (FA) can be a very helpful diagnostic tool by providing visualization of perfusion of choroid, retina, and both deep (prelaminar) and inner surface of the optic disc. The FA filling characteristics can help differentiate optic disc edema secondary to ischemia from other causes. Markedly delayed in choroidal filling is characteristic of AAION. Optic coherence tomography (OCT) is another useful tool (see Chapter 9.2). Sectoral disc edema, retinal nerve fiber layer (RNFL) thickness, and then resolution to normal or atrophy can be well documented.<sup>26</sup> The extent and pattern of RNFL loss can be correlated to visual field loss.<sup>27</sup> This can provide a useful metric against which purported treatment for AION can be assessed.



**Fig. 9.8.5 Typical Temporal Arteritis.** (A) Histological section shows a vasculitis involving all coats of the temporal artery. (B) Increased magnification shows the typical giant cell granulomatous inflammation. (Courtesy Dr. M. M. Rodrigues.)

## Differential Diagnosis

The differential diagnosis of AION includes idiopathic optic neuritis, particularly in patients under 50 years of age; other forms of optic nerve inflammation, such as those related to syphilis or sarcoidosis; infiltrative optic neuropathies; anterior orbital lesions that produce optic nerve compression; and diabetic papillopathy. Diabetic papillopathy (discussed later) may represent a forme fruste AION with reversible signs and symptoms after several months. Optic neuritis may resemble AION with regard to rate of onset, pattern of visual field loss, and optic disc appearance. In most cases, however, the patient's age, lack of pain with eye movement, and pallor or segmental configuration of the disc edema enables differentiation. Early disc filling delay on FA may confirm ischemia. Syphilitic or sarcoid-associated optic neuritis often is associated with other intraocular inflammatory signs, which should prompt further testing. Orbital lesions typically produce gradually progressive visual loss. Associated signs of orbital disease, such as mild exophthalmos, lid abnormalities, or eye movement limitation, may suggest the use of neuroimaging to detect anterior orbital inflammation or tumor.

## Systemic Associations

AAION is known to be a manifestation of temporal arteritis. NAION has been reported in association with a number of diseases that could predispose to reduced perfusion pressure or increased resistance to flow within the optic nerve head. Systemic hypertension has been documented in up to 47% of patients who have NAION<sup>28</sup> and diabetes in up to 40%.<sup>29</sup> Obstructive sleep apnea has been reported in up to 89% of patients with NAION but there are many confounders.<sup>30</sup> Hypercholesterolemia, smoking, anemia, chronic renal failure, and migraine have all been reported as potential risk factors.

Whether cataract surgery has an association with NAION has been controversial. Lam et al. found that in patients with unilateral NAION, the risk of NAION in the fellow eye was increased by 3.6-fold when the fellow



eye underwent cataract surgery.<sup>31</sup> Another study did not find significant temporal relationship.<sup>32</sup>

Carotid occlusive disease itself is not causative with NAION. However, indirect evidence shows increased central nervous system, small vessel, ischemic disease in patients who have NAION, based on magnetic resonance imaging (MRI) data.<sup>33</sup> Studies indicate that cerebrovascular or cardiovascular events are both more common than in the normal population, particularly in patients who have hypertension or diabetes.<sup>34</sup> Subsequent mortality, however, is not affected.

Also, NAION has been reported in association with multiple forms of vasculitis, acute systemic hypotension, and optic disc drusen. Other risk factors have been proposed, such as hyperopia and the presence of human lymphocyte antigen A.<sup>35</sup> Associations of hyperhomocysteinemia with AION, particularly in patients under 50, are inconclusive.<sup>36</sup> Prothrombotic risk factors, such as protein C and S and antithrombin III deficiencies, factor V Leiden mutation, and cardiolipin antibodies, have rarely been reported in association with AION.<sup>37</sup> Screening in patients under age 50 may be considered as treatment and may reduce involvement of fellow eye.

Certain medications have been associated with NAION. The association between amiodarone and NAION has been controversial, as patients taking amiodarone typically carry other vascular risk factors. The association is more likely when the process is insidious, bilateral, and chronic.<sup>38</sup> Thirty-nine cases of NAION have been reported in association with ingestion of phosphodiesterase 5 inhibitor, including sildenafil (Viagra), tadalafil (Cialis), and vardenafil (Levitra).<sup>39</sup> Some authors speculated that these medications induce systemic hypotension exacerbated by nocturnal hypotension in predisposed optic discs. Association with interferon-alpha has also been proposed, possibly secondary to medication-induced systemic hypotension or immune complex deposition.<sup>40</sup>

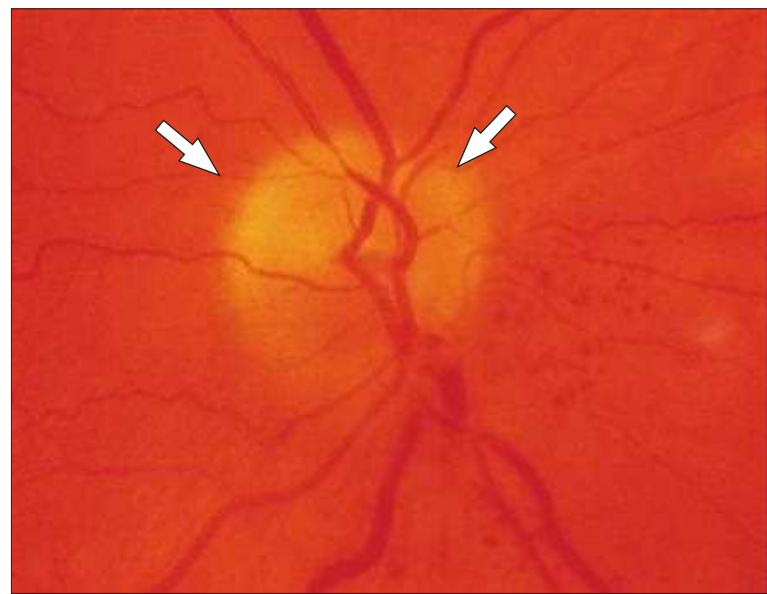
## Treatment

### Arteritic Anterior Ischemic Optic Neuropathy

Early treatment of AAION is essential and must be instituted immediately in any suspected case of temporal arteritis. High-dose systemic corticosteroids are standard; the use of intravenous methylprednisolone at 1 g/day for the first 3 days has been recommended for some AAION patients in the acute phase of severe involvement. Oral prednisone in the range of 60–100 mg/day may be used initially and for follow-up to intravenous pulse therapy; alternate day regimens do not suppress the disease effectively. Treatment usually reduces systemic symptoms within several days. A positive response is so typical that if it does not occur, an alternate disease process should be considered. Treatment is usually continued at high dose for several months before beginning taper. AAION remains a serious ophthalmic condition requiring timely diagnosis and treatment. Studies have undertaken to understand the immunopathology and to guide more targeted therapy.<sup>41</sup> For cases of AAION that do not respond to or are unable to tolerate corticosteroids, investigators have tried corticosteroid-sparing agents such as anti-TNF- $\alpha$  antibodies with various results.<sup>42</sup> More recently, a randomized double-blind placebo-controlled trial (GiACTA) was conducted to investigate the efficacy and safety of tocilizumab as a new adjuvant therapy for AAION.<sup>43</sup> Tocilizumab is a humanized monoclonal anti-IL6 receptor antibody. In the study, tocilizumab was found efficacious for induction and maintenance of remission in patients with AAION on prednisone taper. Relapse-free survival by week 52 was achieved in 85% of patients in the tocilizumab group and only 20% in the placebo group. The time difference to stop corticosteroids was 12 weeks in favor of the tocilizumab group, leading to significantly less cumulative dose of corticosteroids. The long-term efficacy of tocilizumab has not been determined.

### Nonarteritic Anterior Ischemic Optic Neuropathy

There is no proven effective therapy for NAION, and the use of corticosteroids in NAION is highly controversial. Hayreh and Zimmerman studied the effect of oral prednisone in the acute phase of NAION and found significant improvement in visual acuity and visual fields up to 6 months after onset.<sup>44</sup> The rationale for vision improvement is that corticosteroids may alter capillary permeability and reduce optic disc edema, thereby relieving compartment syndrome and improving circulation in the optic nerve head. However, the result of this study is controversial as it was not randomized or blinded, and the noncorticosteroid-treated cohort may have been influenced by a ceiling effect (their visual acuities were often very good to start with). Optic nerve sheath decompression (ONSD) surgery has been attempted, based on the theory that reduction of perineural subarachnoid cerebrospinal fluid pressure might improve local vascular flow



**Fig. 9.8.6 Optic Disc, Nonarteritic Anterior Ischemic Optic Neuropathy.** The disc, 2 months after onset of inferior visual field loss, is segmentally atrophic superiorly (arrows), with sparing and resolving edema inferiorly.

or axoplasmic transport in the optic nerve head and thus reduce tissue injury in reversibly damaged axons.

The Ischemic Optic Neuropathy Decompression Trial compared ONSD surgery in 119 patients with no treatment in 125 controls.<sup>5</sup> The study revealed no significant benefit for treatment and a possible harmful effect; it was recommended that ONSD not be performed for NAION. Hyperbaric oxygen, by marked elevation of the dissolved oxygen content in the blood, provides increased tissue oxygenation that might reduce damage in reversibly injured axons. A controlled clinical pilot study of hyperbaric oxygen in 22 patients who had acute NAION, however, has shown no beneficial effect.<sup>45</sup> Johnson et al.<sup>46</sup> reported a beneficial effect for oral levodopa on the visual outcome for NAION, but the study was controversial,<sup>35</sup> and the effect is considered unproved. Neuroprotective agents have shown a beneficial effect in animal models of optic nerve damage but are not proven to be effective in NAION. The effect of aspirin in reducing risk of fellow eye involvement is also unproved.<sup>47</sup>

## Course and Outcome

### Arteritic Anterior Ischemic Optic Neuropathy

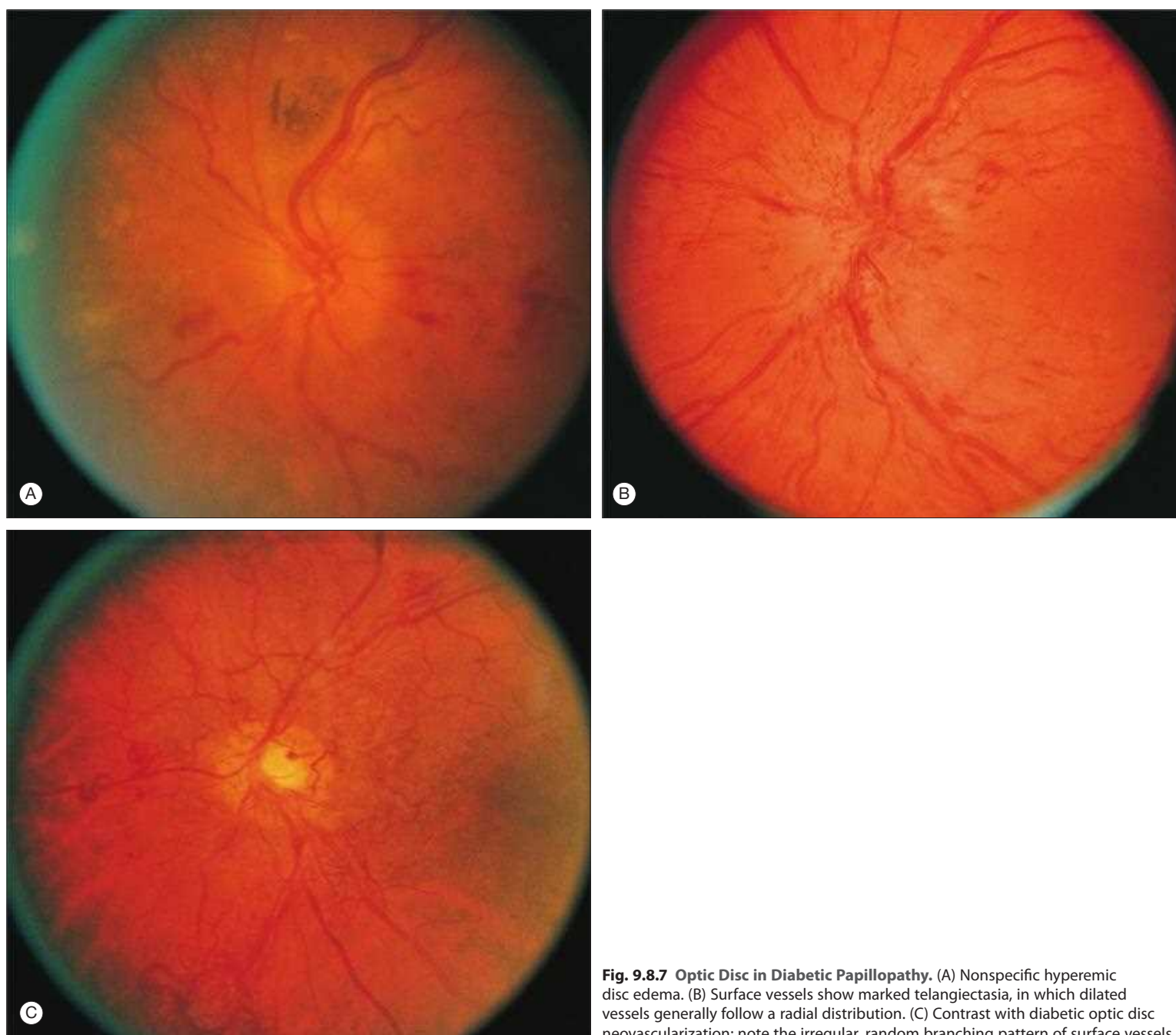
The major goal of therapy in AAION is to prevent visual loss in the fellow eye. Untreated, such involvement occurs in 54%–95% of cases,<sup>48,49</sup> typically within 4 months. With corticosteroid therapy, the rate of such breakthrough is reduced to an estimated 13%. Prognosis for visual recovery in the affected eye that has treatment generally is poor, and worsening of vision in spite of therapy has been reported in 9%–17% of cases.<sup>48</sup> A study reports a 3-day course of induction intravenous corticosteroids (1000 mg/day) may reduce long-term cumulative doses of corticosteroid.<sup>50</sup>

### Nonarteritic Anterior Ischemic Optic Neuropathy

The course of untreated NAION varies considerably. Reports indicate that 24% to 43% of cases demonstrate spontaneous improvement of visual acuity by three Snellen lines or more.<sup>5</sup> Even in the progressive form, improvement has been reported to occur in roughly 30% of cases. Whether NAION is static or progressive, visual acuity and field stabilize after several months. Within 6 weeks, the optic disc becomes visibly atrophic, either in a sectoral (Fig. 9.8.6) or diffuse pattern. Further progression or recurrent episodes are extremely rare after 2 months and, if present, should prompt evaluation for another cause of optic neuropathy.

## POSTERIOR ISCHEMIC OPTIC NEUROPATHY

Ischemia of the optic nerve that does not involve the optic nerve head is termed posterior ischemic optic neuropathy (PION). It presents with acute visual loss associated with signs of optic neuropathy (afferent pupillary defect and visual field loss) in one or both eyes, with initially normal appearance of the optic disc, which subsequently becomes atrophic.



**Fig. 9.8.7 Optic Disc in Diabetic Papillopathy.** (A) Nonspecific hyperemic disc edema. (B) Surface vessels show marked telangiectasia, in which dilated vessels generally follow a radial distribution. (C) Contrast with diabetic optic disc neovascularization; note the irregular, random branching pattern of surface vessels.

The diagnosis of PION is most often made in one of two settings:

- *Vasculitis*, most importantly, giant cell arteritis (GCA); evaluation for GCA should be the primary consideration with this presentation in the elderly, or
- The combination of *systemic hypotension and anemia*, usually related to blood loss either from surgery (coronary artery bypass and lumbar spine procedures most commonly),<sup>51</sup> gastrointestinal bleed, or trauma. This was originally referred to as shock-induced optic neuropathy.

The differential diagnosis includes compressive, inflammatory, and infiltrative optic neuropathies, although the onset in PION is typically more abrupt. In most cases, neuroimaging is indicated to rule out these possibilities.

Sadda et al. reported a multicenter, retrospective review of 72 patients with PION, adding a third classification paralleling the nonarteritic form of AION.<sup>52</sup> The nonarteritic PION group accounted for 38 of the 72 patients, exhibited similar risk factors, and followed a clinical course precisely like that of NAION. Perioperative and arteritic PION was characterized by severe visual loss with little or no recovery. It is important to recognize this nonarteritic form in patients with acute optic neuropathy but no optic disc edema, a scenario that may be mistaken for retrobulbar optic neuritis. Such patients, particularly those with ischemic white-matter lesions on MRI, might be incorrectly begun on immunomodulatory therapy to reduce the risk of multiple sclerosis. This PION mechanism may also present

with disc swelling and hemorrhages and is a form of NAION, although it differs in usually occurring postsurgery or other causes of severe blood loss.

## DIABETIC PAPILLOPATHY

### PATHOGENESIS AND FEATURES

The pathogenesis of diabetic papillopathy is unclear. The most commonly proposed theory suggests diabetic papillopathy to be a mild form of NAION, with reversible ischemia of both the prelaminar and inner surface layers of the optic nerve head.<sup>53</sup> Edema of the optic nerve head in the absence of significant visual dysfunction occurs in several presumed vascular disorders as follows:

- Asymptomatic optic disc edema, which evolves to typical NAION weeks to months after initial symptoms.
- Asymptomatic disc edema of the fellow eye in patients who have NAION, which may either progress to NAION or resolve spontaneously.
- Disc edema in association with systemic hypertension, which resolves without sequelae as blood pressure is normalized.

Diabetic papillopathy fits this category as well. The prominent surface telangiectasias may represent vascular shunting from prelaminar to



ischemic vascular beds. The frequent occurrence of a crowded optic disc in the fellow eye (see later),<sup>54</sup> as in NAION, also supports an ischemic mechanism.

The currently accepted criteria for the diagnosis of diabetic papillopathy include:

- Presence of diabetes (approximately 70% type 1, 30% type 2).
- Optic disc edema (unilateral in roughly 60%).
- Only mild optic nerve dysfunction.

The absence of ocular inflammation or elevated intracranial pressure also is essential to the diagnosis.

Although younger patients predominate (approximately 75% of those reported are under the age of 50 years), those affected may be of any age and typically experience mild visual complaints, such as mild blurring or distortion. Visual acuity is usually only mildly impaired; over 75% of reported cases measured 20/40 (6/12) or better. Macular edema contributes to visual acuity loss in many cases. OCT is invaluable in detecting this. Pain is absent, as are other ocular or neurological symptoms.

The involved optic discs may demonstrate either nonspecific hyperemic edema or marked telangiectasia of the inner surface microvasculature (Fig. 9.8.7A and B); pale swelling typically has been a criterion for exclusion and suggests AION. The surface telangiectasia is so prominent in many cases that it may be mistaken for neovascularization (see Fig. 9.8.7C). The fellow eye frequently demonstrates crowding, with a small cup-to-disc ratio similar to the configuration seen in patients who have NAION.

Diabetic retinopathy usually is present (in more than 80% of reported cases) at the time of onset of papillopathy, but it varies in severity. Often diabetic papillopathy is precipitated by a rapid drop from a very high HbA1C.<sup>55</sup> It is associated with cystoid macular edema in about 25% of cases and neovascularization in approximately 9%.

## COURSE AND OUTCOME

Although systemic corticosteroids have been used in isolated cases, no proven therapy exists for this disorder. Untreated, the optic disc edema

gradually resolves over a period of 2–10 months to leave minimal optic atrophy in about 20% of cases and subtle, if any, visual field loss. Visual acuity at the time of resolution of edema is 20/40 (6/12) or better in about 80% of cases; the remainder of patients suffer visual impairment because of maculopathy. The long-term visual prognosis for patients who have diabetic papillopathy, however, is limited by the associated diabetic retinopathy.

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# Hereditary, Nutritional, and Toxic Optic Atrophies

## 9.9

Rustum Karanjia, Vivek R. Patel, Alfredo A. Sadun

**Definition:** Leber's hereditary optic neuropathy arises from an inherited point mutation in mitochondrial DNA and manifests in young adulthood as a distinctive hereditary optic neuropathy.

Nutritional deficiency states, particularly those that involve lack of certain vitamins (e.g., B12 or folic acid) and amino acids used in mitochondrial metabolism (e.g., homocysteine or methionine), can result in a stereotypical optic neuropathy.

Toxins and antibodies may interfere with mitochondrial metabolism on an acquired basis (e.g., ethambutol), producing an optic neuropathy.

### Key Features

- Symmetrical visual impairments.
- Loss of central visual acuity.
- Dyschromatopsia.
- Centrocecal visual field defects.
- Temporal optic disc pallor.
- Nerve fiber layer loss in the papillomacular bundle.

### Associated Features

- Loss of hearing.
- Peripheral neuropathy.

## INTRODUCTION

Hereditary, nutritional, and toxic optic neuropathies selectively affect the papillomacular bundle (PMB) of the human optic nerve, resulting in a characteristic bilateral central or centrocecal scotoma with preservation of some degree of peripheral vision. This peculiar susceptibility of the PMB appears to be underwritten by genetic or acquired mitochondrial dysfunction.<sup>1</sup> The hereditary causes include the prototypical disease of Leber's hereditary optic neuropathy (LHON), dominant optic neuropathy (Kjer's disease), Friedreich's ataxia, and Wolfram syndrome (characterized by diabetes insipidus, diabetes mellitus, optic atrophy, and deafness—DIDMOAD). The acquired diseases include toxic effects of drugs, including chloramphenicol, ethambutol, and linezolid and dietary deficiencies of B vitamins and folate, which are typified by tobacco-alcohol amblyopia (TAA) and the Cuban epidemic of optic neuropathy (CEON).<sup>1</sup>

The understanding of these optic neuropathies has evolved, but the characterization and study of the prototypical disease of LHON was first described in 1871 as a disease that produced a subacute onset of dyschromatopsia and sequential, bilateral visual loss, primarily in young men.<sup>2</sup> In 1988, Wallace and coworkers<sup>3</sup> identified the genetic defect as a point mutation in the mitochondrial DNA (and hence involving maternal inheritance). Three commonly reported mitochondrial DNA point mutations account for over 90% of the case of LHON. All the mutations affect complex I of the respiratory chain. The resulting impairment of energy production and chronic increase in reactive oxygen species are the underlying pathogenic mutations leading to optic nerve degeneration.<sup>4,5</sup> The fundus appearance is unusual, revealing characteristic optic disc changes and loss of the papillomacular nerve fiber layer.<sup>2</sup>

On the acquired side, TAA refers to a well-described combined toxic and nutritional deficiency. Traquair<sup>6</sup> emphasized that heavy drinking and smoking could lead to a slow, progressive, bilateral visual field loss. TAA

is now thought to result from the cyanide from tobacco and low levels of B12 brought about by poor nutrition and poor absorption associated with alcohol consumption.<sup>7</sup> Deficiencies of B12, other B vitamins, and in particular folic acid are known to result in a similar clinical picture.<sup>8</sup> Furthermore, a number of toxins, such as chloramphenicol, ethambutol, and linezolid, injure the optic nerve and produce a virtually indistinguishable clinical picture.<sup>9–11</sup> Indeed, it is one of the fundamental curiosities of these disorders that they, along with LHON, all have such similar and characteristic clinical manifestations.<sup>12,13</sup> In considering toxic agents that are best known to cause optic neuropathy, it is remarkable that most are known to interfere with mitochondrial oxidative phosphorylation.<sup>13</sup>

## EPIDEMIOLOGY AND PATHOGENESIS

Each of these optic atrophies has its own distinct incidence, prevalence, and pathogenesis. The prevalence of the toxic and nutritional optic neuropathies is dependent on extrinsic factors and thus varies between populations. Again, our knowledge of the hereditary optic neuropathies is best understood through the study of LHON, which is one of the most frequently occurring mitochondrial diseases.<sup>14</sup> The prevalence of LHON is about 1 in 30 000.<sup>15</sup> Penetrance is variable, affecting men more often than women, although the ratio depends on the pedigree.<sup>14,16</sup> The severity of the visual loss is greater for 3460/ND1 and 11778/ND4 and less for the 14484/ND6 mutation.<sup>2</sup>

The PMB is the main locus of the problem, eventually atrophying in most cases.<sup>2,17,18</sup> Injury to the PMB probably begins with impairments in mitochondrial oxidative phosphorylation. The resultant decrease in adenosine 5'-triphosphate (ATP) may compromise axonal transport, which, paradoxically, is highly energy dependent.<sup>19</sup> There is also a concurrent rise in reactive oxygen species (ROS) that can trigger apoptosis.<sup>14</sup>

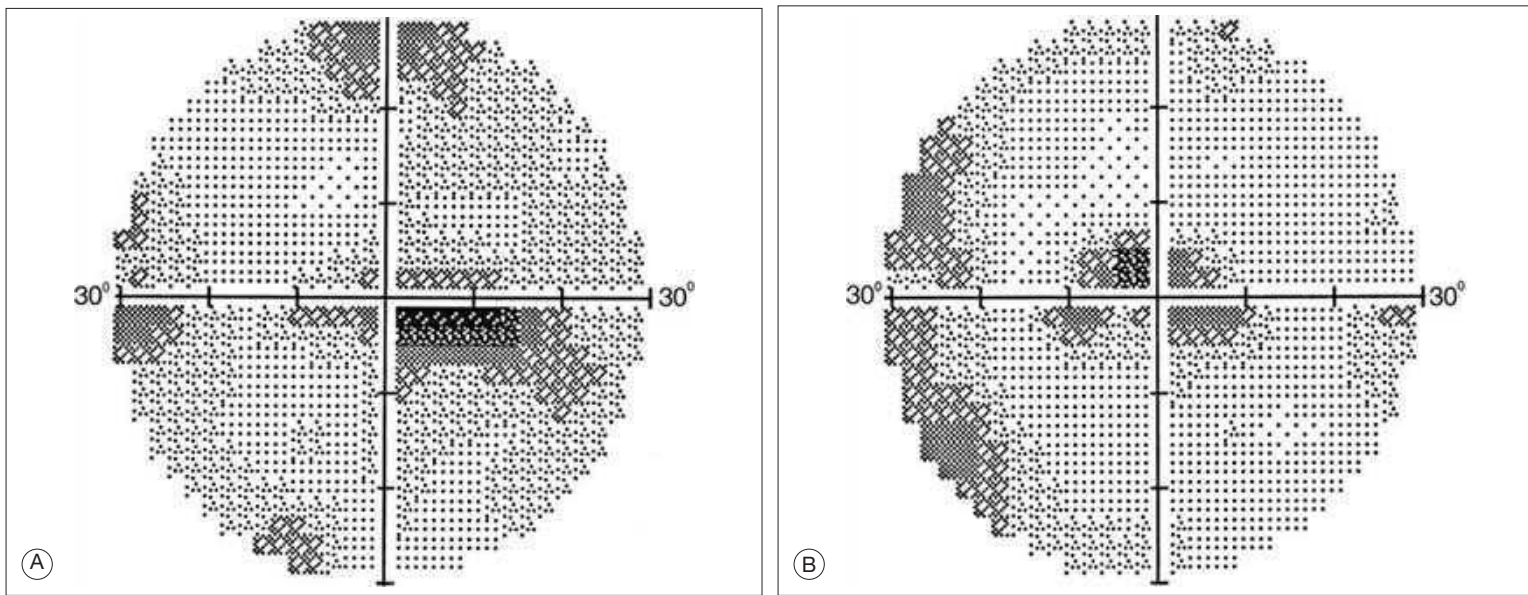
Toxic and nutritional deficiency optic neuropathies are fairly uncommon causes of optic neuropathy in the United States and Western Europe. CEON, however, serves to remind us that these types of optic neuropathies may be far more common in the developing world.<sup>20</sup> This family of diseases makes a resurgence in times of famine, new application of pharmaceuticals, or changes in the workplace that lead to nutritional deficiencies or toxic exposures.

Deficiencies in B-complex vitamins, including B1 (thiamine), B2 (riboflavin), and B12 (cobalamin), as well as folate, are the most commonly implicated nutritional deficiencies leading to nutritional optic neuropathy. Proteins containing sulfur amino acids are also crucial for efficient mitochondrial oxidative phosphorylation. Toxins established most clearly as producers of an optic neuropathy include arsacetin, carbon monoxide, clioquinol, cyanide, ethambutol, hexachlorophene, isoniazid, lead, linezolid, methanol, plasmocid, and triethyl tin. These agents interfere with mitochondrial oxidative phosphorylation.<sup>21–24</sup>

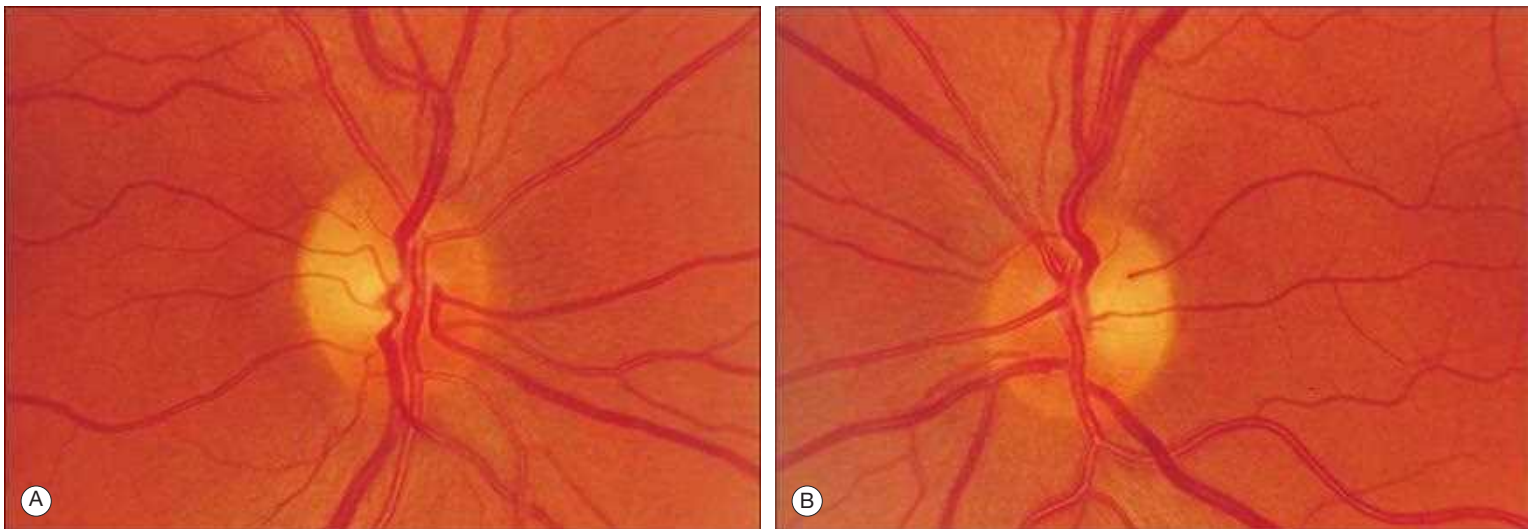
Ethambutol optic neuropathy is a particularly well-characterized and common mitochondrial cause of blindness.<sup>9,10,13</sup> There are an estimated 100 000 new cases of avoidable and permanent visual loss due to ethambutol annually.<sup>9</sup> While there is no universally safe dose of ethambutol (toxicity has been noted at doses <15 mg/kg/day), dosing should take into account the patient's weight, age, and renal function.<sup>9,10</sup> Further, as recommended by the Centers for Disease Control and Prevention, ethambutol should be discontinued once drug-susceptibility tests show it to be unnecessary.<sup>10</sup>

Several other agents less clearly toxic to the optic nerve are carbon disulfide, chloramphenicol, pheniprazine, quinine, and thallium. In addition, toxins such as carbon tetrachloride, cassava, dapsone, and suramin are suspected but unproven causes of optic neuropathy.<sup>22</sup>





**Fig. 9.9.1 Humphrey Visual Field Strategies 30–2.** A large stimulus V was used. (A) Note the centrocecal scotoma that bridges fixation to the blind spot of the right eye. (B) In the left eye, the scotoma seems a little more centralized around fixation. It is notable that this patient, who had tobacco–alcohol amblyopia (mixed toxic and nutritional deficiency optic neuropathy), also had relatively small central scotomas but visual acuities of 20/400 (6/120) in each eye.



**Fig. 9.9.2 Fundus Views Reveal Mild Temporal Optic Disc Pallor.** (A) Right optic disc. (B) Left optic disc. More interesting, however, is the loss of the nerve fiber layer in the papillomacular bundle. This patient, who had tobacco–alcohol amblyopia (mixed toxic and nutritional deficiency optic neuropathy), also had visual acuities of 20/400 (6/120) in each eye, which recovered to only 20/100 (6/30) after changes in habit and diet and vitamin therapy. In this class of optic neuropathies, relatively severely compromised visual acuities and dyschromatopsia often are found with minimal optic disc atrophy.

Similarities in clinical presentations of nutritional and toxic optic neuropathies are likely due to perturbation of the common biochemical pathway responsible for energy metabolism within the optic nerve head. Oxidative phosphorylation within mitochondria involves the process of electron transfer to oxygen and the production of ATP. Vitamins such as B12 and folic acid are crucial to this process. Similarly, agents such as cyanide or formate (a metabolic product of methanol) block this electron transport. The final common product of these deficiencies and toxins is decreased ATP production by mitochondria and the accumulation of ROS.<sup>2,5</sup> Compensatory mechanisms may apply to some cell types, but fibers of the optic nerve—most particularly the PMB—are susceptible due to the long unmyelinated segment in the retina and the consequent inefficiency of unmyelinated axonal conduction.<sup>25</sup>

## OCULAR MANIFESTATIONS

LHON typically begins with the sudden onset of painless monocular visual loss, which the patient may describe as a blurring of vision, but more often as a central dark or gray cloud. This develops first in one eye and then soon after (days to several weeks) afflicts the fellow eye in a similar fashion. In contrast, most patients who have either toxic or nutritional optic neuropathy experience slowly progressive bilateral loss of central vision. Described

below are the ocular manifestations that on the whole are quite similar for all three syndromes (LHON, nutritional, and toxic optic neuropathies).

On examination, patients generally have bilateral impairment of visual acuity that varies from minimal to hand motion vision. The severity of visual acuity loss in the two eyes is usually quite symmetrical. Loss of color vision is more profound than the loss of visual acuity. Very early cases may exhibit isolated dyschromatopsia.<sup>26</sup> The hallmark of these disorders is the visual field defect that consists of a centrocecal scotoma that begins nasal to the blind spot and extends to involve fixation on both sides of the vertical meridian (Fig. 9.9.1). Pupillary reactions are often normal, even in the early monocular stages of LHON. This is because of a relative preservation of the melanopsin retinal ganglion cells that subserve the retinotectal pathway in LHON.<sup>27–29</sup>

A peripapillary microangiopathy may occur in early LHON.<sup>30</sup> Telangiectatic or tortuous blood vessels may be seen around the optic disc, but this occurs transiently and often is overlooked until involvement of the second eye becomes apparent. In nutritional deficiencies and toxic optic neuropathies, the fundus may appear normal. However, a careful examination may reveal nerve fiber layer losses in the PMB, sometimes associated with swelling of the nerve fiber layer in the arcuate bundles above and below the denuded area.<sup>31</sup> Later in the course of the disease, the temporal optic nerve pallor is often noted (Fig. 9.9.2). The mismatch between relatively

mild temporal disc pallor and severe depression of visual acuity, visual field, and color vision may lead to the misconception that the patient is malingering.

## DIAGNOSIS AND ANCILLARY TESTING

A careful history usually provides enough information to make a presumptive diagnosis of LHON. The patient describes the subacute, painless loss of vision monocularly, possibly followed soon after by involvement of the fellow eye. This sequential involvement and the family history help to differentiate LHON from nutritional deficiencies and toxic optic neuropathies. Most often, LHON manifests in men in their late teens or early twenties. It can be differentiated from toxic and nutritional optic neuropathies by the family history, presence of telangiectatic vessels around the optic nerve head during the acute phase, and the likelihood that one eye is affected before the other (not simultaneous occurrence). Optical coherence tomography (OCT) will reveal peripapillary nerve fiber layer thickening early in the disease course followed by thinning as atrophy ensues, while the ganglion cell complex will show progressive atrophy (see Chapter 9.2). The diagnosis is confirmed by laboratory study of the point mutation in the mitochondrial DNA.

Care must be taken to explore all possibilities in terms of diet, medications, and exposures, with an emphasis on recent changes in pattern. Suspected toxicities can be confirmed through serum and urine analysis. In particular, 24-hour urine collection for heavy metal screening may yield unexpected results. In addition to serum vitamin levels for B1, B2, B12, and folic acid, it is often useful to obtain serum pyruvate levels.

## DIFFERENTIAL DIAGNOSIS

The differential diagnosis of toxic and nutritional optic neuropathies includes disorders that cause acute and subacute symmetrical losses in visual acuity and color vision. The similarities between LHON and nutritional deficiency and toxic optic neuropathies have been addressed.

Autosomal dominant optic atrophy (DOA), a nuclear (OPA1) genetic disorder, can be confused with toxic and nutritional optic neuropathies. There is an autosomal dominant family history, and the optic neuropathy occurs slowly and progressively in late childhood.

Chiasmal syndromes sometimes need to be ruled out. Pituitary adenomas or other lesions that compress the optic chiasm generally present with bitemporal visual field loss but without any significant loss of central acuity or color vision. In the early stages, bitemporal field losses may appear similar to centrocecal scotomas, particularly with prefixed chiasm. Occasionally, optic neuritis may occur bilaterally and produce almost any type of visual field defect. If the patient has multiple sclerosis, a number of plaques may be visible on T2-FLAIR sequences in magnetic resonance images; furthermore, most patients who have optic neuritis show dramatic recovery of visual acuity over several weeks.

There is controversy regarding the possibility that amiodarone may cause optic neuropathy. Amiodarone is a benzofuran derivative with vasodilatory and antiarrhythmic properties, used in treating supraventricular and ventricular cardiac arrhythmias. Among the numerous side effects, ranging from mild to life threatening,<sup>32</sup> corneal microdeposits are very common and can even be used to ascertain the therapeutic dosage of the therapy. The keratopathy usually does not cause any serious visual disturbance, but occasionally patients may note halos and mild photosensitivity.<sup>33</sup> Hyperthyroidism, peripheral neuropathy, ataxia, bone marrow depression, and pulmonary toxicity are several of the more severe side effects that are attributed to the use of amiodarone.<sup>32,34</sup>

Some reports suggest that patients on amiodarone therapy may also be at risk of developing an amiodarone-induced optic neuropathy, which is hard to distinguish from nonarteritic anterior ischemic optic neuropathy (AION). The most compelling evidence for the existence of amiodarone-induced AION is the increased incidence of AION among patients receiving amiodarone therapy (1.79%).<sup>35</sup> This is higher than the incidence of AION in the general population age 50 or older (0.3%).<sup>35</sup> However, such a comparison fails to consider that patients on amiodarone therapy have cardiac arrhythmias, hypertension, and other potential risk factors for AION.

Others have suggested that amiodarone produces an optic neuropathy that can be distinguished from AION. Purported amiodarone-induced optic neuropathy may be characterized by the insidious onset of bilateral and symmetrical visual loss with slow progression, whereas AION is characterized by an acute, unilateral visual loss that is rarely progressive. Amiodarone-induced optic neuropathy causes a protracted disc swelling

that tends to stabilize within several months of discontinuation of medication, whereas AION is characterized by resolution of disc edema over several weeks. In amiodarone-induced optic neuropathy, the cup-to-disc ratio is larger than that seen in AION,<sup>35</sup> and the fundus should exhibit bilateral disc edema (Fig. 9.9.3).

Nonetheless, it may be prudent to perform ophthalmological examinations on patients taking amiodarone. Alternative antiarrhythmic therapy may be considered in cases of bilateral disc edema. While a relationship between LHON and AION is tenuous, mitochondrial dysfunction has the potential to underlie a variety of optic neuropathies.<sup>36</sup>

Finally, because the nerve and nerve fiber layer changes in LHON and nutritional and toxic optic neuropathies can sometimes be very subtle, psychogenic visual loss often is considered in the differential diagnosis. Electrophysiological studies can be useful to distinguish organic from inorganic disease (see Chapter 9.27).

## SYSTEMIC ASSOCIATIONS

Multifactorial mixed nutritional optic neuropathies may be associated with neurological symptoms, such as paresthesias, ataxia, or hearing impairment, in addition to visual involvement. However, these are more characteristic of general nutritional deficiencies sometimes found in clusters in equatorial countries and termed tropical amblyopias. These instances are not usually described in cases of toxic exposure or single vitamin deficiency.<sup>37</sup> Visual symptoms may be seen in association with paresthesias and dysesthesias—particularly in the legs—in association with ataxia and hearing loss. This has been described in vitamin deficiencies associated with poor diet, compounded by the ingestion of cassava and by elevated levels of cyanide.<sup>38</sup>

## PATHOLOGY

Much of our understanding of pathology that underlies hereditary optic neuropathies comes from the study of LHON. The discovery of the ND4 mutation by Wallace's group<sup>39</sup> in 1988 opened the door to understanding the complex interplay between mitochondrial and nuclear DNA that underlies energy production in living cells.<sup>39</sup> Sadun et al.,<sup>25</sup> Kerrison et al.,<sup>40</sup> and others have since provided ultrastructural characterizations of the three primary mitochondrial mutations in LHON from genetically characterized pedigrees.<sup>41,42</sup> In addition to severe losses of retinal ganglion cells in the macular area and depletion of the nerve fiber layer, these authors described accumulations of mitochondria in other orbital tissues and noted electron-dense,<sup>43</sup> membrane-bound calcium inclusions in the remaining retinal ganglion cells. These diseased mitochondria appear to be unable to produce as much ATP, but perhaps more significantly, there is an increase in reactive oxygen species (ROS) production.<sup>44</sup> This ultimately leads to the death of the cell.

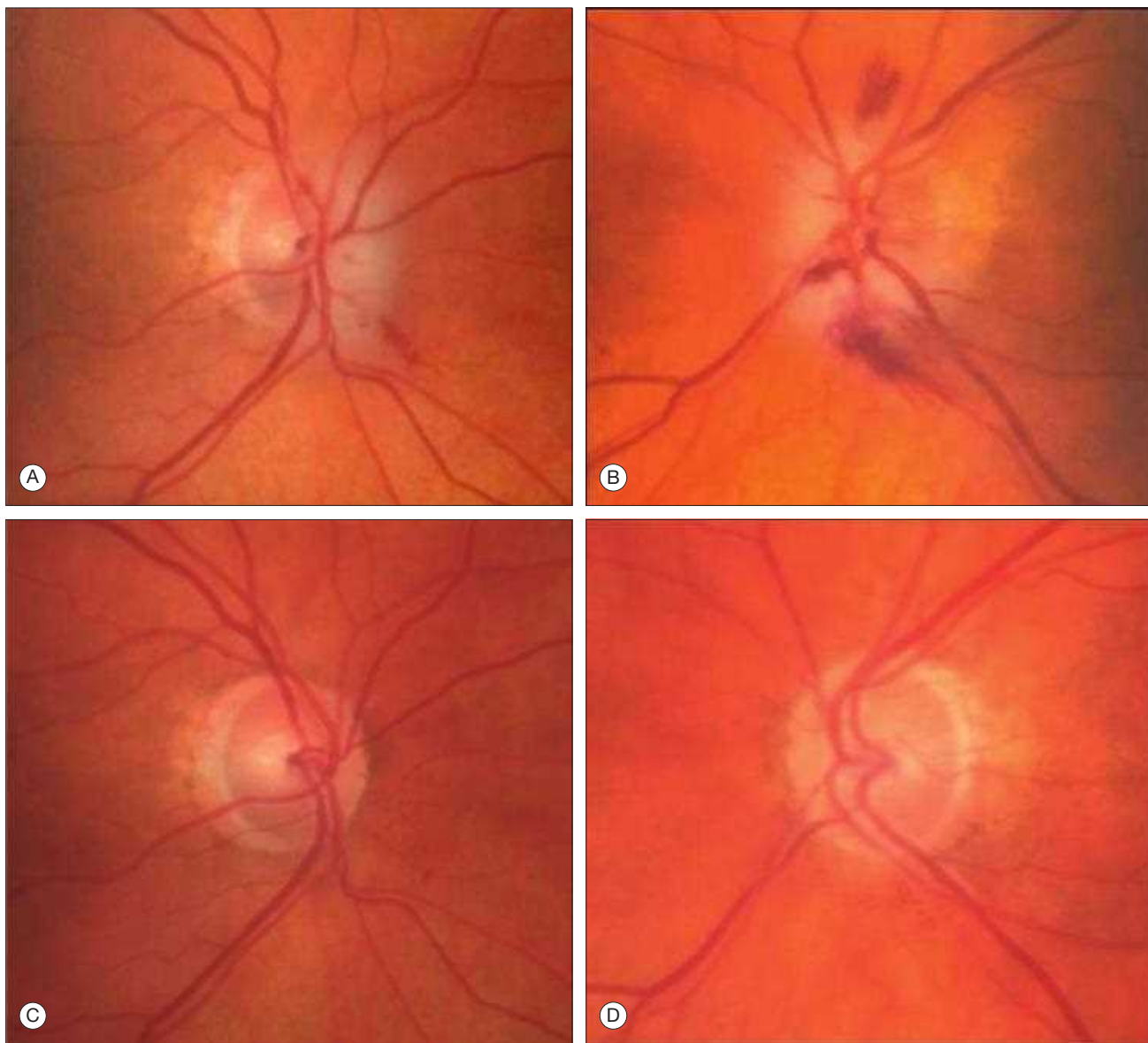
Clinically there are two stages to LHON, carriers who have the mutation and have "normal vision" and affected patients who have the mutation and vision loss. This distinction is perhaps an artifact of our ability to detect changes in asymptomatic carriers. Objective tests such as OCT measurements do show subclinical changes in the optic nerve.<sup>43</sup>

Savini and coworkers<sup>45</sup> have provided further objective evidence that in subclinical LHON, the PMB is affected as shown by the significant increase in RNFL thickness observed by OCT measurements in the temporal quadrant. A thickening of the temporal fibers was detected in all subgroups of unaffected carriers with males having a more diffuse involvement than females. Unaffected male carriers showed a thicker RNFL in the temporal and inferior quadrants and in the 360° average measurement. Unaffected female carriers had an increased thickness in the temporal quadrant when compared with the control group.<sup>45</sup>

These data suggest that the RNFL swells especially in the PMB in the presymptomatic stage of LHON. RNFL thickening of these fibers suggests that selective injury with swelling of RNFL occurs before atrophic changes are established. This offers clinicians the opportunity to more carefully track LHON development in patients in the presymptomatic stage. LHON may manifest with a subclinical phase with axonal thickening and near normal visual function that may or may not precede clinically significant vision loss reflecting the acute phase of axonal injury with clinically significant loss of visual function.

Hence, we are in a paradigm shift in regard to LHON. No longer should we consider this as a disease in which phenotypically normal carriers abruptly transition to affected status. Rather, there may be a complex interplay between compensatory and decompensatory factors that may also represent a window of opportunity for treatment.<sup>46</sup>





**Figure 9.9.3 Fundus Views From a Patient With Amiodarone-Associated Optic Neuropathy.** The patient presented with constricted visual fields and bilateral simultaneous disc swelling (A–B) that resolved with the discontinuation of amiodarone (C–D).

Much of what we have learned about LHON has implications for the other hereditary, nutritional, and toxic optic neuropathies.<sup>47,48</sup> One of the better understood outbreaks of optic neuropathies occurred in Cuba in the early 1990s (CEON). Socioeconomic challenges led to malnutrition, which combined with high levels of tobacco and cassava consumption increased circulating levels of cyanide. The toxicity of cyanide on the mitochondria is well described and indeed most toxic or nutritional optic neuropathies affect mitochondrial energy production leading to cell death.<sup>48,49</sup> Some agents, such as antibiotics, are targeted to enzymes that lead to the death of microorganisms. Mitochondria are in essence bacteria that are living in eukaryotic cells.<sup>50</sup> Thus it is not surprising that antimicrobials, including ethambutol, linezolid, and erythromycin, are able to cause a mitochondrial optic neuropathy by poisoning the energy production of the cells.<sup>51</sup>

The most intriguing aspect of the pathophysiology of all of these optic neuropathies is their preference for the papillomacular bundle. This can, also, be explained by the energy dynamics of the cells involved. RGCs are in part more susceptible to injury than other neurons as they have a long unmyelinated segment and high energy demands. The fibers of the PMB, which subserve the central vision, are the most susceptible RGCs as they have a narrow caliber leading to a relatively high surface area to volume ratio.<sup>2,13,14,52</sup> This, in turn, increases their energy needs and paradoxically limits their ability to compensate for the increased energy demands of defective mitochondria by physically limiting the ability to accumulate more mitochondria.<sup>51</sup> This compensatory accumulation of mitochondria accounts for the electron-dense bodies found in LHON described above.

## TREATMENT

The cause of a toxic or deficiency optic neuropathy should be found and treated early (for example, by cessation of smoking and the administration of vitamins in tobacco–alcohol amblyopia). In the absence of a demonstrable deficiency, no good evidence exists that empirically giving B vitamins is of any benefit. Nonetheless, it is not uncommon to prescribe cyanocobalamin (vitamin B12) in suspected cases of tobacco–alcohol amblyopia and LHON. Idebenone, a quinol analog, has been used recently in a few cases of LHON to ameliorate the net ATP synthesis by providing an alternate pathway, as well as scavenging free radicals with the advantage of concentrating readily in the mitochondria.<sup>53</sup> Patients who have already lost vision in one eye from LHON might be candidates for pharmacological manipulation of mitochondrial metabolism to protect the second eye.<sup>13,36</sup>

Coenzyme Q10 has been proposed as treatment for LHON as it can target the excessive production of ROS. However, there have been no successful case series with this treatment, which is not surprising given the lack of blood–brain barrier penetration by CoQ10.<sup>14</sup> Second (idebenone) and third (EPI-743) generation quinones with better blood brain barrier penetration have been used with greater success.<sup>54–56</sup> These treatments are neither dramatic nor quick to show effect. However, after 1 year of quinone treatment, most patients show some improvement.<sup>54–56</sup>

Other treatment approaches under investigation for LHON include different methods of supporting the electron transport chain stabilization and reducing ROS,<sup>57–59</sup> and new approaches using gene therapy. The



first involves the use of adenovirus-associated vectors (AAV2) to supplement the defective mitochondrial DNA gene product with the unmutated form. Data from animal and preliminary human studies suggest that this treatment approach could correct the underlying genetic defect.<sup>60-63</sup> The second genetic approach seeks to eradicate LHON by replacing the damaged mtDNA with wild-type mtDNA prior to conception. This technology, termed mitochondrial donation, inserts a donor oocyte with wild type mtDNA (which is enucleated and has the nuclear DNA of a woman carrying the mtDNA mutation).<sup>64</sup> There is considerable ethical debate on the future of this therapy,<sup>65</sup> and experimentation with this technology is limited. An adapted approach exploits the presence of both mutant mtDNAs in the oocyte prior to conception and attempts to skew the heteroplasmy in favor of the wildtype.<sup>66</sup> All of these techniques are still investigative and have implications not only for LHON but also other genetic disorders.<sup>47</sup>

## COURSE AND OUTCOME

In many cases, prompt administration of the deficient nutrient (such as a vitamin) or removal of the toxin (such as ethambutol) results in significant recovery over a period of months. However, in cases in which the injury is long-standing, there may be little or no recovery. In LHON, most patients show minimal recovery, although there have been reports of dramatic and late improvements in individuals carrying the 14484 mutation.<sup>67</sup> The 11778 and 3460 mutations carry a less favorable prognosis, with over 75% becoming legally blind in both eyes.<sup>13</sup> Advances with quinone therapy, such as idebenone, have altered the natural history of LHON, often contributing to stabilization of vision and sometimes modest recovery.<sup>54-56</sup> Advances in the genetic therapies, if successful, have the promise to both treat affected carriers and stop germline transmission of LHON-mutated mtDNA.

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# Prechiasmal Pathways—Compression by Optic Nerve and Sheath Tumors

9.10

Michelle Y. Wang, Thomas C. Spoor

**Definition:** Optic nerve dysfunction occurring as a result of compression by a space-occupying lesion, typically tumor or aneurysm, anywhere along the nerve's course from globe to chiasm.

## Key Features

- Progressive visual field deterioration.
- Relative afferent pupillary defect.
- Dyschromatopsia.

## Associated Features

- Proptosis.
- Swollen or atrophic optic disc.
- Retinal and choroidal striae.
- Optociliary collateral vessels.
- Venous stasis retinopathy or central retinal vein occlusion.

## INTRODUCTION

The optic nerve extends from the back of the eye, traverses the orbit, passes through the optic canal, and has a variable intracranial course before it joins with the contralateral optic nerve to form the chiasm (Fig. 9.10.1). Compression by a tumor or an aneurysm may cause optic nerve dysfunction anywhere along its course from globe to chiasm.

Extrinsic optic nerve compression by orbital tumors or apical orbital compression by enlarged dysthyroid extraocular muscles represents an uncommon but potentially treatable cause of optic neuropathy. These tumors may compress the optic nerve at the orbital apex (Fig. 9.10.2).

## EPIDEMIOLOGY AND PATHOGENESIS

Compression of the apical orbital optic nerve by enlarged extraocular muscles is an uncommon manifestation of thyroid orbitopathy (Fig. 9.10.3). The vast majority of patients who have hyperthyroidism have mild,

noninfiltrative orbitopathy. Clinically significant infiltrative orbitopathy occurs in only 3%–5% of the hyperthyroid population.

Encapsulated orbital tumors are quite uncommon. Of these, cavernous hemangiomas are the most common, neurilemmomas are less common, and hemangiopericytomas are even rarer.

## OCULAR MANIFESTATIONS

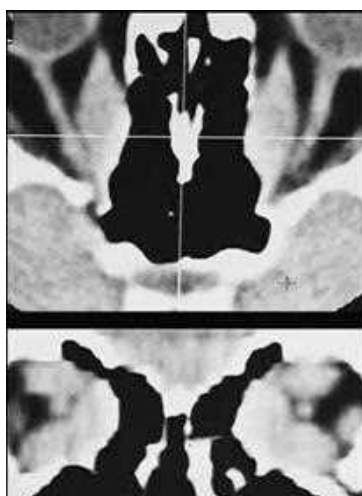
Initially, extrinsic optic nerve compression within the orbit manifests with slowly progressive loss of visual acuity, decreased brightness sensation, and dyschromatopsia. Vision may be good at presentation, but visual field deterioration and relative afferent pupillary defect are seen with progression.



**Fig. 9.10.1** Axial Cadaver Section That Demonstrates the Course of the Optic Nerve From the Globe to the Optic Chiasm. Note the intraorbital, intracanalicular, and intracranial segments of the optic nerve.

**Fig. 9.10.2** Images of a Large Orbit Mass Adjacent or Contiguous With the Optic Nerve. (A) Computed tomography scan (axial). (B) Magnetic resonance imaging shows obvious demarcation between the tumor and the adjacent optic nerve.





**Fig. 9.10.3 Computed Tomography Scans (Axial and Coronal).** The optic nerves are compressed at the orbital apex by enlarged extraocular muscles.

Patients who have large tumors with more anterior optic nerve compression may have a swollen optic disc and choroidal striae. However, anterior orbital tumors more commonly occur with proptosis without compressive optic neuropathy. In patients with thyroid orbitopathy, manifestations such as eyelid retraction and extraocular motility restriction may be seen.

## DIAGNOSIS AND ANCILLARY TESTING

It is key to obtain appropriate imaging studies to visualize the orbital apex. Computed tomography (CT) scanning differentiates optic nerve compression by orbital tumors from apical orbital optic nerve compression by enlarged, dysthyroid extraocular muscles (see Fig. 9.10.2). Magnetic resonance imaging (MRI) scans can help delineate the extent of orbital tumor and facilitate surgical management. Ocular coherence tomography (OCT) may be useful to detect early loss of peripapillary retinal nerve fiber layer (see Chapter 9.2).

## TREATMENT

Treatment of dysthyroid optic neuropathy is to decompress the orbit (more details are discussed in Chapter 12.13). Inflammation may be reduced with systemic corticosteroids or low-dose irradiation, and the orbital apex may be expanded by surgical removal of the orbital walls. In a recent survey, most surgeons prefer a combined approach of floor and medial wall decompression or lateral and medial wall decompression.<sup>1</sup> We favor the initial use of systemic corticosteroids, either intravenous or high-dose oral prednisone 80 mg daily, followed by orbital decompression. Orbital irradiation is reserved for cases refractory to corticosteroids and surgical decompression.

Treatment of optic nerve compression caused by an encapsulated orbital tumor entails surgical removal of the tumor. MRI may help to differentiate the tumor from the optic nerve and ascertain the tumor's position in reference to the optic nerve. The latter is important in planning an appropriate surgical approach for tumor excision.

## OPTIC NERVE COMPRESSION BY OPTIC NERVE AND SHEATH TUMORS

### INTRODUCTION

The optic nerve may be invaded by intrinsic tumors (such as gliomas) arising from the neuroglia or neurons or compressed by extrinsic tumors arising from the meninges (such as meningiomas). Optic nerve gliomas and optic nerve sheath meningiomas are the most common tumors to involve the optic nerve. Less commonly, the optic nerve also may be involved by lymphomas, leukemias, malignant gliomas, and metastatic cancers.

## GLIOMAS AND MALIGNANT GLIOMAS

### Epidemiology and Pathogenesis

Gliomas of the anterior visual pathways are the most common tumors of the central nervous system, accounting for 2% of all gliomas and 5% of



**Fig. 9.10.4 Magnetic Resonance Imaging of a Large Optic Nerve Glioma and Optic Canal.**

childhood gliomas. These tumors occur most commonly during the first two decades of life; 65% occur within the first decade, and 90% occur before 20 years of age. Rarely, a glioma may occur in a previously asymptomatic adult as an expanding orbital mass. Gliomas of the anterior visual pathways account for 65% of all intrinsic optic nerve tumors.<sup>2</sup> Malignant gliomas of the optic nerve are rare.<sup>3,4</sup> Gliomas that involve the intraorbital optic nerve are most common (47%). Those that involve the orbital and intracranial optic nerve are second most common (26%), followed by intracranial and chiasmal involvement (12%) and gliomas confined to the optic chiasm (5%).<sup>4</sup>

## Ocular Manifestations

Patients with optic nerve gliomas usually experience exophthalmos, extraocular motility dysfunction, decreased visual function, and dyschromatopsia accompanied by a relative afferent pupillary defect. The optic disc may be normal, swollen, or atrophic. Central retinal vein occlusion may occur.

Patients who have malignant gliomas of the optic nerve have rapidly progressive, painful visual loss accompanied by signs of an optic neuropathy.<sup>3,4</sup> Initial visual loss may be unilateral or bilateral (chiasmal involvement), but rapid progression to bilateral blindness and death are constant features.<sup>2</sup>

## Diagnosis

Intrinsic enlargement of the optic nerve on MRI is evident in patients who have optic nerve gliomas. The presence and extent of optic nerve gliomas is best demonstrated by MRI (Fig. 9.10.4).<sup>2</sup> Although rarely missed with high-resolution CT scans, optic nerve enlargement by an intrinsic glioma may be confused with compression by a resectable orbital tumor; MRI may help to differentiate these (see Fig. 9.10.3).

For patients who have orbital nerve gliomas and neurofibromatosis type 1, MRI demonstrates a typical double-intensity tubular thickening caused by perineural arachnoid gliomatosis and elongation and downward kinking of the midorbital optic nerves.<sup>5</sup>

Imaging studies of an optic nerve glioma may show enlargement of the optic forearm that arises from secondary meningeal hyperplasia. Therefore, enlargement of the optic forearm is not firm evidence of intracranial extension of an optic nerve glioma.

Imaging studies of malignant gliomas of the optic nerve demonstrate enlargement of the involved regions of the optic nerve and chiasm, although initially normal imaging study results have been reported.<sup>3,4</sup> The diagnosis of this devastating disease should be confirmed by biopsy of the involved portion of the optic nerve.

## Differential Diagnosis

The differential diagnosis of visual loss from optic nerve glioma is the differential diagnosis of any slowly progressive optic neuropathy. Differentiation between gliomas and other causes of optic nerve compression in a child is best accomplished using appropriate imaging studies (see earlier).

## Systemic Associations

Frequently, optic nerve gliomas are found in association with neurofibromatosis type 1 (only rarely with neurofibromatosis type 2), which is present in 25% of patients who have optic nerve gliomas, whereas 15% of patients with neurofibromatosis have optic nerve gliomas. Increased intracranial pressure and chiasmal and optic tract involvement are more common in patients who do not have neurofibromatosis. Precocious puberty is more common in children who have gliomas and neurofibromatosis.<sup>6,7</sup>

## Pathology

Optic nerve gliomas are intrinsic tumors that arise from the neuroglia—usually astrocytes but occasionally oligodendrocytes. Three histopathological patterns exist:

- Transitional areas in which the tumor merges with normal optic nerve and which may be difficult to differentiate from reactive gliosis.
- Areas of tumor necrosis, which may appear as cystic spaces that contain reticulated, myxomatous material.
- Areas where astrocytes may show spindle cell formation and contain cytoplasmic, eosinophilic structures called Rosenthal fibers.

These patterns are characteristic but not diagnostic of optic nerve gliomas.<sup>6</sup> Arachnoid hyperplasia, secondary to infiltration by the glioma through the pia, may mimic an optic nerve sheath meningioma.

Biopsy specimens of malignant gliomas of the optic nerve demonstrate bizarre, atypical malignant astrocytes that separate disrupted myelin sheaths.

## Treatment

Treatment of gliomas of the anterior visual pathways is controversial. If visual function is good, isolated intraorbital optic nerve gliomas may be observed. Visual function may be followed with serial visual field testing, and MRI should be done every 6–12 months to detect any intracranial extension. Most of those tumors grow slowly over time and may be self-limited. Since most observed patients retain stable vision, surgery is rarely necessary.<sup>8</sup> If vision is poor or exophthalmos is excessive and unsightly, the lesion may be removed via a craniotomy and superior orbitotomy. If intracranial extension by a glioma initially confined to the orbit is documented, the tumor can be removed completely via craniotomy in an effort to avoid chiasmal, hypothalamic, or third ventricle involvement. Chemotherapy has increasingly become the initial treatment for infants with optic pathway gliomas as it may help defer radiotherapy until the child has completed development.<sup>9</sup> Radiotherapy may be helpful for tumors involving the chiasm or optic tract. It may also be considered as an adjuvant therapy after surgery or chemotherapy if there is progressive growth in the chiasm. However, radiotherapy is accompanied by a significantly increased risk of second nervous system tumors in patients with neurofibromatosis type 1 as well as growth retardation in infants.<sup>10</sup>

There is no successful treatment for malignant gliomas of the visual pathways.

## Course and Outcome

Optic nerve gliomas are true neoplasms that characteristically demonstrate early growth followed by long periods of stability in many cases. They have a poor prognosis for vision, but if the tumor is confined to the optic nerve, long-term survival is excellent. If the chiasm, hypothalamus, or third ventricle is involved, the prognosis for life diminishes. Once the hypothalamus is involved, mortality rises to over 50%. No therapy exists of proven benefit.<sup>3</sup> Spontaneous regression may occur.<sup>11</sup> There is a tendency for vision in the worse eye to deteriorate and vision in the better eye to remain stable regardless of treatment or neurofibromatosis status.<sup>12</sup>

Patients who have malignant gliomas of the optic nerve experience painful visual loss and rapidly progress to bilateral blindness within 6–8 weeks. Death invariably follows within 6–9 months after the initial symptoms.<sup>3,4</sup>

## OPTIC NERVE SHEATH MENINGIOMAS

### INTRODUCTION

Meningiomas are benign neoplasms that arise from the meningotheelial cells of the meninges. The optic nerve may be compressed by meningiomas



**Fig. 9.10.5** Gadolinium-Enhanced Magnetic Resonance Imaging Demonstrates the Intracranial Extension of an Optic Nerve Sheath Meningioma.

confined to the optic nerve or by orbital extension of intracranial tumors. Slowly progressive, relentless visual loss may be accompanied by proptosis and extraocular motility dysfunction.

## EPIDEMIOLOGY AND PATHOGENESIS

Optic nerve sheath meningiomas represent 1%–2% of all meningiomas. After gliomas, these are the second most common type of optic nerve tumor and primarily affect middle-aged adults, usually women.

## OCULAR MANIFESTATIONS

Slowly progressive visual loss is the hallmark of an optic nerve sheath meningioma. Some patients may present with transient vision loss, which may be gaze evoked. A relative afferent pupillary defect and dyschromatopsia invariably are present. The optic disc may be swollen or atrophic. Retinal and choroidal folds may be evident on fundus examination. Even though optociliary collateral vessels may not always be present, their presence indicates chronic compression of the central retinal vein. Extraocular motility dysfunction is present in some cases.

## DIAGNOSIS

Neuroimaging confirms the diagnosis of optic nerve sheath meningioma. CT scans demonstrate fusiform, tubular, or irregular enlargement of the optic nerve. The borders of the enlarged optic nerve may enhance after administration of intravenous contrast to leave a central, linear lucency within the optic nerve sheath (tram-track sign). Extensive or segmental calcifications also may be present.

MRI fat suppression and gadolinium-diethylenetriamine-pentaacetic acid (Gd-DTPA) enhancement can detect and demarcate precisely the degree of extension of optic nerve sheath meningiomas (Fig. 9.10.5). The majority of intraorbital and intracranial meningiomas are detectable by CT scans, but gadolinium-enhanced MRI can more reliably demonstrate subtle findings (see Fig. 9.10.5). Rarely, isolated small intracanalicular tumors may still be difficult to visualize. Studies with high-quality MRI demonstrate that even with small tumors, intracranial extension is the rule rather than the exception.<sup>13</sup>

## PATHOLOGY

Meningiomas arise from the meningotheelial cells of the arachnoid villi. Histopathology demonstrates patterns of whorls and sheets of meningotheelial cells. A variable amount of fibrous and vascular tissue occurs in fibroblastic pattern meningiomas, with psammoma bodies present in psammomatous and mixed meningiomas.

## TREATMENT

The management of optic nerve sheath meningioma is controversial. Traditionally, treatment is conservative because these tumors tend to grow

very slowly and are not amenable to complete resection without compromising the vascular supply due to its close proximity to the optic nerve and pial vasculature. Most tumor resections result in complete visual loss, except for tumors that are primarily extradural.<sup>14</sup> Therefore, observation, serial automated visual fields, and MRI scans are appropriate for patients who have good vision without evidence of intracranial extension of tumor. In patients who have no useful vision, surgery is warranted when there is intracranial extension or to relieve severe disfiguring exophthalmos. For patients who still have useful vision, surgery should be limited to the intracranial portion.

Conventional radiotherapy can be successful<sup>15</sup>; however, radiation-associated complications limit its use. Stereotactic or conformal fractionated radiotherapy, designed to deliver more focused radiation, allows a high degree of spatial specificity to the tumor. This new technique shows promise in improving long-term visual outcome and minimizing irradiation of the surrounding tissue.<sup>16,17</sup> Stereotactic and conformal fractionated radiotherapy are becoming accepted as the treatments of choice when patients demonstrate progressive vision loss. It is important to maintain long-term follow-up as radiation-induced pathology, including secondary neoplasia, remains a potential risk.

## COURSE AND OUTCOME

The clinical course of optic nerve sheath meningiomas is a slowly progressive, relentless visual loss in the affected eye. The prognosis for life is excellent, with an overall tumor-related mortality of near zero.<sup>14</sup>

## OTHER INTRACANALICULAR AND INTRACRANIAL COMPRESSIVE LESIONS

The optic nerves may be compressed within the optic canal or intracranially by any entity that can compress the optic chiasm, depending on the length of the intracranial optic nerves and their position relative to intracranial structures (e.g., pre- or post-fixed optic chiasm; see Chapter 9.12). Aneurysms, tumors, infection, inflammation, mucocoeles, and processes that involve the sphenoid bone, such as fibrous dysplasia, may cause a compressive optic neuropathy (Box 9.10.1). The involved optic nerves may appear normal, atrophic, swollen, or excavated. Optic disc excavation in the absence of elevated intraocular pressure may indicate a compressive optic neuropathy, especially if accompanied by pallor of the neuroretinal rim.<sup>14</sup>

### BOX 9.10.1 Intracranial Causes of Compressive Optic Neuropathies

#### Inflammation

Neurosarcoidosis

#### Infectious

Tuberculous meningitis

Syphilis-meningitis or gumma

#### Aneurysms

Supraclinoidal

Ophthalmic

#### Tumors

Gliomas

Pituitary adenomas

Meningiomas

- Sphenoid ridge
- Planum sphenoidale, suprasellar, intrasellar

Craniopharyngiomas

Paranasal sinus tumors

Mucocoeles

Fibrous dysplasia

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# Traumatic Optic Neuropathies

Michelle Y. Wang, Thomas C. Spoor

# 9.11

**Definition:** Optic nerve damage after cranio-orbital trauma.

## Key Features

- Decreased visual acuity.
- Visual field defects.
- Relative afferent pupillary defect.

## Associated Features

- Optic nerve infarction.
- Orbital or optic nerve sheath hematoma.
- Central retinal artery occlusion.
- Orbital and optic canal fractures.

## INTRODUCTION

Optic neuropathy may occur directly or indirectly after cranio-orbital trauma. Causes of damage include optic nerve transection, avulsion, ischemia, or orbital hemorrhage and edema. Direct optic nerve injuries arise from penetrating trauma, especially orbital fractures associated with mid-facial fractures, whereas indirect optic nerve injuries occur when the force of impact is imparted into the skull and transmitted to the optic nerve. Orbital hemorrhage compromises the circulation to the optic nerve, resulting in injury secondary to orbital compartment syndrome. Primary injury to the optic nerve fibers by transection or infarction at the time of injury results in permanent damage. However, neural dysfunction secondary to compression within the optic canal as a result of edema and hemorrhage may respond to medical or surgical intervention.

## EPIDEMIOLOGY AND PATHOGENESIS

Traumatic optic neuropathy (TON) occurs in 0.5%–2% of patients who suffer closed head trauma.<sup>1</sup> The optic nerve is enclosed tightly within the bony optic canal; it may be damaged by shearing and avulsion of its nutrient vessels or by pressure transmitted along the bone to the optic canal.

## OCULAR MANIFESTATIONS

A complete history is essential in the diagnosis of TON, which remains a clinical diagnosis. Visual acuity is invariably reduced, often to a significant degree, and is invariably accompanied by an afferent pupillary defect in cases of unilateral optic nerve injury. Patients who have bilateral and symmetric optic nerve dysfunction may demonstrate light-near dissociation, characterized by poor pupillary light responses but intact accommodative pupillary responses. Anterior injuries may cause avulsion of the optic nerve head, appearing as a ring of hemorrhage or a deep pit at the site of injury, as well as compromised retinal circulation resulting in infarction, hemorrhage, or central retinal artery occlusion evident on ophthalmoscopy. More posterior injuries often lead to an afferent pupillary defect and visual loss despite a normal fundus.

## DIAGNOSIS AND ANCILLARY TESTING

Visual fields may help localize the site of optic nerve damage, but testing of visual fields requires a sufficient level of vision, and there is no

pathognomonic field defect in TON. High-resolution computed tomography (CT) is the diagnostic procedure of choice as it can delineate bony fractures better than magnetic resonance imaging (MRI). Treatable causes of optic nerve compression, such as orbital and optic nerve sheath hemorrhages, are detected using CT scans,<sup>1</sup> as are orbital and optic canal fractures. MRI is superior to CT for imaging soft tissues and assessing chiasmal damages. Hyperintensity of the optic nerve on diffusion-weighted image due to restricted diffusion may be an imaging marker for TON.<sup>2</sup>

## DIFFERENTIAL DIAGNOSIS

Traumatic optic nerve injury may sometimes occur even after a relatively minor head injury. Detection of visual loss may be coincident with the traumatic event. The differential diagnosis should include other causes of optic neuropathies and causes of obviously treatable optic nerve compression (Box 9.11.1).

## PATHOLOGY

The optic nerve can be injured anywhere along its course, most commonly at the intracanalicular and intracranial portion. Forces applied to the frontal bone may be transmitted and concentrated at the optic canal.<sup>3</sup> Acceleration and deceleration forces may cause a partial or total avulsion of the retrobulbar optic nerve, contusion necrosis, and shearing of the pial vascular supply to the intracanalicular optic nerve leading to ischemic infarction. The bony canal has very limited space; the middle part of the canal is the narrowest segment, making it the most likely site of injury. Hence even a tiny amount of hemorrhage or swelling may cause optic nerve compression.<sup>4</sup> Orbital hemorrhage or hemorrhage into the optic nerve sheath also may cause progressive visual loss. The intracranial optic nerve may be injured by the falciiform dural fold caused by the force of a shifting brain at the moment of impact. Swelling of the intracanalicular optic nerve causes delayed, progressive visual loss through exacerbation of the ischemic effects of the original injury. Any or all of these mechanisms may be responsible for optic nerve injury.<sup>1</sup>

Optic nerve injuries may be caused by primary or secondary mechanisms. The primary mechanism causes mechanical shearing of the optic nerve and its vasculature, leaving permanent, irreparable damage to the optic nerve. Treatment modalities are potentially effective only for secondary mechanisms, which arise from the force of impact, causing optic nerve swelling at the cellular level and ischemia that further compromises an injured optic nerve.<sup>1</sup> Treatment consists of attempts to limit secondary injury and salvage axons that survive the initial trauma.

### BOX 9.11.1 Differential Diagnosis of Traumatic Optic Neuropathy

- Optic nerve sheath hematoma
- Orbital hematoma
- Subperiosteal hematoma
- Coincident optic neuropathies
- Compression by tumor or aneurysm
- Optic nerve inflammation
- Orbital inflammation
- Sinusitis with orbital involvement
- Ischemic optic neuropathy
- Optic neuritis

## TREATMENT

The primary optic nerve injuries are not treatable. The secondary effects of the primary injury—edema and hemorrhage—may be treatable. Although orbital hemorrhage that compromises the optic nerve warrants immediate decompression by lateral canthotomy and cantholysis, there is no established standard of care for TON secondary to other causes. Patients may improve spontaneously without treatment.<sup>5</sup> However, many suffer severe permanent vision loss. Treatment for TON remains controversial.

Treatment with megadose corticosteroids was initially suggested based, in part, on the success attained in treatment of spinal cord injuries.<sup>6</sup> Treatment should begin within 8 hours of injury. Methylprednisolone 30 mg/kg is administered intravenously over 30 minutes followed by 15 mg/kg 2 hours later. This dosing regimen compensates for the rapid serum half-life of methylprednisolone. Treatment is continued with 15 mg/kg every 6 hours for 24–48 hours. If visual function improves, corticosteroids are tapered rapidly. Administered within 8 hours after injury, megadose corticosteroids have an antioxidant and membrane-stabilizing effect that limits secondary cell damage and increases microcirculatory perfusion.<sup>7</sup>

Some studies show that patients treated with corticosteroids or a combination of corticosteroids and optic canal decompression seem to have better visual prognosis than untreated patients.<sup>5,8–10</sup> Treatment with megadose corticosteroids seems to improve vision more quickly than treatment with high-dose intravenous corticosteroids, but there is no significant difference in the final visual outcome.<sup>11,12</sup> However, the Corticosteroid Randomization After Significant Head Injury (CRASH) trial showed increased mortality among patients with acute head trauma who were treated with high-dose corticosteroids.<sup>13</sup> Given the severity of potential adverse effect and lack of proven clinical efficacy, Steinsapir and Goldberg recommend against the use of corticosteroid in TON.<sup>14</sup>

Surgery is recommended by those who believe that prompt surgical decompression may expand tissue space and relieve compression of the optic nerve.<sup>8</sup> As with any surgical procedure, potential risks must be weighed against possible benefits.

It is important to keep in mind that the benefits of medical, surgical, or combined treatment options have not been clarified by randomized

controlled trial. Therefore, many prefer the safer approach—observation and use of corticosteroids only in selected cases.<sup>15</sup> The International Optic Nerve Trauma Study, the largest unbiased study to date, failed to demonstrate clear benefit for either corticosteroids or optic canal decompression. Hence, it is important to individualize therapy and communicate to the patients and family the uncertain benefits of procedures and the potential harmful side effects prior to initiating any treatment.

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# Lesions of the Optic Chiasm, Parasellar Region, and Pituitary Fossa

9.12

Richard M. Rubin, Alfredo A. Sadun, Alfio P. Piva

**Definition:** Tumors and intracranial processes causing loss of vision and visual field due to involvement of the optic chiasm, its blood supply, or adjacent optic nerve or optic tract.

## Key Feature

- Typical binocular temporal field loss with respect to the vertical midline.

## Associated Features

- Cavernous sinus symptoms such as ocular motor nerve palsies, Horner's syndrome, trigeminal hypoesthesia, or pain.
- Endocrine dysfunction.
- Headache.
- Hydrocephalus.
- Involvement of surrounding structures results in endocrine dysfunction that arises from disruption of the hypothalamic–pituitary axis or in abnormalities of ocular motility, pupillary function, or facial sensation. These signs and symptoms are caused by injury of the cranial nerves or of ocular sympathetic nerves in the cavernous sinus.

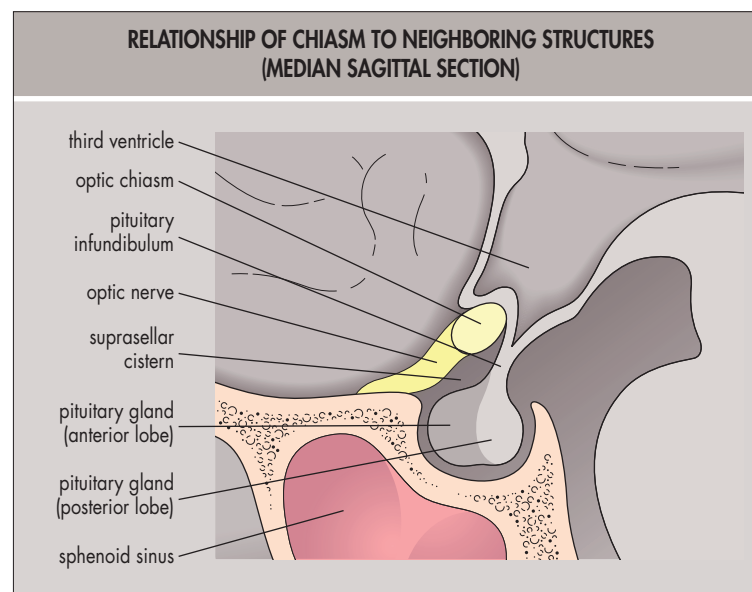
## INTRODUCTION

The word chiasm derives from the Greek letter chi ( $\chi$ ) and in the visual system refers to the appearance of the junction of the two optic nerves where they join to allow the hemidecussation of nasal fibers to the opposite optic tracts and the direct passage of temporal fibers to the ipsilateral optic tracts. Thus all visual information supplied to both eyes from the right visual space is transmitted to the left cerebral cortex, and that supplied from the left visual space is transmitted to the right cerebral cortex.

The unique anatomy of the chiasm and its relationship to other major structures explains the characteristic patterns of visual loss and cranial nerve, neurological, and endocrine dysfunction seen here (Fig. 9.12.1).<sup>1</sup>

## Anatomy

The optic chiasm, a flattened structure, is situated about 10 mm above the pituitary gland, which rests in the sella turcica of the sphenoid bone. These structures are separated by a space called the suprasellar or inferior chiasmatic cistern. The chiasm is also contiguous with the anterior-inferior floor of the third ventricle at the base of the brain. The intracranial optic nerves exit from the optic foramen and rise with a tilt of as much as 45°. Although the chiasm usually hangs directly over the pituitary fossa of the sella turcica, as a result of variations in the lengths of the optic nerves, the chiasm could also have a prefixed (15%) or postfixed (5%) position. Relative to a normal chiasm position, a prefixed chiasm would have a more rostral location, or a somewhat closer-to-the-tuberculum sellae position than normal. A postfixed chiasm would have a more caudal position than normal chiasm or a somewhat closer-to-the-dorsum sellae position (Fig. 9.12.2).<sup>2–5</sup> The pituitary infundibulum, which arises from the hypothalamus (ventral diencephalon) behind the chiasm, extends downward to the posterior lobe of the pituitary (neurohypophysis). The anterior lobe of the pituitary (adenohypophysis) forms embryologically from Rathke's pouch, an embryological structure connected to the pharynx. The chiasm



**Fig. 9.12.1 Median Sagittal Section Through the Chiasm and Relationship of Chiasm to Neighboring Structures.** The optic chiasm is suspended above the pituitary gland and rests in the sella turcica of the sphenoid bone. It is surrounded by cerebrospinal fluid, except posteriorly where it borders the anterior-inferior wall of the third ventricle. (Adapted from Sadun AA, Rubin RM. *Developments in sensory neuro-ophthalmology*. In: Silverstone B, Lang MA, Rosenthal B, et al, editors. *The Lighthouse handbook on vision impairment and rehabilitation*. New York: Oxford University Press; 2000.)

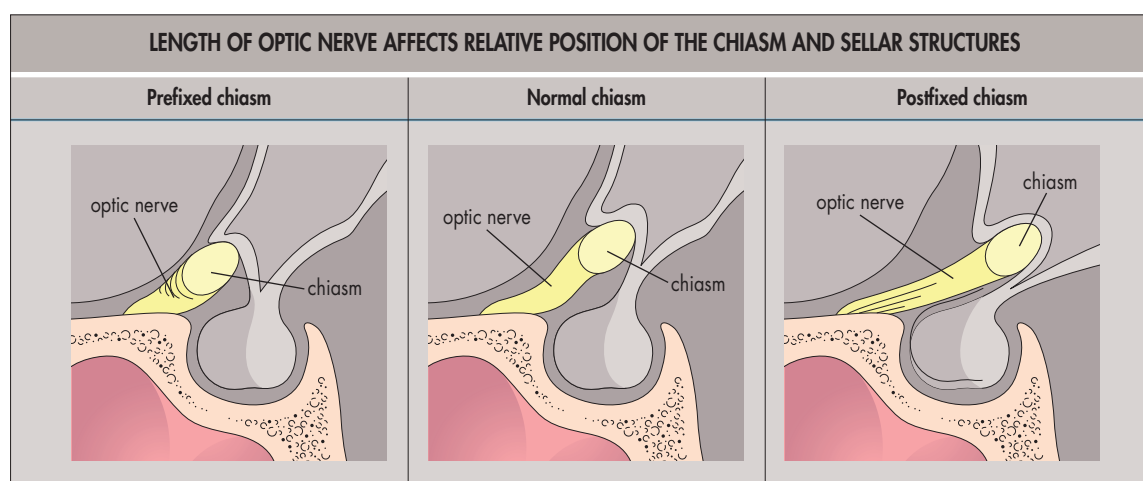
is flanked laterally by the supraclinoid segments of the carotid arteries and inferolaterally by the cavernous sinuses (Fig. 9.12.3).<sup>5,6</sup> The arterial supply of the chiasm is derived from the anterior cerebral and anterior communicating arteries from above and posterior communicating, posterior cerebral, and basilar artery from below as the chiasm is located centrally at the circle of Willis (Fig. 9.12.4).<sup>7–9</sup> Although noted by Michel as early as 1887, Hermann Wilbrand described in several publications, starting in 1904, a group of crossing, inferior nasal quadrant, extramacular ganglion cell axons that loop anteriorly into the posterior portion of the contralateral optic nerve before they turn posteriorly and laterally to head into the optic tract (Wilbrand's knee).<sup>10</sup> In the early 1960s, Hoyt<sup>11–13</sup> and Luis<sup>11,12</sup> confirmed, in the primate chiasm, the presence of Wilbrand's knee and also demonstrated that the arrangement of axons within the optic chiasm is such that superior nasal quadrant retinal fibers remain superior and cross more posteriorly in the chiasm. They also showed that macular fibers cross through the chiasm in its central and posterior portions and that arcuate fibers maintain their relative superior or inferior position while they are passing through the chiasm (Figs. 9.12.5–9.12.7).

However, more recently, Horton<sup>14</sup> suggested that Wilbrand's knee is an artifact of the preparations studied.

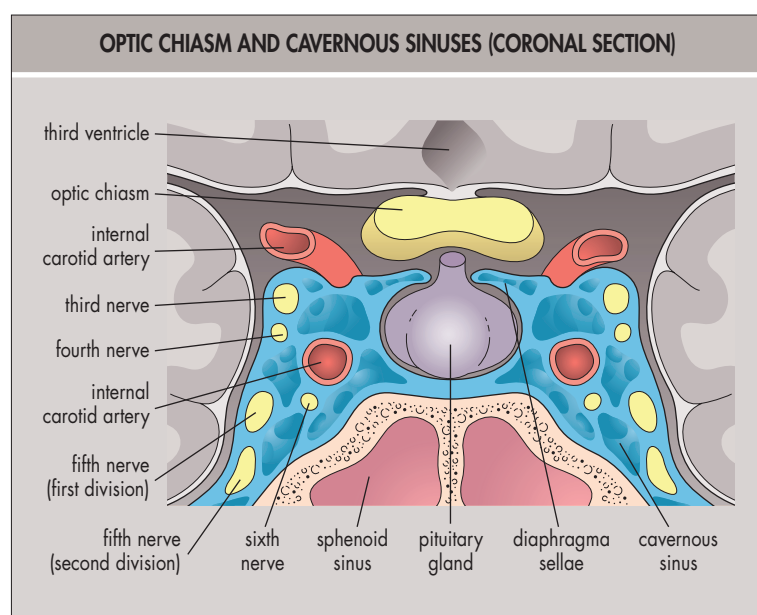
## EPIDEMIOLOGY AND PATHOGENESIS

### Pituitary Adenomas

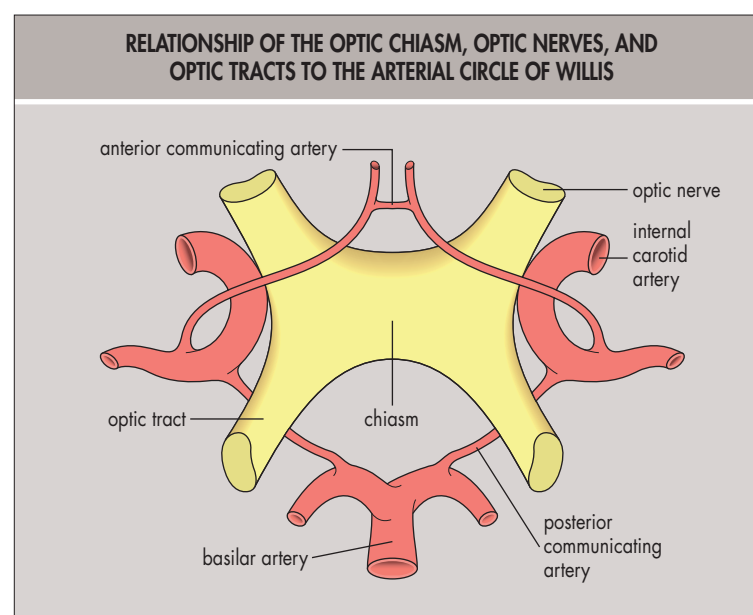
Chiasmal dysfunction most commonly occurs as a result of pituitary adenomas, which make up 12%–15% of symptomatic intracranial neoplasms.



**Fig. 9.12.2** Variation in the Length of the Optic Nerves Alters the Relative Position of the Chiasm to the Sellar Structures. Relative to a normal chiasm position, a prefixed chiasm would have a more rostral location or a somewhat closer-to-the-tuberculum sellae than normal. A postfixed chiasm would have a more caudal position than normal chiasm or a somewhat closer-to-the-dorsum sellae. (Adapted from Rhoton AL, Harris FS, Renn WH. Microsurgical anatomy of the sellar region and cavernous sinus. In: Glaser JS, editor. Neuro-ophthalmology: symposium of the University of Miami and the Bascom Palmer Eye Institute, vol. 9. St Louis: CV Mosby; 1977. p. 75–105.)



**Fig. 9.12.3** Coronal Section Through the Optic Chiasm and Cavernous Sinuses. The chiasm is flanked laterally by the supraclinoid segments of the carotid arteries and inferolaterally by the cavernous sinuses through which pass the oculomotor nerves and first two divisions of the trigeminal nerve. (Adapted from Warwick R. The orbital vessels. In: Warwick, R, editor. Eugene Wolff's anatomy of the eye and orbit. 7th ed. Philadelphia: WB Saunders; 1976. p. 406–17.)



**Fig. 9.12.4** Relationship of the Optic Chiasm, Optic Nerves, and Optic Tracts to the Arterial Circle of Willis. The chiasm passes through the circle of Willis and receives its arterial supply from the anterior cerebral and communicating arteries from above and the posterior communicating, posterior cerebral, and basilar arteries from below. (Adapted from Reed H, Drance SM. The essentials of perimetry: static and kinetic. 2nd ed. London: Oxford University Press; 1972.)

Uncommon before age 20, their incidence increases after the fourth decade of life. Autopsy studies reveal that the prevalence of asymptomatic pituitary adenomas may be as high as 20%–27% and that adenomatous hyperplasia may be found in almost every pituitary gland.<sup>15</sup>

Pituitary tumors may be classified as *benign adenomas*, the most frequent pituitary tumor (Fig. 9.12.8), *invasive adenomas*, which grow and invade adjacent skullbase structures and its meningeal coverings, and *pituitary carcinomas*, very rare entities.

Pituitary apoplexy is the sudden enlargement of a pituitary gland as a result from hemorrhage or infarction (most commonly hemorrhagic infarction) of a pituitary adenoma.<sup>16</sup> Pituitary apoplexy is typically associated with acute headache, visual loss, ophthalmoplegia, facial pain, or facial numbness (Fig. 9.12.9).

The normal pituitary gland also may undergo hemorrhagic or non-hemorrhagic infarction, but such episodes generally do not cause visual loss or chiasmal dysfunction and may go unrecognized until hypopituitarism develops. Predisposing factors include pregnancy, estrogen therapy, obstetrical hemorrhage (Sheehan's syndrome), diabetes mellitus, bleeding disorders, long-term anticoagulation, blood dyscrasias, radiation therapy, trauma, angiography, atheromatous emboli, cardiac surgery, coughing, positive pressure ventilation, and vasoactive agents.

The presentation of acute pituitary apoplexy is variable and its course is unpredictable, therefore it should be considered in any patient with abrupt neuro-ophthalmological deterioration associated with headache. Although early investigators suggested pituitary apoplexy occurs primarily

in patients with large macroadenomas, it is now evident that tumors of almost any size may undergo hemorrhagic necrosis.<sup>17,18</sup>

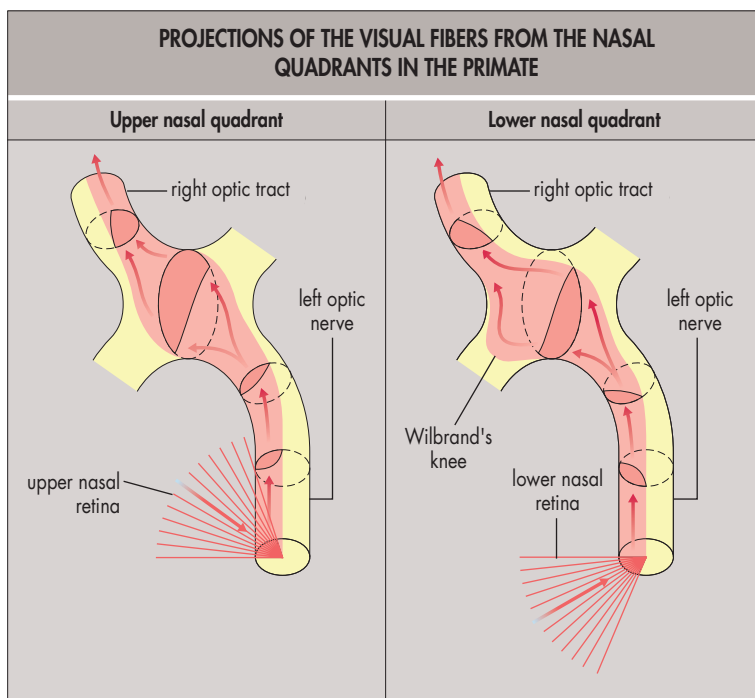
Lymphocytic adenohypophysitis, an immune-mediated diffuse lymphocytic infiltration of the pituitary gland, has been reported to cause chiasmal syndrome from suprasellar extension.<sup>19</sup> This uncommon condition has been reported in women only, and more than one-half of the cases have been found to occur during the perinatal period.

## Meningiomas

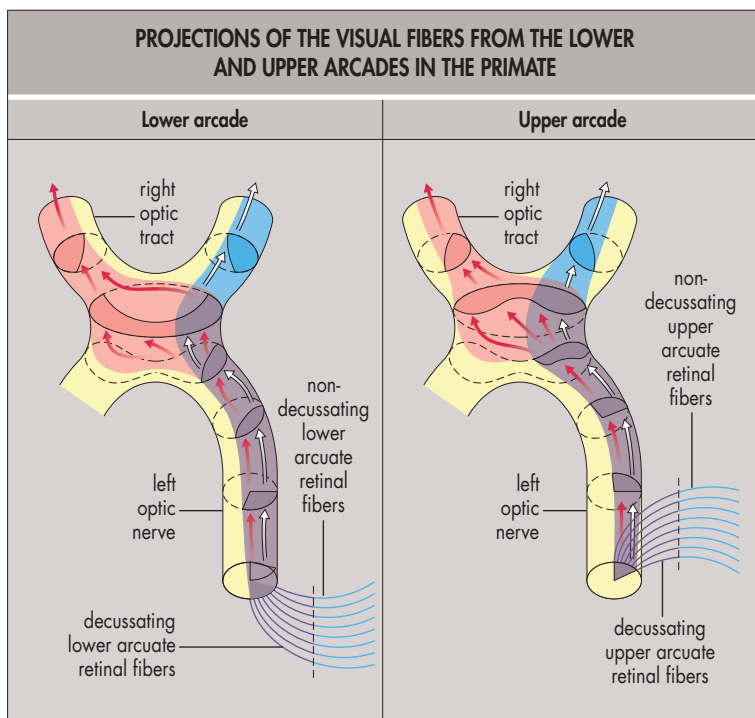
In 1929, Cushing and Eisenhardt<sup>20</sup> described the syndrome of bitemporal visual field defects and primary optic atrophy, which occurred with a normal sella turcica as examined by radiography. These findings were most often associated with suprasellar meningiomas, aneurysms, and occasionally with craniopharyngiomas. Suprasellar meningiomas of the sphenoid planum or tuberculum sellae may compress the chiasm from below. Occasionally, the chiasm may be compressed posteriorly by meningiomas that arise from the diaphragma sellae or pituitary infundibulum, laterally by medial sphenoid ridge meningiomas, or above by olfactory groove subfrontal meningiomas (Fig. 9.12.10).

Meningiomas represent 13%–18% of all primary intracranial tumors. The incidence of these tumors increases with age. In one study of 464 patients who had meningiomas, 94% were over 30 years of age.<sup>21</sup> According to other reports, less than 2% of meningiomas occur in patients under 20 years of age, and in this age group, only 2%–4% of primary intracranial

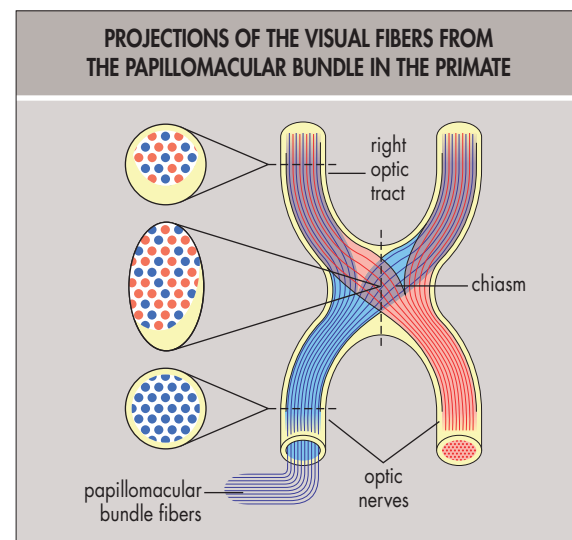




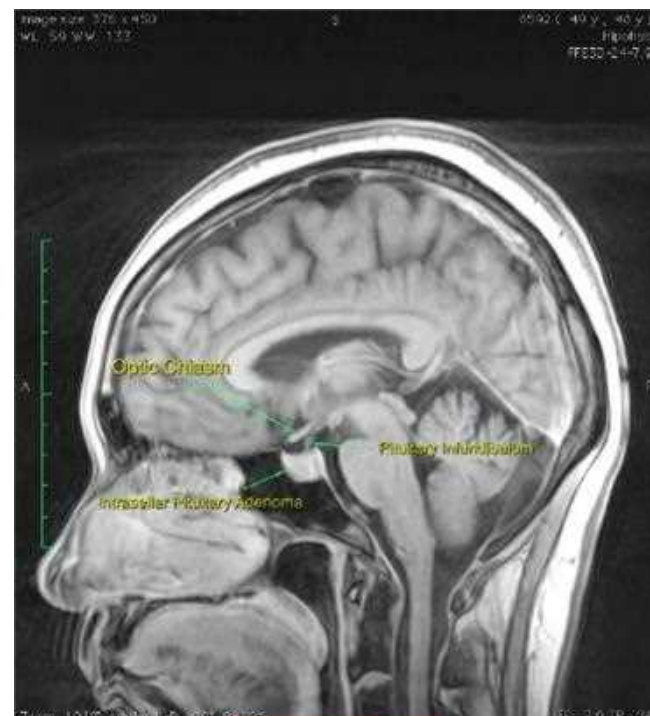
**Fig. 9.12.5 Projections of the Visual Fibers From the Upper and Lower Nasal Quadrants in the Primate.** Upper nasal quadrant retinal fibers remain superior and cross more posteriorly in the chiasm. Lower nasal quadrant retinal fibers remain inferior, cross more anteriorly in the chiasm, loop anteriorly into the terminal portion of the contralateral optic nerve (Wilbrand's knee), and head into the optic tract. (Adapted from Hoyt WF, Luis O. Visual fiber anatomy in the infrageniculate pathway of the primate: uncrossed and crossed retinal quadrant fiber projections studied with Nauta silver stain. Arch Ophthalmol 1962;68:94–106. Figure 8, p. 99.)



**Fig. 9.12.6 Projections of the Visual Fibers From the Lower and Upper Arcades in the Primate.** Arcuate fibers maintain their relative superior or inferior positions as they pass through the chiasm. Upper arcuate fibers enter the medial portion of each optic tract and lower arcuate fibers enter the lateral portion of each optic tract. A vertical line through the foveal center divides the nasal decussating from the temporal nondecussating fibers. (Adapted from Hoyt WF. Anatomic considerations of acute scotomata associated with lesions of the optic nerve and chiasm: a Nauta axon degeneration study in the monkey. Bull Johns Hopkins Hosp 1962;111:57–71.)



**Fig. 9.12.7 Projections of the Visual Fibers From the Papillomacular Bundle in the Primate.** Macular fibers crossing through the chiasm do so in its central and posterior portions. (Adapted from Hoyt WF, Luis O. The primate chiasm: details of visual fiber organization studied by silver impregnation techniques. Arch Ophthalmol 1963;70:69–85. Figure 3, p. 72.)



**Fig. 9.12.8 Pituitary Tumor with Intrasellar Expansion.** Chiasm is easily visible above the tumor, which is separated by a cerebrospinal fluid cistern. The pituitary infundibulum, which arises from the hypothalamus (ventral diencephalon) behind the chiasm, extends downward to the posterior lobe of the pituitary (neurohypophysis).

neoplasms are meningiomas.<sup>22</sup> Meningiomas that occur in adults are known to occur 2–3 times more frequently in women, but this predilection is not found with children. Estrogen and progesterone receptors play a role in the growth of meningiomas.<sup>23–25</sup>

Von Recklinghausen's syndrome (neurofibromatosis-1 [NF-1]), an autosomal dominant inherited condition, is associated with meningiomas, often more than one in a single patient.<sup>26</sup> Multiple meningiomas have an incidence of 1% to 2% in most series. Also, cases of familial meningiomas have been reported. Both familial or multiple meningiomas may or may not be associated with von Recklinghausen's syndrome.

## Craniopharyngiomas

In children and young adults, embryonic vestigial epithelial remnants of Rathke's pouch between the anterior and posterior lobes of the pituitary



**Fig. 9.12.9 Pituitary Apoplexy (T1-Weighted Magnetic Resonance Image).** Pituitary apoplexy in a 32-year-old woman who presented with acute left eye visual loss, headache, and diplopia. Examination showed left side optic neuropathy, bitemporal asymmetric visual field loss, with decreased corneal reflex. Note pituitary macroadenoma necrosis. A large necrotic cyst produces chiasmatic compression and cavernous sinus syndrome with oculomotor paresis.



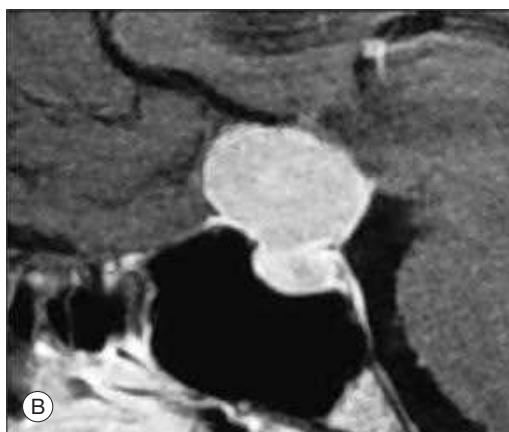
**Fig. 9.12.11 Cystic Craniopharyngioma Growing Down Toward the Optic Chiasm.** 12-year-old boy presented with progressive visual loss and bitemporal hemianopia.



**Fig. 9.12.12 Glioma of the Optic Nerve, Chiasm, and Hypothalamus in a 13-Year-Old Girl.** Invasion of the hypothalamus or third ventricle dramatically increases the mortality rate from this tumor.



**Fig. 9.12.10 (A) Coronal view.** Tuberculum sellae meningiomas slowly grow posteriorly contacting the optic chiasm. Note optic chiasm is visible as a thin tissue layer draped to the tumor dome. (B) Sagittal view. Infundibular meningiomas may produce chiasmatic compression as the tumor grows rostrally. Note normal pituitary gland inside sella turcica below tumor.



may develop into a benign, frequently cystic tumor called craniopharyngioma (Fig. 9.12.11). Such tumors may occur at any age but have a bimodal incidence, the first peak occurs during the first two decades of life and the second between 50 and 70 years of age. They account for 2%–4% of intracranial neoplasms, 8%–13% of pediatric intracranial neoplasms, 20% of suprasellar masses in adults, and 54% of suprasellar masses in children.<sup>27</sup> Suprasellar, intrasellar, and (rarely) intrachiasmal involvement may be seen. Extension into the third ventricle is common and may lead to hydrocephalus. Rare posterior extension has been documented in association with ventral brainstem and cerebellar compression.<sup>28,29</sup>

## Optic Gliomas

Primary optic pathway gliomas are pilocytic astrocytomas that affect the visual pathways at any location, from the lamina cribrosa, optic nerves, chiasm, or postchiasmatic structures (Fig. 9.12.12).

These tumors often have an indolent clinical course but may be associated with extensive loss of vision from intrinsic involvement by the tumor in the optic pathway.

Unlike with most tumors, there are no reliable histopathological factors predicting outcome in any particular case. Traditional histopathological techniques have not been reliably predictive of clinical course. It is immunogenic characteristics of each tumor (or cell clusters within each tumor) that seems to explain wide differences in the clinical course.<sup>30</sup>

Although patients may be diagnosed at any age, the majority are diagnosed during the first two decades of life. Women and girls are affected as often as men and boys. Many gliomas that infiltrate the chiasm also involve the hypothalamus. Although most are sporadic, up to one-third may be associated with neurofibromatosis type 1.<sup>31–34</sup> Gliomas in adults tend to be more malignant.<sup>35,36</sup>

## Other Causes of Chiasmatic Syndrome

Less common neoplasms that affect the chiasm include chordoma (a type of tumor that arises from the remnants of notochord cells that become sequestered during development), germinoma, endodermal sinus tumor,

leukemia, Hodgkin's and non-Hodgkin's lymphoma, nasopharyngeal carcinoma, and metastatic carcinomas. Non-neoplastic mass lesions that may compress the chiasm include sphenoid sinus mucocoele, arachnoid cyst, Rathke's cleft cyst, epidermoid cyst, fibrous dysplasia, histiocytosis X, dolichoectasia of the internal carotid artery, and aneurysm of the large vessels of the circle of Willis or internal carotid artery. Cavernous hemangiomas, arteriovenous malformations, and venous angiomas may implicate the optic chiasm, bleed into the chiasm, and cause a chiasmal apoplexy. Not infrequently the chiasm also may be compressed from above when obstructive hydrocephalus leads to an enlarged third ventricle.<sup>37</sup> Blindness is often an accompanying symptom of acute hydrocephalus.

Extension of the normal subarachnoid space with prolapse and flattening of the chiasm into an enlargement of the sella turcica is known as empty sella syndrome. As a result of the richly anastomotic blood supply of the chiasm, infarction requires multiple vessel involvement, such as with systemic vasculitis, radiation vasculopathy, or bilateral carotid occlusive disease.<sup>38</sup>

Inflammatory and infectious causes include sarcoidosis, syphilis, other granulomatous diseases, arachnoiditis, abscess, demyelination disease, and lymphoid hypophysitis. Head trauma also may result in a chiasmal syndrome. Postulated mechanisms include tears in the chiasm, contusion necrosis, compression from brain swelling, and delayed hemorrhage. Toxins have been implicated as causes of chiasmal injury. The mechanisms of injury include direct toxicity from chloramphenicol, isoniazid, ethambutol, hexachlorophene, vincristine, and ethchlorvynol, and hemorrhage associated with ethanol-induced coagulopathy. Congenital chiasmal dysplasia may be found in rare cases.

## OCULAR MANIFESTATIONS

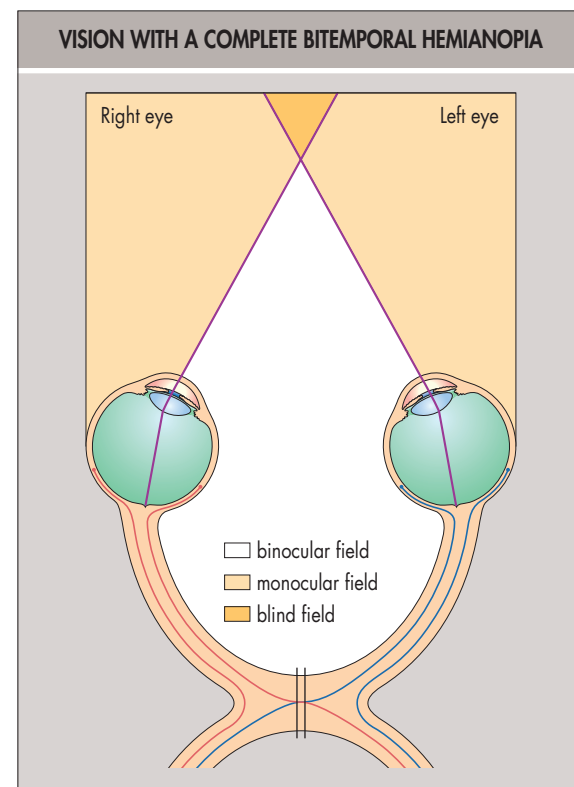
### Signs and Symptoms of Chiasmal Lesions

Chiasmal lesions cause loss of vision and visual field defects related to involvement of the chiasm itself, its blood supply, the adjacent optic nerve, or the optic tract. Patients who have chiasmal involvement may be unaware of any deficit, may complain of difficulties related to unrecognized loss of their peripheral field, or may complain of unilateral or bilateral central or peripheral visual loss. If a complete bitemporal hemianopia is present, the affected person may experience loss of depth perception at near, the phenomenon of disappearance of an object as the point of fixation moves forward and leaves the object in an area of blindness behind (Fig. 9.12.13), and "double vision" as a result of overlap or separation of the hemifields associated with a pre-existing phoria, a "hemifield slide" (Fig. 9.12.14).

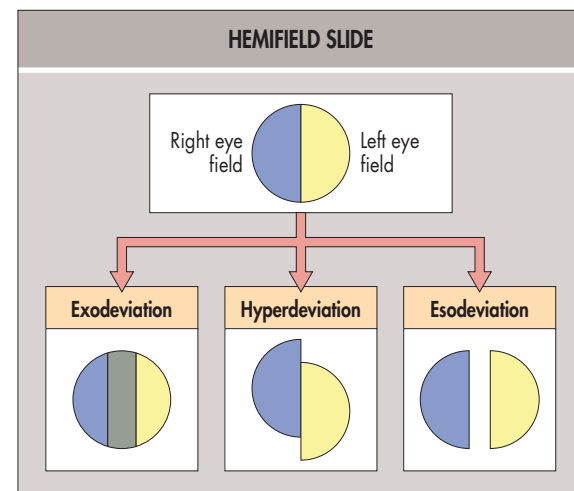
Generally, extrinsic mass lesions become apparent with gradually progressive depression of monocular or binocular vision. However, pituitary adenomas, craniopharyngiomas, or aneurysms may cause acute worsening or fluctuations of vision and can be mistaken for optic neuritis.<sup>39-41</sup> Fluctuation of vision over weeks and months also has been described in some cases of meningiomas, and optic disc pallor may be a late finding with these tumors. Response to treatment with systemic corticosteroids may further mimic the clinical picture of retrobulbar optic neuritis.

The pattern of field loss may suggest the presence of a lesion and further help to localize it (Fig. 9.12.15). Compression of the anterior angle of the chiasm may cause a junctional scotoma, which is a central scotoma, or blindness in one eye plus a contralateral superotemporal defect. Hemianopic arcuate scotomas also may indicate early anterior chiasmal compression. Compression of the body of the chiasm from below, because of a pituitary adenoma for example, generally causes a bitemporal superior quadrantanopia or bitemporal hemianopia. Huber<sup>42</sup> noted that the visual loss associated with sellar meningiomas was more likely to be monocular or markedly asymmetrical if bilateral. Bitemporal inferior quadrantanopia or bitemporal hemianopia occurs with compression of the body of the chiasm from above (e.g., because of a craniopharyngioma). Compression of the posterior chiasm and its decussating nasal fibers may cause bitemporal hemianopic scotomas, but Traquair suggested that this pattern of field loss also may denote a rapidly growing tumor.<sup>43</sup> Less commonly, lateral compression of the margins of the chiasm (e.g., because of dolichoectasia of the carotid siphon or compression of the chiasm into lateral structures) may cause a nasal or binasal hemianopia. Regardless of the pattern, respect for the vertical midline is a feature that helps to differentiate true chiasmal field patterns from other causes.

Because the chiasm is composed of the axons of retinal ganglion cells, chronic involvement (>6 weeks) of the chiasm often leads to nerve fiber layer defects or optic atrophy. When the body of the chiasm is involved, a temporal or "bow-tie" pattern that corresponds to retinal fibers that



**Fig. 9.12.13 Vision With a Complete Bitemporal Hemianopia.** Relative to the point of fixation is a triangular region of blindness behind, a triangular region of binocular vision in front, and regions of monocular vision to each side. As a result, an object may disappear as the point of fixation moves forward and leaves the object in an area of blindness behind. (Adapted from Kirkham TH. The ocular symptomatology of pituitary tumors. *Proc R Soc Med* 1972;65:517-18.)



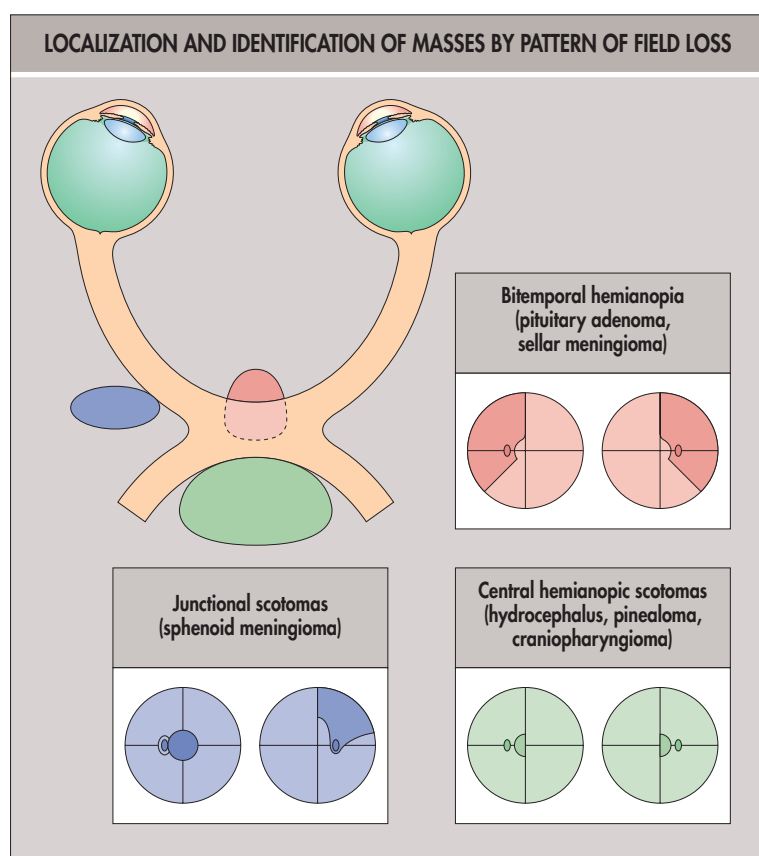
**Fig. 9.12.14 Phenomenon of "Hemifield Slide."** In patients affected by a complete bitemporal hemianopia, pre-existing phorias may result in separation of the hemifields vertically (hyperdeviation) or horizontally (esodeviation) or in double vision if the intact nasal hemifields overlap (exodeviation). (Adapted from Kirkham TH. The ocular symptomatology of pituitary tumors. *Proc R Soc Med* 1972;65:517-18.)

originate nasal to the fovea may occur (Fig. 9.12.16). However, this appearance often is not apparent, because nondecussating fibers frequently are damaged, as well particularly with compressive lesions. Optic atrophy also may be a late sign of chiasmal compression and is associated with a poorer postoperative visual acuity.

### Signs and Symptoms of Parasellar Lesions

Parasellar involvement manifests with abnormalities of ocular motility, pupillary function, or facial sensation from injury to the third, fourth, ophthalmic, maxillary, and mandibular cranial nerves or the ocular sympathetic nerves in the parasellar region. Injury to these structures within the cavernous sinus may be associated with complaints of diplopia, ptosis, unequal pupil size, accommodative difficulty, facial pain or numbness, or





**Fig. 9.12.15 Localization and Probable Identification of Masses by Pattern of Field Loss.** Junctional scotomas occur with compression of the anterior angle of the chiasm (sphenoid meningioma). Bitemporal hemianopia results from compression of the body of the chiasm from below (e.g., because of pituitary adenoma, sellar meningioma). Compression of the posterior chiasm and its decussating nasal fibers may cause central bitemporal hemianopic scotomas (e.g., because of hydrocephalus, pinealoma, craniopharyngioma).

eye pain. Signs include ocular motor nerve palsies, decreased sensation in the areas innervated by the first and second divisions of the trigeminal nerve, or Horner's syndrome. Multiple cranial nerve involvement is more suggestive of invasive malignant tumors.

Lesions that block the normal cerebrospinal fluid circulation by obstruction of the foramen of Monroe may result in hydrocephalus. Ocular examination may reveal vertical gaze abnormalities, convergence retraction nystagmus, pupillary light-near dissociation, and papilledema.

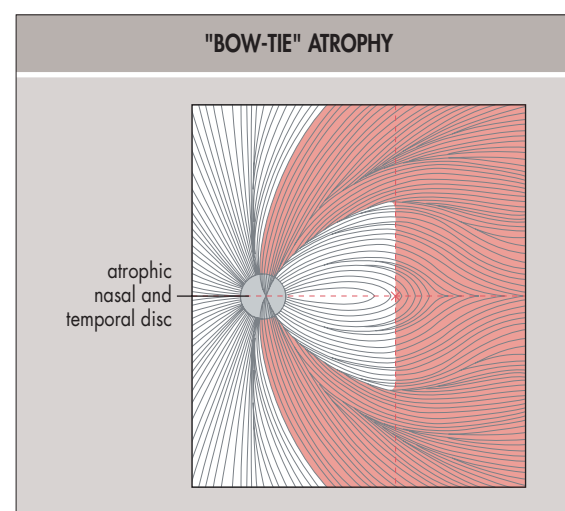
An unusual form of dissociated nystagmus, termed see-saw nystagmus, occasionally accompanies mass lesions in the chiasmal region and diencephalon. Also, it may be seen transiently immediately after brain-stem stroke, or subsequent to severe head trauma after a delay of weeks to months, or as a variant of congenital nystagmus. See-saw nystagmus manifests as alternating intorsion and elevation of one eye with extorsion and depression of the fellow eye and may result in complaints of oscillopsia. It ceases when the eyes are closed and does not occur in blind patients, which suggests a role for vision in its pathogenesis. A lesion has been postulated that involves the interstitial nucleus of Cajal and its connections or damage to the ocular counter-rolling mechanism mediated by the inferior olivary nucleus.

Chiasmal gliomas in young children have been reported to cause nystagmus, which may be the initial sign of chiasmal or parachiasmal involvement. The nystagmus, which is usually pendular and asymmetrical, may mimic spasmus nutans (even head nodding).

## DIAGNOSIS

### Visual Field Testing

The primary role of the clinician in the diagnosis of chiasmal disorders is to assess visual function accurately, interpret the results correctly, and thus localize the anatomical region that is affected. Visual field tests may provide a strong indication of direct chiasmal involvement, and failure to perform and properly interpret visual field tests is a common cause for delay in the diagnosis of chiasmal disorders. It is important to establish that the



**Fig. 9.12.16 "Bow-Tie" Atrophy.** Chronic compression of the decussating visual fibers of the chiasm leads to atrophy of the corresponding nasal retinal nerve fibers that enter the optic disc nasally and temporally. At the disc, this atrophy appears in a bow-tie pattern.



**Fig. 9.12.17 Pituitary Adenoma With Chiasmal Compression.** Coronal view magnetic resonance scan from a 59-year-old woman who has a bitemporal hemianopia demonstrates a pituitary adenoma that bows the chiasm upward toward the third ventricle. The chiasm is thinned and draped over the mass.

vertical midline forms the border of the field depression and accordingly to rule out nonchiasmal temporal field loss that does not respect the vertical midline. Although a peripheral hemianopic step along the vertical midline is characteristic, early chiasmal compression often lacks a clear vertical step. Most often, temporal paracentral depression occurs because the chiasm has macular projections through most areas. A good strategy to establish a field defect attributable to chiasmal disease is to test either a single central isopter or static threshold sensitivity within the central 15°–20° from fixation and to compare changes in color perception as colored objects pass across the vertical midline through central fixation.

## Neuroimaging

Prompt magnetic resonance imaging (MRI) is indicated for the patient who has symptoms or signs referable to the chiasm or parachiasmal region (see Fig. 9.12.17, Fig. 9.12.9, and Fig. 9.12.10). It is the study of choice for most sellar and parasellar lesions, but high-resolution computed tomography (CT) with fine cuts (1.5–3 mm) of axial and coronal views is also an important imaging aid when planning surgical resection of such lesions. Both modalities provide about equivalent ability to detect lesions in the parachiasmal regions. The advantages of MRI are a better definition of the anatomical relationships to surrounding structures, the absence of artifacts from bone, and the ability to provide axial, coronal, and sagittal

views without special image reconstruction. However, CT provides superior abilities in the detection of tumoral calcifications, of bony erosion and destruction by meningiomas and craniopharyngiomas, and of hyperostosis from meningiomas. Intravenous contrast and enhancement agents (such as paramagnetic gadolinium-pentetic acid for MRI and radiopaque iodine for CT) are used to demonstrate lesions that may not be visualized on noncontrast studies.

## Other Diagnostic Testing

Complete endocrinological evaluation should be done in assessment of lesions that involve the pituitary-hypothalamic axis. Lumbar puncture also may be required if an inflammatory or infectious cause is suspected. Magnetic resonance angiography or cerebral angiography may be indicated when vascular causes or cavernous sinus invasion are suspected, or to further characterize or delineate mass lesions and their blood supply. The current sensitivity of MRI or CT often obviates the need for angiography. Some clinicians still use arteriography to absolutely rule out a suprasellar aneurysm or to define the position of the carotid arteries prior to surgery. However, due to high quality of imaging provided by MRI, transsphenoidal resections of pituitary tumors usually are accomplished safely without prior angiography.<sup>44</sup>

## DIFFERENTIAL DIAGNOSIS

Several conditions may mimic the visual field defects associated with chiasmal syndromes. Retinal conditions (such as nasal sector retinitis pigmentosa), optic disc anomalies (such as tilted optic discs), and papilledema with greatly enlarged blind spots may cause bilateral temporal field loss. Bilateral centrocecal scotomas caused by bilateral optic nerve disease may be difficult to differentiate from posterior chiasmal compression that affects the macular projections unless careful attention is paid to the vertical midline. Visual obstruction from overhanging redundant lid tissue, refractive scotomas, psychogenic visual loss, and test artifacts also may simulate chiasmal field patterns.

## SYSTEMIC ASSOCIATIONS

Headache, usually frontal in location, frequently accompanies pituitary adenomas, pituitary apoplexy, and meningiomas and may be attributable to a stretched diaphragma sellae. Hydrocephalus caused by normal cerebrospinal fluid circulation blockage may lead to headache, gait difficulties, somnolence, and eventually urinary incontinence.

Abnormalities of pituitary endocrine dysfunction cause a variety of symptoms and signs. Many of them are very typical of a specific kind of hormone-producing tumor. Typical features such as thick lips, enlarged eyebrows, increased hand and feet size, large tongue, and metabolic changes including diabetes mellitus and hypertension are common in *acromegaly*. Amenorrhea–galactorrhea syndrome in women and impotence in men are typical features of prolactin-producing tumors, and changes in body habitus, including a full-moon face and centripetal obesity, are associated with Cushing's disease.

Hypothalamic dysfunction also may manifest as urinary frequency as a result of diabetes insipidus, heat or cold intolerance caused by a disturbance of temperature regulation, behavioral changes, lethargy, decreased libido, or disturbance of appetite. In children, delay or arrest in sexual development, precocious puberty, or infantile emaciation may occur.

## PATHOLOGY

### Pituitary Adenomas

Adenomas are by far the most common tumors of the pituitary gland. Tumors usually arise as a discrete nodule from the anterior part of the gland, called adenohypophysis; such microadenomas are soft and vary in color from gray–white to pink or red, depending on the degree of vascularity. As the tumor progressively grows, the normal pituitary gland is pushed away toward the periphery, affecting its normal function. This is the reason many patients with large pituitary adenomas suffer from hypopituitarism (lack or low normal pituitary hormone levels).

Often, the pituitary function (or lack of it) is the most relevant clinical criteria when classifying these kinds of tumors. Functional pituitary tumors are pituitary adenomas that produce hormones. Functional pituitary tumors are therefore classified according to the kind of hormone they produce as:

- Prolactin-(PRL) producing, also known as prolactinomas.
- ACTH-producing, which are adenomas associated with Cushing's disease.
- GH-producing, which are adenomas associated with acromegaly and/or gigantism.
- TSH-producing tumors are considered very rare.

Because they do not produce abnormal hormone levels, nonfunctional adenomas are generally diagnosed due to chiasmatic syndrome or sometimes as an incidental finding during a brain scan for an unrelated reason.

Pituitary adenomas are classified according to size as microadenomas or macroadenomas. Microadenomas are less than 10 mm in their largest diameter, whereas macroadenomas are greater than 10 mm in their largest diameter. In addition, pituitary adenomas may be distinguished anatomically and radiologically as intrapituitary, intrasellar, or extrasellar. Invasive adenomas, which account for approximately 35% of all pituitary neoplasms, may invade the dura mater, cranial bone, cavernous sinus, or sphenoid sinus.<sup>45</sup> Such a finding does matter; according to the World Health Organization, adjacent structure invasion such as cavernous sinus, ethmoid and/or sphenoid sinus, dorsum sellae, or clivus erosion are loosely correlated with tumor recurrence.

Pituitary adenomas can also be classified according to the histological staining affinities of the cell cytoplasm, size, endocrine activity, pathological characteristics, hormone production and contents, ultrastructural features, granularity of the cell cytoplasm, cellular composition, cytogenesis, and growth pattern.<sup>46,47</sup> Recent classifications, however, omit criteria based on tinctorial stains (i.e., acidophilic, basophilic, and chromophobic) because of the poor correlation between staining affinities of the cell cytoplasm and other pathological features of pituitary tumors, such as the type of hormone produced and cellular derivation. A unifying pituitary adenoma classification incorporates the histological, immunocytochemical, and electron microscopic studies of the tumor cells and stresses the importance of hormone production, cellular composition, and cytogenesis. Therefore, pituitary adenomas are named as lactotroph (PRL-producing) adenomas, corticotroph (ACTH-producing) adenomas, somatotroph (GH-producing) adenomas, and thyrotroph (TSH-producing) adenomas. Other tumors may be found to be producers of more than one hormone (plurihormonal adenomas), and up to one-third may be composed of endocrinologically inactive cells (null cell adenomas). In a series of 1000 pituitary tumors surgically resected, Wilson<sup>48</sup> found that just over 77% were secretory (41% prolactin, 19% growth hormone, 17% adrenocorticotropin, and 0.2% thyrotropin). Occasionally, pituitary tumors are associated with other endocrine tumors in the pancreas and parathyroid gland (multiple endocrine neoplasia type 1).

Immunohistochemical analysis is also important as a predictor of future tumor recurrence; elevated mitotic index, a Ki-67 labeling index higher than 3%, and extensive p53 expression are indicators of aggressive behavior.

### Meningiomas

Meningiomas probably derive from cap cells that line the outer surface of the arachnoid (where they serve as the interface between the dura and arachnoid) and within the stroma of the choroid plexus. Histologically, meningiomas are categorized into:

- Syncytial tumors in which the cell borders are indistinct because the cell membranes intertwine extensively.
- Transitional tumors composed of plump polygonal cells and concentrically wrapped spindle cells that form whorls.
- Fibroblastic meningiomas composed of interlacing bundles of elongated cells that simulate fibroblasts.
- Angioblastic meningiomas in which prominent, thin-walled capillaries are found interspersed between the tumor cells.

A characteristic histopathological feature of many meningiomas, especially those in which whorls are prominent, is the presence of psammoma bodies. These structures contain concentric layers of calcium salts, which appear to be deposited within degenerating whorl cells. Whorls and psammoma bodies, characteristic of transitional meningiomas, also may be found (but to a lesser degree) in fibroblastic meningiomas. Malignant meningiomas are rare and usually show cellular pleomorphism and mitoses. However, tumors that appear histologically benign and show rapid growth, local invasion, and metastasis may be determined malignant on the basis of biological behavior.

## Craniopharyngiomas

Craniopharyngiomas may be solid or cystic; the cysts contain an oily fluid, with cholesterol clefts derived from degenerating epithelial cells and keratin. Histologically, the tumor's solid portions may be composed of areas of trabeculae of stratified squamous epithelium supported by a vascularized connective tissue stroma and of areas of peripheral, basal palisading cells that surround layers of stratified squamous epithelial cells, which may form "horny pearls" of keratinized cells. Calcification and deposition of lamellar bone are found frequently. The tumors are surrounded by a capsule of stratified squamous epithelium and often dense gliosis.

## Optic Pathway Gliomas

In children, most gliomas are astrocytomas that consist of pilocytic cells (spindle-shaped cells with hair-like filaments) and stellate cells. Less often, the tumors may comprise evenly distributed oligodendrocytes with dark, round nuclei surrounded by clear halos that may stain with Alcian blue. These tumors have a benign appearance histologically. Eosinophilic hyalinization of apparently degenerated neuroglial cells may form elongated structures called Rosenthal fibers. Formation of microcystic, acellular spaces that contain mucoid material is common. The benign tumors, which are more common in children, are distinct from the aggressive, malignant glioblastoma multiforme that predominates in adults.

## TREATMENT, COURSE, AND OUTCOME

### Pituitary Adenomas

Surgery is the first line of treatment for most symptomatic pituitary adenomas.

Surgery is indicated for all chiasmatic syndrome-producing tumors that will not adequately respond to medical treatment, which is all pituitary tumors, except prolactin-producing and some GH-producing adenomas.

The nonsurgical treatment of pituitary tumors is nonetheless of paramount importance.

The medical treatment of pituitary tumors that are prolactin secreting consists of bromocriptine (an agonist of dopamine D2 receptors) or cabergoline (a dopamine receptor macrolide)<sup>49</sup> and other dopamine agonists that suppress further growth and reduce its size. Normal systemic prolactin levels may be achieved via medical treatment in up to 90% of microadenomas and in more than 70% of macroadenomas.<sup>50</sup> After the institution of bromocriptine therapy, shrinkage of tumor volume and reduction in serum prolactin may occur within days, and maximal shrinkage in tumor size appears to be obtained within 6 weeks. Improvements in visual acuity and field defects may be sustained using bromocriptine therapy in 80%–90% of patients.<sup>51</sup> Unfortunately, about 15% of prolactinomas do not respond adequately to dopamine agonist treatment. Symptomatic pituitary tumor patients that are intolerant, unlikely to respond (cystic prolactinomas), or fail to respond to medical therapy are usually treated by surgical resection, most frequently by the transsphenoidal route.

Prolactinoma treatment success rates depend on the initial tumor size and prolactin levels. In patients with intrasellar microadenomas with prolactin levels under 155 ng/mL, 86% were found to have long-term remissions after transsphenoidal surgical removal.<sup>50</sup> Failure to obtain long-term remission after surgery correlates with higher initial prolactin levels, especially over 200 ng/mL.<sup>52</sup> Overall, recurrence of prolactinomas and pituitary adenomas that secrete growth hormone was 15% at 1 year after transsphenoidal surgery. Pretreatment with bromocriptine does not seem to improve surgical cure rates. Improvement in vision after surgery may be delayed, and final visual outcome is not determined until 10 weeks postoperatively. Improvement does not usually extend beyond 3–4 months.

Some growth hormone-secreting tumors may also respond to bromocriptine, though better results are obtained using octreotide, a somatostatin analog. Response rates of about 80% have been reported.<sup>53</sup>

Symptomatic pituitary tumor patients that are intolerant, unlikely to respond, or fail to respond to medical therapy usually are treated by surgical resection, most frequently by the transsphenoidal route.

## Surgical Treatment

Transsphenoidal approach can be used for 95% of pituitary tumors. Endoscopic techniques have gained much popularity among well-trained otolaryngology–neurosurgery teams. The endoscope provides panoramic magnified views of the sellar anatomy during both the approach and the

resection of tumors itself. The option of using angled endoscopes allows surgeons to inspect for residual tumor, particularly along the cavernous sinus walls and the suprasellar region. During the last decade endoscopic techniques have dramatically improved, and it may become the surgical treatment of choice for many pituitary tumors. Neuronavigation systems are an excellent tool during such surgeries, in particular during recurrent adenomas surgery in which the midline anatomy has been distorted by previous transsphenoidal surgery.

Craniotomy is reserved for very large invasive pituitary adenomas in which vascular control and neural tissue dissection are better served by direct observation and manipulation of tissues.

## Radiation Therapy

Incompletely resected tumors and those unresponsive to hormone therapy are considered for postoperative radiation therapy. Fractions must not exceed 200 cGy daily because of the increased incidence of radionecrosis. Extensive extrasellar extensions usually are treated with surgical decompression followed by irradiation of residual tumor, because a 40% incidence of microscopic dural invasion makes complete resections difficult or impossible to obtain with surgery alone.<sup>54</sup> Patients who have pituitary adenomas that do not immediately threaten vision may be considered as candidates for stereotactic radiosurgery, such as with proton beam, cobalt-60 gamma knife, or linear accelerator therapy.<sup>55</sup> Although endocrine deficit is commonly associated with these modalities, other complications are infrequent and tumor recurrence is rare.

Pituitary apoplexy, which may be life threatening, is treated with high-dose systemic corticosteroids and hormone replacement and may require medical management of either diabetes insipidus or inappropriate antidiuretic hormone secretion. Transsphenoidal decompression of the sella is indicated if rapid visual loss and decrease in level of consciousness occur.

## Meningiomas

The preferred management of meningiomas that involve the intracranial optic nerves and chiasm is surgical removal.<sup>56</sup> Surgical debulking alone, radiation therapy alone, or combination therapy may be performed if vital structures are densely surrounded by tumor. Postoperative radiation therapy of incompletely resected tumors appears to extend the period to tumor recurrence. However, because the tumors grow slowly and this treatment carries the risk of radiation vasculopathy, adjunctive radiation therapy is used only in cases in which progression follows incomplete resection. Another option in some patients includes hormone therapy using the progesterone antagonist mifepristone, which has resulted in reduced tumor size as shown by neuroimaging or improved visual fields in 5 out of 14 patients.<sup>57</sup>

Location of the tumor and duration of visual symptoms are the most important predictors of visual recovery after surgical removal. Meningiomas of the tuberculum sellae and sphenoid wing are generally completely resectable, whereas complete removal of clinoidal meningiomas or diaphragma sellae meningiomas is most unlikely to be complete. Complete gross excision alone does not rule out recurrence. One study showed a 19% 5-year probability of recurrence or progression of parasellar meningiomas despite "complete excision."<sup>58</sup> Visual improvements after tumor resection largely depend on the degree of visual compromise prior to surgery. Long-standing visual symptoms are often associated with large, difficult-to-resect lesions and optic atrophy.

## Craniopharyngiomas

The preferred treatment of craniopharyngiomas remains controversial and is usually customized individually.<sup>59</sup>

Although complete surgical resection of craniopharyngiomas can usually be accomplished through craniotomy, subdiaphragmatic and cystic craniopharyngiomas may be approached transsphenoidally. Intracavitary placement of radioactive or chemotherapeutic agents, including phosphorus-32 colloid,<sup>60</sup> yttrium-90 colloid, bleomycin,<sup>61</sup> or alpha interferon<sup>62</sup> within cystic tumors, has been attempted with some success.<sup>63</sup> Cystic tumors are particularly difficult to manage.

Recurrence is frequent with craniopharyngiomas and usually occurs during the first 2 years after surgery. Due to the tumor's tight attachments to the hypothalamic region, aggressive resections may delay recurrences but lead to greater mortality, as well as visual, endocrine, and neurological morbidity.<sup>64</sup> A review of ambitious attempts at complete surgical removal



showed a 25% operative mortality, a 71% 11-year mortality, and residual tumor in over 75% of those autopsied.<sup>65</sup> Adjunctive radiation therapy improved median survival after extensive subtotal resection from about 3 years to more than 10 years and may achieve remission rates greater than 90%.<sup>66,67</sup> However, adjunctive irradiation is reserved for patients over 5 years of age because of the complications of severe intellectual impairment and profound growth retardation that occur in children.

Visual recovery occurs in only 50% of patients after tumor resection, and the recovery seen within the first month is all that is expected. Lifelong endocrine replacement is expected in most patients after surgery or radiation therapy or both.<sup>68</sup>

## OPTIC GLIOMAS

The treatment of optic chiasmatic–hypothalamic gliomas remains controversial.<sup>69,70</sup> Patients with gliomas that involve the chiasm alone have a mortality of 28% because of the eventual involvement of the hypothalamus or third ventricle.<sup>69</sup> Invasion of the hypothalamus or third ventricle dramatically increases the mortality rate to more than 50% over 15 years (see Fig. 9.12.10).<sup>69</sup> Surgical intervention does not constitute a definitive treatment for these tumors once there is chiasmal or hypothalamic involvement and may be associated with significant visual morbidity and potential mortality. However, studies show benefit from tumor resection in those who have demonstrated rapid expansion of the suprasellar mass with visual deterioration or progressive neurological deficits.<sup>70,71</sup> Shunting procedures are of clear benefit when hydrocephalus is present, and hormone replacement is indicated when endocrine dysfunction occurs. Chemotherapy for progressive chiasmal gliomas has shown promise and in children offers a safer

alternative to radiotherapy.<sup>72</sup> Radiotherapy may be considered in children over the age of 5 years if progression occurs and chemotherapy has been ineffective.

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# Lesions of Retrochiasmal Pathways, Higher Cortical Function, and Nonorganic Visual Loss

9.13

Andrew W. Lawton, Michelle Y. Wang

**Definition:** The retrochiasmal pathways are anatomic brain partitions carrying parallel streams of information diverted to appropriate areas of the brain for identification, storage, and retrieval.

## Key Features

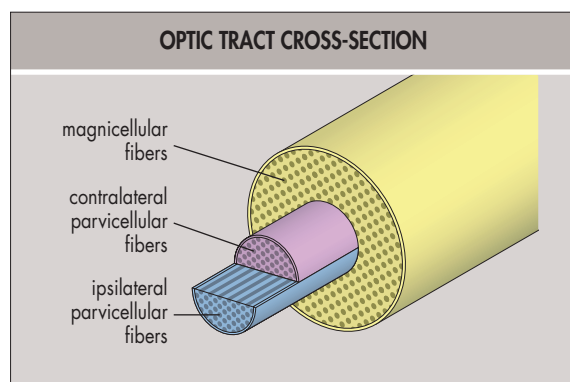
- Lesions of numerous areas of the brain produce characteristic interruptions of pathway functions and visual processing.
- Careful analysis of visual fields and function can localize white matter and cortical lesions accurately.
- Because patients with conversion reactions and malingerers may have complaints that mimic those caused by retrochiasmal pathway and cortical injuries, careful evaluation is necessary to avoid unnecessary testing, patient discomfort, and incorrect diagnoses.

## RETROCHIASMAL PATHWAYS AND HIGHER CORTICAL FUNCTION

### OPTIC TRACTS

The optic tracts connect the optic chiasm to the lateral geniculate nuclei. An injury to an optic tract may yield a relative afferent pupillary defect in the contralateral eye. Because of the temporal crescent, the temporal visual field is 50% larger than the nasal field of the contralateral eye. Hence the nasal retina produces axons that constitute approximately 55% of the contralateral optic tract.

The optic tracts do not maintain a strict retinotopic architecture: Tract lesions therefore result in incongruous visual field defects (Fig. 9.13.1). Fibers from corresponding parts of the retinas do not pair in the optic tracts. Larger diameter, faster-conducting axons predominate superficially under the pia. These fibers correspond to the magnocellular layers in the lateral geniculate nuclei. The parvocellular axons dominate the center of the optic tract, with fibers from the opposite eye running in the deepest dorsal regions. The ipsilateral parvocellular fibers sit slightly ventrally. Optic tract axons achieve this orientation by the time they arrive during axonogenesis.



**Fig. 9.13.1 Optic Tract Cross-Section.** Note that the parvocellular fibers run centrally and the magnocellular fibers peripherally.

## LATERAL GENICULATE BODIES

The lateral geniculate bodies are the first sites at which information from corresponding axons arising from the retinal ganglion cell layers pair together. Early embryos do not have this orientation of fibers.<sup>1</sup> The axons rearrange themselves into regular layers. The retina directs the rearrangement process via generation of electrical impulses even before the system is visually active. These impulses arise from ganglion and amacrine cells prior to the appearance of photoreceptors.

Myelinated nerve fibers divide each lateral geniculate body into six neuronal layers.<sup>2</sup> The layers are numbered ventral to dorsal. Axons from the contralateral eye synapse in layers 1, 4, and 6; axons from the ipsilateral eye synapse in layers 2, 3, and 5.

The layers of the lateral geniculate body may be categorized by neuronal size. Large, magnocellular neurons (M cells) predominate in layers 1 and 2; small, parvocellular neurons (P cells) constitute layers 3–6. At this level, visual processing is divided into at least two parallel pathways. The parvocellular pathway involves color perception and visual resolution (high spatial frequency contrast sensitivity), whereas the magnocellular pathway deals with motion detection and lower contrast, lower spatial frequency.

Several authors propose additional parallel pathways.<sup>3</sup> Primate research shows that numerous small neurons (koniocellular or K cells) sit in the interlaminar zones and superficial layers of the lateral geniculate. They receive input from the retina and the region of the superior colliculus. The koniocellular pathways apparently modulate information derived from the other two pathways.

The lateral geniculate nuclei are also organized by retinotopic visual field loci. The macula tends to project to the caudal 75% of the nucleus. These fibers straddle the midline of the nucleus and form a rhombus. The unpaired sections of the visual fields appear to project peripherally within the nucleus. Fibers from the superior retina tend to migrate medially in the lateral geniculate nuclei; those from the lower retina tend to move laterally.

## OPTIC RADIATIONS

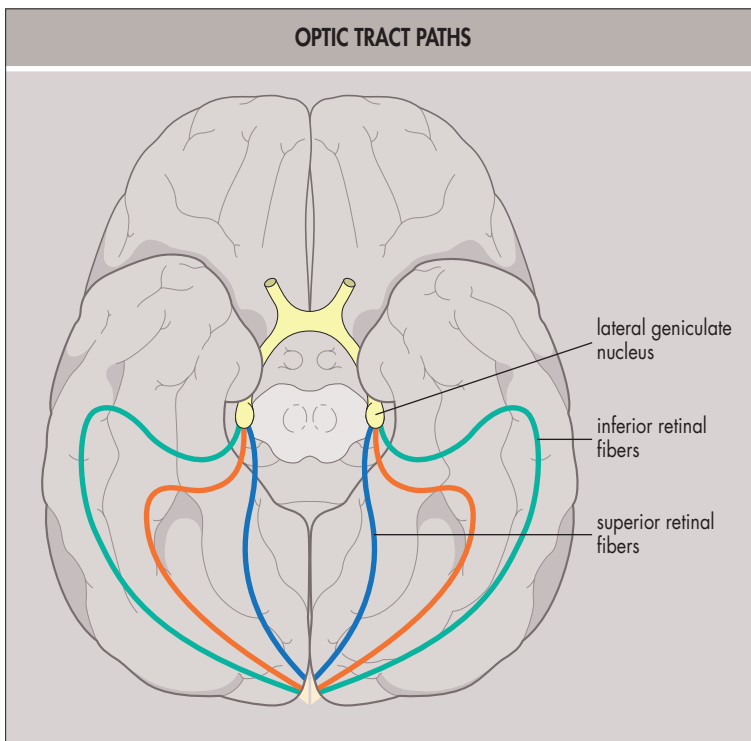
Axons arising in the lateral geniculate nuclei form the optic radiations and project to the calcarine cortex. Superior retinal fibers course inferiorly in the radiations and the inferior retinal fibers migrate superiorly (Fig. 9.13.2). Axons corresponding to central vision travel between the two other bundles.<sup>4</sup>

The fibers from the inferior retina travel deep within the parietal lobe relatively close to the internal capsule and to a tract that carries pursuit information from both occipital lobes to the ipsilateral paramedian pontine reticular formation. The superior retinal fibers course ventrally into the temporal lobe in an arc (Meyer's loop) around the temporal horn of the lateral ventricle.<sup>5</sup> These geographical relationships gain considerable importance in localizing a lesion of the visual pathways.

## HIGHER CORTICAL FUNCTION

Information from the optic tracts projects via the radiations to the calcarine cortices of the medial occipital lobes. This visual cortex performs multiple processing functions to prepare information for detailed analysis elsewhere in the brain.





**Fig. 9.13.2 Optic Tract Paths.** Fibers that correspond to the inferior retina course rostrally and laterally into the temporal lobes to form Meyer's loop through the temporal lobe. The superior retinal fibers take a much more direct course through the parietal lobes.

The visual cortex (Brodmann area 17, V1) straddles the calcarine sulci. The neurons of V1 receive information via the myelinated stripe of Gennari. Information from central vision projects to the caudal half of the visual cortex, while peripheral vision projects rostrally.

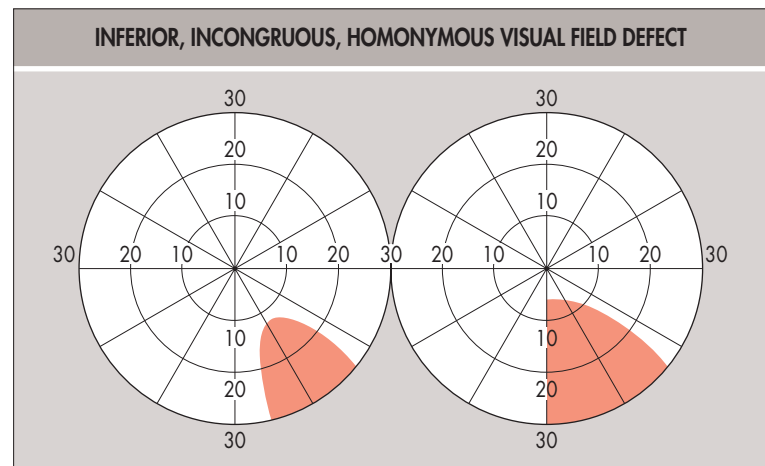
The calcarine cortex plays a smaller role in visual processing than previously theorized. It is a coordination center where information from both hemifields is paired into parallel, vertically oriented, ocular dominance columns.<sup>6</sup> Because the temporal field from the contralateral eye is considerably larger than the nasal field from the ipsilateral eye, each calcarine cortex receives unpaired information from the contralateral eye; this forms the "temporal crescent." This information is processed most anteriorly and aids in the diagnosis and localization of occipital lobe lesions. Connections between the two hemispheres via the corpus callosum allow synchronization and combination of information generated by both fields.<sup>7</sup>

The visual cortex contains four basic types of cells that respond in specific and characteristic ways to retinal stimuli.<sup>8</sup> Circularly symmetrical cells react to small lights independent of movement or orientation. Simple cells respond to a moving light or a dark line or pattern with a specific orientation and direction of motion that projects on the center of their field. Simple cells may turn either "on" or "off" in response to the stimulus. Complex cells respond to linear stimuli almost anywhere in their field but are less specific as to orientation. They also may be "on" or "off" cells. Hypercomplex cells are similar to complex cells but require a linear stimulus of a specific length. The information generated among all these cells is synchronized through the extensive interconnection between visual cortical areas.<sup>9</sup> As a result of this exchange of information, certain stimuli in patterns "pop out" and catch an individual's attention, whereas other details (small gaps in a large pattern especially outside the central 15° or the defect associated with the blind spot) may "fill in" and disappear into the background.<sup>10</sup>

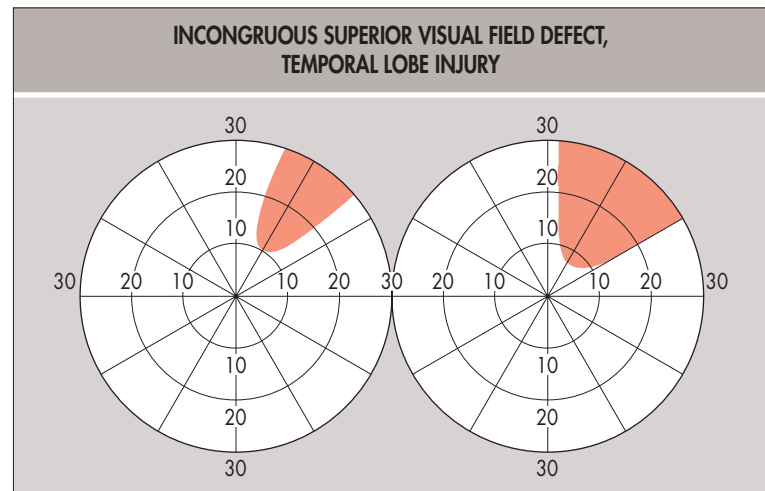
## TOPOGRAPHICAL DIAGNOSIS OF RETROCHIASMAL DISEASE

Lesions involving the visual pathways tend to produce some form of homonymous hemianopia. A total homonymous hemianopia involving the temporal crescent is nonlocalizing. In most cases, however, careful examination of the visual field and associated clinical findings yields clues to the location of a lesion.

Lesions isolated to the optic tracts account for less than 5% of patients with a homonymous hemianopia. Injury to the optic tracts tends to produce exceedingly incongruous field defects. Because the optic tracts include



**Fig. 9.13.3 Inferior, Incongruous, Homonymous Visual Field Defect.** Injuries to the parietal lobe tend to spare central fixation, as is characteristic of temporal lobe lesions.



**Fig. 9.13.4 Visual Field Defect, Temporal Lobe Injury.** Interruption of this segment of the optic radiations yields an incongruous, superior, homonymous visual field defect, more dense above than below—the "pie-in-the-sky" pattern.

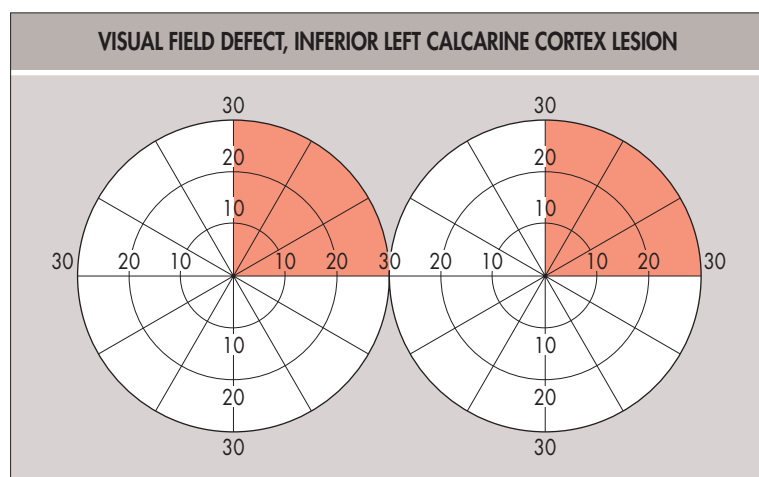
fibers of the afferent pupillary pathway, patients with optic tract lesions tend to demonstrate a relative afferent pupillary defect in the contralateral eye and, eventually, optic atrophy on one or both sides. Patients may demonstrate a larger pupil on the side of the hemianopia (Behr's pupil) or pupillary hemiakinesia (Wernicke's pupil).

Lesions to the lateral geniculate nuclei also tend to produce an incongruous homonymous hemianopia. The vascular supply of the lateral geniculate nucleus may include the adjacent thalamus and corticospinal tracts, which provides additional neurological data to localize a lesion clinically. Because pupillary fibers leave the optic tracts rostral to the lateral geniculate nuclei, lesions here do not produce afferent pupillary defects.

Lesions of the deep parietal lobe may involve the superior (superior and peripheral retinal) fibers of the optic radiations. This damage results in a wedge-shaped, inferior, contralateral homonymous hemianopia (Fig. 9.13.3). Because the optic radiation fibers are still orienting themselves for cortical innervation, the hemianopia is incongruous. Because the macular fibers pass between the parietal and temporal fibers, the defect generally spares central vision. The lesion may involve the posterior limb of the internal capsule and produce a contralateral hemiplegia and hemianesthesia. Involvement of the pursuit pathways, headed for the ipsilateral paramedian pontine reticular formation, tends to result in an alteration of optokinetic nystagmus—the patient cannot pursue stimuli moving toward the side of the lesion and does not generate optokinetic nystagmus in that direction.

Damage to the temporal optic radiations interrupts the inferior (inferior and peripheral retinal) fibers of Meyer's loop. The typical visual field defect is an incongruous, wedge-shaped, superior homonymous hemianopia sparing central vision (Fig. 9.13.4). Injury to adjacent structures may yield memory loss, hearing loss, and auditory hallucinations.

Lesions of the calcarine cortex tend to be silent other than for visual field defects. These defects tend to be highly congruous (Fig. 9.13.5).



**Fig. 9.13.5 Visual Field Defect, Inferior Left Calcarine Cortex Lesion.** Note the high congruity and involvement of fixation.

Preservation of the temporal crescent identifies a defect as cortical. Patients may show sparing of central vision (macular sparing); this phenomenon generally results from separate arterial supply between the occipital pole and the rostral calcarine cortex.

Horton and Hoyt<sup>11</sup> mapped the visual cortex in depth by correlating magnetic resonance imaging (MRI) findings and visual dysfunction in patients with occipital lobe lesions. Information from the central 10° of vision involves more than 50% of the caudal striate cortex. Lesions that spare only the temporal crescent are unusual; the central 1° of vision and the entire temporal crescent engage an equivalent cortical volume.

Improved neuroimaging techniques now simplify the evaluation of patients with homonymous hemianopia (see Chapter 9.1). MRI is the method of choice for watershed lesions, small-vessel disease, thrombotic infarction, leukodystrophy, primary or secondary neoplasia, demyelinating white matter disease, shear injuries, or contusion. The MRI should include contrast and noncontrast multiplanar T1- and T2-weighted images. Lesions dominated by blood (acute subarachnoid or intraparenchymal hemorrhage, for example) show poorly on MRI. Noncontrast computed tomography (CT) studies are more productive in these cases. A lumbar puncture may be the only conclusive tool for finding blood.

## CORTICAL REPRESENTATION OF VISION

### INTRODUCTION

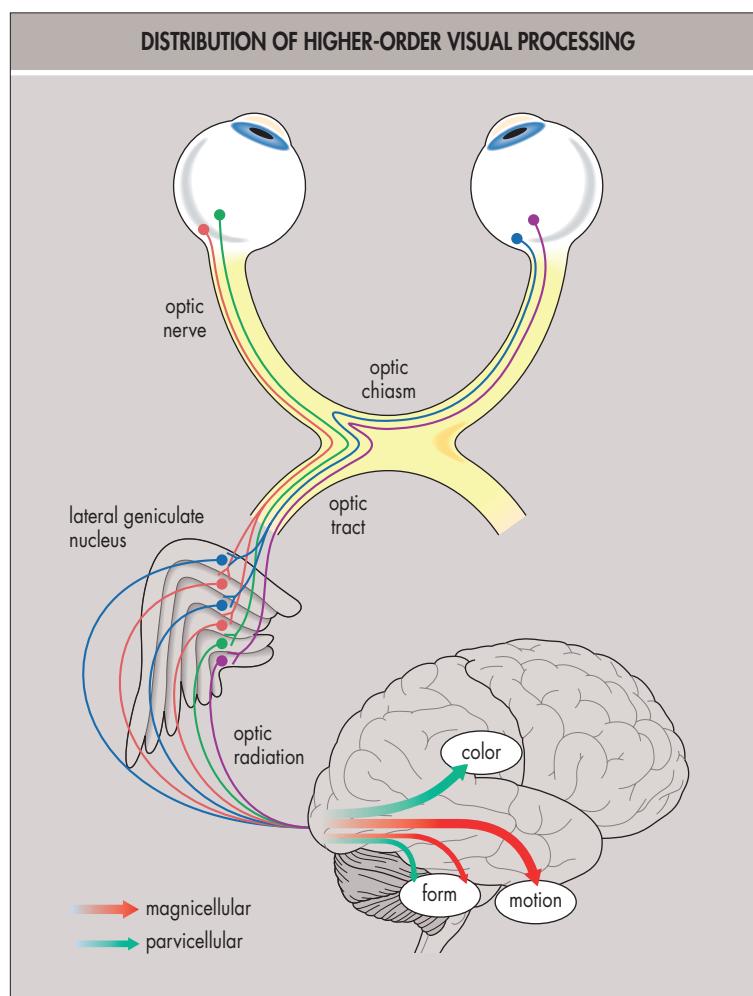
The visual association areas of the brain create an image of the world through complex combinations of information from several parallel pathways. The brain separates information by position and category and correlates this information with surrounding objects and associated sounds (Fig. 9.13.6). The brain must maintain a reference library of previously viewed images ready for instantaneous recall that can be applied in unfamiliar contexts. An understanding of the relationship of cortical visual processing pathways enables the recognition of characteristic syndromes by clinical features.

### OBJECT IDENTIFICATION AND MEMORY

Identification of an object requires the ability to retain an image in memory and use this image for future comparison. A patient may be able to identify objects by touch but not by sight.<sup>12</sup> This syndrome comes from damage to the ventrolateral occipital lobes. In contrast, damage to the superior posterior parietal cortex causes difficulty in making the movements needed to manipulate objects despite a preserved ability to describe the objects and their orientation.<sup>13</sup>

One theoretical basis for this separation of function targets visual association areas in the medial occipital lobes.<sup>14</sup> Injury to the right occipital lobe results in failure to identify complex objects (including faces, i.e., prosopagnosia) in general. Apparently, in many animals this area helps to sort out various types of visual stimuli.<sup>15</sup> A lesion in the left occipital lobe yields impairment of recognition of objects with numerous parts, including words.

A second theory concentrates on the connections among lobes of the brain<sup>16</sup> and postulates that primate brains separate visual information into



**Fig. 9.13.6 Distribution of Higher-Order Visual Processing Among Different Cortical Areas.** The magnocellular system (inferior stream) is concerned generally with the location and motion of objects, whereas the parvocellular system (superior stream) is concerned with the fine resolution (acuity), form, and color of objects.

dorsal and ventral streams. The ventral stream originates in the primary visual cortex, projects to the inferotemporal region, and carries information needed to identify objects and their positions in space. The dorsal pathway transmits the information on size, shape, and orientation needed to grasp the object. One stream may be damaged without injuring the other.

The positron emission tomography (PET) scanner provides assistance in resolution of these two theories. Sine-wave gratings yield activity restricted to the striate and extrastriate cortices.<sup>17</sup> Faces stimulate the right parahippocampal region and both fusiform and anterior temporal cortices. Simple objects activate the left occipitotemporal cortex alone. Farah<sup>18</sup> provides an excellent synopsis of the theories of image generation.

Lack of image recognition, however, does not mean an individual cannot see an image clearly.<sup>19</sup> Patients with prosopagnosia fail in selecting two matching faces from a picture set. Invert the faces, however, and the patients fare much better. Inverting the face apparently allows the brain to treat faces as simple objects.

When an image is repeated in a series, necessitating the recurrent identification of the same object, the brain adds another region to the loop. The prefrontal cortex becomes active on PET scan during this task.<sup>20</sup> Although long-term memory for vision is a temporal lobe function, short-term visual memory is a frontal lobe function.

The inability to identify objects visually, however, does not necessarily affect a person's generation of a mental image. Despite a deficit in naming seen objects, patients may copy visual objects, generate accurate pictures from the memory of an object, or draw a picture based upon tactile examination of an object.<sup>21</sup> Ironically, when shown these drawings, patients do not recognize them as their own.

Stimulation of storage areas may produce accurate visual hallucinations that may occur as a release phenomenon resulting from visual loss<sup>22</sup> or abnormal electrical stimulation.<sup>23</sup> Visual hallucinations may result in isolated midbrain injury,<sup>24</sup> although the exact mechanism remains undetermined.

## READING AND DYSLEXIA

Reading represents a very specialized form of visual processing. The unimpaired reader can recognize even sloppy and garbled writing. Multiple regions of the brain are involved, and injury to any of these areas produces recognizable syndromes.

The primary center for reading and writing language appears to be in the dominant angular gyrus in the parietal lobe.<sup>25</sup> Alexia (the inability to read) with agraphia (the inability to write) results from destruction of this area; exceptions to this rule do exist.<sup>26</sup> Alexia without agraphia results from disconnection of the dominant angular gyrus from input from both occipital lobes.<sup>27</sup> This syndrome most commonly results from an infarct in the distribution of the left posterior cerebral artery.

Dyslexia represents a very special form of alexia.<sup>28</sup> By definition, patients with developmental dyslexia have a discrepancy between the acquisition of reading skills and other intellectual abilities, and this disability is not related to environmental conditions, sensory deficits, or acquired neurological disorders.

Investigators have failed to determine a specific site for the origin of developmental dyslexia. One proposal postulates that developmental dyslexia results from deficiencies and depletion in magnocellular pathways<sup>29</sup> based on decreased numbers of magnocellular neurons in the lateral geniculate nuclei from postmortem studies in dyslexic patients. These patients also had decreased responses to low spatial frequency patterns. This theory is not universally accepted, however. It has been challenged,<sup>30</sup> and the definitive answer to an anatomical cause of developmental dyslexia awaits further clinical research.

Phonological dyslexia represents a disorder of association between sounds (phonemes) and letters (graphemes). Some evidence now exists that phonological dyslexia may result from abnormal development of the dominant inferior frontal lobe in areas responsible for control of tongue and lip articulator movements.

## COLOR PERCEPTION

The pathway for the interpretation of color remains separate from those responsible for object identification. PET scanning findings indicate that the lingual and fusiform gyri become stimulated when a normal individual scans for a colored target.<sup>31</sup> Patients who have lesions that cause visual agnosia may maintain the ability to identify the color of objects.<sup>32</sup>

Patients who have acquired central cerebral achromatopsia (inability to identify colors) may have complete loss or miss only one primary color.<sup>33</sup> The isolation of single-color defects links came from research performed in macaque monkeys that showed that an area of prestriate cortex, identified as area V4, contains neurons that respond to specific color stimuli.<sup>34</sup>

Patients with cerebral achromatopsia generally describe objects as “washed out” or “faded.” Patients may still be able to use contrast clues to separate the edge of one intense color from another. If two colors or a color and a shade of gray match pseudoisochromatically, however, patients demonstrate a distinct inability to isolate colored targets. Despite the achromatopsia, other parts of the parvocellular system may remain intact. Patients may have normal visual acuity and contrast sensitivity. Postmortem and radiological studies of these patients reveal bilateral lesions of the inferior occipital cortex.

## INTEGRATION OF VISUAL-AUDITORY SPACE

The brain frequently receives contradictory information from the visual and auditory systems. For example, when an individual watches a movie, an image is seen directly ahead, but sounds are heard from numerous speakers throughout the theater. The brain integrates this information to provide a meaningful and logical integrated experience.

The ability to reconcile auditory and visual cues appears to be learned.<sup>35</sup> This reconciliation is a complicated task, because visual information is received by direct stimulation of an individual retina, whereas auditory localization requires a binaural triangulation of sound. The complexity heightens when the individual or the target moves.

The brain prioritizes visual input.<sup>36</sup> If a sound seems to originate from a seen object, the brain transfers the perception of that sound to the visible source. The process of correlation occurs in the midbrain tectum.

## MOTION DETECTION

Once the brain identifies an object, it must localize that object in relation to the perceiver and the environment and determine the relative rate of

motion of the object to the perceiver. The observer also may be moving, and multiple environmental targets may be moving in different directions. The brain has developed efficient mechanisms to resolve these factors. Injuries may result in the ability to perceive motion in an otherwise blind field or to lose motion detection while the image of the object is preserved.<sup>37</sup>

The primary step in motion detection involves neurons in area V1 of the calcarine cortex supplied by the magnocellular pathway. Motion-sensitive neurons react to movement in a specific direction.<sup>38</sup> The information from these individual neurons then travels to an area (referred to as MT or V5) in the medial temporal lobe. In primates, MT sits in the posterior segment of cortex, bordering the superior temporal sulcus. Almost 100% of the neurons in MT demonstrate directional sensitivity. Evidence suggests that MT represents the first area in which the information related to motion becomes attached to a texture, color, or pattern.<sup>39</sup>

Unfortunately, for simplistic views of motion detection, a moving object in the environment generates multiple bits of information in the MT region. Some bits may appear contradictory. The brain must integrate these signals to form one coherent, three-dimensional representation of relative motion. Approximately 25% of neurons in MT do not react just to linear motion in a single direction but to motion in multiple vectors. These cells may be responsible for motion integration.

## NONORGANIC VISUAL LOSS

Nonorganic (or functional) visual loss represents one of the most difficult challenges faced by ophthalmologists. Nonorganic visual loss cannot be explained by physical examination or ancillary testing and generally falls into one of two categories—conversion reaction or malingering.

Patients with a conversion reaction, previously called hysterical blindness, react to environmental stress. Adolescents seem particularly prone to this kind of response. Because a conversion reaction alleviates tension, patients generally show a flat, relaxed affect despite severe visual complaints. Patients with a conversion reaction appear to honestly believe they are disabled. They tend to be cooperative with testing.

Malingering patients mimic visual loss consciously to obtain an external secondary gain. Their visual complaints appear out of proportion to the underlying original injury. Physicians must take great care with this diagnosis and not equate failure to find a diagnosis with malingering; this diagnosis requires forms of documentation for clinicians as well as judge and jury.

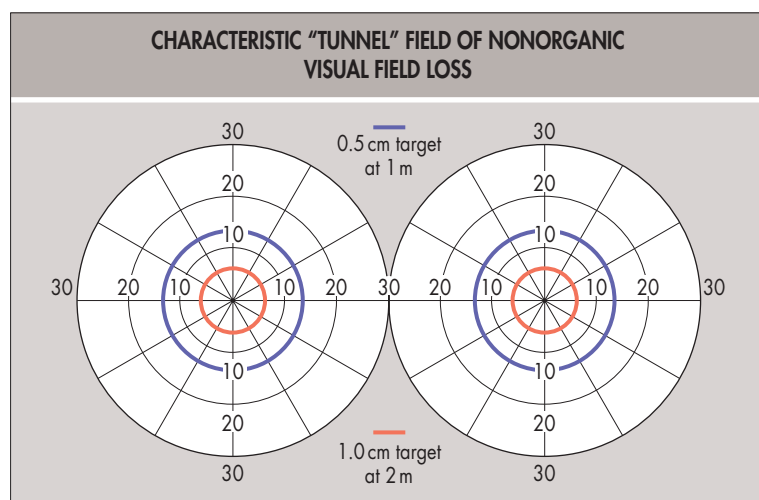
To evaluate patients who have nonorganic visual loss, the examiner starts with the smallest letters possible, in most cases the 20/10 (6/3) line. The physician should pause at each letter and demonstrate concern and confusion that the patient cannot identify these letters. After making the point that the next letters are much larger, the examiner shifts to the 20/15 (6/4.5) line and repeats the process. By the time the patient looks at the 20/20 (6/6) or 20/25 (6/7.5) line, the power of suggestion has set in and the patient generally is convinced the letters are now large enough to read. This technique works well with complaints of either monocular or binocular visual loss.

A 4-diopter prism is an indispensable tool in the evaluation of the visual acuity of patients who have nonorganic monocular visual complaints. The examiner occludes the patient’s “bad” eye, then places the prism over the patient’s “good” eye such that the base is up and the apex splits the pupil. If the prism is positioned in just the right spot, the patient experiences monocular vertical diplopia. The examiner asks the patient if both of the perceived lines appear equally clear; the answer will be “yes.” Once the patient is certain that this test measures the function of the “good” eye, the tester simultaneously uncovers the “bad” eye and slides the prism downward to cover the “good” eye completely. The patient now experiences binocular diplopia but intellectually remains convinced of a monocular phenomenon. At this point, the patient often reads well down the eye chart without hesitation, even when asked to attend to the upper line that corresponds to the “bad” eye.

The red–green eyeglasses provided with the Worth four-dot test may be useful. The examiner asks the patient to put on the glasses and then inserts the red–green filter installed in the vision chart projector. The patient sees the letters on the red half of the eye chart with the eye covered by the red lens and the letters on the green half with the eye covered by the green lens. The patient often progresses well down the eye chart before realizing overachievement has occurred.

The red–green eyeglasses may be used with the Ishihara color plate series as well. If a patient complains of poor vision in one eye, have the patient put on the red–green glasses with the green lens over the “good” eye and the red lens over the “bad” eye. Under normal circumstances, an individual can read the Ishihara numbers through the red lens but





**Fig. 9.13.7 Characteristic "Tunnel" Field of Nonorganic Visual Field Loss.** Paradoxically, the visual field appears to expand as the patient approaches the screen. Such a pattern does not correspond to any known ocular or central nervous system lesion.

not the green lens. If the subject who has nonorganic complaints reads the numbers under the above circumstances, this discrepancy confirms better-than-stated ocular function.

Ophthalmologists often use phoropters and trial frames to confuse patients regarding which eye they are using and obtain a measure of visual acuity. These methods may fail, however, when patients are malingerers. Patients may close an eye surreptitiously and determine which eye they are using. Optokinetic nystagmus only helps ascertain that vision is grossly intact in each eye. A positive test suggests vision is at least 20/400.

Perimetry remains an excellent tool for the evaluation of nonorganic complaints. Both confrontational and tangent screen techniques yield the best information, because they allow variable test distances. Patients who are determined to produce a factitious visual field defect may confound Goldmann and automated perimetry techniques easily, however.

The most common defect discovered during perimetry is a tunnel field. If a visual field is constricted because of organic disease, the absolute size of an isopter for a given test object increases as the distance from the screen increases. Patients who have tunnel fields, however, tend to have field constriction, but they always generate the same absolute size of an isopter on the tangent screen no matter what the test distance (Fig. 9.13.7). The examiner may enhance this tendency by using large, easily discriminated pins to mark the edge of an isopter. Testing at two distances is necessary, however, because several medical conditions (end-stage glaucoma, end-stage papilledema, tapetoretinal degeneration, chiasmal compression, or bilateral occipital lobe infarcts) may produce authentic generalized constriction of the visual field.

The tangent screen may prove useful in another way for the evaluation of patients who have unilateral visual complaints. In one method the visual field is tested for the "good" eye and the location of the blind spot determined. The examiner then tests the "bad" eye and elicits the characteristically small tunnel field inside the blind spot. Finally, the physician evaluates the patient with both eyes open. Patients who have nonorganic complaints frequently lose the blind spot from the "good" eye even though the claimed field for the "bad" eye was smaller than 10°. Occasionally, patients tested in this manner may yield totally inexplicable and impossible visual field changes under binocular conditions. For example, a patient who has a full field in one eye and a tunnel field in the other may report a hemifield loss on the side of the "bad" eye with both eyes open.

Should a patient claim severe bilateral vision loss and be noncompliant on perimetry testing, the examiner must take every opportunity to observe the patient's behavior. If the patient can accurately fix on the examiner's location, a peripheral field much larger than stated is indicated. Patients who have small, bilateral tunnel fields may be able to maneuver easily without bumping into objects. Patients may pick up or take objects held well away to one side, which indicates they can see the objects. Finally, patients who feel no one is watching may perform tasks inconsistent with their level of claimed disability.

Tests for stereoscopic vision may assist the evaluation of patients who have nonorganic complaints. Patients often become intrigued with the challenge of stereoacuity testing and perform at a level well beyond that

claimed under other conditions. Levy and Glick proposed a table estimating the level of visual acuity of the patient's worse eye based on Titmus stereoacuity.<sup>40</sup> The proposed estimate is helpful and has been recently revised.<sup>41</sup>

The examiner may be able to use motility testing to advantage. If a patient complains of a tunnel field, the tester should evaluate saccades initially with two targets very close together. The examiner gradually increases the distance between the two targets and asks the patient to continue to make saccades back and forth. Because a saccade requires voluntary generation to a visible target, patients who have organic visual loss do poorly but those with nonorganic complaints may perform well.

Appropriate evaluation of the pupils constitutes a critical part of the examination of patients who have nonorganic disorders. Asymmetrical visual acuity or field loss between the two eyes must result from intraocular disease or lesions of the optic nerves. Although intraocular disease may not cause an afferent pupillary defect, the examiner usually is able to identify the lesion visually. Unilateral optic nerve disease must produce a relative afferent pupillary defect on the side of the lesion. A patient who complains of markedly poor vision in one eye only, has normal ocular examination findings, and a normal response of the pupils to a light in the "bad" eye is likely to have a nonorganic syndrome.

In certain circumstances, ancillary testing may prove helpful. Electroretinography (ERG) has become a useful tool for nonorganic visual loss evaluation (see Chapter 9.27). Depending on the extent and pattern of vision loss, full field ERG or multifocal ERG may be considered. If a patient generates complaints or findings that suggest a retrochiasmal lesion, imaging studies may be used to identify or eliminate such a lesion as a cause. Should the examiner need further documentation, visual evoked response testing that gives a normal latency and amplitude essentially rules out organic disease as a cause of serious injury to the afferent visual pathway. Malingering patients, however, may prove uncooperative and thwart the efforts of the electrophysiology technician.

Once the examiner has established a patient's complaints as nonorganic, all appropriate findings must be documented carefully in the patient record. The physician must perform all critical tests in the presence of a reliable witness who can corroborate the results in a courtroom.

In most instances, patients who have a conversion reaction respond very favorably to a report of a healthy visual system. The physician must remember that these patients' complaints stem from anxiety; assuaging that anxiety allows the patient to "recover" without stigma. The patient and family must understand that a conversion reaction represents an adaptation to stress; they must work to alleviate the cause of this stress to prevent the development of other somatic complaints.

Malingering patients react poorly to confrontation. Because they seek secondary gain, they immediately challenge demonstrations of their abilities. A good approach is to state that because the physician has not examined the patient previously, an organic lesion may have existed at one time. The examiner can then express concern and relief that the patient's problem has resolved so well and avoid confrontations.

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# Disorders of Supranuclear Control of Ocular Motility

9.14

Patrick J.M. Lavin, Sean P. Donahue, Reid A. Longmuir

**Definition:** Loss of voluntary saccades (fast) and pursuit (slow) eye movements from interruption of neural pathways that carry commands from the cerebral cortex to the ocular motor nuclei in the brainstem.

## Key Features

- Disconjugate eye movement disorders and gaze palsies from lesions that involve the prenuclear pathways between the gaze centers and the ocular motor nuclei.
- Abnormal voluntary saccades, pursuit or vergence eye movements.
- Preservation of reflex eye movements (vestibulo-ocular, optokinetic, and Bell's phenomenon).

## Associated Features

- Pyramidal signs (e.g., pseudobulbar palsy, limb weakness, spasticity, hyperreflexia, and extensor plantar responses).
- Extrapyramidal signs (e.g., bradykinesia, dystonia, rigidity, and tremor).
- Evidence of disorders that cause supranuclear gaze palsies (e.g., traumatic or degenerative, demyelinating, neoplastic or vascular diseases).

## INTRODUCTION

With the exception of reflex eye movements (vestibulo-ocular and optokinetic) and the fast phases of nystagmus, cerebral structures determine when and where the eyes move, while the brainstem centers determine how they move.<sup>1</sup>

The final common pathways for eye movements are located in “gaze centers” in the brainstem (Fig. 9.14.1). The paramedian pontine reticular formation (PPRF) contains the premotor substrate for ipsilateral horizontal gaze; and the midbrain reticular formation (MRF) mediates vertical gaze, vergence eye movements, and ocular counter-rolling (Fig. 9.14.2). The PPRF and MRF receive input from a number of “higher” centers, including the cerebral hemispheres, superior colliculus, vestibular nuclei, and cerebellum (see Fig. 9.14.1). They innervate the three ocular motor nuclei. Supranuclear gaze palsies result from interruption of the neural pathways that carry commands for voluntary saccades and pursuit before they reach the brainstem eye movement “generators.”

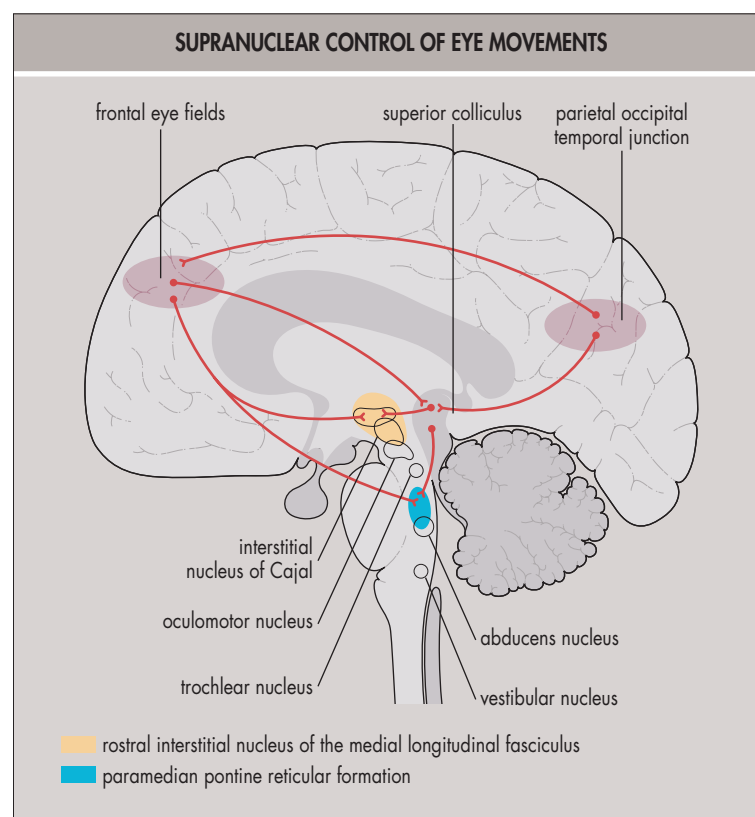
## ANATOMY OF EYE MOVEMENT

### Anatomy of Supranuclear Eye Movement Control

Eye movements are divided broadly into two types (Box 9.14.1):

- Fast eye movements (saccades) that move the eyes from one target to another.
- Slow eye movements that allow the eyes to follow a target when the target, the head, or both are moving.

Slow eye movements may be conjugate (e.g., pursuit,) or disconjugate (e.g., vergence).<sup>2</sup> The initiation and generation of saccades and pursuit is complex and dealt with in greater detail elsewhere.<sup>1,2</sup> The fast phases of nystagmus (see Chapter 9.18) are also saccades (see Box 9.14.1).



**Fig. 9.14.1 Supranuclear Control of Eye Movements.** The pontine horizontal gaze center (blue) and the vertical gaze center in the midbrain (yellow) receive input from the frontal eye fields to initiate saccades and from the parietal occipital temporal junction to control pursuit. These gaze centers control ocular motility by innervating the ocular motor nerve nuclei (III, IV, and VI).

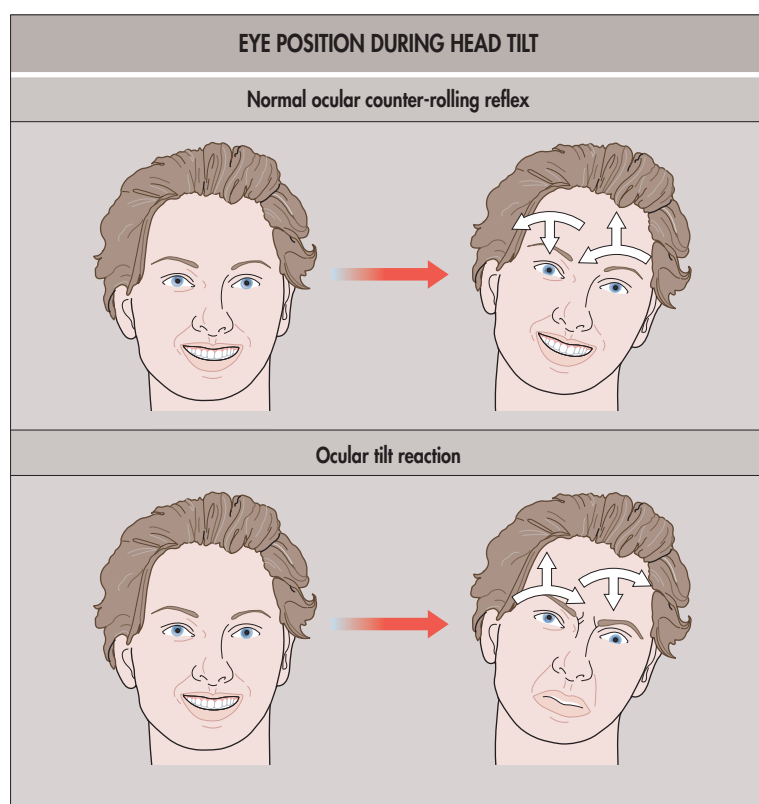
### Horizontal Eye Movements

The contralateral frontal lobe, particularly the frontal eye field, is responsible for generating horizontal saccades. Each frontal eye field projects to the contralateral PPRF, which innervates the abducens nucleus. Pursuit eye movements are triggered by the ipsilateral posterior parietal lobe (see Fig. 9.14.1), which projects to the PPRF and then to the abducens nucleus. About 60% of the neurons in the abducens nucleus innervate the ipsilateral lateral rectus muscle; the remaining 40% project, via the medial longitudinal fasciculus (MLF), to the contralateral medial rectus subnucleus in the oculomotor nuclear complex (Fig. 9.14.3). Thus, activation of the PPRF or the abducens nucleus generates ipsilateral horizontal gaze; conversely, damage to either of these structures results in an ipsilateral gaze palsy.

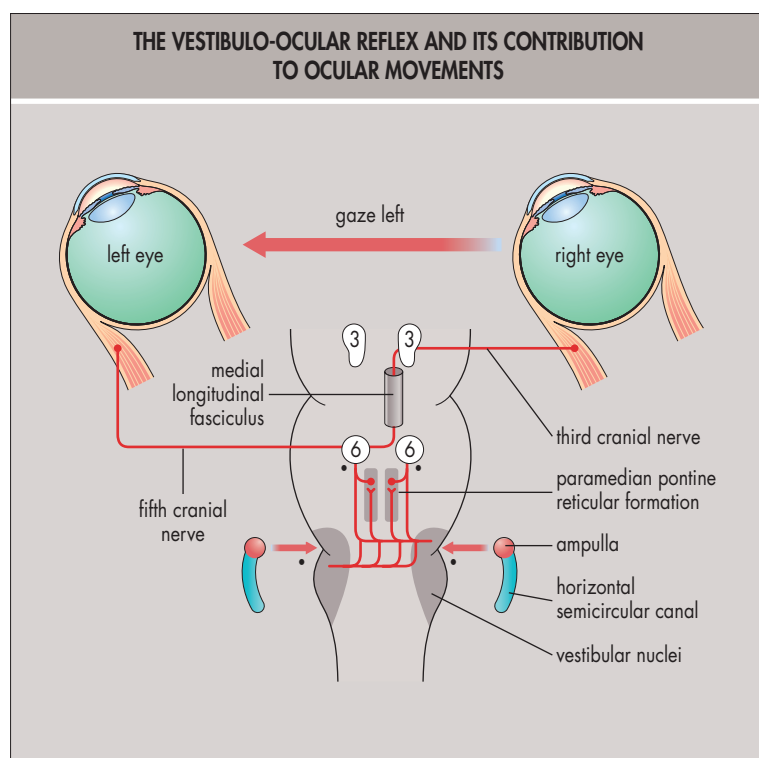
### Vertical Eye Movements

The premotor substrate for vertical gaze lies primarily in the MRF. The rostral interstitial nucleus of the medial longitudinal fasciculus (riMLF) contains neurons for both upward and downward saccades. Their axons relay to neurons in the interstitial nucleus of Cajal, which discharge in relation to vertical eye position and play a role in vertical pursuit and eye position. The neurons for upward saccades innervate both ipsilateral





**Fig. 9.14.2 Eye Position During Head Tilt.** The normal ocular counter-rolling reflex maintains relative eye position when the head is tilted. As the head tilts to the left, the right eye excyclotorts and falls while the left eye rises and incyclotorts. The ocular tilt reaction occurs after brainstem injury and is paradoxical. Patients have a head tilt, bilateral torsion, and a sense of a torted vertical meridian all to the same side.



**Fig. 9.14.3 The Vestibulo-Ocular Reflex and Its Contribution to Horizontal Eye Movements.** The semicircular canals respond to rotational acceleration of the head by driving the vestibulo-ocular reflex to maintain the eyes in the same direction in space during head movement. Fibers from the horizontal semicircular canal travel first to the vestibular nuclei and then to each paramedian pontine reticular formation. Excitatory projections that travel to the contralateral sixth cranial nerve nucleus and via the medial longitudinal fasciculus to the ipsilateral medial rectus subnucleus cause gaze to the left. In a similar manner, inhibitory projections are sent to the antagonist ipsilateral lateral rectus and contralateral medial rectus.

### BOX 9.14.1 Types of Eye Movements

#### Saccades or Fast Eye Movements (Velocity Up to 800/Second)

Voluntary (internally triggered)  
Reflexive (externally triggered—by visual or auditory stimuli)  
Spontaneous (searching, rapid eye movements of sleep)  
Fast phases of nystagmus (physiological or pathological)

#### Slow Eye Movements (Velocity Up to 70/Second)

Smooth pursuit  
• Foveal pursuit  
• Full-field pursuit (optokinetic slow phase)  
Vestibular slow phase (includes torsional movements)  
Vergence

#### Other Ocular Oscillations (e.g., Opsoclonus, Flutter)

and contralateral oculomotor and trochlear nerve nuclei (Fig. 9.14.4). The neurons that mediate downward saccades only innervate the oculomotor and trochlear nerve nuclei ipsilaterally (see Fig. 9.14.1). The riMLF and the interstitial nucleus of Cajal also are involved in the generation of ipsilateral torsional eye movements.

The supranuclear pathways for vertical saccades travel from both frontal eye fields to innervate the riMLF on each side in the MRF (see Fig. 9.14.4). Vertical saccades require simultaneous activation of both frontal eye fields.

### Slow Eye Movements

Slow eye movements help maintain fixation on a target to stabilize the image on the fovea when either the subject or object is moving. Four types of slow eye movements occur, namely, pursuit, optokinetic, vestibular, and vergence.

### Pursuit Eye Movements

Pursuit eye movements allow the eyes to track a moving object at velocities up to 70°/second and have a latency of about 125 milliseconds.<sup>2</sup> The generation of pursuit eye movement consists of three essential elements<sup>1,3</sup>:

- A sensory component driven by an image moving across the fovea.
- A motor component generated near the parieto-occipito-temporal junction that projects to the ipsilateral PPRF.
- An attentional-spatial component for concentration on selected targets and orientation in space.

### Vestibular System

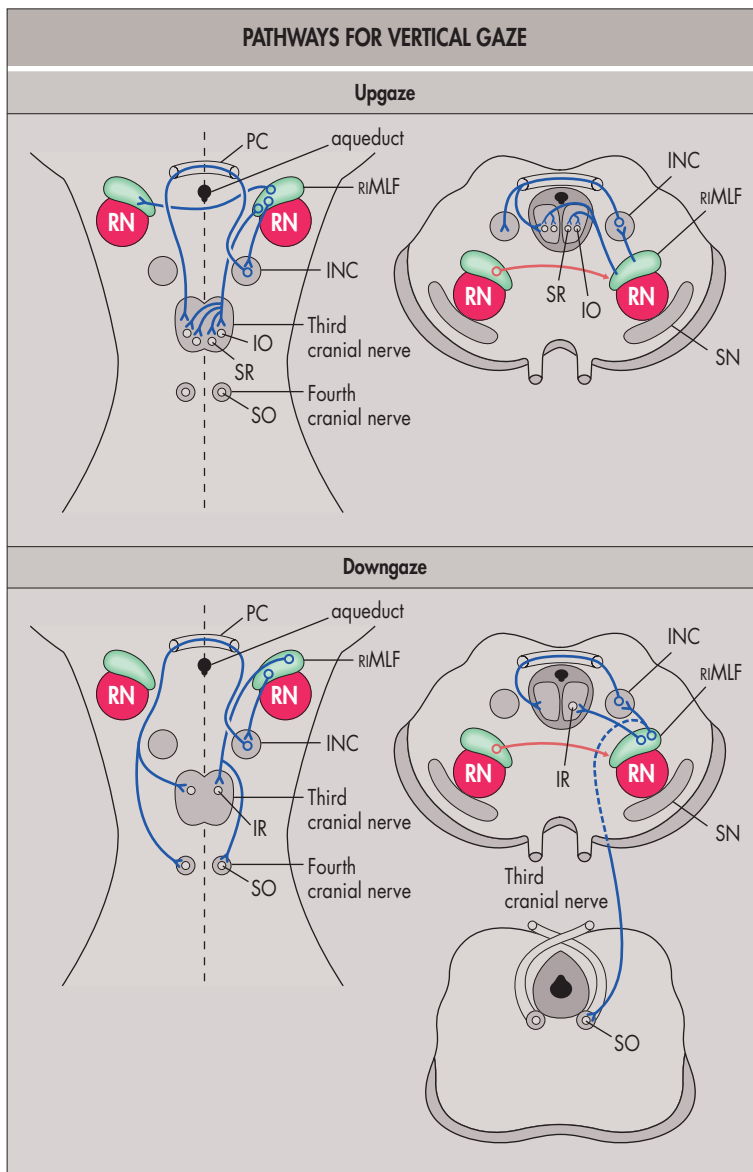
Vestibular eye movements maintain foveation when the head moves in any direction or plane, including the horizontal (yaw), vertical-sagittal (pitch), or vertical-coronal (roll) planes. For example, if the subject's head turns 10° to the right, the eyes rotate 10° to the left to maintain fixation of a stationary object (see Fig. 9.14.2). The latency for vestibular responses is about 10 milliseconds.

### Optokinetic System

The optokinetic system complements the vestibulo-ocular system when it becomes inadequate, as with sustained head rotation when the eyes reach the limit in the orbit. In humans the optokinetic system is tested predominantly by foveal fixation and pursuit and, to a lesser extent, by moving visual field stimulation. The latter is tested clinically by rotating an image of the environment around the patient or by turning the patient in a revolving chair so the environment appears to be moving relative to the patient.

### Vergence System

The vergence system enables eyes to move disconjugately in the horizontal plane and allows binocular fixation of an object that moves toward (convergence) or away (divergence) from the subject. The main stimuli for vergence movements are retinal blur (object unfocused) and diplopia (fusional disparity); convergence is associated with accommodation and pupillary miosis (the near triad). The pathways that generate vergence eye movements are not known precisely, but the occipital lobe, midbrain, and cerebellum play significant roles.



**Fig. 9.14.4 Pathways for Vertical Gaze.** Uppgaze pathways originate in the rostral interstitial nucleus of the medial longitudinal fasciculus and project dorsally to innervate the oculomotor and trochlear nerves, traveling through the posterior commissure. Lesions to both axon bundles are necessary to produce upgaze paralysis. Uppgaze paralysis is a feature of the dorsal midbrain syndrome as a result of the lesion's effect on the posterior commissure. Downgaze pathways also originate in the rostral interstitial nucleus of the medial longitudinal fasciculus but probably travel more ventrally. Bilateral lesions also are needed to affect downgaze and usually are located dorsomedial to the red nucleus. *INC*, Interstitial nucleus of Cajal; *IO*, inferior oblique subnucleus; *IR*, inferior rectus subnucleus; *PC*, posterior commissure; *riMLF*, rostral interstitial nucleus of the medial longitudinal fasciculus; *RN*, red nucleus; *SR*, superior rectus subnucleus.

## DIAGNOSTIC TESTING

Techniques used in the examination of the ocular motor system fall into six categories, reviewed in detail by Borchert.<sup>3</sup>

### Saccades

The patient is asked to alternate fixation rapidly between two targets, such as a finger and the examiner's nose. Both horizontal and vertical saccades are tested and observations are made with respect to latency, velocity, and accuracy.

Abnormalities in saccadic accuracy include overshooting (hypermetria) or undershooting (hypometria) the target and indicate cerebellar pathology. Gross abnormalities are clinically obvious, but detection of subtle changes requires quantitative oculography.<sup>2</sup>

### Fixation

The patient looks at a stationary, accommodative target projected in the distance while the examiner checks fixation both monocularly and binocularly. Fixation should be steady without nystagmus or other significant ocular oscillations. Small eye movements such as square wave jerks of less than 1–2° are normal and do not impair vision.

### Pursuit

The patient is asked to fixate a small object, such as a pen, and follow it slowly through the extent of horizontal and vertical versions. The patient's eyes should pursue the target smoothly. If the pursuit system is defective, or the target moves too quickly, the eyes fall behind and make "catch-up saccades" (saccadic or cogwheel pursuit) to refixate the target.

Also, pursuit may be evaluated while testing the patient's ability to suppress the vestibulo-ocular reflex (VOR). Have the patient sit on a rotatable stool and fixate one of his or her own thumbs at arm's length, then rotate the stool so that the patient's head, arm, and thumb move as one. A normal subject can suppress the induced VOR by maintaining fixation on the thumb, even in darkness or with the eyes closed—VOR suppression probably involves the same pathways as smooth pursuit. This technique particularly helps differentiate real from psychogenic visual loss, because blind patients also can suppress the VOR whereas psychogenic patients appear unable to follow a target smoothly.

### Vergence Eye Movements

The patient is instructed to follow a target as it is moved toward (convergence) and then away (divergence) from their face.

### Ocular Alignment

Ocular alignment is covered in more detail in the section on strabismus (see Chapter 11.3). Ocular alignment is determined by simultaneous prism and cover testing (for tropias) and by alternate cover testing (for phorias, and to measure the basic deviation) while in the proper cycloplegic refraction and fixating an accommodative target.

### Differentiating Supranuclear From Nuclear and Infranuclear Lesions

If the patient has a gaze palsy, the physician determines whether the eyes can be moved reflexively in the direction of the "paresis" in two ways:

#### Oculocephalic (Doll's Eyes) Reflex

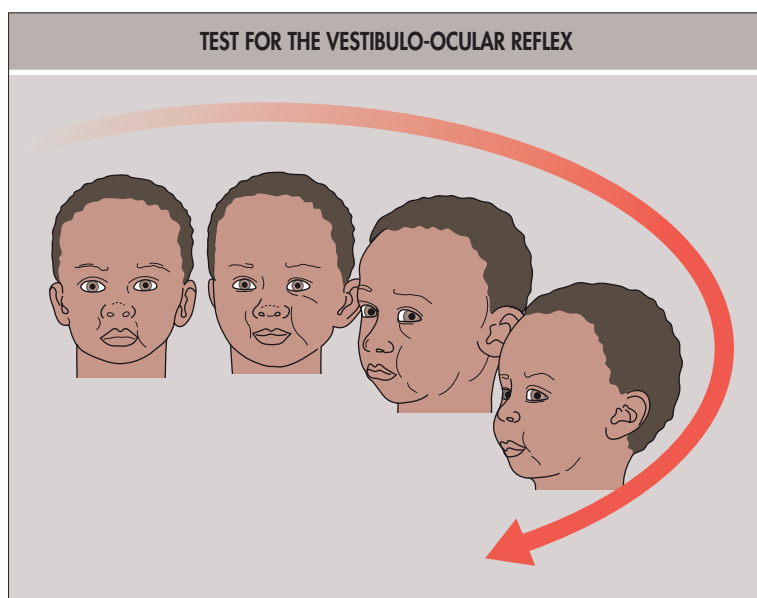
The oculocephalic (doll's eyes) reflex is performed by tilting the head forward 30° and fixating a distant target. The head is then rotated in the direction opposite the gaze palsy. This maneuver uses direct projections from the vestibular system to the ocular motor nuclei (see Fig. 9.14.3). Gaze palsies caused by lesions of the cerebral cortex typically can be overcome by vestibulo-ocular testing. In prenuclear, nuclear, or infranuclear lesions, the reflex does not overcome the palsy.

#### Vestibulo-Ocular Reflex Testing

The patient's head is tilted back 60° and the external auditory meatus irrigated with either cool or warm water to stimulate the horizontal semicircular canal. In normal subjects and patients with supranuclear gaze palsies, cool water stimulation causes the eyes to deviate slowly toward the irrigated side resulting in nystagmus with the fast (corrective) phase to the opposite side. When warm water is used, the fast phase is toward the stimulated ear. The mnemonic COWS (cool, opposite, warm, same) refers to the direction of the fast phase of the nystagmus. In comatose patients no corrective (fast) phase occurs, so with cold water the eyes deviate tonically toward the irrigated ear. Simultaneous bilateral caloric testing may be used to evaluate vertical eye movements, but this is less reliable than oculocephalic testing.<sup>2</sup>

## DISORDERS OF SUPRANUCLEAR OCULAR MOTILITY

Supranuclear ocular motility disturbances result from interruption of the neural pathways before they reach the eye movement generators. They



**Fig. 9.14.5 The Child Is Spun Around the Examiner to Test the Vestibulo–Ocular Reflex.** The slow tonic phase produces gaze in the direction of the spin; fast phase corrective saccades occur to drive the eyes back. In congenital ocular motor apraxia (congenital saccadic palsy), fast phases are absent and the eyes are driven tonically in the direction of the spin.

may be divided into two groups—disorders of gaze and disorders of vergence eye movements. Gaze palsies affect conjugate eye movements and are characterized by loss of voluntary gaze, in one or more directions, while sparing reflex movements, such as the VOR, optokinetic nystagmus (OKN), and Bell's phenomenon. Disorders of vergence eye movements are disconjugate. Skew deviation and the ocular tilt reaction, which also spare the final common pathway for extraocular eye movements and may also affect reflex eye movements, are referred to in this chapter as prenuclear.<sup>1</sup>

## Congenital Gaze Palsies

Congenital ocular motor apraxia (COMA) or, more correctly, congenital saccadic palsy,<sup>1,2</sup> is more common in boys than in girls; these children find it difficult to initiate saccades and have variable impairment of pursuit. Vertical eye movements remain intact. In early infancy, blindness may be suspected because of the inability to fixate or follow objects. However, after a few months head control is achieved and the patient moves the eyes by thrusting the head in the direction of the target. As the head overshoots the target, the eyes follow the head movement and take up fixation. The head thrusts, usually accompanied with blinks, become less noticeable with time. Confirmation of saccadic palsy is made by spinning the infant around the examiner (Fig. 9.14.5). The eyes move conjugately and slowly in the direction of the spin, but because of the impaired saccades, no corrective horizontal fast phases are seen. COMA may be associated with posterior fossa abnormalities and developmental delay. Ocular motor disorders resembling COMA may be seen in a number of conditions, including Aicardi's syndrome, dysgenesis of the corpus callosum or cerebellum, ataxia telangiectasia, Cockayne's syndrome, Joubert's syndrome, Pelizaeus-Merzbacher's disease, and succinic semialdehyde dehydrogenase deficiency.

Congenital vertical ocular motor apraxia is rare<sup>4</sup> and must be differentiated from metabolic and degenerative disorders, such as neurovisceral lipidosis, and from stable disorders such as birth injury, perinatal hypoxia,<sup>4</sup> and, occasionally, Leber's congenital amaurosis.

Familial horizontal gaze palsy with scoliosis (HGPS) is an autosomal recessive disorder characterized by paralysis of horizontal gaze from birth, progressive scoliosis, impaired optokinetic reflex, and VOR, but intact convergence and vertical eye movements. Some patients may have fine pendular horizontal nystagmus, facial myokymia, facial twitching, hemifacial atrophy, and situs inversus of the optic discs.<sup>2,5</sup>

## Acquired Gaze Palsies

Acquired horizontal supranuclear gaze palsies may occur with stroke, head injury, tumors, seizures and, rarely, with metabolic disease. This subject is reviewed in detail elsewhere.<sup>1</sup> Because these patients have cognitive dysfunction, they can be difficult to examine.

## BOX 9.14.2 Causes of Slow Saccades

Acquired immunodeficiency syndrome dementia complex  
Amyotrophic lateral sclerosis  
Anticonvulsant toxicity (consciousness usually impaired)  
Ataxia telangiectasia  
Hexosaminidase A deficiency  
Huntington's disease  
Internuclear ophthalmoplegia  
Joseph's disease  
Lesions of the paramedian pontine reticular formation  
Lipid storage diseases  
Lytico-bodig disease  
Myasthenia gravis  
Myotonic dystrophy  
Nephropathic cystinosis  
Ocular motor apraxia  
Ocular motor nerve or muscle weakness  
Progressive supranuclear palsy  
Spinocerebellar degeneration (e.g., olivopontocerebellar degeneration)  
Wernicke's encephalopathy  
Whipple's disease  
Wilson's disease

Acute hemisphere stroke can cause a transient gaze deviation.<sup>1</sup> Usually, the eyes are deviated toward the side of the lesion because of paresis of gaze to the hemiplegic side. After about 5 days the intact hemisphere usually takes over and both the gaze paresis and ocular deviation resolve.

Ictal conjugate ocular deviation (seizure activity) occurs as a result of irritative lesions.<sup>6,7</sup> Such lesions “activate” the involved frontal eye field and cause the eyes to deviate away from the damaged hemisphere (adversive gaze deviation). Usually, such ocular deviation is associated with or immediately followed by adversive nystagmoid eye movements. Afterward, because of postictal paralytic conjugate ocular deviation, gaze transiently deviates toward the involved hemisphere as part of Todd's paralysis.

The PPRF may be injured by a variety of lesions including ischemia, hemorrhage, neoplasm, infection, demyelination, and paraneoplastic disorders. A lesion that affects the ipsilateral abducens nucleus or PPRF causes an ipsilateral gaze palsy. A rostral PPRF lesion spares the VOR, whereas a caudal lesion does not. As a result of the proximity of the abducens nucleus and the facial nerve fasciculus, ipsilateral facial weakness typically occurs with caudal PPRF lesions. Rarely, the first-order (central) sympathetic fibers are involved, causing an associated ipsilateral Horner's syndrome.<sup>8</sup>

Wrong-way eyes is the term given to conjugate eye deviation to the “wrong” (hemiplegic) side, that is, away from the lesion and toward the hemiplegic side (contraversive gaze deviation).<sup>9</sup> It may occur with supratentorial lesions, particularly thalamic hemorrhage, but also with ischemic stroke. This can also occur with large perisylvian or lobar hemorrhage or irritative lesions.

Incomplete lesions of the PPRF result in difficulty maintaining eccentric gaze and produce gaze-paretic (gaze-evoked) nystagmus. When the eyes drift back to the primary position, the patient makes corrective saccades back to the eccentric target, which results in gaze-evoked nystagmus.

Bilateral lesions of the PPRF may cause complete loss of voluntary horizontal gaze. Large lesions may extend into the ventral pons, injuring the corticospinal tracts, and render the patient quadriplegic, causing the locked-in syndrome.<sup>10</sup> Such patients appear unconscious, but volitional vertical eye and lid movements are spared, differentiating the locked-in syndrome from coma. Ocular bobbing can occur in this setting (see Chapter 9.18).

Slow saccades occur with pontine disease and a number of disorders listed in Box 9.14.2.<sup>1</sup>

## Disorders of Pursuit

The horizontal pursuit pathways control ipsilateral tracking. The final common motor pathway extends from the parieto-occipito-temporal junction via the dorsolateral pontine nuclei, to the ipsilateral gaze center in the PPRF. With rare exceptions, lesions of the pursuit pathways cause impaired ipsilateral tracking; because the pursuit pathways probably decussate twice,<sup>11</sup> a unilateral midbrain lesion can cause impaired contralateral pursuit.<sup>12</sup> The frontal eye fields, superior colliculi, and cerebellum also contribute to pursuit drive.



Pursuit deficits range from absence of tracking eye movements to saccadic (cogwheel) pursuit. Global impairment of smooth pursuit is a common, nonspecific finding.

Injury to the pursuit pathways also affects the slow phase of OKN, easily demonstrated by rotating an optokinetic drum so that the stripes move toward the affected hemisphere. Because of the proximity of the pursuit pathways to the afferent visual pathways, lesions can cause a contralateral homonymous hemianopia as well.

Balint's syndrome is characterized by apraxia of gaze (inability to look at different parts of the visual field), simultanagnosia (inability to attend simultaneously to different parts of the visual field), and optic ataxia (mislocalization when reaching for, or pointing to, objects). It occurs with bilateral injury to the parieto-occipital region, usually as a result of a prolonged episode of hypotension causing watershed (distal territory) infarction, but also in posterior reversible encephalopathy syndrome (PRES) and in degenerative disorders such as posterior cortical atrophy.<sup>13,14</sup>

## Internuclear Ophthalmoplegia

Injury to the MLF, between the abducens nucleus and the contralateral medial rectus subnucleus of the oculomotor nerve, interrupts transmission of neural impulses to the ipsilateral medial rectus muscle (see Fig. 9.14.3). This impairs adducting saccades of the ipsilateral eye, which become either slow or absent. On attempted lateral gaze, away from the side of the lesion, the abducting eye overshoots the target (dysmetria), giving the appearance of dissociated (disconjugate) nystagmus. If the internuclear ophthalmoplegia (INO) is bilateral, abduction saccades also may be slow because of impaired inhibition of resting tone in the medial rectus muscle. Upward beating and torsional nystagmus are frequently present, particularly if both MLFs are affected. A subtle INO may be demonstrated when the patient makes repetitive horizontal saccades, which disclose slow adduction of the ipsilateral eye. Convergence may be preserved. Other clinical features associated with INO include skew deviation, defective vertical smooth pursuit, impairment of the vertical VOR, as well as impaired ability to suppress or cancel the vertical VOR.

INO also may occur with a variety of disorders that affect the brainstem (vascular, demyelinating, and metastatic) and must be differentiated from the pseudo-INO of myasthenia gravis, paraneoplastic strabismus, or a long-standing exotropia.

The one-and-a-half syndrome occurs with damage to the caudal pons that involves the ipsilateral MLF and either the ipsilateral PPRF or the abducens nucleus. It results in an ipsilateral gaze palsy with an ipsilateral INO (see Fig. 9.14.3). The only intact horizontal movement is abduction of the contralateral eye. If the facial nerve nucleus or fasciculus is involved, oculopalatal myoclonus (a vertical oscillation of the eyes, palate, and other muscles of branchial origin) may develop later.<sup>15</sup> The most common causes of the one-and-a-half syndrome are multiple sclerosis and brainstem stroke, followed by metastatic and primary brainstem tumors. Ocular myasthenia gravis may cause a pseudo-one-and-a-half syndrome.<sup>16</sup>

## Disorders of Vertical Gaze

Isolated midbrain lesions can cause disorders of vertical gaze (see Fig. 9.14.4) and occur with a variety of diseases (Box 9.14.3). Disorders of vertical gaze, particularly downgaze, often are overlooked in patients with brainstem vascular disease, because damage to the nearby reticular activating system impairs consciousness.

Supranuclear upgaze palsies occur with lesions at or near the posterior commissure and with bilateral lesions in the pretectal area (see Fig. 9.14.4). Extrinsic compression of the posterior commissure or pretectal region causes loss of the pupillary light reflex but spares accommodation and convergence (light-near dissociation). Paralysis of upgaze, light-near dissociation of the pupils, impaired convergence, lid retraction, and convergence retraction nystagmus are features of the dorsal midbrain (Parinaud's) syndrome. This condition is most commonly seen in the setting of pineal region tumors, primary brainstem tumors, and midbrain stroke.<sup>17</sup>

Convergence retraction nystagmus is a uniquely localizing sign of injury to the dorsal midbrain region. It is not true nystagmus but a saccadic disorder<sup>2</sup> that is elicited best by rotating an optokinetic drum with the stripes moving downward. When the patient attempts to make corrective upward saccades to refixate, the eyes converge and retract in the orbits because of synchronous co-contraction of the extraocular muscles.

Downgaze palsy occurs with bilateral lesions of the rostral interstitial nucleus of the MLF or its projections (see Fig. 9.14.4). With the exception of occlusion of the posterior thalamosubthalamic branch of the posterior

### BOX 9.14.3 Disorders of the Midbrain That Affect Vertical Gaze

#### Extrinsic Lesions

Pineal region tumors  
Vascular malformations and aneurysms  
Hydrocephalus (failed ventricular shunt)  
Parasitic cysts

#### Intrinsic Lesions

Primary brainstem tumor (glioma, ependymoma)  
Metastatic brainstem tumor  
Third ventricular tumors  
Pituitary adenomas  
Stroke

- Infarction
- Hemorrhage (thalamic, pretectal)

Trauma (surgery, head injury)  
Multiple sclerosis  
Infection (syphilis, encephalitis)  
Lipid storage disease  
Transtentorial herniation  
Kernicterus  
Wernicke's syndrome  
Bassen-Kornzweig syndrome  
Vitamin B12 deficiency  
Jejunal ileal bypass

cerebral artery (Percheron's artery), such discrete lesions are rare; involvement of the midbrain rather than the thalamus is responsible for the paralysis.<sup>18</sup> More commonly, bilateral involvement of the pathways for downgaze and for upgaze occurs as part of diffuse neurological disorders. Rarely, a unilateral lesion of the midbrain tegmentum may result in impaired downward, as well as upward, saccades.<sup>2</sup>

Progressive supranuclear palsy (Steele-Richardson-Olszewski syndrome), a neurodegenerative disorder, occurs in about the sixth decade. It is characterized by vertical supranuclear gaze palsy, particularly for downward gaze, postural instability, and unexplained falls. In addition, nuchal rigidity, Parkinsonism, pseudobulbar palsy, and dementia may be present. Early visual symptoms include blurred vision (making it difficult to see food on a plate and to read), diplopia, burning eyes, and photophobia. As the disease progresses, horizontal eye movements become impaired as well; and eventually a global gaze paresis develops.<sup>2</sup>

Wilson's disease (hepatolenticular degeneration) is associated with a Kayser-Fleischer ring, caused by the accumulation of copper in Descemet's membrane. Eye movement abnormalities are unusual, but slow saccades and supranuclear upgaze palsies may occur.

Kernicterus (neonatal jaundice) can cause upgaze paresis, which usually is supranuclear.<sup>19</sup> Horizontal saccades may be slow in Huntington's disease. Patients find it difficult to initiate saccades and frequently use blinks and head thrusts to facilitate eye movements. Vertical saccades are affected more than horizontal saccades. Fixation instability is prominent.

Tonic upward deviation of gaze (forced upgaze) is rare but may be seen in unconscious patients.<sup>1</sup> It can also be observed in oculogyric crisis, which is often triggered by neuroleptic medications. Rarely, tonic upward gaze deviation may be psychogenic, but it can be overcome by cold caloric stimulation of the semicircular canals.

Benign paroxysmal tonic upward gaze usually starts during the first year of life, lasts about 2 years, and has no known cause. This phenomenon can occur with cystic fibrosis.<sup>20</sup> Tonic upgaze may be seen in normal infants during the first months of life.<sup>21</sup>

Tonic downward deviation of gaze (forced downgaze) is associated with medial thalamic hemorrhage, acute obstructive hydrocephalus, severe metabolic or hypoxic encephalopathy, or massive subarachnoid hemorrhage. When associated with lid retraction, the pupils may be buried below the lower lids (setting sun phenomenon). In this setting, elevated intracranial pressure is a major concern. The eyes may be converged, as if looking at the nose.<sup>22</sup> Preterm infants with intraventricular hemorrhages also may have tonic downward deviation with skew deviation and esotropia.<sup>23</sup> Tonic downward deviation of the eyes may occur as a transient phenomenon in otherwise healthy neonates. It also can be induced in infancy by sudden exposure to bright light.

Skew deviation is a vertical divergence of the ocular axes caused by a "prenuclear" lesion of the vertical vestibulo-ocular pathways in the

brainstem or cerebellum. Skew deviation usually is comitant and frequently associated with cyclotorsion of one or both eyes. When the skew deviation is noncomitant it can mimic a partial third or fourth cranial nerve palsy. Exotropia is often present in combination with skew deviation and internuclear ophthalmoplegia. Skew deviation occurs most commonly with vascular lesions of the pons or lateral medulla (Wallenberg's syndrome). With lesions of the midbrain or upper pons, the contralateral eye is lower (contraversive skew), but with lesions of the lower pons or medulla the ipsilateral eye is lower (ipsiversive skew).<sup>24</sup>

With alternating skew deviation, the hypertropia changes with the direction of gaze. The adducting eye usually is hypotropic, thus mimicking superior oblique overaction. Alternating skew deviation occurs with lesions of either the upper midbrain region involving the interstitial nucleus of Cajal or the cervicomedullary junction or cerebellum. In the latter situation, ataxia and downbeat nystagmus usually are associated.<sup>25</sup> Paroxysmal or periodic alternating skew deviation occurs with midbrain lesions; the hypertropia changes in a regular or irregular manner over periods of seconds to minutes.

Ocular counter-rolling, a normal vestibular reflex, allows people to maintain horizontal orientation of the environment while the head tilts to either side (see Fig. 9.14.2). When the head is tilted to the left, the left eye rises and incyclotorts as the right eye falls and excyclotorts.

The ocular tilt reaction is a special type of skew deviation associated with cyclotorsion of both eyes and paradoxical head tilt all to the same side—that of the lower eye (see Fig. 9.14.2). A tonic (sustained) ocular tilt reaction occurs with lesions of the ipsilateral utricle, vestibular nerve or nuclei, or a lesion in the region of the contralateral interstitial nucleus of Cajal and medial thalamus. A phasic (paroxysmal) ocular tilt reaction occurs with lesions of the ipsilateral interstitial nucleus of Cajal and may respond to baclofen.

Dissociated vertical deviation is an asymmetrical, bilateral phenomenon that occurs with early disruption of fusion (congenital esotropia, infantile cataract). Usually it is manifest during periods of inattention in which the deviating eye elevates, abducts, and excyclotorts. The cause remains unclear, but it is an exception to Hering's law of equal innervation. When manifest, it is best treated by unilateral or bilateral superior rectus recession.<sup>26</sup>

Congenital monocular elevator deficiency, previously known as double elevator palsy, is characterized by congenital limitation of elevation of one eye. Most patients are hypotropic in the primary position but use a chin-up head position to allow fusion. A ptosis or pseudoptosis, in which the upper lid of the affected hypotropic eye appears ptotic because the eye is lower, is almost always present. Monocular elevator deficiency is believed to result from a prenuclear congenital unilateral midbrain lesion because the affected eye usually is elevated by Bell's reflex. Furthermore, because the elevator muscles of the affected eye (inferior oblique and superior rectus) are innervated by their respective subnuclei within the third cranial nerve nucleus but on opposite sides of the midline, a single unilateral lesion must be prenuclear rather than nuclear.

In long-standing monocular elevator deficiency, the inferior rectus muscle may become tight, which may be treated using recession. If no restriction occurs, a full tendon vertical transposition (Knapp procedure) of the horizontal muscles is recommended.<sup>27</sup> Other disorders that may cause inferior rectus restriction, such as thyroid orbitopathy and orbital floor fractures, must be excluded.

Monocular supranuclear (prenuclear) elevator palsy is an acquired limitation of elevation of one eye on attempted upgaze. Patients remain orthotropic in primary position and downgaze is intact. This disorder occurs with unilateral vascular or neoplastic lesions of the midbrain.<sup>1</sup> The affected eye usually is elevated by Bell's reflex or by vestibular stimulation.

## OCULAR MOTILITY DISORDERS AND THE CEREBELLUM

The cerebellum coordinates the different motor and sensory inputs to the ocular motor system and ensures that the eyes move smoothly and accurately. Ocular motility signs indicative of cerebellar disease are listed in Box 9.14.4. The dorsal vermis and fastigial nuclei determine the accuracy of saccades by adjusting their amplitude. Lesions of the dorsal vermis and fastigial nuclei result in saccadic dysmetria. The flocculus is responsible for the stabilization of images on the fovea, particularly after a saccade. Lesions of the flocculus result in gaze-holding deficits, such as gaze-evoked, rebound, or downbeat nystagmus, impaired smooth pursuit, inability to cancel the VOR by the pursuit system, and inability to suppress

### BOX 9.14.4 Ocular Motility Signs Indicative of Cerebellar Disease

Saccadic dysmetria (inaccurate saccadic amplitude; over- or undershooting a visual target)  
Saccadic pursuit  
Unstable fixation (square wave jerks)  
Impaired vestibulo-ocular reflex suppression  
Gaze-evoked nystagmus  
Vertical nystagmus  
Increased vestibulo-ocular reflex gain

nystagmus (and vertigo) by fixation. The nodulus influences vestibular eye movements and vestibulo-optokinetic interaction. Lesions of the nodulus may produce periodic alternating nystagmus.

Posterior fossa tumors may become apparent with strabismus; acute comitant esotropia may be the first sign.<sup>28</sup> Affected children usually are older than those who have infantile or accommodative esotropia and develop nystagmus or other neurological signs.<sup>29</sup> Failure to regain fusion after spectacle, prism, or surgical therapy is common and indicates need for neuroimaging.<sup>28</sup> Congenital or acquired cerebellar defects may be associated with a variety of ocular motility disorders. Patients with COMA may have midline cerebellar defects.<sup>30</sup> Chiari malformations may be associated with downbeat nystagmus, gaze-evoked nystagmus, skew deviation, or divergence-insufficiency esotropia. Familial cerebellar degeneration may be associated with vergence disorders.<sup>31,32</sup>

## OCULAR MOTILITY DISORDERS AND THE VESTIBULAR SYSTEM

The vestibular system stabilizes images on the retina during head movements; the semicircular canals respond to the rotational acceleration of the head by driving the VOR to maintain the direction of gaze in space (on target) during head movements: the otolith (utricle or saccule) respond to linear acceleration and static head tilt responds to gravity. This network is discussed in greater detail elsewhere.<sup>33,34</sup> Disruption of the vertical VOR pathway (peripheral vestibular system, vestibular nuclei, cerebellar inputs, MLF, or cranial nerve subnuclei) causes skew deviation.

## VERGENCE DISORDERS

Convergence paralysis occurs with midbrain lesions and may be associated with other features of the dorsal midbrain syndrome. Lack of effort, however, is the most common cause of poor convergence. Degenerative disorders, such as cerebellar degeneration, Parkinson's disease, and progressive supranuclear palsy, also may be associated with poor convergence. The absence of other midbrain signs and the lack of pupillary constriction on attempted convergence may differentiate psychogenic convergence from organic disease.

Convergence insufficiency is an idiopathic condition that also may in part be related to effort. It is seen in young individuals who complain of diplopia or eye strain in association with near work (asthenopia).<sup>31</sup> This condition is often responsive to "pencil pushups."

Divergence insufficiency is characterized by uncrossed horizontal diplopia at distance in the absence of other neurological symptoms or signs. Patients have intermittent or constant esotropia that is greater at distance than at near. Abduction is full. The origin of divergence insufficiency is unclear, but it may result from a break in fusion later in life or occur in patients with cerebellar degeneration.<sup>32</sup> The condition is treated easily with base-out prisms for the distance correction and rarely requires extraocular muscle surgery.

Divergence paralysis is a controversial entity that is difficult to differentiate from bilateral sixth cranial nerve palsies. Such patients usually have horizontal diplopia at distance with full versions, but abducting saccades are slow. Patients who have bilateral sixth cranial nerve palsies who recover gradually often go through a phase in which the esotropia is comitant and versions are full and thus mimic divergence paralysis.

Spasm of the near reflex is characterized by intermittent episodes of convergence, miosis, and accommodation. Symptoms include double or blurred vision. The patient is esotropic, particularly at distance, and has extreme miosis. Spasm of the near reflex is commonly psychogenic in origin. Patients who have psychogenic spasm of the near reflex often have

associated somatic complaints and behavioral abnormalities, which include blepharoclonus on prolonged lateral gaze. Uncorrected high hyperopia may mimic spasm of the near reflex, but a careful cycloplegic refraction will reveal an accommodative esotropia. The correct management consists of prescribing the full cycloplegic refraction.

Central disruption of fusion, also called posttraumatic fusion deficiency, occurs after moderate midbrain injury and causes intractable diplopia, despite the patient's ability to fuse intermittently and even achieve stereopsis briefly.<sup>33</sup> Prism therapy or surgery is ineffective. Central disruption of fusion also may be associated with brainstem tumors, stroke, neurosurgical procedures, removal of long-standing cataracts, and uncorrected aphakia. It must be differentiated from psychogenic disorders of vergence and bilateral superior oblique palsies; the latter usually cause intolerable cyclodiplopia.

The hemislide phenomenon occurs when patients who have large visual field defects, particularly dense bitemporal hemianopias, develop diplopia. They have difficulty maintaining fusion because they can no longer suppress any latent deviation as a result of loss of overlapping areas of field.

Ocular neuromyotonia is a brief, involuntary, intermittent myotonic contraction of one or more muscles of the extraocular. Although the mechanism is unclear, it is included here because it must be differentiated from other vergence disorders. Ocular neuromyotonia usually results in esotropia of the affected eye with accompanying failure of elevation and depression of the globe and may be provoked by prolonged eccentric gaze. It may be associated with signs of aberrant reinnervation of the third cranial nerve. Usually, the pupil is fixed to both light and near stimuli. Causes include radiation therapy and, less commonly, compressive lesions such as cavernous sinus meningiomas, pituitary adenomas, and, rarely, dolichoectatic vessels. Occasionally no cause is found. It must be differentiated from superior oblique myokymia and the spasms of cyclic oculomotor palsy (see Chapter 9.18). Ocular neuromyotonia responds to carbamazepine and other antiepileptic drugs.

## DEVELOPMENT OF THE OCULAR MOTOR SYSTEM

Maturation of the nervous system continues after birth and is particularly rapid during the first few months of life. At birth the vestibular system is the most developed of the ocular motor subsystems and may be tested by rotating the infant (held at arm's length). The VOR is well developed by the end of the first postnatal week.<sup>34</sup> Smooth pursuit movements occur in neonates but only with large targets (such as a human face) that move at low velocities. The pursuit system does not mature fully until the late teens. The saccadic system also is immature in the neonate. Vertical saccades mature more slowly than horizontal saccades and may not be detected for

the first month after birth. Vergence movements are also slow to mature but are seen after about the first month.

## Transient Ocular Motility Abnormalities in Infancy

Several benign transient ocular motility disorders occur in infancy. Neonatal strabismus occurs in up to one-third of healthy neonates; an esotropia that persists beyond 3 months or an exotropia that persists beyond 4 months postnatally is abnormal.<sup>35</sup> Tonic downward ocular deviation occurs in approximately 2% of otherwise healthy neonates<sup>36,37</sup> and is similar to the "sunset" sign seen in infants with hydrocephalus but resolves spontaneously. Lid retraction, either spontaneous or associated with sudden darkness, may be noted. Tonic upgaze is less common than tonic downgaze but is well described<sup>32,38</sup> and also usually resolves. Skew deviation occurs in healthy infants and usually resolves,<sup>37</sup> but a substantial number of them develop strabismus.

Premature infants, especially those with intraventricular hemorrhages, may develop tonic downward and esotropic ocular deviations similar to that in adults with acquired thalamic lesions. Although the upgaze palsy typically resolves, the esotropia persists and requires surgery.<sup>1</sup>

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# Nuclear and Fascicular Disorders of Eye Movement

9.15

Sean P. Donahue, Reid A. Longmuir

**Definition:** Eye movement disorders caused by damage to the ocular motor nerve nuclei (third, fourth, or sixth cranial nerves) or to the ocular motor nerve fascicles within the brainstem.

## Key Features

- Diplopia.
- Incomitant ocular deviation.
- Concomitant localizing neurological signs.

## Associated Features

- Additional cranial nerve palsies.
- Supranuclear disorders of motility.
- Long tract signs.

## INTRODUCTION

Eye movement commands are carried from the cerebral cortex and higher brainstem structures to the ocular motor nerve nuclei. These commands are then sent to the individual extraocular muscles by the third, fourth, and sixth cranial nerves. Eye movement abnormalities resulting from damage to the structures that carry commands to the ocular motor nerve nuclei are considered supranuclear or prenuclear in origin (see Chapter 9.14). Abnormalities resulting from damage to the ocular motor nuclei and their respective cranial nerves are considered infranuclear abnormalities.

An infranuclear ocular motor nerve palsy can be caused by damage anywhere from the nucleus to the extraocular muscle. Nuclear ocular motor palsies occur at the level of the ocular motor nucleus; fascicular nerve palsies are caused by lesions to the nerve fibers that travel from the nucleus and exit the brainstem into the subarachnoid space.

Nuclear and fascicular ocular motor nerve palsies produce characteristic ocular abnormalities, depending on the loss of the function of the innervated extraocular muscle. Acute palsies produce an incomitant strabismus that is greatest in the field of action of the paretic muscle. Palsies of the third nerve are also associated with abnormal pupillary and lid function. Fourth nerve palsies are almost always associated with additional complaints of torsion or with a head tilt or turn.

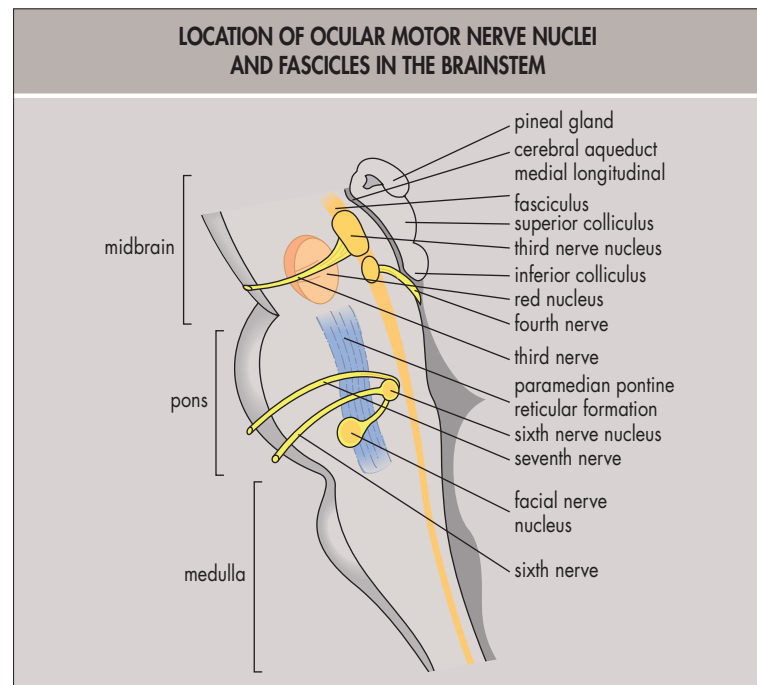
Nuclear and fascicular nerve palsies often are associated with other neurological signs because of the large number of structures located nearby (Fig. 9.15.1). Detailed knowledge of the neuroanatomy of the midbrain and pons enables the clinician to localize these lesions with great accuracy.

## EPIDEMIOLOGY AND PATHOGENESIS

Ocular motor nerve palsies typically become apparent in one of the following four ways<sup>1</sup>:

- Isolated nerve palsies with no other signs or symptoms.
- Isolated nerve palsies with associated symptoms.
- Nerve palsies associated with palsies of other cranial nerves.
- Nerve palsies with neurological signs other than cranioneuropathies.

Each of these four presentations has a different corresponding differential diagnosis. Unfortunately, most of the reports in the literature that



**Fig. 9.15.1 Location of Ocular Motor Nerve Nuclei and Fascicles in the Brainstem.** Note the relationship of the cranial nerve nuclei and fascicles to the medial longitudinal fasciculus, red nucleus, paramedian pontine reticular formation, and facial nerve nucleus and fascicle. The fourth nerve exits dorsally, whereas the third and sixth nerves exit ventrally.

consider the causes of ocular motor nerve palsies<sup>2-5</sup> do not classify the palsies in this manner.

Because nuclear and fascicular disorders are highly localizable, it is better to localize the lesion and then consider the causes based on the patient's age and history (Boxes 9.15.1–9.15.3). Most nuclear and fascicular disorders of eye movement are caused by vascular disease (infarction, hemorrhage from arteriovenous malformation), demyelination, and tumor (metastatic or primary). Infectious, inflammatory, and traumatic causes are less likely. Congenital oculomotor nerve palsy can arise from brainstem disorders in some patients,<sup>6-8</sup> who often have other brain anomalies and brainstem syndromes. Although thyroid disease and myasthenia can mimic isolated cranial nerve palsies, neither is associated with neurological deficits of brainstem function.

## OCULAR MANIFESTATIONS

### Palsies of the Third Cranial Nerve

The oculomotor nerve innervates four extraocular muscles (medial rectus, inferior rectus, superior rectus, and inferior oblique) in addition to the levator palpebrae and the pupillary sphincter.

The degree of involvement of each of these six structures can be quite variable. When the palsy is complete, there is complete ptosis with a dilated pupil that responds to neither light nor near vision. The eye is deviated out and usually, but not always, down. Functioning of the other ocular motor nerves can be assessed in this situation by evaluation of abduction (sixth

### BOX 9.15.1 Etiology of Oculomotor Nerve Palsies of the Nucleus and Fasciculus—Third Nerve Palsies

#### Children

- Congenital
  - With neurological abnormalities
  - With aberrant reinnervation
  - With cyclical oculomotor spasm
- Vascular (arteriovenous malformation)
- Primary tumor
- Metastatic tumor

#### Young Adults

- Demyelinating
- Vascular (hemorrhage or infarction)
- Tumor

#### Older Adults

- Vascular (infarction)
- Tumor

### BOX 9.15.2 Etiology of Oculomotor Nerve Palsies of the Nucleus and Fasciculus—Fourth Nerve Palsies

#### Intrinsic Midbrain Lesions

- Trauma (anterior medullary velum)
- Tumor
  - Medulloblastoma
  - Ependymoma
  - Metastatic
- Demyelination
- Stroke
  - Ischemic
  - Hemorrhagic
- Arteriovenous malformation

#### Extrinsic Midbrain Lesions

- Tumor
  - Pinealoma
  - Metastatic
- Hydrocephalus
- Aqueductal stenosis

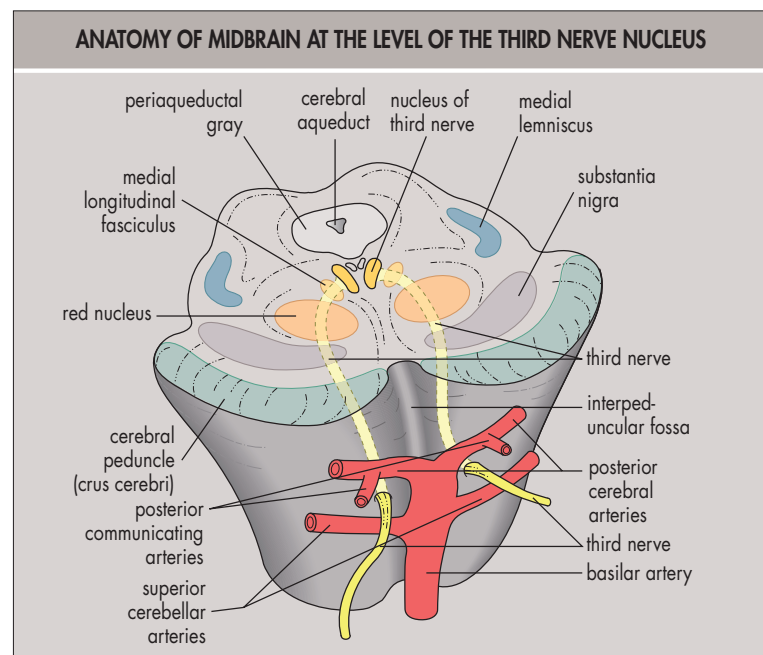
### BOX 9.15.3 Etiology of Oculomotor Nerve Palsies of the Nucleus and Fasciculus—Sixth Nerve Palsies

- Vascular disease
  - Hemorrhage
  - Infarction (anteroinferior cerebellar artery; paramedian perforating arteries)
- Demyelinating disease
- Trauma
- Tumor
  - Glioma
  - Astrocytoma
  - Ependymoma
  - Medulloblastoma
  - Metastatic
  - Infiltrative
- Other

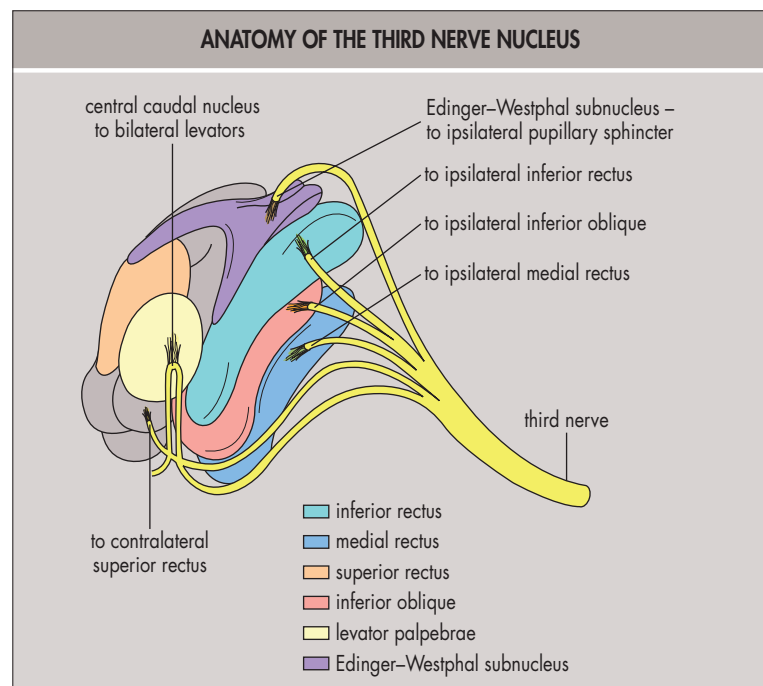
cranial nerve) and by observing incyclotorsion on attempted depression in adduction (fourth cranial nerve).

## Third Cranial Nerve Nuclear Lesions

The third nerve nucleus is located in the midbrain near the cerebral aqueduct at the level of the superior colliculus (Fig. 9.15.2). Each extraocular muscle that receives innervation from the third nerve has a corresponding subnucleus (Fig. 9.15.3). A single central nucleus (central caudal nucleus) innervates both levator palpebrae muscles. Distinct, bilateral subnuclei



**Fig. 9.15.2 Anatomy of Midbrain at the Level of the Third Cranial Nerve Nucleus.** The fascicles of the third nerve pass through the red nucleus, substantia nigra, and crus cerebri before they exit into the interpeduncular fossa. The medial lemniscus is nearby. Note the intimate relationship of the oculomotor nerve to the medial longitudinal fasciculus, periaqueductal gray, and the cerebral aqueduct.



**Fig. 9.15.3 Anatomy of the Third Cranial Nerve Nucleus.** The third nerve nucleus consists of a single, central, caudally located nucleus for the levator palpebrae, paired bilateral subnuclei with crossed projections that innervate the superior recti, and paired bilateral subnuclei with uncrossed projections that innervate the medial recti, inferior recti, and inferior oblique muscles. Parasympathetic input to the ciliary body and iris sphincter arises from the Edinger-Westphal nucleus. (From Warwick R. Representation of the extraocular muscles in the oculomotor nuclei of the monkey. *J Comp Neurol* 1953;98:449–503.)

exist for the extraocular muscles. An additional bilateral subnucleus, the Edinger-Westphal nucleus, provides parasympathetic input to the pupillary sphincter.<sup>9</sup>

Projections from the subnuclei to their targets all are uncrossed (each subnucleus innervates the ipsilateral corresponding extraocular muscle), with two exceptions—the single central caudal nucleus sends projections to both levator muscles, and the superior rectus subnucleus projection is crossed. Thus, the right superior rectus subnucleus innervates the left superior rectus muscle, and vice versa.



TABLE 9.15.1 Syndromes of the Third Cranial Nerve Fasciculus

Location	Eponym	Findings
Red nucleus	Benedikt's syndrome	Intention tremor, ataxia, contralateral sensation loss (if medial lemniscus involved)
Crus cerebri	Weber's syndrome	Contralateral hemiparesis

### BOX 9.15.4 Daroff's Rules for Third Cranial Nerve Nucleus Palsies

#### Conditions That Obligate Nucleus Involvement

- Bilateral third nerve palsy without ptosis (bilaterally spared levator function)
- Unilateral third nerve palsy with contralateral superior rectus abnormality and bilateral partial ptosis

#### Conditions That Exclude a Nucleus Lesion

- Unilateral ptosis
- Unilateral internal ophthalmoplegia
- Unilateral external ophthalmoplegia associated with normal contralateral superior rectus function

#### Conditions That Neither Exclude Nor Obligate a Nucleus Lesion

- Bilateral total third nerve palsy
- Bilateral ptosis
- Bilateral internal ophthalmoplegia
- Bilateral medial rectus palsy
- Isolated unilateral single muscle involvement (except levator and superior rectus)

From Daroff RB. Oculomotor manifestation of brainstem and cerebellar dysfunction. In: Smith JL, editor. Neuro-ophthalmology: Symposium of the University of Miami and Bascom-Palmer Eye Institute, vol. 5. Hallandale: Huffman; 1971. p. 104–21.

The evolution of the crossed connections may have occurred to facilitate vestibular innervation. Because the trochlear nerve also undergoes a decussation, each cyclovertical muscle and its corresponding yoked muscle pair have nuclei on the same side of the brain. The right inferior oblique subnucleus and the left superior rectus subnucleus are both located on the right; the left inferior rectus subnucleus and the right superior oblique subnucleus are both located on the left. This allows the direct innervation of a yoked muscle pair from the corresponding semicircular canal without a decussation and is important in the vestibular–ocular counter-rolling reflex.

Although the anatomy of the third nerve nucleus is complex, it allows for precise localization. Daroff<sup>10</sup> has proposed clinical rules that obligate or exclude nuclear involvement (Box 9.15.4). Because the central caudal subnucleus sends projections to both levator muscles, a bilateral third nerve palsy that spares the lid on both sides obligates a rostral nuclear lesion. The crossed projection of the superior rectus subnucleus underlies the observation in that unilateral third nerve lesions with contralateral superior rectus involvement obligate a nuclear lesion, whereas a third nerve palsy with no contralateral superior rectus abnormality cannot be caused by a nuclear lesion.

## Third Cranial Nerve Fascicular Palsies

After leaving the nucleus, the axons of the oculomotor neurons travel through the midbrain. Within the midbrain, they pass near or through two important structures before exiting into the subarachnoid space of the interpeduncular fossa (the red nucleus and the crus cerebri). Lesions that damage the third nerve fascicle within the red nucleus cause a contralateral intention tremor and ataxia. Because the nearby medial lemniscus carries sensory fibers for light touch and proprioception on the contralateral side, these modalities also may be impaired or absent. Lesions of the cerebral peduncle damage corticospinal tract fibers and produce a contralateral hemiparesis. Each of these syndromes has a specific eponym (Table 9.15.1).

Typically, fascicular third nerve palsies affect all functions of the third nerve equally, with the degree of pupil involvement being proportional to the lid and motility defects. However, isolated extraocular muscle pareses can result from fascicular third nerve lesions.<sup>11,12</sup> Divisional oculomotor paresis also can be caused by brainstem lesions.<sup>13</sup> The “isolated,” pupil-sparing third nerve palsy seen in adults with vascular disease may also result from fascicular damage.<sup>14</sup>

Most fascicular third nerve lesions have vascular causes (hemorrhage, infarction). Metastatic or infiltrative disease is less common; demyelinating disease is rare, even in patients with known multiple sclerosis. Because fascicular third nerve palsies are typically ischemic in nature, they may have varying degrees of recovery. Aberrant regeneration, however, does not occur. Patients who have aberrant regeneration after an acquired third nerve palsy must be considered to have a compressive lesion of the third nerve.

## Congenital Third Cranial Nerve Palsies

Congenital oculomotor nerve palsies are rare and are often associated with neurological abnormalities.<sup>6,7,15</sup> Aberrant regeneration is common,<sup>16</sup> which, if present, argues against a nuclear lesion. Loewenfeld and Thompson<sup>16</sup> speculated that perinatal damage to the third nerve causes retrograde degeneration of the oculomotor nucleus, which then is reinnervated haphazardly.

Some patients with congenital oculomotor nerve palsies develop cyclic oculomotor spasm.<sup>16</sup> Typical cases have a slow alternation between a parietic phase, in which the lid droops, the pupil dilates, and the eye turns out, and a spastic phase, in which the lid elevates, the pupil constricts, accommodation occurs, and the eye adducts. These cycles usually persist throughout life. Cyclical oculomotor spasm usually is not associated with acquired lesions of the third nerve.

## Palsies of the Fourth Cranial Nerve

Superior oblique palsy is the most common cause of acquired vertical diplopia and can be either congenital or acquired. Patients who have acquired superior oblique palsies have diplopia that is often worse in downgaze, and they often complain of tilting of their vision. Subjective image separation increases with gaze in the direction opposite the side of the palsy and with head tilt toward the side of the palsy. Motility testing in the acute phase usually demonstrates poor depression in adduction. Orthoptic measurements show hypertropia of the affected eye, with the hypertropia increasing with gaze to the side opposite the palsy and with head tilt toward the side of the palsy. The most common cause of an isolated, acquired fourth nerve palsy is trauma (see Box 9.15.2).<sup>17–19</sup>

Congenital fourth nerve palsies can become apparent at any age. Young children often exhibit abnormal head postures, whereas older individuals typically experience intermittent vertical diplopia. Patients who have congenital fourth nerve palsies have large vertical fusional amplitudes, and old photographs demonstrate a consistent head tilt. Motility often is full in these patients. Orthoptic testing yields results similar to those for acquired fourth nerve palsies.

Although both congenital and acquired fourth nerve palsies usually are isolated, additional neuro-ophthalmological findings occasionally are present that help to localize the lesion and determine whether imaging studies are warranted. Because the fourth nerve fasciculus is quite short, most brainstem-localizing fourth nerve palsies usually involve both the nucleus and the fasciculus.

## Fourth Cranial Nerve Nuclear and Fascicular Lesions

The fourth nerve nucleus is in the midbrain at the level of the inferior colliculus (see Fig. 9.15.1). It lies just caudal to the third nerve nucleus and receives prenucleus input from the vestibular system, the medial longitudinal fasciculus, and the rostral interstitial medial longitudinal fasciculus. The fasciculus of the trochlear nerve travels dorsally to exit the lower midbrain just caudal to the inferior colliculus, near the tentorium. Because the nerve decussates in the anterior medullary velum, fourth nerve nuclear and fascicular palsies are usually associated with superior oblique dysfunction on the contralateral side (Table 9.15.2), but cases of ipsilateral fascicular fourth nerve palsy have been reported in patients with lesions located precisely after the decussation.<sup>20</sup>

Isolated lesions that affect only the trochlear nerve nuclear or fascicular are rare. Most lesions of the area that surrounds the fourth nerve nucleus and fasciculus also affect neighboring structures. Both extrinsic (tumor, hydrocephalus) and intrinsic (tumor, stroke, demyelination, arteriovenous malformation) lesions of the brainstem may damage the trochlear nerves or nucleus and often produce an associated upgaze palsy or features of the dorsal midbrain syndrome (see Box 9.15.2). Lesions that damage the fourth nerve within the dorsolateral midbrain also can damage the first-order

**TABLE 9.15.2 Syndromes of the Fourth Cranial Nerve Nucleus and Fasciculus**

Site of Damage	Laterality of Superior Oblique Palsy	Clinical Manifestations
Pretectal area	Contralateral	Vertical gaze palsy Dorsal midbrain syndrome
Descending sympathetic pathways	Contralateral	Ipsilateral Horner's syndrome
Superior cerebellar peduncle	Contralateral	Ipsilateral dysmetria
Medial longitudinal fasciculus	Contralateral	Ipsilateral internuclear ophthalmoplegia
Brachium of superior colliculus	Contralateral	Contralateral relative afferent pupillary defect Contralateral pupil homonymous hemianopia Normal visual fields
Anterior medullary velum	Bilateral	"V"-pattern esotropia Reversing hypertropias on side gaze >10° excyclotorsion

(descending) sympathetic fibers to produce a contralateral fourth nerve palsy with an ipsilateral Horner's syndrome.<sup>21</sup> Damage to both trochlear nerve fascicles at their decussation within the anterior medullary velum produces a bilateral superior oblique palsy, which is often asymmetrical. These patients can have a V-pattern esotropia, reversing hypertropias on gaze and tilt, and greater than 10° of subjective excyclotorsion.<sup>22</sup> These patients may also show features of dorsal midbrain syndrome.<sup>23</sup>

An interesting fascicular syndrome of the fourth nerve involves the brachium of the superior colliculus.<sup>24</sup> Pupillomotor fibers pass through this structure as they travel from the optic tract to the pretectum. These fibers subserve the pupillary light reflex from the contralateral visual field. Because the retinogeniculate pathway has already separated from the pupillary pathways, conscious light detection is not affected, but the pupillary light reflex is. Patients who suffer lesions in this area have normal visual fields but a small (0.6–0.9 log unit) relative afferent pupillary defect in the eye contralateral to the lesion, consistent with an optic tract lesion. The fourth nerve palsy is also on the contralateral side (the fascicle is damaged before the decussation).

## Palsies of the Sixth Cranial Nerve

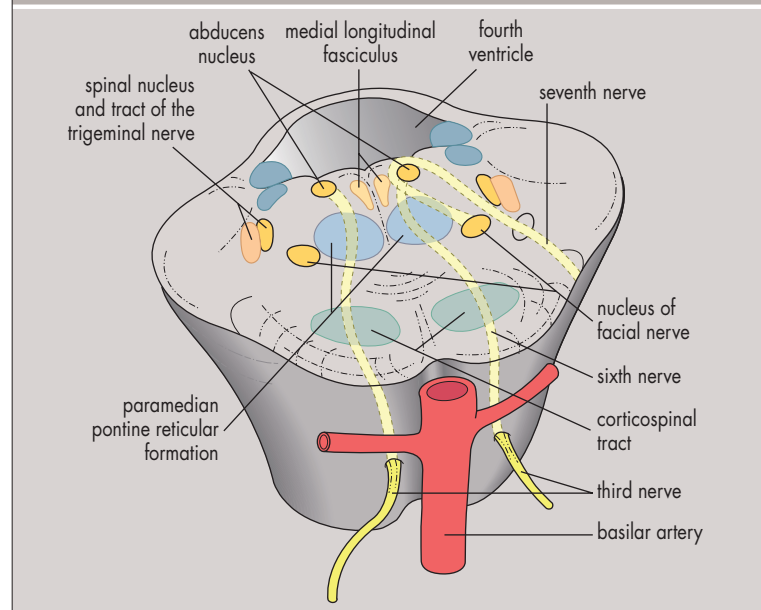
The sixth nerve innervates the ipsilateral lateral rectus muscle and produces abduction. Damage to the sixth nerve produces an esotropia that is worse in the field of action of the involved sixth nerve and greater at distance than at near. Most patients are able to fuse with a face turn toward the side of the palsy (gaze away from the palsy). The pupil is not affected. Patients who have long-standing sixth nerve palsies can develop tightening and contracture of the medial rectus, which causes a restrictive strabismus with positive forced ductions. Occasionally, patients who have long-standing sixth nerve palsies may have associated vertical diplopia and hypertropia.<sup>25</sup> Nuclear and fascicular lesions of the sixth nerve typically have characteristic findings.

## Sixth Cranial Nerve Nuclear Palsies

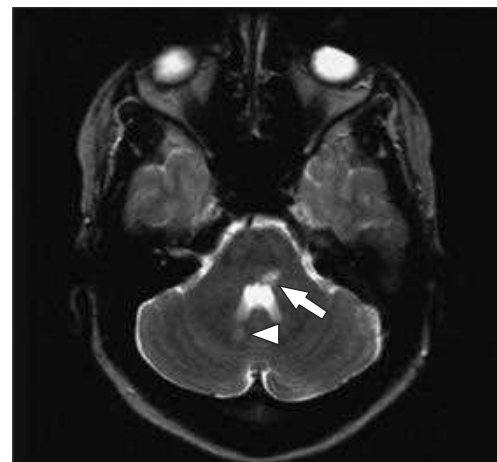
The sixth nerve nucleus is in the pons, just ventral to the floor of the fourth ventricle. The fascicle of the facial nerve wraps around the sixth nerve nucleus (Fig. 9.15.4). The sixth nerve nucleus contains bodies of two types of neurons—most project directly to the lateral rectus muscle, but about 40% of the cells in the abducens nucleus are interneurons, which project, via the medial longitudinal fasciculus, to the contralateral medial rectus subnucleus and cause adduction of the contralateral eye. Thus, the sixth nerve nucleus, like the paramedian pontine reticular formation, is a gaze center. Damage to the sixth nerve nucleus or to the caudal paramedian pontine reticular formation produces an ipsilateral gaze palsy that cannot be overcome by vestibular testing. Because all nuclear sixth nerve palsies produce a gaze palsy, an abduction deficit not associated with contralateral adduction weakness cannot arise from damage to the nucleus.

The location of the sixth nerve nucleus within the brainstem produces several possible associated deficits when a nuclear sixth nerve palsy is present (Box 9.15.5). The intimate relationship between the facial nerve

**ANATOMY OF THE SIXTH NERVE NUCLEUS IN THE PONS**



**Fig. 9.15.4 Anatomy of Sixth Cranial Nerve Nucleus in the Pons.** The abducens nucleus is surrounded by the facial nerve fasciculus after it originates from its nucleus and is associated intimately with the medial longitudinal fasciculus. Abducens fascicles traverse the paramedian pontine reticular formation and the corticospinal tract before leaving the lower ventral pons. The vestibular nuclei and spinal nucleus and tract of the trigeminal nerve are nearby in the lateral pons.



**Fig. 9.15.5** T2-weighted magnetic resonance imaging scan of a 33-year-old woman who has a left abduction deficit, gaze paretic nystagmus on left gaze, and left facial weakness. The cause of this nuclear sixth nerve lesion (long arrow) most likely was demyelinating disease. A second lesion can be seen in the right cerebellum (arrowhead).

## BOX 9.15.5 Sixth Cranial Nerve Syndromes of the Nucleus and Fasciculus

### Sixth Nerve Nucleus Palsies

- One-and-a-half syndrome (obligate)
- Foville's syndrome
- Gaze palsy
- Peripheral facial palsy (likely)

### Fascicular Sixth Nerve Palsies

- With contralateral hemiplegia (Raymond's syndrome)
- Facial weakness (Millard–Gubler syndrome)

fasciculus and the sixth nerve nucleus produces an ipsilateral peripheral facial nerve palsy in nearly all cases of abducens nuclear injury (Fig. 9.15.5).

When damage from either the sixth nerve nucleus or the paramedian pontine reticular formation also involves the ipsilateral medial longitudinal fasciculus, a characteristic motility pattern is produced, consisting of an ipsilateral gaze palsy with an ipsilateral internuclear ophthalmoplegia. The ipsilateral eye cannot adduct or abduct, and the contralateral eye can only abduct. This syndrome is called *one-and-a-half syndrome*.<sup>26</sup>

Most nuclear abducens palsies are caused by infarction (anteroinferior cerebellar or paramedian perforating arteries), demyelination, or

compression (intrinsic pontine tumors). Infiltrative disease, hemorrhage, and trauma are less likely causative factors (see [Box 9.15.3](#)).

## Sixth Cranial Nerve Fascicular Palsies

Nearly all fascicular lesions of the abducens nerve are associated with distinctive neurological findings that result from damage to the surrounding neurological structures of the pons (see [Box 9.15.5](#)). These eponymous syndromes and their findings are listed in [Box 9.15.5](#). Because most lesions can affect both the dorsal and the ventral pons, a clinical overlap exists between these syndromes.

Common causes of fascicular lesions include infarction, compression (cerebellar pontine angle tumor or glioma), infiltration, and demyelination and vary with the age of the patient.<sup>1,3,27</sup> Hemorrhage, trauma, and infection are less likely (see [Box 9.15.3](#)).

Classic teaching in pediatric ophthalmology held that isolated sixth nerve palsies in childhood should be considered the result of a pontine glioma until proven otherwise.<sup>27</sup> However, the definition of isolated palsy used in the study by Robertson et al. meant that no other cranial nerve palsies existed and not that the remainder of the neurological examination was normal. Most children with pontine gliomas develop other neurological findings within a few weeks, and therefore a careful neuro-ophthalmological examination with close follow-up probably is all that is necessary in children (under age 14 years) who have truly isolated idiopathic sixth nerve palsies.

## DIAGNOSIS

Complete third nerve palsy is recognized by the simultaneous presence of ptosis, mydriasis, and paralysis of adduction, elevation, and depression. The eye is turned “down and out” because of the unopposed actions of the lateral rectus and superior oblique muscles. Fourth nerve palsy is diagnosed in the presence of hypertropia, which is worse in opposite gaze and in same-sided head tilt (Parks-Bielschowsky three-step test), along with excyclotorsion on the affected side. Sixth nerve palsy is seen as an abduction deficit, with decreased abducting saccadic velocity. Diagnosis of isolated cranial nerve palsy is covered in greater detail in Chapter 9.16.

## Palsies of the Third Cranial Nerve

Attention should be paid to vertical gaze abnormalities because the centers for vertical gaze are in close proximity to the oculomotor nucleus and also are often damaged. Magnetic resonance imaging (MRI) is the best method by which to assess the integrity of midbrain structures in patients who have acute palsies. The neuroradiologist should be informed of the clinical localization so that attention can be directed to this area.

## Palsies of the Fourth Cranial Nerve

Patients who have acquired fourth nerve palsies with localizing signs should undergo imaging studies, with attention paid to the areas suggested by the clinical findings. Patients who have no risk factors for vascular disease, no history of trauma, and no findings suggestive of a decompensating congenital fourth nerve palsy should undergo imaging studies.

## Palsies of the Sixth Cranial Nerve

Patients who have brainstem findings need further assessment with MRI and appropriate management.

## TREATMENT, COURSE, AND OUTCOME

### Palsies of the Third Cranial Nerve

In many patients with microvascular oculomotor nerve palsies, there is improvement eventually. Ptosis is advantageous because it prevents

diplopia. Strabismus correction and lid surgery are needed to restore binocularity in patients whose condition does not improve spontaneously; the chapter author waits for a period of 6 months for stable measurements to occur before suggesting surgical alignment.

## Palsies of the Fourth Cranial Nerve

Palsies of the fourth nerve that result from vascular disease or trauma often resolve spontaneously over 3–6 months. During this time, Fresnel prisms can be placed over spectacles to allow fusion. However, this often is fraught with difficulty because the deviation is usually quite incomitant and torsion cannot be corrected. Patients who have fourth nerve palsies that arise from compressive lesions often do not experience improvement in their condition and require surgery.

Surgical options for the treatment of superior oblique palsy are complex and are beyond the scope of this chapter. Congenital superior oblique palsies often are associated with abnormalities of the insertion of the superior oblique tendon.

## Palsies of the Sixth Cranial Nerve

Nearly all patients who have sixth nerve palsies experience diplopia. During the acute phase, this condition is best managed by patching the paretic eye or by frosting a spectacle lens. Prisms usually are not well tolerated because of the magnitude and incomitance of the deviation. Botulinum toxin injection probably does not decrease the need for later surgical intervention of unilateral sixth nerve palsy.<sup>28,29</sup>

Surgical intervention for sixth nerve palsy is indicated when the deviation has been stable for a minimum of 6 months. The choice of surgical procedure for chronic sixth nerve palsies depends on the recovery of function of the lateral rectus muscle, which can be assessed by determining the saccadic velocity. Patients who experience good return of function usually do quite well with an ipsilateral recess–resect procedure, whereas those having poor lateral rectus function need transposition. Patients who have little or no lateral rectus function need muscle transposition surgery.

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# Paresis of Isolated and Multiple Cranial Nerves and Painful Ophthalmoplegia

9.16

Adam DeBusk, Mark L. Moster

**Definition:** Dysfunction of one or more of the three cranial nerves that move the eyes.

## Key Features

- Diplopia.
- Dysconjugate gaze.

## Associated Features

- Ptosis.
- Pupillary abnormalities.
- Pain.
- Proptosis.
- Chemosis.
- Arterialization of conjunctival vessels.

## INTRODUCTION

One of the common clinical presentations in neuro-ophthalmology involves dysfunction of the ocular motor nerves—third (oculomotor nerve), fourth (trochlear nerve), and sixth (abducens nerve) cranial nerves. In this chapter, the anatomy of the peripheral course of the ocular motor nerves is reviewed, and various clinical syndromes are discussed. The syndromes include isolated involvement of each nerve, involvement of multiple cranial nerves simultaneously, involvement of the third, fourth, and sixth cranial nerves with other neurological or orbital symptoms and signs, and involvement of these cranial nerves in severe pain. An approach to the differential diagnosis of patients who seek treatment for involvement of the ocular motor nerves and guidelines for evaluation and treatment are also given.

## ANATOMY

The clinical localization and subsequent differential diagnosis of cranial neuropathies requires knowledge of the anatomy of the third, fourth, and sixth cranial nerves. The anatomy within the brainstem is covered in Chapter 9.15; here, the relevant anatomy of the motor nerves from the brainstem exit to the eye is given (Fig. 9.16.1).

The third cranial nerve exits the midbrain ventrally to enter the subarachnoid space. It continues forward and laterally, passes between the posterior cerebral artery and superior cerebellar artery, and then runs alongside the posterior communicating artery. The nerve pierces the dura to enter the cavernous sinus, where it runs along the lateral wall, superior to the fourth cranial nerve. It enters the orbit via the superior orbital fissure. In the anterior cavernous sinus, it divides into the superior and inferior divisions. The superior division ascends lateral to the optic nerve to supply the superior rectus and levator palpebrae superioris muscles. The inferior division divides into branches that supply the inferior rectus, inferior oblique, and medial rectus muscles and the pupillary sphincter. Parasympathetic preganglionic fibers travel along the branch to the inferior oblique and terminate in the ciliary ganglion near the apex of the extraocular muscle cone lateral to the optic nerve. The postganglionic

fibers from the ciliary ganglion travel in the short ciliary nerves, along with the sympathetic fibers, to enter the globe at the posterior aspect near the optic nerve. They terminate in the ciliary body and iris, and control pupillary constriction and accommodation via the ciliary muscles.

The fourth cranial nerve exits the midbrain dorsally and crosses to the opposite side, within the anterior medullary velum, just below the inferior colliculi. The nerve courses forward within the subarachnoid space around the cerebral peduncle and runs between the posterior cerebral and superior cerebellar arteries, along with the third nerve. The fourth cranial nerve pierces the dura at the angle between the free and attached borders of the tentorium cerebelli to enter the cavernous sinus. It runs within the lateral wall of the cavernous sinus, just below the third cranial nerve and above the first division of the fifth cranial nerve (trigeminal nerve). It enters the orbit via the superior orbital fissure, but runs outside the annulus of Zinn and diagonally across the levator palpebrae superioris and superior rectus muscle to reach the superior oblique muscle. It supplies the superior oblique muscle, the main action of which is incyclotorsion. Secondary actions are depression of the eye in the adducted position and abduction of the eye.

The abducens nerve exits the brainstem at the junction of the pons and pyramid of the medulla, and ascends through the subarachnoid space along the surface of the clivus. It runs forward over the petrous apex of the temporal bone, beneath the petroclinoid ligament, and through Dorello's canal to enter the cavernous sinus. In the cavernous sinus, it runs lateral to the internal carotid artery, but medial to the third and fourth cranial nerves and the first and second divisions of the fifth cranial nerve, which run in the lateral wall. It enters the superior orbital fissure, within the annulus of Zinn to innervate the lateral rectus muscle.

## OCULAR MANIFESTATIONS

### General Symptoms

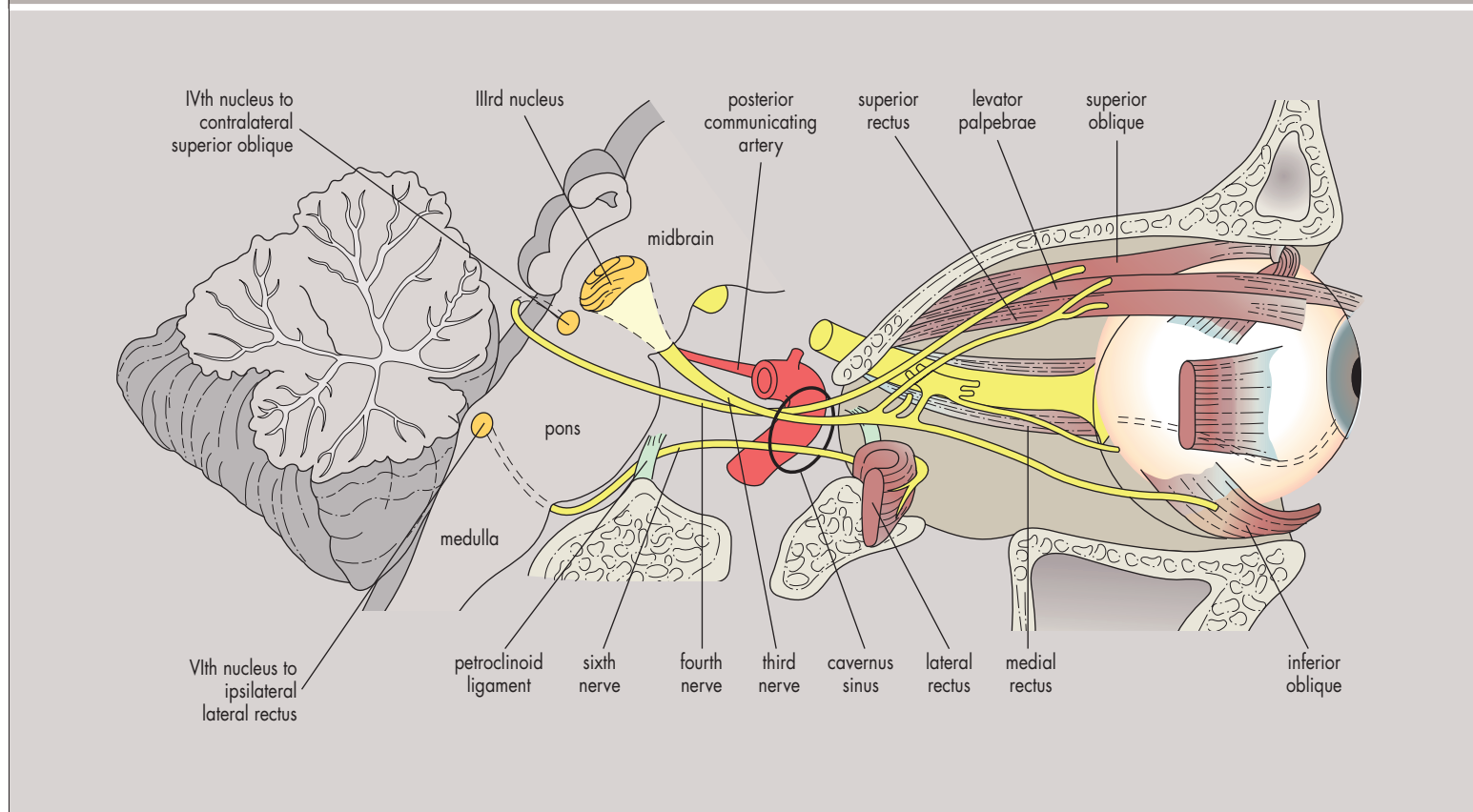
The usual symptom associated with dysfunction of the ocular motor nerves is binocular diplopia. Diplopia occurs when an object projects onto retinal points that do not correspond in both eyes. The diplopia is worst in the direction of action of the weak muscle(s), but it may not occur with poor visual acuity, ptosis, or a history of congenital strabismus.

On examination, a patient who has binocular diplopia demonstrates an ocular deviation. Numerous examination techniques are available to measure ocular deviations, including prism lenses with the cover–uncover or alternate cover technique, the red glass test, the Maddox rod, and the Hess or Lancaster screen. Proficiency in at least one of these techniques (see Chapter 11.3) is necessary to adequately assess patients with diplopia.

An ocular deviation that is variably present when fusion is broken is termed *phoria*, whereas an intermittently or constantly manifest deviation under binocular conditions is referred to as *tropia*. When a measured deviation is similar in all gaze directions, it is a *comitant* deviation; when it varies by direction it is *incomitant*. Congenital strabismus most often presents with a comitant deviation.

Acquired cranial neuropathies appear with a ductional deficit on examination that corresponds to weakness in the appropriate muscle(s) innervated by the cranial nerve(s) involved. In a more subtle deficit, ductions may appear full, but an incomitant deviation greatest in the direction of action of the paretic muscle is seen. When a cranial neuropathy is chronic, spread of comitance may occur, and the deviation mimics that of congenital strabismus.

## THIRD, FOURTH, AND SIXTH CRANIAL NERVES, LATERAL VIEW



**Fig. 9.16.1** Lateral view of third, fourth, and sixth cranial nerves from the brainstem nuclei to the orbit. The third nerve exits the midbrain anteriorly, crosses near the junction of the internal carotid and posterior communicating artery in the subarachnoid space, and enters the cavernous sinus, where it runs in the lateral wall. The fourth nerve exits the midbrain posteriorly and crosses to the opposite side, to move forward in the subarachnoid space and into the cavernous sinus. The sixth nerve exits the pons anteriorly, ascends along the clivus bone, crosses the petrous apex, and descends below the petroclinoid ligament to enter the cavernous sinus, where it runs between the lateral wall and the carotid artery.

## Isolated Cranial Neuropathies

In this section, the assessment of patients affected by isolated involvement of the third, fourth, or sixth cranial nerve, with no other neurological or ophthalmologic signs, is discussed.

### Isolated Sixth Cranial Nerve Palsy

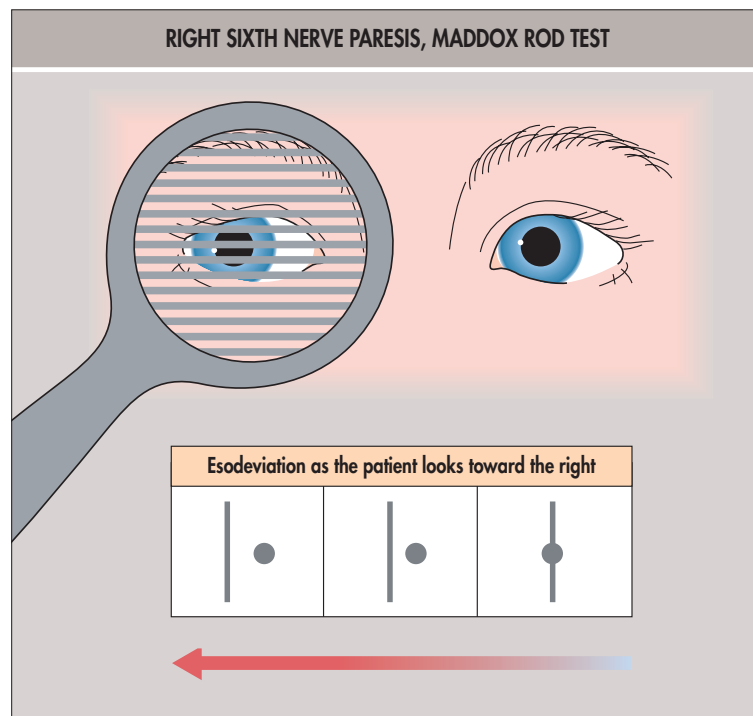
An isolated sixth nerve palsy appears with a unilateral abduction deficit of variable degree, from a complete inability to abduct past the midline to a mild incomitant esodeviation greatest on lateral gaze. Abduction saccades in the affected eye are slow. The history consists of binocular uncrossed diplopia, worse in the direction of the lesion and worse at distance than at near. [Fig. 9.16.2](#) demonstrates the deviation seen when using a Maddox rod in a patient who has a right sixth nerve palsy.

Congenital sixth nerve palsy is rare and may be related to birth trauma. The deficit resolves in the first month of life.<sup>1,2</sup> Other congenital abnormalities of the sixth nerve, such as Mobius' syndrome and Duane's retraction syndrome, show additional findings and are discussed in the section on [differential diagnosis](#).

Traumatic sixth nerve injury is often associated with fractures of the petrous bone or clivus. Other clinical findings include mastoid ecchymosis (Battle's sign) and cerebrospinal fluid (CSF) otorrhea. Head trauma with subsequent elevated intracranial pressure may cause unilateral or bilateral sixth nerve palsy. Causes of chronic sixth nerve palsy include those of acute sixth nerve palsy but more often are from a compressive lesion.<sup>3-5</sup>

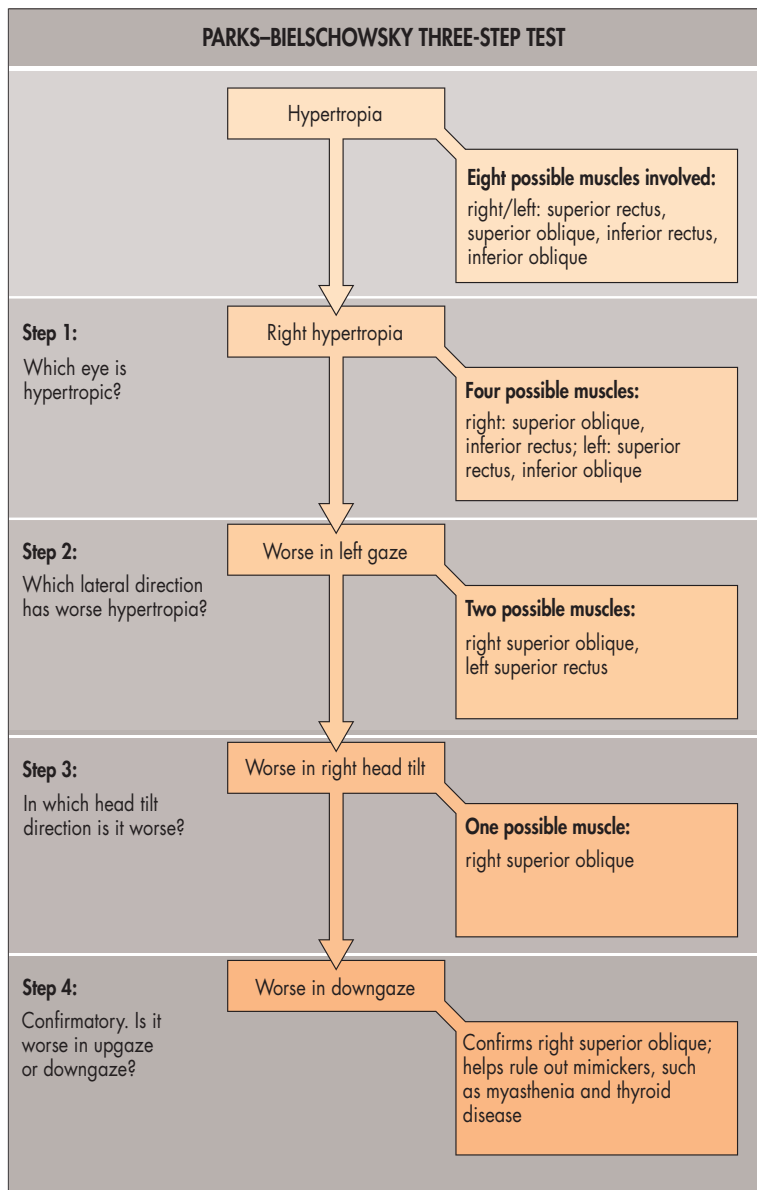
Recurrent sixth nerve palsy may occur as a benign syndrome in children or as a presentation of skull base tumor, and remission of a sixth nerve palsy may occur in either.<sup>6-9</sup> A hypoplastic Dorello's canal has also been reported as a cause of recurrent sixth nerve palsy in children.<sup>10</sup>

Although each series reviews patients differently, some generalizations are apparent from reports of isolated and nonisolated sixth nerve palsy.<sup>1,2,11-18</sup> In adults, an isolated sixth nerve palsy is more likely to be ischemia than a nonisolated sixth nerve palsy, which is more likely



**Fig. 9.16.2** Right Sixth Cranial Nerve Palsy Evaluated by the Maddox Rod Test. A Maddox rod is placed in front of the patient's right eye. Subjective deviation between the light and the line is noted by the patient in different positions of gaze. An esodeviation greatest as the patient looks to the right is consistent with a right lateral rectus muscle weakness.





**Fig. 9.16.3 Parks–Bielschowsky Three-Step Test.** In a patient who has a vertical deviation because of a weakness in a single muscle, this three-step test determines which muscle is weak. Step four confirms that the correct muscle has been identified and helps to rule out other causes of vertical deviation.

inflammation, tumor, trauma, or aneurysm. Additionally, tumor is a more common cause of sixth nerve paresis in young adults and children than in older patients.<sup>19</sup>

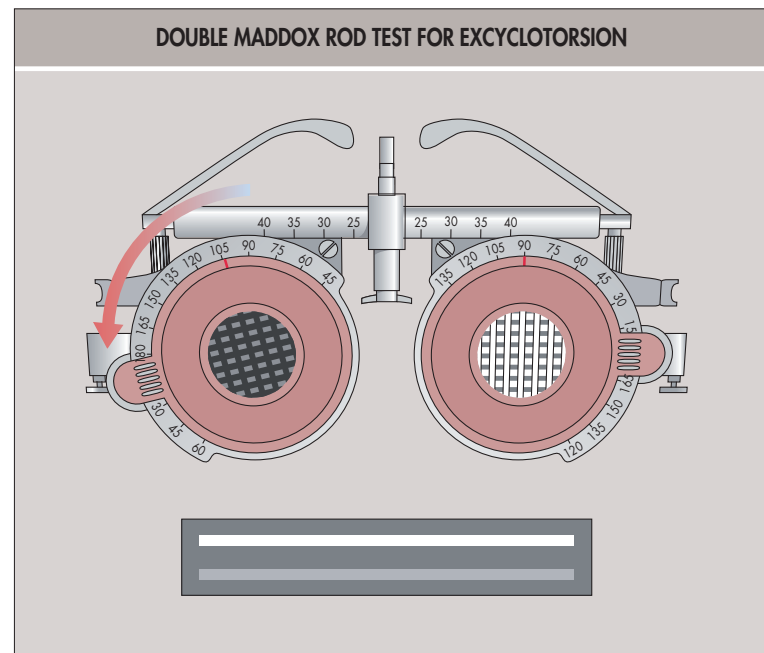
### Isolated Fourth Cranial Nerve Palsy

A fourth nerve or trochlear palsy manifests with an isolated, vertical, diagonal, or cyclotorsional diplopia that is worse when looking down and to the side opposite the lesion. It is the most common cause of vertical diplopia. Examination using the Parks–Bielschowsky three-step test (Fig. 9.16.3) shows a hyperdeviation that is worse on contralateral gaze, as well as ipsilateral head tilt. A fourth step that demonstrates that the deviation is worse in downgaze than upgaze is confirmatory. With time, spread of comitance may develop. Double Maddox rod testing shows excyclotorsion (Fig. 9.16.4)—if the excyclotorsion is  $>10^\circ$ , fourth nerve paresis is likely to be bilateral.

### Isolated Third Cranial Nerve Palsy

Patients who have third nerve palsy have a history of horizontal and/or vertical binocular diplopia, ptosis, and/or complaints of enlarged pupil or difficulty in focusing, with involvement of accommodation (Fig. 9.16.5); various combinations of these may occur.

The major causes of isolated third nerve palsy can be categorized by vasculopathic infarction, vasculitic infarction (as in giant cell arteritis [GCA]), compressive (usually from aneurysm), trauma, meningeal inflammation (e.g., with infection or tumor), ophthalmoplegic migraine, or



**Fig. 9.16.4 Double Maddox Rod Test for Excyclotorsion.** A red Maddox rod is placed in front of the right eye and a white Maddox rod in front of the left eye in a trial frame or phoropter. In a patient who has vertical diplopia, one line is above the other. With excyclotorsion, the two lines are not parallel but cross each other. One of the Maddox rods is then rotated until the two lines appear parallel. The degree of rotation required (in this case about  $12^\circ$ ) to make the lines parallel determines the degree of excyclotorsion.

demyelination. Other rare causes include complication of internal carotid artery dissection or occlusion<sup>20,21</sup> or toxicity of chemotherapy.<sup>22</sup>

Several series have looked at the causes of isolated and nonisolated third nerve paresis.<sup>10,13,14,16–18,23–25</sup> From these studies, third nerve paresis is associated more frequently with aneurysm than are fourth or sixth nerve pareses. Ophthalmoplegic migraine is only associated with a third nerve paresis. As with the sixth nerve paresis, isolated lesions are more often ischemic than nonisolated ones.

In vasculopathic third nerve palsy, pain often precedes the onset of ptosis or diplopia, the pupillary reaction is usually spared, and the pupil does not become enlarged. However, in up to 53% of cases, the pupil may be involved, usually with less than 1 mm of anisocoria.<sup>26–28</sup> Clinical associations include diabetes, hypertension, or other atherosclerosis risk factors. The natural course of a vasculopathic, isolated third nerve palsy is one of recovery over weeks to months, usually 3 months. The pupil is spared because the infarction occurs in the center of the nerve, and the pupillary fibers are located in the nerve periphery where there is good collateral blood supply.

Compression of the third nerve from an expanding aneurysm at the junction of the internal carotid and posterior communicating arteries is a true neuro-ophthalmic emergency. Such compressions are usually painful and almost always involve the pupil. However, numerous case reports of isolated third nerve palsy caused by expanding aneurysms show that the pupil may be spared initially.<sup>29</sup> Often, these patients have only partial ptosis and extraocular muscle involvement, and, with very rare exceptions, the pupil becomes involved within 1 week of symptom onset. This situation is one of the few life-threatening emergencies in neuro-ophthalmology, and appropriate diagnosis and treatment are lifesaving.

In contrast to acute third nerve palsy, a slowly progressive third nerve palsy that involves the pupil usually is a sign of an enlarging cavernous sinus lesion.

What has been called “ophthalmoplegic migraine” in the past is likely a misnomer. This refers to a syndrome that consists of migraine-type headache and a third nerve palsy; the pupil is usually involved. Most patients (82% in one series) have an antecedent worsening in migraine severity that precedes the oculomotor paresis and is intense, continuous, and located in the orbital region.<sup>30</sup> As the paralysis reaches its maximum, the headache begins to recede. The initial presentation is usually in childhood, multiple attacks may occur, and a family history of migraine is often present. The third nerve palsy may last from hours to weeks, and permanent deficits occur after repeated attacks.<sup>31</sup> Magnetic resonance imaging (MRI) shows enlargement and enhancement of the third nerve as it exits the brainstem, which is more prominent during the attack.<sup>32</sup>



**Fig. 9.16.5 Isolated Third Nerve Palsy in the Setting of Herpes Zoster Ophthalmicus.** At the time of acute illness. Note the presence of herpes zoster lesions in the distribution of the first division of the fifth nerve. Third nerve palsy consists of ptosis, adduction, elevation, and depression deficit with preserved abduction.

A case of recurrent postviral oculomotor paresis at age 11 months and 39 months has been described, with corticosteroid response and enhancement of the cisternal portion of the oculomotor nerve during the episodes.<sup>33</sup> Other causes of isolated third nerve palsy in the subarachnoid space include trauma, infectious, and neoplastic meningitis.

Aberrant regeneration may occur with recovery of a third nerve because of a structural lesion, but not an ischemic lesion. The abnormal activation of one part of the third nerve is found when another part should be in action. For instance, if fibers originally destined for the medial rectus now supply the levator palpebrae superioris or innervate the pupil, then on adduction of the eye the lid elevates (so-called lid-gaze dyskinesia) or the pupil constricts, respectively. This may give rise to pupillary light-near dissociation. Another common pattern of aberrant regeneration is elevation of the eyelid on downgaze, referred to as pseudo-Von Graefe phenomenon, because fibers destined for the inferior rectus now go to the levator palpebrae superioris. Co-contraction of vertically acting muscles may limit vertical excursion of the eye and be associated with retraction of the globe.

Primary aberrant regeneration refers to the findings above, but with no antecedent third nerve palsy. This suggests a compressive lesion of the third nerve that slowly evolves with ongoing recovery to produce the aberrant regeneration without clinical realization of a third nerve palsy. This occurs most often from internal carotid artery aneurysms, meningiomas, or neurinomas in the cavernous sinus.

Rarely, aberrant regeneration may occur between the sixth and third nerves. For example, on attempted abduction, the lid elevates and the eye adducts. This has been described after trauma with initially complete ophthalmoplegia.

### Divisional Third Cranial Nerve Palsy

The third nerve divides in the anterior cavernous sinus into a superior and inferior division. Either division may be affected by lesions, most commonly structural in the anterior cavernous sinus or orbit. A superior division third nerve palsy manifests with an isolated elevation deficit and ptosis of one eye. A characteristic example is caused by an ophthalmic artery aneurysm. An inferior division third nerve palsy may cause mydriasis and an adduction and depression deficit without ptosis or elevation deficit. Divisional palsies have been described as far posteriorly as the anterior midbrain, likely because fibers have segregated into different portions of the nerve at this point. In addition, cases exist of benign, remitting pareses of either division of the third nerve.<sup>34</sup>

## Nonisolated Cranial Neuropathies

When an ocular motor nerve paresis is accompanied by additional findings, the approach to evaluation changes. Associated findings suggest the localization and character of the lesion. Long-tract findings, alterations in consciousness, or other cranial neuropathies result from brainstem lesions, and these are covered in Chapter 9.15. When there is only cranial nerve involvement, the likely localization includes the subarachnoid space, cavernous sinus, and orbit. Proptosis, chemosis, and visual loss occur with orbital lesions, and these are covered in Chapter 12.10.

In this section, nonisolated cranial neuropathies are reviewed. They are subdivided into categories of multiple cranial neuropathies, bilateral cranial neuropathies, and lesions in the subarachnoid space that may cause both multiple unilateral or bilateral cranial neuropathies.

### Multiple Cranial Neuropathies

In contrast with isolated mononeuropathies, involvement of more than one ocular motor nerve rarely results from vasculopathic lesions. The involvement of multiple nerves enables localization of the responsible lesion, usually in the cavernous sinus, superior orbital fissure, or orbital apex. In numerous series, common causes include tumor, inflammation, trauma, and aneurysm.<sup>14,16,17</sup> Because the first division of the fifth cranial nerve may also be involved in such lesions, pain may be a prominent feature.

Typically, fourth nerve paresis is associated with hyperdeviation, most noticeable when the eye is adducted. In the presence of a third nerve paresis, the eye does not adduct, which makes it difficult to determine the presence of a coexisting fourth nerve paresis. In this situation, the eye is examined carefully for intorsion of the globe on attempted downgaze by visualization of a conjunctival vessel, from which secondary action of the fourth nerve is assessed (Fig. 9.16.6).

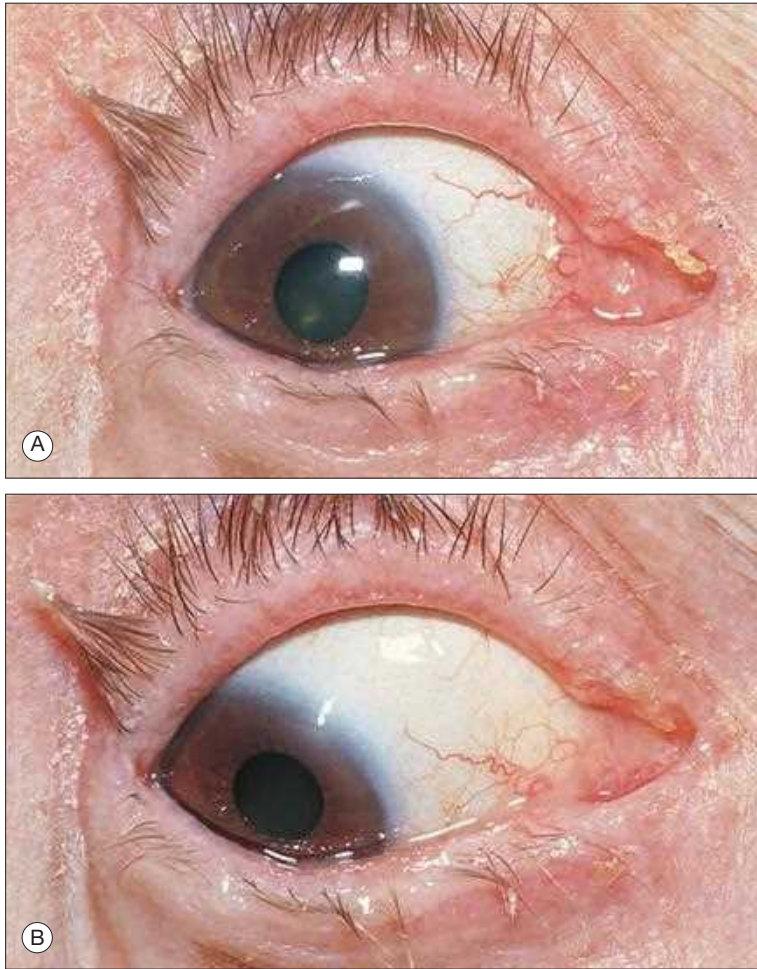
On occasion, the third and fourth cranial nerve nuclei may be involved together in the brainstem, usually with other neurological deficits. These cranial nerves may be involved together in the subarachnoid space also, as discussed below.

Because the sixth nerve crosses along the petrous apex, a syndrome that includes sixth nerve palsy, facial pain, hearing loss, and (sometimes) facial paralysis may occur. This is known as Gradenigo's syndrome and may result from infectious mastoiditis, tumor, trauma, aneurysm of the petrosal segment of the internal carotid artery, or inferior petrosal sinus thrombosis. Petrous bone fractures involve combinations of the fifth, sixth,



seventh, and/or eighth cranial nerves and other findings of hemotympanum, Battle's sign (mastoid hematoma), and CSF otorrhea.

The cavernous sinus consists of a plexus of veins. Within the venous plexus lies the sixth nerve, and within the lateral wall of the cavernous sinus lies the third nerve, fourth nerve, first division of the fifth nerve, and, posteriorly, the second division of the fifth nerve. Within the cavernous sinus, the sympathetic fibers form a nerve plexus along the carotid artery (Fig. 9.16.7).



**Fig. 9.16.6 Demonstration of Intact Fourth Cranial Nerve in the Presence of a Third Nerve Paresis.** (A) The patient's right eye is exotropic from a complete third nerve palsy. (B) However, an intact fourth nerve is noted on attempted downgaze because of incyclotorsion of the eye. This is best seen by comparison of the conjunctival vessels in (A) with their position in (B) on attempted downgaze.

The superior orbital fissure contains the same nerves as the anterior cavernous sinus. Therefore, the signs and symptoms of cavernous sinus and superior orbital fissure lesions may be the same. The findings include involvement of any of the above cranial nerves in isolation or in various combinations, including the second division of the fifth nerve if a lesion is in the posterior cavernous sinus. The pupil may be involved, spared, or appear spared with concomitant oculosympathetic and parasympathetic involvement. Various degrees of pain may be involved and, if pain is severe, "painful ophthalmoplegia syndrome" is diagnosed.<sup>35</sup>

Broad categories of diseases that involve the cavernous sinus include neoplasms, inflammation, infection, vascular lesions, and trauma.<sup>36–38</sup> Neoplastic lesions include local metastatic disease from nasopharyngeal cancer, olfactory neuroblastoma, adenoid cystic carcinoma, cylindroma, ameloblastoma, and squamous cell carcinoma, or disease that spreads from distant lesions, which includes carcinoma, sarcoma, multiple myeloma, and lymphoma. Local spread of benign tumors includes pituitary adenoma, meningioma, craniopharyngioma, neurilemmoma, and epidermoid tumor. Chordomas, chondromas, and giant cell tumors may also spread in the cavernous sinus. Meningiomas may arise in the cavernous sinus itself. Neuromas, neurofibromas, or schwannomas may occur on the gasserian ganglion or the other cranial nerves.

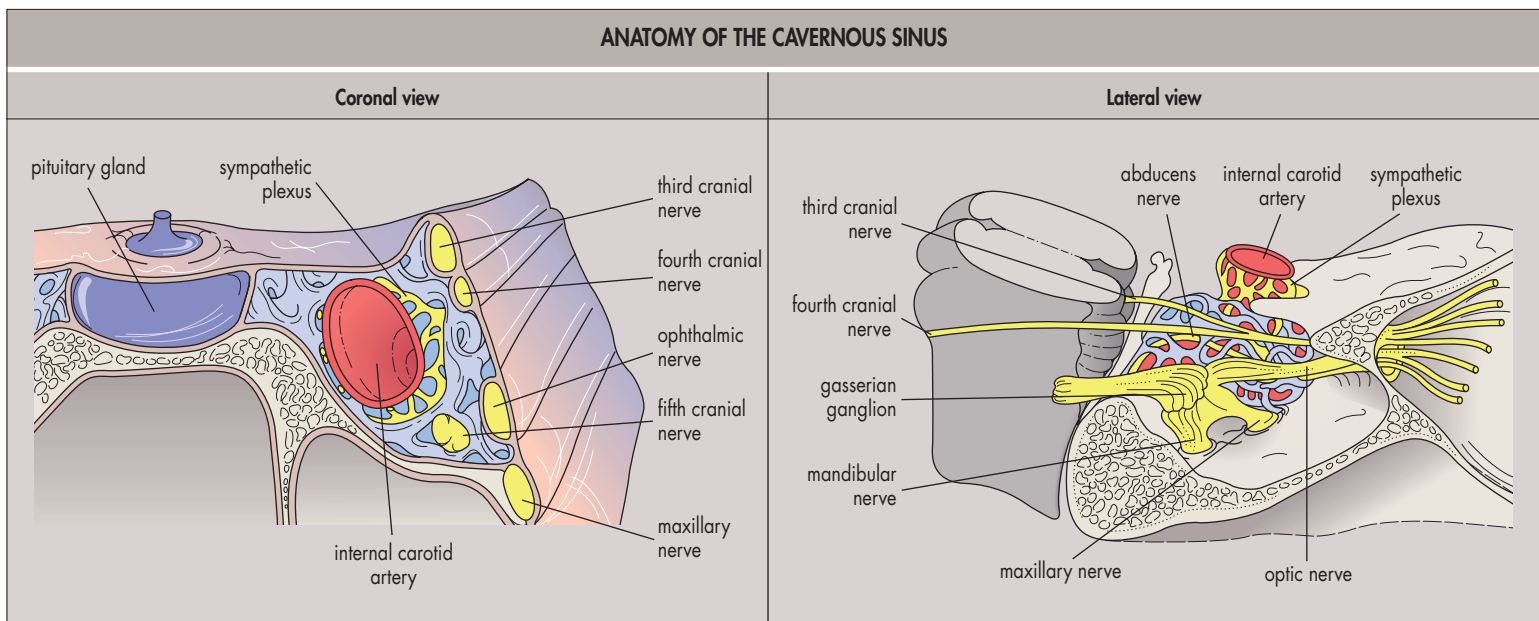
Pituitary apoplexy is a clinical syndrome caused by sudden enlargement in a pituitary tumor as a result of acute hemorrhage or edema. Previous symptoms may have been present, but the lesion can also present acutely. Features are variable and include acute and severe headache, diplopia with ophthalmoplegia from cavernous sinus involvement, visual loss from optic nerve, chiasm, or tract involvement, meningismus from hemorrhage into the subarachnoid space, and endocrine insufficiency.

Inflammatory lesions may be both infectious and noninfectious. Bacterial infections may cause cavernous sinus thrombosis, which causes a unilateral or bilateral cavernous sinus syndrome, proptosis, and chemosis associated with signs of fever, depressed mental status, and signs of sepsis. Direct extension of infection or a mucocoele from the paranasal sinuses may cause compression of the cavernous sinus.

Mucormycosis is a life-threatening infection that may affect the cavernous sinus, superior orbital fissure, or orbit. Multiple cranial neuropathies may occur relatively rapidly in a predisposed patient who is diabetic or immunosuppressed. Often an indicative eschar is seen in the nose. An occlusive vasculitis may occur, affecting the brain or eye. A high index of suspicion is required to make the diagnosis.

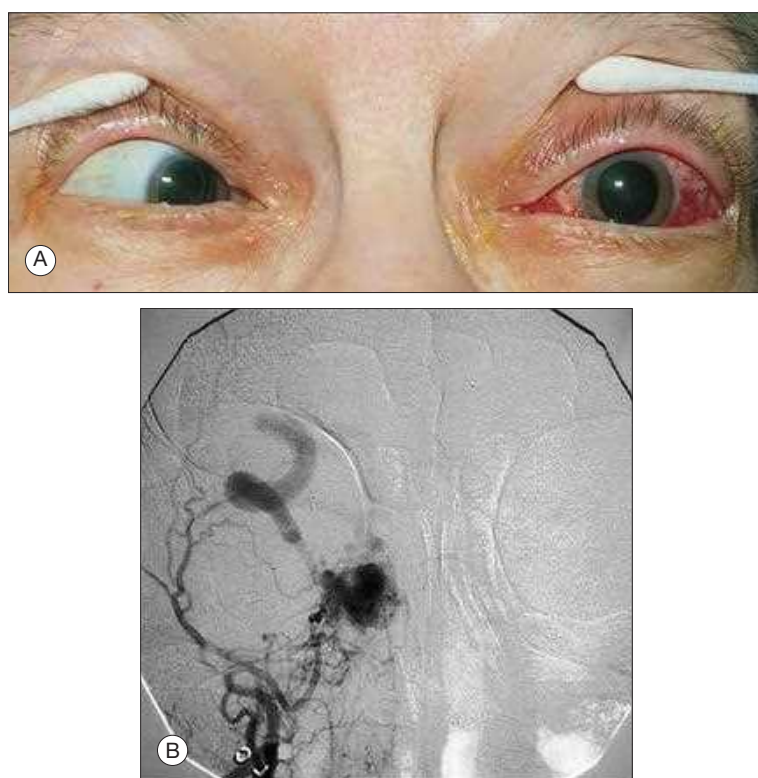
Aspergillosis also may involve the orbital apex or cavernous sinus. Rarely, other infections, such as syphilis or tuberculosis, may affect the cavernous sinus. Herpes zoster, usually ophthalmic but even with cervical involvement, may be followed by abnormalities of the cavernous sinus. Typically, an isolated ocular motor nerve becomes affected following involvement of the first division of the fifth cranial nerve.<sup>39,40</sup> Occasionally, multiple cranial nerves are affected.

Inflammatory, noninfectious lesions include sarcoidosis, Wegener's granulomatosis, eosinophilic granuloma, and the idiopathic Tolosa–Hunt



**Fig. 9.16.7 Anatomy of the Cavernous Sinus.** Coronal and lateral views. (From Kline LB. The Tolosa–Hunt syndrome. *Surv Ophthalmol* 1982;27:79–95.)





**Fig. 9.16.8 Dural Arteriovenous Fistula.** (A) Patient had diplopia that resulted from a left sixth nerve palsy, Horner's syndrome, proptosis, chemosis, and injection with arterIALIZATION of the conjunctival vessels. (Pupils are pharmacologically dilated.) (B) Arteriogram demonstrates filling of the cavernous sinus and a huge dilated superior ophthalmic vein in the arterial phase of an external carotid artery injection in the same patient.

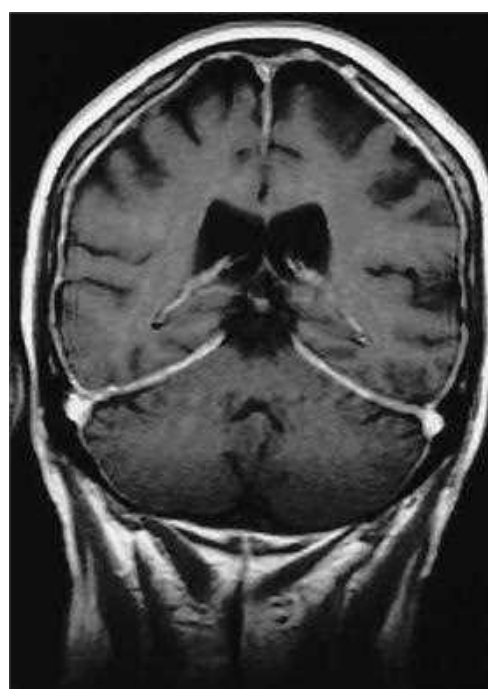
syndrome; the last causes painful ophthalmoplegia of combinations of the ocular motor nerves, most frequently the third nerve. The pain is described as "gnawing" or "boring" and may precede ophthalmoplegia. Other findings include Horner's syndrome, proptosis, optic nerve involvement, fifth nerve (divisions 1–3) involvement, or seventh nerve palsy.<sup>35,41,42</sup> The symptoms last for days to weeks and spontaneous remissions occur, with or without residual deficits. Recurrences may occur at intervals of months to years.

Vascular causes of a cavernous sinus syndrome include carotid artery aneurysm, cavernous sinus thrombosis, direct carotid artery to cavernous sinus fistula, and dural arteriovenous fistula. Intracavernous carotid artery aneurysms are saccular aneurysms that develop most commonly from atherosclerosis. They cause slowly progressive ophthalmoplegia through enlargement, often with aberrant regeneration, and may cause an acute carotid cavernous fistula if they bleed. Trauma to the internal carotid artery may also cause a direct carotid cavernous fistula.

A direct carotid cavernous fistula can cause cavernous sinus syndrome, as well as headache, facial pain, severe proptosis, chemosis, and injection of the eye, with arterIALIZATION of conjunctival and episcleral vessels. Often pulsatile tinnitus and an orbital bruit occur, and retinal venous engorgement and hemorrhage, central retinal vein occlusion, retinal ischemia, serous retinal or choroidal detachment, and anterior ischemic optic neuropathy may also be seen. Intraocular pressure may be elevated and angle-closure or neovascular glaucoma may develop.

A less serious fistula results from a dural arteriovenous connection in which multiple dural vessels that come off the arterial system connect directly with the cavernous sinus. This occurs most often in older women and has a subacute or chronic course. The findings include the above cranial neuropathies, as well as proptosis, orbital bruit, and conjunctival injection, none as severe as those associated with a direct internal carotid cavernous fistula. The more subtle clinical picture means that these patients are often misdiagnosed with chronic conjunctivitis, episcleritis, or thyroid ophthalmopathy (Fig. 9.16.8).

Involvement of the sixth nerve with loss of tearing and sometimes sensory loss in the second division of the fifth nerve localizes a lesion to the sphenopalatine fossa, usually from metastatic tumor or nasopharyngeal carcinoma. Poliomyelitis may involve one or more cranial nerves, most often the sixth cranial nerve.



**Fig. 9.16.9** Magnetic resonance image (with gadolinium) of a patient with bilateral sixth cranial nerve palsy. The palsy resulted from intracranial hypotension after lumbar spine surgery. Note the diffuse enhancement of the meninges.

### Bilateral Ophthalmoplegia

Bilateral ophthalmoplegia, a unique variant of the syndrome of multiple cranial neuropathy, refers to the involvement of more than one of the above cranial nerves, including at least one on each side. This implies a lesion that is large enough to cause deficits bilaterally or is situated in a location such that bilateral cranial nerves are involved.

Mobius' syndrome is a congenital syndrome associated with bilateral sixth nerve or horizontal-gaze paresis and seventh nerve (facial nerve) paresis and other deficits, which may include tongue atrophy, hand and face deformities, and other malformations. Bilateral sixth nerve paresis is seen in posterior fossa or clivus lesions, including clivus meningioma, chordoma, chondroma, or chondrosarcoma, as well as spread of nasopharyngeal carcinoma. An epidural hematoma in this area can also cause bilateral sixth nerve paresis.<sup>43</sup> This may occur because the two sixth nerves run adjacent to each other along the clivus or because sixth nerve palsies are nonlocalizing.

Increased intracranial pressure of any cause may produce unilateral or bilateral sixth nerve palsy by downward pressure and shift of the brainstem. This is because the sixth nerve is fixed as it exits the pons and as it pierces the dura to enter Dorello's canal under the petroclinoid ligament. Papilledema inevitably is present. Myelography, spinal anesthesia, or even lumbar puncture can cause a bilateral sixth nerve paresis through a similar mechanism of downward shift of the brainstem from a pressure differential. However, there is intracranial hypotension, and diffuse enhancement of the meninges may be seen on MRI (Fig. 9.16.9). Dolichoectasia or aneurysm of the basilar artery also may cause unilateral or bilateral sixth nerve paresis. In bilateral sixth nerve paresis, ischemic causes are less frequent and trauma is more common than in unilateral cases.<sup>15</sup> Bilateral sixth nerve palsy must be distinguished from nonorganic convergence spasm.

Bilateral fourth nerve paresis may be seen after head trauma. Trauma likely involves the nerves in the area of decussation in the anterior medullary velum. Bilateral fourth nerve paresis also may be seen with hydrocephalus, tumor, arteriovenous malformation, or demyelinating disease.

With bilateral fourth nerve paresis, right hyperdeviation in left gaze or right head tilt and left hyperdeviation in right gaze or left head tilt occur. In primary position, depending on the relative symmetry of the bilateral fourth nerve paresis, orthophoria, or right or left hyperdeviation may occur. An additive effect of exocyclodeviation occurs, with the result that greater than 10° of exocyclotorsion is often seen. Because a tertiary action of the superior oblique muscle is abduction, loss of action of both superior obliques in downgaze causes a relative esodeviation in downgaze, which results in a characteristic "V"-pattern horizontal deviation.

Rarely, bilateral simultaneous ophthalmoplegia may have a vasculopathic cause.

### Subarachnoid Involvement

With subarachnoid involvement, signs of multiple cranial nerve involvement may occur on one or both sides, as well as headache, stiff neck, photophobia, and fever. Causes include subarachnoid hemorrhage, trauma,

infectious or neoplastic meningitis, idiopathic intracranial hypertension (pseudotumor cerebri), tumors on the sixth nerve, or tumors in the clivus that compress the sixth nerve. With elevated intracranial pressure, papilledema occurs.

Infectious meningitis may arise from bacterial, fungal (mainly cryptococcal), tuberculous, or syphilitic causes, or from Lyme disease. Inflammatory meningitis occurs with sarcoidosis.

Patients with human immunodeficiency virus (HIV) may develop cranial neuropathies, associated with mostly secondary infectious causes (toxoplasmosis and cryptococcus) and with numerous other symptoms and signs. In one series of patients with HIV and neurological involvement, 17% had sixth nerve palsy, 9% third nerve palsy, and 1% fourth nerve palsy.<sup>44</sup>

### Nonisolated Third Cranial Nerve Palsies

Nonisolated third nerve palsies occur in the subarachnoid space and are accompanied by meningeal signs. The processes are similar to those described above—mainly infectious, neoplastic, or traumatic. However, one additional nonisolated third nerve syndrome occurs with uncus herniation through the tentorium, with large hemispheric mass lesions (e.g., tumor, hemorrhage, or infarct with edema). The patient has a corresponding neurological deficit and is lethargic. The third nerve is compressed against the tentorial edge, petrous ridge, and clivus by the uncus of the temporal lobe. Usually, pupillomotor fibers are involved first. Rarely, upward herniation from a mass in the posterior fossa may cause a third nerve palsy.

## DIAGNOSIS

Although the above history and examination techniques should enable specific identification of the dysfunctional nerve(s), the associated findings (“the company it keeps”) are perhaps even more critical. Associated findings, such as involvement of other cranial nerves, other neurological deficits, or findings suggestive of an orbital process ultimately help localize the lesion and differentiate the likely causes.

In some instances, the cranial neuropathy is truly isolated to only the third, fourth, or sixth nerve. These cases necessitate a unique approach.

The evaluation of patients for ophthalmoplegia depends on the age of the patient. In infants, a congenital deficit or birth trauma is considered; in children, a postviral syndrome, trauma, or posterior fossa tumor; in young adults, trauma, multiple sclerosis, aneurysm, or arteriovenous malformation; and in older adults, diabetes, hypertension, atherosclerosis, tumor, or GCA.

The character of the onset and progression is an important indicator of etiology. Acute onset occurs with vascular, inflammatory, or traumatic causes. Progressive deficits are consistent with mass lesions, such as tumor or aneurysm. Intermittent symptoms suggest myasthenia gravis.

Although cranial neuropathy commonly results from trauma, such deficits only rarely occur with mild trauma. In these instances, an underlying structural lesion, such as aneurysm or tumor, often is present.<sup>45</sup>

### Isolated Cranial Neuropathies

Isolated cranial neuropathies are occasionally seen with intrinsic brainstem lesions. These are discussed in Chapter 9.15.

#### Isolated Sixth Cranial Nerve Palsy

In a child who has an acquired, isolated sixth nerve paresis, early investigation with MRI is reasonable because of the frequent presentation of tumor with sixth nerve paresis.

In an older person, with or without a history of diabetes or hypertension, an erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), platelet count, blood pressure recording, hemoglobin A1c, and serologies may be indicated. The patient may be followed up clinically, but if no improvement occurs over a few months or if the early clinical features deviate from the expected course, then neuroimaging, preferably with MRI, is required. The imaging must focus on the course of the sixth nerve, including the pons, clivus, petrous apex, cavernous sinus, and orbit. Some experts advocate MRI in all patients with isolated cranial neuropathy because up to 12% may have lesions that may benefit from early treatment, including pituitary apoplexy.<sup>13,46</sup> CSF and nasopharyngeal examination are considered if there is a high suspicion of nonvasculopathic etiology and no other cause is found.

In a young adult, particularly without evidence of hypertension or diabetes, the above serological tests and neuroimaging studies are performed, and, if negative, a CSF examination is a reasonable approach. If no

abnormality is found, the patient is followed up at regular intervals and re-evaluated at 6 months if resolution does not occur.

#### Isolated Fourth Cranial Nerve Palsy

The evaluation of patients affected by isolated fourth nerve paresis depends on the age group and setting. A history of significant trauma or evidence of a congenital fourth nerve paresis with decompensation requires no further workup.

In older patients with vascular risk factors, ESR, CRP, and platelet count are performed to rule out GCA (see Chapter 9.22), and the patient may be followed up clinically. Without this history, blood pressure, blood glucose, ESR, CRP, and platelet count are checked. If no resolution occurs within 6 months, neuroimaging, preferably with MRI, should be performed. Examination of CSF may be considered as well, although, without other neurological symptoms or signs, the diagnostic yield will be low. Some experts advocate early neuroimaging.<sup>13</sup>

In children and young adults who have no history of trauma or evidence to suggest a congenital cause, neuroimaging and a search for vasculitis are indicated. CSF examination is indicated if no clear cause can be established and if the deficit does not resolve.

#### Isolated Third Cranial Nerve Palsy

In adults of vasculopathic age, the most important issue is whether the pupil is involved or not. If the pupil is spared with otherwise *complete* involvement of ocular motility and ptosis, the patient is over 50 years of age, and he or she has diabetes and/or hypertension, a diagnosis of vasculopathic third nerve paresis may be presumed. Since aneurysms that do not at first involve the pupil have been described, the patient is followed carefully for the first week, and if the pupil becomes involved, further evaluation is indicated.<sup>47,48</sup> Some clinicians perform MRI on all isolated cranial neuropathies at presentation, and in particular for a third nerve palsy where aneurysm is a possibility MRI and magnetic resonance angiogram (MRA) or computed tomography (CT) and computed tomographic angiography (CTA) are reasonable.<sup>13</sup> One study found other etiologies in presumed vasculopathic ocular motor palsies in 16.5% of cases. When third nerve palsies and GCA cases were removed, the rate dropped to 4.7%. This might suggest that it is important to image third nerve palsies even when presumed to be vasculopathic.<sup>49</sup>

If the pupil is involved, the appropriate evaluation must be pursued until aneurysm is excluded adequately. The reliability of noninvasive imaging is dependent on the training and experience of the interpreting radiologist.<sup>50</sup> Initially, MRI or, if not available, CT, with and without contrast, is carried out for subarachnoid blood and evidence of aneurysm. If negative, MRA or CTA may show an aneurysm. However, in some centers, the sensitivity of MRA and CTA is not considered sufficient to exclude an aneurysm. In this situation, urgent catheter angiography must be carried out. If an aneurysm is found, emergency neurosurgery or interventional occlusion is necessary to prevent subarachnoid hemorrhage.

There is also controversy surrounding proper testing for the presentation of partial ptosis with ophthalmoparesis, with complete sparing of the pupil. Many investigators evaluate this similarly to a pupil-involving third nerve paresis, whereas others investigators monitor the patient carefully for pupillary involvement. The authors' opinion is that these patients should undergo neuroimaging.

Although aneurysmal compression must be excluded, other masses also cause relative pupillary spared third nerve palsies.<sup>51</sup> Therefore, in addition to MRA or CTA, standard MRI or CT is required.

If a pupil-sparing third nerve paresis does not resolve within the expected 3–6 month period or signs of aberrant regeneration are observed, further workup, including MRI, vasculitis workup, and, if no diagnosis has been confirmed, CSF examination, is indicated.

In children, many cases have a congenital etiology, and no further workup is indicated. In such patients, third nerve palsy often is incomplete and associated with signs of aberrant regeneration. If a difficult delivery was involved, trauma is the most probable cause. In those conditions that are acquired, angiography is likely indicated. Although the youngest reported age for a child with posterior communicating artery aneurysm is 7 years<sup>52</sup>, even infants may have an arteriovenous malformation or cavernous carotid aneurysm causing oculomotor palsy.<sup>53</sup>

If the history is suggestive of so-called ophthalmoplegic migraine, MRI will show enlargement and enhancement of the third nerve.<sup>32</sup>

In adults below the vasculopathic age, all acquired third nerve palsies should be investigated with MRI, blood tests (ESR, Lyme titer, glucose, antinuclear antibody [ANA]) to rule out vasculitis or infection, and CSF examination if no other cause is found.

## Nonisolated Cranial Neuropathies

### Multiple Cranial Neuropathies

The management of patients with cavernous sinus and superior orbital fissure lesions depends on the age of the patient, acuteness of presentation, speed of progression, presence of pain, history of systemic diseases or tumors, and accompanying features. Patients who have fever, somnolence, or a toxic appearance must be evaluated rapidly for evidence of cavernous sinus thrombosis or mucormycosis. Those who seek treatment acutely with prominent vascular features, with arterialization of conjunctival vessels, proptosis, and bruits, must be evaluated for direct carotid cavernous fistula.

The workup includes neuroimaging with MRI, with and without gadolinium. If MRI is contraindicated, CT, with and without contrast, using very thin axial and coronal sections, is indicated. Most often, the structural lesion is imaged by one of these techniques. For a dural arteriovenous fistula or direct fistula, MRA, orbital color doppler imaging, as well as conventional angiography, may be performed. In rare instances, CSF examination is helpful. When appropriate, blood tests, such as level of angiotensin-converting enzyme, and Lyme titer, are considered.

When a mass lesion consistent with tumor is found, metastasis must be considered and the diagnosis established by biopsy of lesions elsewhere. With primary tumors, biopsy of the cavernous sinus lesion is often necessary.

With the onset of painful ophthalmoplegia consistent with idiopathic inflammation, a course of corticosteroids should be considered. A positive response to corticosteroids has been used as diagnostic support for Tolosa–Hunt syndrome. However, since similar responses may occur in association with tumors, such as chordoma, giant cell granuloma, lymphoma, epidermoid, and other inflammatory conditions. This diagnosis must be made with caution as a diagnosis of exclusion. Differential diagnostic considerations for the presentation of painful ophthalmoplegia are listed in [Box 9.16.1](#). Evaluation to exclude the above causes of the cavernous sinus syndrome, as well as numerous other conditions, includes neuroimaging, complete blood count, ESR, rapid plasma reagin, fluorescent treponema antibody, ANA, Lyme titer, serum protein electrophoresis, and, occasionally, nasopharyngeal and CSF examinations. Neuroimaging results may be normal or may show a lesion consistent with inflammation. With recurrent episodes consistent with Tolosa–Hunt syndrome, biopsy of any lesion

noted on neuroimaging is indicated to rule out other entities. In the few cases reviewed pathologically, idiopathic chronic granulomatous inflammation and thickened fibrous tissue is seen.

When a patient with a known or occult pituitary adenoma has acute onset of painful ophthalmoparesis, pituitary apoplexy may be found by demonstration of acute hemorrhage or swelling of the pituitary adenoma on neuroimaging. These patients undergo transsphenoidal hypophysectomy and treatment for possible acute pituitary insufficiency.

To diagnose direct or indirect carotid cavernous fistula, arteriography is the definitive diagnostic procedure. However, MRI and MRA may demonstrate enlargement of the superior ophthalmic vein or the actual fistula. Other helpful procedures include CTA, Doppler ultrasound, orbital color Doppler, and measurement of ocular pulse amplitude. Reversal of flow, arterial pulsations, and arterialization may be demonstrated in the superior ophthalmic vein. Orbital color Doppler results may be as high as 96% sensitive for carotid cavernous fistula with anterior manifestations. However the specificity is low at 41%.<sup>54</sup>

### Bilateral Ophthalmoplegia

Neuroimaging that includes the course of each nerve involved is performed in those who have bilateral simultaneous ophthalmoplegia. If negative, CSF examination is carried out, and serological evaluations for collagen vascular disease, arteritis, syphilis, and Lyme disease, are performed. Wernicke's encephalopathy should be considered in cases of bilateral ophthalmoplegia.

## DIFFERENTIAL DIAGNOSIS

Numerous disorders that affect ocular motility may mimic and appear identical to a cranial neuropathy. These processes include restrictive ophthalmopathies, such as thyroid disease; neuromuscular diseases, such as myasthenia; and polyneuropathies, such as the Miller–Fisher variant of the Guillain–Barré syndrome.

The major examination technique used to exclude a restrictive process is the forced duction examination, in which a forceps or cotton-tipped swab is used to overcome the ductional deficit in the eye. A positive sign of restriction is when the deficit cannot be overcome because of resistance. Another sign of restrictive disease is an elevation of intraocular pressure when the eye moves in the direction of the restriction.

## Isolated Cranial Neuropathies

### Isolated Sixth Cranial Nerve Palsy

The differential diagnosis of a sixth nerve paresis includes Duane's retraction syndrome, thyroid or other restrictive ophthalmopathy, myasthenia gravis, spasm of the near reflex, or breakdown of a previous esophoria.

Duane's syndrome is a congenital abnormality that occurs in three different forms, which share palpebral fissure narrowing and globe retraction when the eye is adducted. Type I consists of an abduction deficit that mimics a sixth nerve paresis, type II consists of an adduction deficit, and type III includes both an abduction and adduction deficit ([Fig. 9.16.10](#)). MRI has revealed the absence of the ipsilateral abducens nerve in type I Duane's syndrome and in some of those with type III. Patients with type II had preserved abducens nerves. Pathologically, there is abnormal development of the abducens nucleus and innervation of the lateral rectus by branches of the oculomotor nuclei. During adduction, co-firing of the medial and lateral recti produces retraction of the globe. Duane's syndrome is bilateral in 18% of cases and familial in 10%.<sup>55,56</sup> Compared to sixth nerve pareses, patients with type I tend to have greater abduction deficit, less esotropia in primary gaze, and less distance–near disparity.<sup>57</sup> But the clearest distinction is that Duane's syndrome, unlike sixth nerve palsy, does not cause diplopia. Spasm of the near reflex is most often a nonorganic, functional disorder in patients who have psychogenic disease or in malingerers, but it rarely is seen in organic disease.<sup>58</sup> It presents with an abduction deficit that arises from substitution of convergence for lateral gaze. The diagnosis is made by finding the other features of the near reflex, mainly miosis, on attempted lateral gaze. Ductions tested with the other eye covered usually are normal.

Restrictive ophthalmopathy of the medial rectus most often results from thyroid disease, which is associated with other orbital signs, such as proptosis, injection, chemosis, lid retraction and lag. Other restrictive processes include trauma and orbital myositis. Forced duction testing result is positive.

Myasthenia may be differentiated on history and examination by the features of fatigability and variability. Evaluation with office testing (ice

### BOX 9.16.1 Differential Diagnosis of Painful Ophthalmoplegia Syndrome

- Trauma
- Aneurysm
  - Intracavernous carotid artery
  - Posterior cerebral artery
  - Basilar artery
- Carotid cavernous fistula
- Cavernous sinus thrombosis
- Tumors
  - Primary intracranial
  - Local or distant metastasis
  - Pituitary apoplexy
  - Meningeal carcinomatosis or lymphomatosis
- Infection
  - Mucormycosis or other fungal infection
  - Herpes zoster
  - Tuberculosis
  - Bacterial sinusitis, mucocoele, periostitis
  - Syphilis
- Inflammation
  - Sarcoid
  - Wegener's granulomatosis
  - Tolosa–Hunt syndrome
  - Orbital pseudotumor
  - Giant cell arteritis
  - Ischemic
  - Diabetes
  - Hypertension
- Ophthalmoplegic migraine





**Fig. 9.16.10 Duane's Syndrome (Type III).** (A) Abduction deficit. (B) Adduction deficit, retraction of globe, and narrowing of palpebral fissure on adduction of the right eye. (Adapted from Moster ML. Complications of cancer therapies. In: Miller N, Newman NJ, editors. Walsh & Hoyt's Neuro-ophthalmology, 5th ed. Baltimore: Williams & Wilkins; 1997.)

test, sleep test, or Tensilon test), acetylcholine receptor antibody, and single-fiber electromyography establishes the diagnosis.

Patients who have worsening congenital esophoria or compensated esotropia, often in times of stress or infection, may give a history consistent with sixth nerve palsy. However, a relatively comitant deviation and the presence in old photographs favor this diagnosis.

### Isolated Fourth Cranial Nerve Palsy

The differential diagnosis of isolated fourth nerve paresis includes myasthenia gravis, thyroid ophthalmopathy and other orbital restrictive processes, Brown's syndrome, skew deviation, and overaction of the inferior oblique muscle associated with congenital strabismus. Associated signs in thyroid ophthalmopathy and myasthenia gravis are noted above for sixth nerve paresis.<sup>59</sup> Skew deviation, a supranuclear vertical deviation that results from brainstem disease, is often associated with other neurological findings. There may be a comitant or incomitant pattern of deviation that does not correspond with the three-step pattern of a fourth nerve paresis. A decrease in vertical hypertropia by greater than or equal to 50% from the upright position to the supine position may also suggest skew deviation.<sup>60</sup> The ocular tilt reaction, a form of skew deviation that most closely mimics a fourth nerve paresis, appears with hypotropia, head tilt toward the hypotropic eye, and conjugate torsion toward the hypotropic eye.<sup>61</sup> In addition, excyclotorsion may not be present with myasthenia, skew deviation, and thyroid disease, but is invariably present with an isolated fourth nerve paresis.

Brown's syndrome causes diplopia because of an elevation deficit in adduction, in which the involved eye is hypotropic; forced duction test is positive. When congenital, this syndrome results from a short or tethered superior oblique tendon, but the acquired syndrome may be a result of tenosynovitis, adhesions, metastasis, or trauma. Brown's syndrome actually mimics an inferior oblique paresis; the latter may be differentiated by concomitant overaction of the superior oblique muscle, an "A"-pattern horizontal deviation, and a negative forced duction test.

### Isolated Third Cranial Nerve Palsy

The differential diagnosis of isolated third nerve palsy is not as lengthy as for fourth and sixth nerve palsies because of the many structures innervated by the third nerve and the characteristic findings. Nonetheless, in the absence of pain or pupil involvement, myasthenia gravis must be considered. Restrictive ophthalmopathy may mimic parts of a third nerve paresis but does not involve the pupil. If caused by thyroid ophthalmopathy, lid retraction is more commonly present than ptosis, and there are often other orbital findings. A supranuclear lesion may involve ptosis and an elevation deficit but shows improved motility with oculoccephalic maneuvers.

## Nonisolated Cranial Neuropathies

It is important in the diagnosis of simultaneous palsies of the ocular motor nerves to differentiate these from ophthalmoparesis that arises from orbital inflammatory disease, such as Graves' ophthalmopathy or orbital pseudotumor, ocular myopathies (e.g., chronic progressive external ophthalmoplegia), disorders of neuromuscular transmission (e.g., myasthenia gravis or botulism), and polyneuropathies (e.g., Miller-Fisher variant of Guillain-Barré syndrome). Demyelinating disease, basilar artery ischemia or aneurysm, skull base tumors, Wernicke's encephalopathy, and supranuclear gaze palsies also must be included in the differential diagnosis of nonisolated cranial neuropathies.

## TREATMENT

Besides treatment for the specific cause of the cranial neuropathy, the symptom of diplopia must be addressed. Acutely, occlusion of either eye using a patch or opaque tape over glasses is treatment good option, particularly in patients who are expected to recover. With chronic diplopia, prisms may be helpful for a subgroup of patients, especially when the deviation is relatively comitant. Eventually, with chronic, stable deviations, strabismus surgery (see Chapter 11.13) may be useful.

Some clinicians have used botulinum toxin injections, particularly early in fourth or sixth nerve paresis, to promote more rapid fusion during recovery. However, botulinum treatment does not hasten ultimate recovery.<sup>62</sup> In chronic cranial nerve paresis, botulinum treatment may be used; for instance, in fourth nerve paresis, it may be injected into the ipsilateral inferior oblique or the contralateral inferior rectus.

## Nonisolated Cranial Neuropathies

The Tolosa-Hunt syndrome is exquisitely sensitive to corticosteroids—pain resolves almost immediately, and ophthalmoplegia resolves subacutely with 60–80 mg/day of oral prednisone with a gradual taper. However, recurrences may not respond as well.

Direct internal carotid cavernous fistulas are treated with intra-arterial balloon occlusion of the connection between the carotid artery and cavernous sinus. Occasionally, neurosurgery is required, with occlusion of the carotid artery both above and below the site of the fistula.

Dural arteriovenous fistulas may be followed clinically if no threat to vision exists. In over 50% of patients, the fistula spontaneously undergoes thrombosis and resolves, particularly after angiography. In addition, training the patient to perform occlusion of the carotid artery intermittently during the day with digital pressure (provided no serious cerebrovascular disease is present) may allow for spontaneous thrombosis to occur. On some occasions, spontaneous thrombosis may be associated with retinal vein occlusions and visual loss. If there is a threat to vision, selective arteriography with occlusion of the feeder vessels is performed. Catheter angiography is also important to assess the presence of cortical venous drainage, which is associated with an increased risk of intracranial hemorrhage.

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# Disorders of the Neuromuscular Junction

9.17

Lauren T. Phillips, Deborah I. Friedman

**Definition:** A disorder of the neuromuscular junction, caused by an antibody-mediated autoimmune attack on postsynaptic acetylcholine receptors or the altered presynaptic release of acetylcholine.

## Key Feature

- Ocular or generalized muscle weakness.

## Associated Features

- Ptosis and ocular motility disturbances.
- Facial, trunk, and limb weakness.
- Speech and swallowing dysfunction.
- Respiratory compromise.
- Autonomic nervous system dysfunction.

## MYASTHENIA GRAVIS

### Introduction

Of all the disorders of the neuromuscular junction (Table 9.17.1), myasthenia gravis is the most common.<sup>1</sup> It is a disorder caused by an antibody-mediated autoimmune attack on the acetylcholine (ACh) receptors at the neuromuscular junction. The hallmark of myasthenia gravis is fluctuating muscle weakness that worsens with exertion and improves with rest. Ocular manifestations, such as ptosis and diplopia, are present frequently at onset and eventually are present in most patients. A subset of patients has only ocular symptoms.

### Epidemiology and Pathogenesis

The prevalence of myasthenia gravis is rising, largely as a result of longer lifespans. An estimated 8–10 cases per 1 million persons occur annually.<sup>2</sup> Women are affected twice as frequently as men. The incidence has one peak in the second and third decades, affecting mostly women, and another in the sixth and seventh decades, involving mostly men. However, the disease can occur at any age. Patients age greater than 50 years are more likely to require hospitalization for myasthenia gravis.<sup>3</sup> Younger patients, who are more likely to have thymic hyperplasia, often have human lymphocyte antigen (HLA-B8 and HLA-DR3) patterns. There is an association with HLA-B7 and HLA-DR2 in patients age greater than 40 years.<sup>4,5</sup> The neuromuscular junction is composed of the motor axon terminal, the synaptic cleft, and the postsynaptic surface of the muscle cell (Fig. 9.17.1), in which deep infoldings occur. ACh is stored in vesicles in the cytoplasm of the nerve terminal and mediates neuromuscular transmission. Depolarization of the axon by an action potential causes release of ACh into the synaptic cleft by calcium-dependent, voltage-dependent exocytosis. Ordinarily, more ACh than is needed to produce neuromuscular transmission is released, and this creates a safety factor. Once released, the ACh diffuses across the synaptic cleft to the postsynaptic folds.

The postsynaptic folds contain the ACh receptors and acetylcholinesterase, the enzyme that hydrolyzes ACh. In general, the receptors are located on the tips of the folds, and acetylcholinesterase is concentrated deeper within the synaptic folds. When two ACh molecules bind to a receptor, conformational changes occur, and an ion channel opens, resulting in a local depolarization and subsequent muscle contraction. An additional safety factor exists at this level because the potential generally exceeds the threshold required for depolarization of a muscle fiber (end-plate potential). Innervated receptors undergo continuous turnover, with a half-life of 8–11 days.

In myasthenia gravis, the major pathological changes are found at the postsynaptic membrane, with loss and simplification of the postjunctional

TABLE 9.17.1 Disorders of Neuromuscular Transmission

Disorder	Cause	Location	Defect	Symptoms	Treatment
Myasthenia gravis	Autoimmune	Postsynaptic	Antibodies to ACh receptor	Ptosis, diplopia Weakness, improves with rest	Pyridostigmine (Mestinon), corticosteroids, immunosuppressants; thymectomy
Botulism	<i>Clostridium botulinum</i> infection	Presynaptic	Impaired ACh release	Ptosis, diplopia, tonic pupils, accommodative impairment, bulbar weakness, cholinergic blockade	Respiratory support Antitoxin BabyBIG-IV (Infantile)
Lambert–Eaton myasthenic syndrome	Paraneoplastic	Presynaptic	Impaired ACh release	Rarely ptosis, diplopia, proximal muscle weakness Autonomic dysfunction	Treat malignancy 3,4-diaminopyridine, corticosteroids, immunosuppressants
Organophosphate toxicity	Insecticides Chemical warfare	Synaptic	Inhibits acetylcholinesterase	Rapid respiratory failure Muscle twitching then paralysis Mental status changes Pupillary miosis	Atropine, pralidoxime
Black widow spider ( <i>Latrodectus mactans</i> ) bite	$\alpha$ -Larotoxin	Presynaptic	Increased ACh release	Autonomic hyperactivity, vasoconstriction Painful, rigid abdomen	Calcium, magnesium, atropine, antivenin; warming
Tick paralysis	Toxic	Presynaptic	Impaired ACh release	Irritability, pain, paralysis Respiratory paralysis Late signs—unreactive pupils, ophthalmoplegia	Remove tick, supportive measures
Scorpion toxin	Toxic	Presynaptic	Increased ACh release	Agitation, respiratory failure, blurred vision, abnormal eye movements, jerking of extremities, autonomic dysfunction	Calcium, atropine, antivenin, supportive measures

ACh, acetylcholine.



folds, reduced numbers of ACh receptors, and a widened synaptic cleft. New receptors are synthesized, but they are not incorporated into the damaged postsynaptic membrane, which results in loss of receptors at the junction. The synapses of patients with myasthenia gravis contain about one third the number of ACh receptors found in those of healthy controls. The number of receptors seems to parallel the severity of weakness. With a reduced number of receptors, the end-plate potential is inadequate to generate contraction of some muscle fibers; this produces the characteristic muscle weakness. Normally, a decline (“rundown”) occurs in the amount of ACh released by successive muscle contractions. At myasthenic junctions, the rundown produces progressive failure of neuromuscular transmission because of the reduced number of receptors. This accounts for the muscular fatigability that is the hallmark of the disease.

The muscular abnormalities in myasthenia gravis result from an antibody-mediated process that likely originates in the thymus gland. The antibodies both accelerate the rate of degradation of ACh receptors and block ACh-binding sites. B cells produce the autoantibodies, but T cells also are important in the autoantibody response of myasthenia gravis. In myasthenia gravis, T and B cells produced by the thymus gland are more responsive to the ACh receptor compared with their counterparts in peripheral blood. Of patients who have myasthenia gravis, 75% have thymic abnormalities; of these, 85% have thymic hyperplasia, and 15% have thymomas. Perhaps the strongest evidence for the importance of the thymus gland in the pathogenesis of myasthenia is the effectiveness of thymectomy.<sup>6</sup>

Congenital myasthenic syndromes (CMSs) are rare, inherited disorders caused by various genetic defects of the neuromuscular junction. Patients may present with fatigable weakness of ocular, extraocular, and limb muscles. Electrodiagnostic testing typically shows a decremental response to slow repetitive nerve stimulation or characteristic compound motor action potential after-discharges. CMSs are not antibody-mediated and

therefore are not treated with immunotherapy. Rather, treatment options include quinidine sulfate, fluoxetine, salbutamol, or acetylcholinesterase inhibitors, depending on the region of defect.<sup>7</sup> CMS will not be discussed in further detail here.

## Ocular Manifestations

Ocular symptoms, that is, ptosis and diplopia, are present at onset in about 70% of patients and eventually are present in 90%. Ptosis, either isolated or associated with extraocular muscle involvement, often is the first symptom. The ptosis may be unilateral or bilateral, symmetrical or asymmetrical, and often it is more pronounced as the day progresses. Of the patients with myasthenia gravis, 15% have only ocular symptoms and signs.<sup>1</sup>

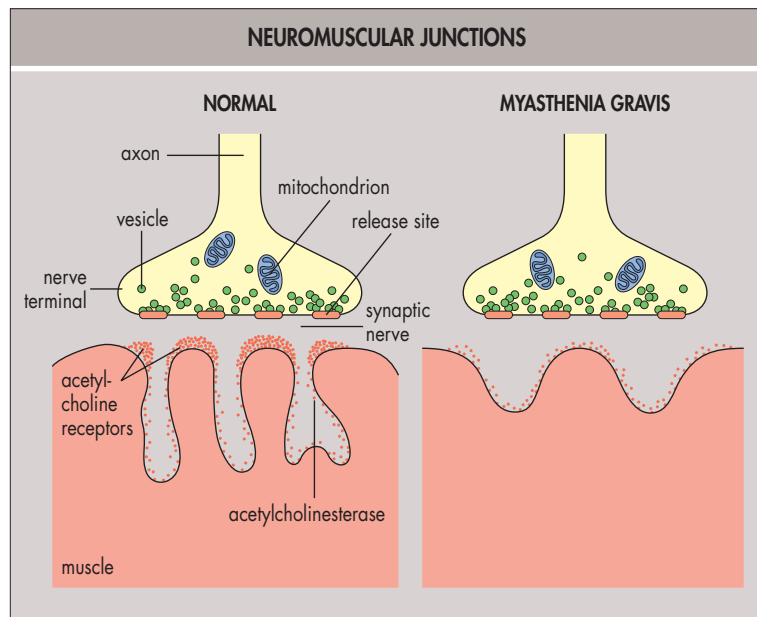
Involvement of the extraocular muscles varies from single-muscle paresis to total ophthalmoplegia. Myasthenia gravis may simulate ocular motor nerve palsy, unilateral or bilateral internuclear ophthalmoplegia, or gaze palsy. When the levator palpebrae superioris also is involved, the disease may mimic pupil-sparing third nerve palsy. Patients experience diplopia, which usually fluctuates throughout the day; sometimes the disease produces vertical separation of images, and at other times, it causes horizontal diplopia. The diplopia may be intermittent. Other motility abnormalities include saccadic dysmetria and decreased final saccadic velocity, small “quiver” eye movements, and gaze-evoked nystagmus.<sup>8</sup> Nystagmus occurs because of muscle fatigue; isolated nystagmus as a sign of myasthenia gravis is rare. For practical purposes, the pupils are normal in myasthenia gravis. Although anisocoria, impaired accommodation, and sluggishly reactive pupils have been described, the abnormalities are subtle and not clinically significant.

## Diagnosis

The diagnosis of myasthenia gravis is usually suspected from the patient’s symptoms and the results of the physical examination. The presence of ptosis and extraocular muscle weakness that either fluctuates or does not conform to any pattern of ocular motor nerve paresis raises the suspicion of myasthenia gravis. Many ocular signs may be present on physical examination. With unilateral ptosis, the other eyelid may appear retracted, exhibiting Hering’s law of equal innervation. If the ptotic eyelid is lifted manually, the ptosis worsens on the contralateral side (“see-saw ptosis”) (Fig. 9.17.2). This finding is not exclusive to myasthenia but is frequently present in patients who have the condition. Cogan’s lid twitch and Beinfang’s signs demonstrate the rapid recovery and easy fatigability of the levator. When the patient looks down for 10–20 seconds and then rapidly looks up to primary position, the upper eyelids often overshoot (retract) and then settle back into a stable position; a downward drift of the lids or several twitches may be observed (Cogan’s) or after 5 seconds of forced lid closure (Beinfang’s). Prolonged upgaze produces muscle fatigue, with eyelid droop or downward drift of the eyes. As the patient attempts repeated large-amplitude saccades, slowing of the eye movements may occur with repetition. Ice placed on a ptotic lid may prolong the time for which the ACh receptor channels open and produce clinical improvement. The ice test is a sensitive and specific test for myasthenia gravis.<sup>9–11</sup>

With generalized myasthenia gravis, muscle strength testing reveals weakness, usually more prominent proximally. Individual muscles weaken with repetitive testing; the strength improves after a brief period of rest.

A combination of physical examination, pharmacological tests, blood tests, and electrodiagnostic tests is often needed to confirm the diagnosis. If a demonstrable, measurable abnormality is present on the examination, administration of an acetylcholinesterase inhibitor produces increased strength of myasthenic muscles.<sup>12</sup> The most commonly used agent is intravenous edrophonium (Tensilon®) because of its rapid onset



**Fig. 9.17.1 Neuromuscular Junctions.** In myasthenia gravis, acetylcholine is released from presynaptic vesicles and diffuses across the synaptic cleft to the postsynaptic receptors. Acetylcholinesterase, located deep within the synaptic folds, hydrolyzes acetylcholine. There is also a simplification of the postsynaptic site with a reduced number of receptors. (From Drachman DB. Myasthenia gravis. *N Engl J Med* 1994;330:1797–810.)



**Fig. 9.17.2 Myasthenia Gravis.** (A) Right ptosis and compensatory left upper lid retraction. (B) On looking right note right abduction deficit and left lid retraction to compensate for right ptosis. (C) On sustained upgaze, right upper lid becomes fatigued.

of action (30 seconds) and short duration of action (5 minutes). Baseline readings are taken for the pulse, blood pressure, and the physical sign to be measured (e.g., measurement of the palpebral fissures and levator function or quantitation of subtle motility deficits using a Maddox rod or Hess screen).<sup>13</sup> The patient should be warned of potential side effects, including diaphoresis, abdominal cramping, nausea, vomiting, salivation, and lightheadedness.

Although the complication rate is very low, the most dangerous complication of intravenous edrophonium administration is heart block, and atropine sulfate should be made available immediately (0.4–0.6 mg, adult dose).<sup>14</sup> Alternatively, patients may be pretreated with intramuscular or subcutaneous atropine. The patient's pulse and blood pressure are monitored during the test. Ten milligrams are drawn into a tuberculin syringe. After administration of an initial test dose of 2 mg intravenously, the patient is observed for 1 minute while the pulse is monitored. Most patients with ocular myasthenia improve with the test dose. If no improvement and no adverse reaction occur, an additional 4 mg is administered. The remaining 4 mg can be used if no effect is seen. The presence of eyelid fasciculations indicates that an adequate dose was injected. Intramuscular neostigmine (Prostigmin®) is useful in children who may not cooperate with intravenous injections. Neostigmine (1.5 mg for adults or 0.04 mg/kg for children, mixed with 0.6 mg atropine sulfate) produces observable effects within 15 minutes; peak action occurs 30 minutes after injection.

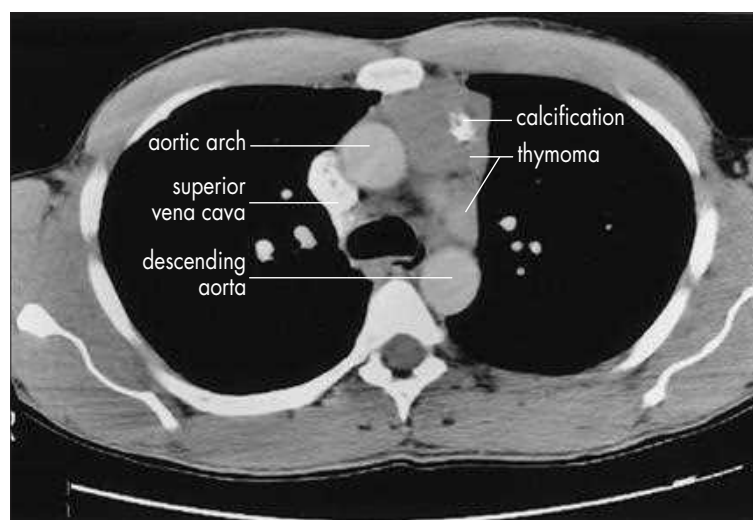
A safe alternative to the edrophonium test is the sleep test.<sup>15</sup> After the baseline deficit has been documented, the patient rests quietly with eyes closed for 30 minutes. The measurements are repeated immediately after the patient “wakes up” and opens the eyes. Alternatively, an ice pack is placed over closed lids for a few minutes. Improvement after rest is characteristic of myasthenia gravis.

A serum assay for anti-ACh receptor antibodies should be obtained for all patients who have suspected myasthenia gravis. Antibody titers do not correlate with the severity of the disease and typically are not serially measured to assess response to immunotherapy. The binding antibody is obtained most commonly, being detected in approximately 90% of patients who have generalized myasthenia gravis and 70% of patients who have ocular myasthenia. Blocking antibodies are present in approximately 60% of patients who have generalized myasthenia and 50% of patients who have ocular disease, and rarely are present (1%) without binding antibodies. Muscle-specific kinase (MuSK) antibodies are present in 40% of patients with generalized myasthenia when other antibodies are not detected. However, MuSK antibodies are rarely detected in purely ocular disease.<sup>16</sup> Several other antibodies have been described in association with myasthenia gravis; the clinical significance of these is being characterized. Serological testing for antilow density lipoprotein receptor-related protein 4 (anti-LRP4), anti-titin, and antiryanodine receptor (anti-RyR) antibodies is commercially available. Seronegative patients comprise 10%–15% of those with myasthenia gravis.<sup>1</sup> These patients should have antibody tests repeated within 12 months following presentation, and the clinical diagnosis should be reassessed, as needed.

Electrophysiological tests are useful for the diagnosis of myasthenia gravis if other tests are inconclusive. Repetitive supramaximal motor nerve stimulation (1–3 hertz [Hz]) produces a progressive decremental response of the compound muscle action potentials during the first four or five stimuli. This technique shows abnormalities in 40%–90% of patients who have myasthenia gravis and results are more likely to be positive with severe disease. Single-fiber electromyography (SFEMG) demonstrates “jitter,” which indicates the variability of propagation time to individual muscle fibers supplied by the same motor neuron. Intermittent “blocking” caused by failure of conduction at the neuromuscular junction also may occur. The sensitivity of SFEMG is approximately 90%.<sup>17</sup> In particular, SFEMG of the superior rectus and levator palpebrae muscles is extremely sensitive for the detection of ocular myasthenia gravis.<sup>18</sup> Conversion from ocular to generalized disease is less likely with normal SFEMG findings of the upper extremities.<sup>19</sup>

Because 10%–15% of patients who have myasthenia gravis have a thymic tumor, chest imaging (contrast-enhanced computed tomography or magnetic resonance imaging) is mandatory, even for patients with solely ocular findings (Fig. 9.17.3). Plain chest radiography alone is not adequate for this purpose. The persistence of a thymus gland in a patient age greater than 40 years or an increase in size on serial imaging studies raises the suspicion that a thymoma is present.

Other testing is directed toward associated systemic autoimmune diseases and treatment. Because 5% of patients who have myasthenia gravis have coexistent thyroid disease, thyroid function tests should be obtained for all patients. Complete blood count, antinuclear antibody analysis, and



**Fig. 9.17.3 Computed Tomography of the Chest With Contrast Enhancement.**

A large, multilobulated thymoma in a 32-year-old man with ocular myasthenia gravis. The mass is in proximity to the aortic arch and the ascending aorta. A focal calcification is present anteriorly. The patient's ptosis and diplopia remitted after removal of the thymoma.

erythrocyte sedimentation rate typically are tested in patients who have confirmed myasthenia gravis. If treatment with corticosteroids is planned, diabetes and tuberculosis should be excluded. Neuroimaging of the brain may be considered for atypical cases that are antibody negative and refractory to treatment (Table 9.17.2).

## Systemic Associations

Generalized myasthenia gravis develops in the majority of patients. The nonocular symptoms include facial weakness, jaw weakness dysarthria, dysphagia, nuchal muscular weakness, and limb weakness. Erector spinae involvement may cause inability to maintain an erect posture. Most patients feel tired with reduced stamina. In severe cases, weakness of the muscles of the chest and diaphragm produces dyspnea and orthopnea. A pronounced drop in the vital capacity leads to myasthenic crisis, which requires mechanical ventilation and aggressive treatment.

Approximately 12% of neonates born to mothers with myasthenia develop transient neonatal myasthenia gravis as a result of maternal transmission of autoantibodies through the placenta; these trigger independent antibody production by the infant. Affected neonates have generalized weakness, with difficulty eating, respiratory weakness, a poor cry, and facial weakness, which are noticed shortly after birth. The symptoms last for several weeks and then resolve without recurrence. Treatment is supportive.

Thymic enlargement and thymoma frequently are present in patients who have myasthenia gravis. Other autoimmune disorders, such as thyroid disease, systemic lupus erythematosus, neuromyelitis optic spectrum disorders, and pernicious anemia, are found with increased frequency in patients with myasthenia gravis.

## Treatment

The major therapies for myasthenia gravis are as follows:

- Acetylcholinesterase inhibitors.
- Immunosuppression.
- Symptomatic treatment of ocular abnormalities.
- Avoidance of agents that worsen neuromuscular transmission.
- Thymectomy in some cases.

Acetylcholinesterase inhibitors raise the safety factor for neuromuscular transmission by preventing the degradation of ACh. These agents provide symptomatic improvement in muscle weakness. However, because of their rapid effectiveness and lack of long-term side effects, they often are the first agents used in the treatment of myasthenia. Pyridostigmine (Mestinon®), the most commonly used drug, has a duration of action of 2–8 hours. It is most useful for the treatment of systemic weakness of myasthenia gravis and may not improve the diplopia. The usual starting dose is 30–60 mg every 4 hours while the patient is awake. Larger doses or more frequent dosing intervals may be used, as needed. Above 120 mg every 3 hours, no additional effectiveness is likely and a risk exists

TABLE 9.17.2 Differential Diagnosis of the Neuromuscular Junction

Disorder	Pupils	Ocular Motility	Lids	Other Ocular Findings	Other Systemic Findings
Myasthenia gravis	Normal	Fluctuating ophthalmoparesis	Ptosis Cogan's lid twitch sign	—	Fluctuating weakness that improves with rest
Thyroid eye disease	Normal	Restricted EOM Positive forced duction testing	Lid retraction Lid lag Lid edema	Conjunctival infection Keratoconjunctivitis sicca Exophthalmos Optic neuropathy	Symptoms of hyperthyroidism may be present
Botulism	Dilated, poorly reactive Light–near dissociation	Ophthalmoparesis	Ptosis	—	Limb weakness, bulbar signs Respiratory failure Urinary retention Constipation
Lambert–Eaton myasthenic syndrome	Usually normal	Usually normal	Usually normal	Keratoconjunctivitis sicca	Autonomic and limb weakness that improves with repetitive testing
Guillain–Barré syndrome	Normal or poorly reactive	Normal or ophthalmoparesis	Ptosis	—	Facial diplegia Limb weakness +/- sensory symptoms Areflexia Respiratory failure
Progressive external ophthalmoplegia	Normal	Slowly progressive Symmetrical ophthalmoparesis	Slowly progressive Ptosis	May have pigmentary retinopathy	Varying degrees of multisystem involvement due to mitochondrial disorder

EOM, extraocular movement.

of cholinergic crises. A delayed-release preparation taken at bedtime is useful for patients who have profound weakness upon awakening in the morning. The most common side effects from these agents are gastrointestinal disturbances (nausea, diarrhea, cramping) and muscle twitching. Overdosing results in sialorrhea, blurred vision, and worsening weakness (cholinergic crisis). It may be difficult to distinguish between cholinergic crisis caused by medication and worsening of the disease. Diplopia often does not improve with pyridostigmine and may be treated with immunosuppressive agents.<sup>20</sup>

Thymectomy is indicated for all patients who have a thymoma. A study of patients age 18–65 years with generalized nonthymomatous myasthenia gravis, with disease duration of less than 5 years, showed that thymectomy is beneficial for patients with ACh receptor antibody–positive myasthenia gravis. Extended transsternal thymectomy improved clinical outcomes over a 3-year period.<sup>6</sup> Guidelines and consensus statements recommend thymectomy for patients with early-onset generalized myasthenia gravis, usually those with detectable muscle antibody tests. Thymectomy may be considered in seronegative or ocular myasthenia gravis if the disease is refractory to standard immunotherapy.<sup>20,21</sup> ACh receptor antibodies status does not seem to influence the efficacy of the surgery, but active ectopic rests of thymic tissue portend a worse prognosis.<sup>22</sup> A transsternal approach is preferable because it allows for adequate visualization of the thoracic cavity and total thymus removal. Robotic techniques shorten the operative time and hold promise as less invasive techniques for extended thymectomy; ectopic rests of thymic tissue may remain undiscovered with use of the less invasive transcervical technique.<sup>23</sup> The morbidity and mortality rates from thymectomy are quite low. Because any surgical procedure may worsen myasthenia, some patients benefit from a short course of plasmapheresis preoperatively. Radiotherapy to the thymus gland is not effective.

Immunosuppressants, mainly cytotoxic agents and corticosteroids, treat the disease directly and are generally employed in patients who do not improve satisfactorily with acetylcholinesterase inhibitors. It may be several weeks to months before these medications take effect. Corticosteroids, most commonly prednisone, are used most frequently, and various dosing strategies are employed. Daily administration of high doses (60–100 mg) may produce substantial worsening within the first 2 weeks after initiation and should be used with caution, particularly in corticosteroid-naïve patients. Other regimens use increasing, daily, low doses of prednisone, or alternate-day dosing. Alternate-day dosing has the advantage of fewer side effects, and many patients who have purely ocular symptoms improve on a low dosage (20–30 mg) of alternate-day therapy. Corticosteroid monotherapy may reduce the risk of generalization in patients with ocular myasthenia gravis, although this issue remains controversial.<sup>20,24,25</sup> The risks of long-term prednisone administration include peptic ulcer, osteoporosis, femoral neck fracture, diabetes, skin breakdown, weight gain, and cushingoid features. Appropriate medical precautions and monitoring are required. To minimize the complication rate, the lowest dosage of prednisone possible should be used, and other immunosuppressant agents added, if needed.

Azathioprine, cyclosporine, and mycophenolate mofetil are utilized for the long-term management of myasthenia gravis and may be used in combination with prednisone and pyridostigmine.<sup>1,2</sup> These medications

have fewer long-term side effects compared with prednisone. Rituximab is reserved for patients with severe disease.<sup>2</sup> However, rituximab is well tolerated and effective in treating myasthenia gravis, particularly in patients with MuSK antibodies.<sup>26</sup> Blood counts, liver function, and renal function must be monitored, with a small possibility that a neoplasm will develop after many years of treatment. Plasmapheresis effectively reduces circulating autoantibodies. It is typically reserved for patients in myasthenic crisis or is used preoperatively for thymectomy in patients who have severe weakness. Improvement is rapid, but transient. Like plasmapheresis, intravenous immunoglobulin produces rapid improvement through a difficult period of myasthenic weakness (400 mg/kg per day for 5 days).<sup>2</sup> Patients in myasthenic crisis require aggressive respiratory support, often need intubation and mechanical ventilation, and are best managed in the intensive care unit.

As a rule, ptosis typically responds to treatment but diplopia may be refractory. Ocular symptoms can be treated symptomatically as other therapies are initiated, or when these are ineffective. Lid crutches or eyelid tape may be beneficial for patients who have ptosis, but ptosis surgery should be reserved for patients who are stable over long periods of time and refractory to other treatments. Diplopia is managed using patching or prisms; strabismus surgery is inappropriate for patients who have active myasthenia gravis.<sup>20</sup>

Medications that lower the safety factor of neuromuscular transmission should be avoided in patients who have myasthenia. Penicillamine causes a myasthenic syndrome that may be associated with autoantibody production. Many antibiotics decrease the production or release of ACh, including the aminoglycoside agents (streptomycin, neomycin, kanamycin, gentamicin, tobramycin, amikacin, viomycin), bacitracin, polymyxins (polymyxin A and B, colistin), and the monobasic amino acid antibiotics (lincomycin and clindamycin). Rarely, worsening of myasthenia occurs with erythromycin or following iodinated contrast dye administration. All neuromuscular blocking agents, such as botulinum toxin, curare, and depolarizing agents, should be used with caution. Chloroquine, lithium, and magnesium affect both presynaptic and postsynaptic transmission. Antiarrhythmic agents, including procainamide and quinidine, can cause or worsen myasthenia gravis. Phenytoin, beta-blockers, cisplatin, phenothiazines, statins, and tetracyclines may have similar effects.

## Course and Outcome

Despite its ominous name, myasthenia gravis is seldom fatal; most patients experience remission or good control of their symptoms with treatment. Of those patients who have only ocular symptoms and signs at onset, 10%–20% undergo spontaneous remission and 50%–80% develop generalized disease, almost always within 2 years of onset of the disorder.<sup>27</sup> The majority of patients who continue to have only ocular symptoms 2 years after presentation never develop generalized disease.<sup>1</sup> Patients who have ocular myasthenia who are 50 years of age or older are more likely to progress to generalized myasthenia, whereas a younger age at onset carries a better prognosis.

In adults, the disease is most labile during the first 10 years; most deaths occur during the first year. The long-term prognosis is poorer when



a thymoma is present. When death is caused by myasthenia gravis, usually it is because of respiratory failure with secondary cardiac dysfunction.<sup>28</sup>

## BOTULISM

### Introduction

Botulism is a potentially life-threatening disorder caused by the toxin of *Clostridium botulinum*. Three types exist—food-borne, wound, and infantile. The clinical picture is characterized by rapidly evolving cranial nerve and respiratory weakness with autonomic dysfunction. Associated symptoms include hyposalivation, dysphagia, dysarthria, respiratory failure, muscular weakness, constipation, urinary retention, nausea, and vomiting.

### Epidemiology and Pathogenesis

Botulism, caused by the neurotoxin elaborated by *Cl. botulinum*, may take many forms. Its site of action is the presynaptic nerve terminal, where it prevents the release of ACh. The preformed toxin may be ingested, as in food-borne botulism, or gain access by wound infection. Alternatively, the bacterium or spore may colonize the gastrointestinal tract, as in infant botulism. Inhaled botulism via aerosolization of the toxin is a potential bioterrorism weapon.<sup>29</sup>

At least eight types of toxin have been described, but only three forms commonly affect humans. Type A botulism is usually the most severe form of the disease. In the United States, an estimated 145 cases of botulism are reported yearly—15% food-borne, 65% infant botulism, and 20% wound.<sup>29</sup>

Historically, classic or food-borne botulism was caused by inadequately cleaned, smoked, salted, or dried fish or meat. Contemporary risk factors include commercial or home-prepared condiments, vegetables, nonacid foods, and preserved raw fish.<sup>29</sup> Plastic food storage bags and containers provide a near-perfect anaerobic environment for growth of *Cl. botulinum*. Vehicles for food-borne botulism vary by region worldwide.<sup>29</sup>

Infant botulism occurs during the age range 2–6 months in previously healthy infants. The course is subacute and may be difficult to diagnose until the child becomes severely ill. The classic source of infection is honey. Transmission of spores from adults to infants is possible from soil contamination of clothing. A similar infection can be seen in adults who have achlorhydria, following gastrointestinal operations, and who have blind loops of the bowel.

Wound botulism was once an uncommon form of botulism but is increasing in incidence as a result of intravenous heroin abuse and cocaine abuse associated with necrotic nasal passages.<sup>30</sup>

### Ocular Manifestations

Ophthalmic manifestations are not likely to occur in isolation but are part of a systemic illness. Diplopia and ptosis occur with varying degrees of ophthalmoparesis. Internal ophthalmoplegia with accommodation paresis produces blurred vision. The pupils often are abnormal, with a poor reaction to light. Pupillary light–near dissociation may be observed during the acute infection and occasionally persists after recovery.<sup>31</sup> Quivering eye movements have been described. Hypolacrimation is often found.

### Diagnosis

The diagnosis is based on the symptoms and signs, the circumstances of infection, electrophysiological studies, and isolation of the organism or toxin.

When botulism is suspected, stool, gastric aspirate or vomitus, and at least 20 mL of serum should be collected for analysis. If the source of contaminated food is available, it may be submitted to the relevant health department for evaluation. Identification of botulinum toxin in serum and stool is performed using a mouse bioassay. A Tensilon test result is almost always negative. Electrophysiological studies are very helpful and show changes similar to those seen in the Lambert-Eaton syndrome (discussed later).

### Differential Diagnosis

The Guillain–Barré syndrome, Miller–Fisher syndrome, and poliomyelitis resemble botulism clinically. Myasthenia gravis spares the pupils and is more gradual in onset. Tick paralysis, diphtheria, organophosphate toxicity, shellfish toxicity, ischemic locked-in syndrome, and hypokalemic periodic paralysis are other diagnostic considerations.

## Systemic Associations

Symptoms of food-borne botulism begin 12 hours to 8 days after ingestion of the toxin. Typically, the patient is conscious and afebrile. The characteristic systemic symptoms include hyposalivation and respiratory failure, urinary retention, constipation, and vomiting. Limb weakness may resemble that of Guillain–Barré syndrome, with ascending or descending paralysis. The reflexes are often normal or hypoaactive. Prominent bulbar symptoms and cranial nerve palsies may develop. At worst, the patient is “locked in,” unable to move or respond, but fully awake.

In wound botulism, symptoms begin 4–18 days after injury and are identical to those of food-borne botulism.

Infant botulism causes constipation and weakness, with descending paralysis.<sup>32</sup> The infant has a poor suck, a weak cry, and becomes hypotonic. Impairment of extraocular movement, facial weakness, and cranial nerve palsies are common. Dilated pupils, respiratory arrest, and death may follow. The course often is insidious and mistaken for failure to thrive.

### Treatment

The most important aspect of treatment is supportive, with mechanical ventilation, when necessary. If the patient is not allergic to horse serum (pretesting for hypersensitivity is required), heptavalent botulinum antitoxin is administered in a single treatment.<sup>29</sup> Human-derived botulinum immunoglobulin (“BabyBIG-IV”) is effective for treating infant intestinal botulism. Recovery occurs spontaneously as new synapses develop; this may take 6–12 months.

## LAMBERT–EATON MYASTHENIC SYNDROME

### Introduction

First described in 1953 as a triad of muscle weakness, autonomic dysfunction, and hyporeflexia, the Lambert–Eaton myasthenic syndrome (LEMS) shares clinical features with myasthenia gravis. Unlike myasthenia gravis, LEMS is a presynaptic disorder of neuromuscular transmission affecting voltage-gated calcium channels (VGCC).<sup>33,34</sup> This rare disorder is associated with a malignancy, such as small cell lung carcinoma (SCLC) in at least 50% of cases.<sup>33</sup> Symptoms of LEMS typically precede the diagnosis of the neoplasm.

### Epidemiology and Pathogenesis

Median onset of the paraneoplastic form is around age 60 years.<sup>34</sup> Smoking is a risk factor because of the high association with bronchogenic carcinoma. About 3% of patients who have SCLC have LEMS.<sup>33</sup> The non-neoplastic form is associated with pernicious anemia, thyroid disease, Sjögren’s syndrome, and other autoimmune disorders.<sup>35</sup> Myasthenia gravis and LEMS may occur concurrently.

Symptoms are caused by impaired release of ACh from the nerve terminal. End-plate potentials are too small to generate an action potential. Striated muscle, glands, and smooth muscle are affected. Calcium and guanidine increase neurotransmitter release, which results in improved strength.

### Ocular Manifestations

In contrast to myasthenia gravis, ocular manifestations are not prominent. Decreased lacrimation leads to keratoconjunctivitis sicca, which is the predominant ocular complaint. Ptosis and intermittent diplopia may occur. Sluggishly reactive pupils and tonic pupils are infrequent.<sup>36</sup> Slowed saccadic velocities that normalize after exercise have been described. There is one report of a patient with ophthalmoparesis and pseudo-blepharospasm.<sup>37</sup>

### Diagnosis

Rapid onset and progression of symptoms over weeks to months are common in the paraneoplastic form. The nonneoplastic variety has an insidious onset with mild, stable symptoms. Patients generally have proximal muscle weakness and leg pain. Autonomic involvement is present in 80%–96% of cases, which results in dry mouth, constipation, hypohidrosis, impotence, orthostatic hypotension, and urinary retention.<sup>38,39</sup> Unlike myasthenia gravis, muscle strength improves following voluntary contraction or repetitive testing. Paradoxical lid elevation may occur after

prolonged upgaze.<sup>40</sup> The deep tendon reflexes are hypoactive or absent at rest and increase with voluntary muscle contraction.

Electrophysiological studies confirm the diagnosis. Low rates of nerve stimulation (2–3 Hz) produce a decremental response, but high rates (20–50 Hz) cause a two- to 10-fold incremental increase in the compound action potential. SFEMG shows changes similar to those found in myasthenia gravis. The Tensilon test result is negative, and anti-ACh receptor antibodies are not present. VGCC antibodies are found in 85%–90% of patients with LEMS and in 100% of patients with SCLC and LEMS.<sup>39,41,42</sup> Sry-like high-mobility group box antibodies occur frequently in SCLC–LEMS.<sup>33</sup>

## Differential Diagnosis

Disorders that produce proximal muscle weakness may resemble myasthenic syndrome. Myasthenia gravis usually can be excluded clinically, with its prominent ocular and facial involvement. Guillain–Barré syndrome, polymyositis, lumbosacral plexopathies, and polyradiculopathies can be excluded by electrophysiological testing and neuroimaging.

## Systemic Associations

More than 80% of the associated malignancies are SCLCs. Other tumors associated with LEMS include small cell carcinoma of the cervix or the prostate, adenocarcinoma, and lymphoma. Myasthenic syndrome may precede the detection of the malignancy by up to 7 years and rarely follows detection of the tumor.<sup>35</sup> If no malignancy is found, repeated investigations are warranted. Other laboratory testing includes thyroid function tests, complete blood count, erythrocyte sedimentation rate, antinuclear antibodies, anti-Ro, and anti-La (SS-A, SS-B) to evaluate for the association of the nonneoplastic form with pernicious anemia, thyroid disease, Sjögren's syndrome, and other autoimmune disorders.

## Treatment

3,4-Diaminopyridine blocks potassium channels and enhances the release of ACh from the presynaptic nerve terminal. A definite and sustained response to aminopyridines occurs in most patients.<sup>33</sup> Treatment with

corticosteroids and azathioprine, mycophenolate, cyclosporine, rituximab, intravenous immunoglobulin, or plasmapheresis usually leads to improvement in strength if symptomatic treatment is ineffective.<sup>33</sup> It may take several months for immunosuppressants to be effective. Anticholinesterases may be useful. Magnesium may worsen the weakness. Other medications that decrease neuromuscular transmission should be used with caution. Treatment of the underlying carcinoma may produce improved strength.<sup>33</sup>

## Course and Outcome

The presence or absence of malignancy largely determines the prognosis. Those patients who have lung cancer should be screened regularly for recurrence within the first 4 years of diagnosis and advised to stop smoking. Most patients can lead a moderately active lifestyle with treatment but should avoid vigorous exercise.

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# Ocular Myopathies

Michelle Y. Wang, Richard M. Rubin, Alfredo A. Sadun

# 9.18

**Definition:** Ocular myopathies involve pathology of the extraocular muscles that results in ophthalmoplegia and other disorders of ocular motility.

## Key Features

- Limitations of motility.
- Inflammation.
- Exophthalmos.
- Pain.
- Diplopia.

## Associated Features

- Some are acquired and of known mechanism (thyroid orbitopathy).
- Some are acquired and consequent to other processes (certain forms of myositis).
- Some are congenital but may not manifest until late adulthood (mitochondrial).

## INTRODUCTION

Diseases that involve metabolic abnormalities, atrophy, infiltration, or inflammation of the ocular muscles may appear as weakness or restriction. Except for thyroid orbitopathy, most of these conditions are uncommon or rare. The three sections of this chapter independently cover mitochondrial myopathies, dystrophic myopathies, and inflammatory and infiltrative myopathies. Thyroid orbitopathy will be discussed in Chapter 12.13.

## MITOCHONDRIAL MYOPATHIES

### Epidemiology and Pathogenesis

Mitochondria are cytoplasmic organelles that produce energy for cell functions, maintenance, repair, and growth through the enzymatic processes of oxidative phosphorylation. A group of neurodegenerative and myopathic syndromes result from disorders of mitochondrial metabolism that cause defects in the energy cycle of susceptible tissues.<sup>1</sup> The tissues most reliant on mitochondrial energy are those of the central nervous system, heart, muscles, kidneys, and endocrine organs. Hence, these tissues are most likely to show various clinical manifestations of mitochondrial dysfunction.

Each mitochondrion possesses 2–10 mitochondrial DNA genomes made up of a closed circle of 16 569 nucleotide base pairs. The mitochondrial DNA encodes for 13 polypeptides essential in oxidative phosphorylation and the production of mitochondrial proteins. Nuclear DNA encodes for an additional 56 subunits of the electron transport chain and for genes required for replication, transcription, and translation of the mitochondrial genes.

Mitochondrial DNA has unique genetics for several reasons, including its cytoplasmic location and the multiple DNA copies that exist in each cell. Mitochondrial DNA is inherited maternally because it is transmitted via oocyte cytoplasm. In addition, new mutations often result in heteroplasmy, a mixed intracellular population of normal and mutant DNA molecules. Also, multiple random and asymmetrical mitochondrial divisions lead to replicative segregation and eventually homoplasmy, such that each cell possesses only pure mutant mitochondrial DNA. Thus, the relative proportion of normal and mutant mitochondrial DNA may vary from cell to cell and from individual to individual.

The variable phenotypic expressions of mitochondrial dysfunction likely arise from interplay of the unique features of mitochondrial inheritance that cause heteroplasmy and homoplasmy, the modifying contribution of nuclear DNA under the influence of Mendelian genetics, the deterioration of mitochondrial function with aging, and the different energy requirements of specific tissues.

The most common mitochondrial disorder to affect muscles is chronic progressive external ophthalmoplegia (CPEO) and its best known subtype, Kearns–Sayre syndrome.<sup>2</sup> Less common mitochondrial myopathies of ophthalmic importance include mitochondrial encephalopathy with lactic acidosis and stroke-like syndrome (MELAS), myoclonic epilepsy with ragged red fibers (MERRF), mitochondrial neurogastrointestinal encephalomyopathy (MNGIE), and the ataxia neuropathy syndromes (ANSs), including sensory ataxia neuropathy dysarthria ophthalmoplegia (SANDO).<sup>3–5</sup>

Mitochondrial disorders that affect tissues other than muscle during early childhood include Alpers' disease, Menkes' disease, and Leigh's syndrome/neurogenic muscle weakness, ataxia and retinitis pigmentosa (NARP). Leber's hereditary optic neuropathy (LHON), the most frequent mitochondrial disorder, manifests later in life.<sup>6</sup> It is the first maternally inherited disorder that has been associated with mitochondrial DNA point mutation. A more in-depth discussion is provided in Chapter 9.9.

## Ocular Manifestations

Patients who have CPEO often exhibit initial bilateral ptosis that is followed by limitation of ductions in all directions and marked delay of saccades. Downward gaze may be spared until late in the course. Curiously, despite ocular misalignment, these patients rarely complain of diplopia. Weakness of the orbicularis oculi and facial muscles is found commonly, and pigmentary retinopathy may be associated.

Kearns–Sayre syndrome, in particular, is characterized by the triad of external ophthalmoplegia, pigmentary retinopathy, and cardiac conduction block during the first or second decade of life (early-onset CPEO). Peripapillary pigment atrophy and salt-and-pepper retinal pigment epithelial changes are most striking in the macula. True bone spicule pigmentary retinopathy as seen in retinitis pigmentosa is not typical in Kearns–Sayre syndrome.<sup>7</sup>

MELAS syndrome manifests with ptosis and external ophthalmoplegia, in addition to the commonly associated visual disturbances, which may include hemianopia or cortical blindness. Eventually, MERRF develops into progressive optic atrophy. MNGIE is characterized by progressive ptosis, external ophthalmoplegia, and glaucomatous-like optic neuropathy.<sup>8</sup> Patients with ataxia neuropathy syndromes, including SANDO, display axonal sensory neuropathy affecting proprioception, variable degrees of cerebellar ataxia and progressive external ophthalmoplegia in about half of cases.<sup>5</sup>

## Diagnosis

The possibility of muscle disease should be considered whenever ophthalmoplegia does not correspond to the pattern of cranial nerve palsy and when there is acquired ptosis. Most diagnoses are made through a process of exclusion and imaging studies.

Diagnoses of mitochondrial disorders often are supported by histopathological and biochemical evidence of mitochondrial dysfunction. Specific identification of an enzyme defect may confirm the diagnosis. Generally, to show abnormalities in patients who have mitochondrial cytopathies, substrates of oxidative phosphorylation from serum and cerebrospinal fluid (CSF), which include glucose, lactate, and pyruvate, and the pH of venous blood during fasting are all measured. Elevation of CSF protein levels also may help in the diagnosis of CPEO and MELAS syndrome.

Electrocardiography should be performed in all patients suspected of mitochondrial cytopathies, to detect any life-threatening cardiac conduction abnormalities. Neuroimaging may help in the assessment for other causes of neurological deficits. In CPEO, magnetic resonance imaging (MRI) of the orbits demonstrates significant symmetrical extraocular muscle atrophy involving all four recti.<sup>9</sup> Migratory waxing and waning of stroke-like lesions with a predilection for the parietal, temporal, and occipital cortex are commonly found on neuroimaging in MELAS syndrome.<sup>10</sup>

Genetic analysis for mitochondrial DNA mutations from blood leukocytes or muscle biopsy may show a characteristic mutation in MELAS syndrome. Poor correlation exists between specific mitochondrial DNA mutations and CPEO because CPEO may exhibit a clinical picture related to a final common pathway of impaired mitochondrial energy production in muscle from a variety of mutations. Myasthenia and diseases of glycolipid metabolism, lysosomal or glycogen storage, peroxisome dysfunction, and acquired viral, toxic, and endocrine myopathies and encephalopathies also must be ruled out. Electromyography helps differentiate myopathic causes from neuropathic causes of muscle weakness.

## Systemic Associations

When ocular findings of CPEO occur in association with other neurological deficits, the term “CPEO plus” is used. Systemic findings of CPEO include short stature, peripheral neuropathy, ataxia, spasticity, somatic muscle weakness, vestibular dysfunction, and deafness.<sup>11</sup> Lactic acidosis resulting from defective aerobic metabolism is often found. Abnormalities of cardiac conduction and of the central nervous system, which include cerebellar dysfunction and elevated CSF protein exceeding 100 mg/dL, are associated with Kearns–Sayre syndrome.<sup>12</sup> Cardiac conduction disturbances have an onset typically 10 years after ptosis appears and may result in sudden death. Endocrine dysfunction may include hypoparathyroidism, diabetes mellitus, hypogonadism, or growth hormone deficiency. In CPEO and Kearns–Sayre syndrome, the brain eventually may undergo spongiform degeneration, with the clinical picture of dementia. Basal ganglia calcifications may occur.

Seizures, vomiting, lactic acidosis, episodes of hemiparesis, and stroke-like events during childhood or early adulthood characterize MELAS. Although partial recovery from these stroke-like episodes is the rule, severe neurological damage eventually results. Typically, MERRF occurs during the second decade of life with myoclonus, followed by ataxia, weakness, and seizures. Progressive ophthalmoplegia with peripheral neuropathy, leukoencephalopathy, and gastrointestinal dysmotility have been reported in MNGIE.<sup>13</sup>

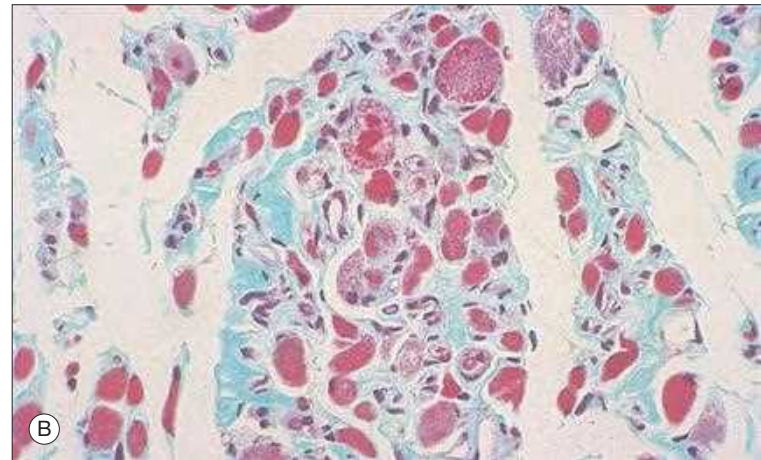
## Pathology

Biopsy of skeletal muscle reveals “ragged red fibers” that stain red or purple using a modified Gomori’s trichrome stain (Fig. 9.18.1). The mitochondria of the involved muscle fibers are concentrated peripherally and may show increased staining for the mitochondrial enzyme succinate dehydrogenase. Biochemical abnormalities of oxidative phosphorylation, such as patchy cytochrome-*c* oxidase deficiency, may be detected by muscle biopsies as well. Orbicularis oculi muscle can mimic mitochondrial cytopathy in normal persons age greater than 40 years and thus diagnosis would still need to be confirmed with skeletal muscle and/or genetic studies.<sup>14</sup>

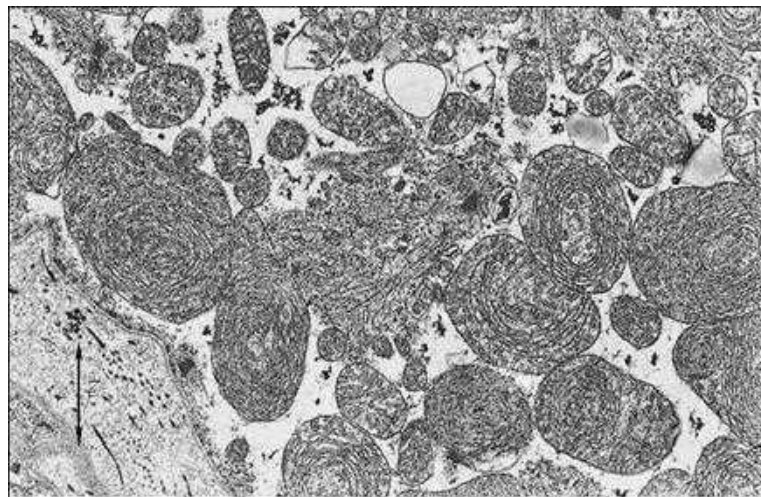
The ultrastructural appearances of skeletal muscle mitochondria are varied and may show enlarged mitochondria that contain crystal-like inclusions; changes in the number, shape, or regularity of cristae; or emptiness, vacuolization, or triglyceride accumulation within mitochondria (Fig. 9.18.2). The mitochondria often are increased in number and size. Such morphological changes may be found in other muscle disorders, such as the muscular dystrophies or polymyositis. Histopathologically, the retinal findings in Kearns–Sayre syndrome suggest retinal pigment epithelial dysfunction rather than photoreceptor disease.<sup>15</sup>

## Treatment

There is no effective treatment for mitochondrial disorders. However, some trials have shown promising trends. Coenzyme Q10 (CoQ10), essential for normal mitochondrial function and deficient in a proportion of patients who have CPEO and Kearns–Sayre syndrome, has been associated with improved exercise tolerance, cardiac function, and ataxia in some patients with Kearns–Sayre syndrome.<sup>16</sup> CoQ10, along with creatine and lipoic acid, have shown promising results in improving surrogate markers of cellular



**Fig. 9.18.1 MELAS Syndrome.** (A) Complete external ophthalmoplegia in a 20-year-old woman. (B) Microscopic section of degenerated extraocular muscles stained with trichrome shows “ragged red fibers.”



**Fig. 9.18.2** Viewed under an electron microscope, the abnormal mitochondria in a case of chronic progressive external ophthalmoplegia appear as electron-dense and globular. The normal arrangement of cristae is not seen.

energy dysfunction in patients with CPEO, Kearns–Sayre syndrome, and MELAS.<sup>17</sup> Other treatments, such as thiamine, also aim to bypass or enhance oxidative phosphorylation but only occasionally have been shown to improve exercise tolerance, cardiac conduction, or lactic acidosis. CoQ10 and these other treatments do not improve the ophthalmoplegia, retinopathy, or ptosis in patients who have CPEO or Kearns–Sayre syndrome. However, modified CoQ10 has led to second- and third-generation quinones, idebenone, and EPI-743, that have shown promising results in some LHON cases, providing new direction for possible therapy targeting mitochondrial disorders.<sup>18–20</sup>

Complaints that arise from ptosis often are handled by ptosis crutches or a careful surgical approach, in which the lid is raised minimally by addressing the visual obstruction, rather than the cosmetic appearance.





**Fig. 9.18.3** Slit-lamp view of a "Christmas tree cataract" in myotonic dystrophy. Note the iridescent or colored refractile flecks.

Overly aggressive attempts to treat the ptosis may result in exposure keratopathy and corneal ulceration because of weak orbicularis oculi muscles and a poor Bell's reflex. Symptomatic ocular deviations may be treated successfully with strabismus surgery.

Periodic evaluation by a cardiologist is indicated in Kearns–Sayre syndrome. In some instances, placement of a pacemaker for prophylactic pacing or for treatment of symptomatic cardiac block is necessary to prevent sudden death. The systemic use of corticosteroids is contraindicated in Kearns–Sayre syndrome because of the possible precipitation of coma and death from hyperglycemic acidosis.<sup>21</sup> Genetic counseling should be offered to all patients who have mitochondrial cytopathies.

## Course and Outcome

CPEO is a slowly progressive loss of lid and extraocular motor function. The diplopia may or may not worsen because the symmetry of the ophthalmoplegia may prevent strabismus. However, small ptosis correction may be required. In severe cases that have more generalized manifestations, such as in Kearns–Sayre syndrome, retinopathy and cardiac problems may develop. Patients who have MELAS, MERRF, or MNGIE may develop several systemic and neurological deficits.

## DYSTROPHIC MYOPATHIES

### Epidemiology and Pathogenesis

Three forms of muscular dystrophy of ophthalmological importance exist, all of which involve progressive weakness of the skeletal muscles. Myotonic dystrophy, like the other forms, involves difficulties with relaxation of skeletal muscles after contraction. Myotonic dystrophy is an autosomal dominant condition in which the first symptoms usually appear during the teenage years or in young adulthood. Several large pedigrees have been identified.

Oculopharyngeal dystrophy usually develops later in life. The first symptom often is difficulty in swallowing, with ptosis occurring later. A significant French Canadian autosomal dominant pedigree has been identified, in which the original ancestor immigrated to Quebec in 1634.<sup>22</sup> Autosomal recessive and sporadic inheritances also have been reported.

Fukuyama's congenital muscular dystrophy is an autosomal recessive condition most often found in people of Japanese descent. Unlike the other two forms above, in Fukuyama's congenital muscular dystrophy, manifestations and death occur in early childhood.

### Ocular Manifestations

In myotonic dystrophy, abnormalities in the extraocular muscles are accompanied by involvement of other muscles, including the levator muscle, and result in slowly progressive bilateral ptosis. Other ocular findings include cataracts, described as "Christmas tree cataracts" (Fig. 9.18.3) for their multiple refractile colors.

In oculopharyngeal dystrophy, dysphagia is followed soon by bilateral ptosis which, over a period of years, is followed by external ophthalmoplegia



**Fig. 9.18.4** Front View of a Patient Who Has Myotonic Dystrophy. The muscle wasting gives the characteristic drawn appearance of "hatchet facies."

and weakness of the orbicularis. The patient, despite a remarkable lack of ocular motility, may not complain of diplopia because often the limitations of eye movement are so symmetrical that no strabismus occurs.

In Fukuyama's congenital muscular dystrophy, in addition to the weakness of the orbicularis and a strabismus, nystagmus, anterior polar cataracts, optic nerve atrophy, and a chorioretinal degeneration with retinosischisis or detachment occur as well.<sup>23</sup>

## Diagnosis

Electromyography, which demonstrates characteristic spontaneous, high-frequency bursts, confirms diagnoses of all forms of dystrophic myotonias. Furthermore, all dystrophic myotonias are evident clinically by blepharospasm, or the inability of the patient to open the eyes after they have been forcibly closed for some time. Only myotonic dystrophy has intraocular findings, such as "Christmas tree cataracts." Both myotonic dystrophy and oculopharyngeal dystrophy have external ophthalmoplegia, but Fukuyama's congenital muscular dystrophy does not. In all three dystrophies, biopsy reveals characteristic histopathology.

## Systemic Associations

In myotonic dystrophy, involvement of the muscles of the head and neck gives the characteristic narrow, drawn facial appearance or "hatchet facies" (Fig. 9.18.4). Involvement of cardiac muscles may result in congestive heart failure. Dysphagia, constipation, and incontinence are not uncommon. In some cases, mental retardation occurs, and in men, testicular atrophy and premature baldness are frequent. In oculopharyngeal dystrophy, the bulbar musculature is affected frequently and temporalis wasting occurs. Patients have difficulty swallowing without aspirating. Other bulbar and limb girdle muscles become involved later. In Fukuyama's congenital muscular dystrophy, the proximal muscle groups are involved the most. Mental retardation, seizures, severe motor development delay, and cortical blindness are common.

## Pathology

Rows of nuclei run down the centers of the muscle fibers. In myotonic dystrophy, the myofilaments and sarcoplasmic reticulum are disrupted, and accumulations of impaired mitochondria may be found. In oculopharyngeal dystrophy, tubulofilamentous intranuclear inclusion bodies are seen on ultrastructural examination of muscle biopsies. In Fukuyama's syndrome, the same changes are confined largely to the proximal muscle groups.

## Treatment

For all three muscular dystrophies, treatment consists of symptomatic support. The cataracts of myotonic dystrophy may be removed. Foot braces



and other devices are available to provide support for those with foot drop or other skeletal muscle weakness. All patients affected by dystrophic myopathies need to be referred to neurologists.

## Course and Outcome

Progressive atrophy of the skeletal muscles leads to a variety of systemic difficulties. In myotonic dystrophy, the patient develops difficulty climbing stairs and, eventually, even with walking and holding the head up. Vision may be maintained after cataract surgery. In oculopharyngeal dystrophy, dysphagia is most problematic. Difficulty swallowing and many other serious medical problems limit the lifespan of patients with Fukuyama's congenital muscular dystrophy.

## INFLAMMATORY AND INFILTRATIVE MYOPATHIES

### Epidemiology and Pathogenesis

#### *Orbital Myositis*

The most common cause of primary muscle dysfunction is inflammation. Inflammation or secondary ischemia related to swelling (tissue compartment syndrome) may lead to fibrosis and scarring within an extraocular muscle. Orbital congestion may cause a restrictive component. Orbital pseudo-tumor, or idiopathic orbital inflammation, is usually characterized by extraocular muscles involvement in addition to other orbital structures, such as the lacrimal gland and orbital fat.

Idiopathic orbital myositis refers to nonspecific orbital inflammation. This orbital inflammation may extend anteriorly to involve the posterior globe (posterior scleritis) or lacrimal gland (dacryoadenitis), or posteriorly as orbital apex syndrome, superior orbital fissure syndrome, or cavernous sinus, as Tolosa–Hunt syndrome. When orbital pseudo-tumor involves primarily the muscles (myositis), it tends to occur unilaterally (although bilateral involvement may occur up to 25% of the time) in young adults, with women being affected more frequently than men.

A variety of granulomatous, infectious, neoplastic, and vasculitic disorders may masquerade as isolated myositis.

### Ocular Manifestations

Generally, orbital inflammatory diseases are associated with significant extraocular muscle involvement. The myositis may be isolated to a single muscle, but most often it affects several muscles. The pain often is most severe when ductions away from the most affected muscle are attempted. Patients also frequently experience gaze-evoked diplopia. Local orbital signs, such as exophthalmos and injection, are common. Children are more apt to have bilateral orbital involvement, may develop spontaneous orbital hemorrhage, and are less likely to have an associated systemic disease.

### Diagnosis

In orbital myositis, the involved extraocular muscle usually is enlarged on orbital imaging. Enhancement of the muscle, and particularly its tendon insertion into the globe, may help distinguish myositis from thyroid orbitopathy. A careful review of systems is critical to rule out granulomatous inflammatory diseases, thyroid orbitopathy, infection, and neoplasm. The diagnosis of orbital pseudo-tumor or idiopathic orbital myositis is one of exclusion and can be made only after the appropriate investigations have been carried out. In many cases, the clinical picture is sufficiently clear, and a trial of glucocorticoids may be initiated. An orbital biopsy is indicated, especially if the orbital inflammation is refractory to glucocorticoids or returns after the glucocorticoids have been tapered.

### Systemic Associations

Myositis may be associated with systemic inflammatory disease, such as Crohn's disease, systemic lupus erythematosus, rheumatoid arthritis, sarcoidosis, granulomatosis with polyangiitis, Churg–Strauss syndrome, ankylosing spondylitis, and giant cell arteritis.<sup>24</sup>

Infectious myositis may result from orbital cellulitis or trichinosis, but usually the cause is never determined.<sup>25</sup> Orbital cellulitis may be bacterial and originate from the paranasal sinuses, or fungal in association with metabolic acidosis or diabetes mellitus.

Other infiltrative processes such as amyloidosis and lymphoma may limit extraocular muscle relaxation.<sup>26</sup> Neoplasms may extend locally into or metastasize directly to a muscle.<sup>27</sup>

In recent years, immunoglobulin G4 (IgG4)–related systemic disease (IgG4-RD) has gained increasing attention as a multisystem immune-mediated inflammatory condition, which may affect multiple organs, such as the pancreas, salivary glands, and orbits.

### Pathology

In idiopathic orbital myositis, a polymorphous, chronic inflammatory infiltration is the most common finding. In chronic idiopathic pseudo-tumor, large amounts of fibrovascular stroma also may be seen. Pathological differentiation of orbital pseudo-tumor, benign lymphoid hyperplasia, monomorphous lymphoid lesions, and malignant lymphoma may be difficult. Immunological cell markers and gene rearrangement studies can help distinguish these entities. However, 15%–20% of patients who have polyclonal cell markers eventually may develop monoclonal malignant lymphoma.

Various specific causes of myositis have their own characteristic histopathological features. For example, in cases of foreign bodies, granulomatous inflammation with multinucleated giant cells is found. Polymorphonuclear leukocytes are seen in association with various infections. Eosinophilic infiltration is seen in trichinosis or other parasitic infections. An eosinophilic hyaline accumulation often occurs surrounding the blood vessels or in round globules within the extraocular muscles. In orbital myositis with plasma cell or lymphoproliferative infiltration, an associated amyloidosis may occur.

Some of the idiopathic orbital inflammatory cases were later found to be related to IgG4. The hallmarks of IgG4-RD are dense lymphoplasma-cytic infiltrations with predominance of IgG4-positive plasma cells, fibrosis, and obliterative phlebitis.<sup>28</sup> Increased numbers of eosinophils may be seen. An elevated IgG4+/IgG+ plasma cell ratio may be even more helpful than absolute tissue IgG4+ plasma cell counts, which differ depending on the affected organs.

### Treatment

Treatment should be directed to address the underlying cause. Infection and malignancy should be ruled out before initiating corticosteroid therapy. High-dose, daily glucocorticoids usually reverse the disease process effectively and eliminate the pain. Inadequate treatment may result in recurrence, but once the desired effect occurs, the glucocorticoids must be tapered slowly over several weeks or months and discontinued. Nonsteroidal anti-inflammatory drugs are less effective than glucocorticoids but have fewer side effects. Immunosuppressive agents may be used in refractory cases. Rarely, in those patients who do not respond or who become glucocorticoid dependent, low-dose radiation therapy (2000 cGy) may induce remission effectively, but this may lead to secondary neoplasms decades later. However, many inflammatory and infiltrative myopathies initially respond to such treatment, only to recur. Furthermore, treatment may not only obfuscate the natural history of the disease but may make the diagnosis by biopsy more difficult. Hence, it often is prudent to complete the diagnostic workup, which includes orbital biopsy for atypical cases, prior to anti-inflammatory treatment.

### Course and Outcome

Idiopathic orbital myositis usually responds very well to systemic glucocorticoids. In most cases, the diagnostic workup does not yield any causative factor and recurrences are not very common. Such patients do well and show no evidence of any ophthalmological sequelae.

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# Nystagmus, Saccadic Intrusions, and Oscillations

Peter A. Quiros, Melinda Y. Chang

# 9.19



**Definition:** Typically involuntary and rhythmic fixation instabilities; nystagmus arises from an inability to maintain fixation due to slow drift, while saccadic intrusions and oscillations result from instability of spontaneous rapid eye movement.

## Key Features

- Inability to maintain or achieve proper fixation.
- Decreased visual acuity.
- Oscillopsia.

## Associated Features

- Central nervous system abnormalities.
- Strabismus.
- Albinism.

## INTRODUCTION

Nystagmus, saccadic intrusions, and saccadic oscillations are fixation instabilities that usually are involuntary and rhythmic. They may impair vision, and many are signs of neurological disease. By recognizing the specific type of nystagmus or instability, the ophthalmologist can localize central nervous system (CNS) as well as peripheral lesions, determine which follow-up tests are appropriate (e.g., magnetic resonance imaging [MRI]), and often initiate treatment.

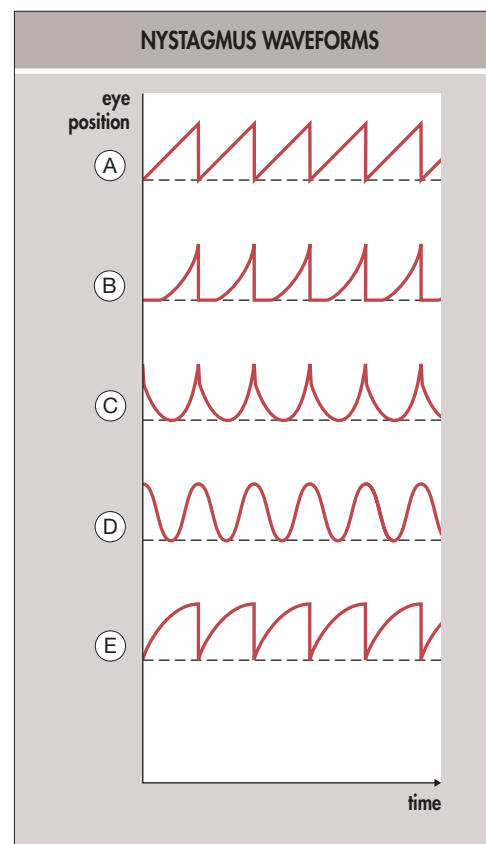
## EPIDEMIOLOGY AND PATHOGENESIS

Abnormalities of the vestibulo-ocular, otolithic-ocular, smooth pursuit, optokinetic, vergence, and eccentric gaze-holding systems are implicated in most forms of nystagmus.<sup>1</sup>

## OCULAR MANIFESTATIONS

Nystagmus is caused by an abnormality in a slow eye movement system or in the system that holds fixation. Abnormal slow eye movements cause a drift away from the intended fixation target or direction of gaze. A more rapid eye movement in the opposite direction is then initiated to carry the eyes back to the intended position. Nystagmus waveforms can be jerk or pendular (Fig. 9.19.1). If the corrective movements are faster than the drift, the waveform is termed *jerk*. The slow movements are the slow phase, and the refixation saccades are fast phases. The direction of jerk nystagmus is designated by the direction of the fast components; for example, fast components to the right indicate “right-beating” jerk nystagmus. When the corrective movements also are slow eye movements, the waveform is pendular. These represent the two main types of nystagmus. Nystagmus, by definition, must have a slow phase, thus being differentiated from saccadic intrusions.

Saccadic intrusions are caused by abnormalities in the saccadic eye movement system. Abnormal saccades move the eyes away from the intended direction of gaze, and corrective saccades carry the eyes back. In saccadic intrusions, such as square-wave jerks and macrosquare-wave jerks, brief pauses, or intersaccadic intervals, occur between the opposing



**Fig. 9.19.1 Nystagmus Waveforms.** The horizontal dashed lines indicate the intended position of gaze. (A) Jerk nystagmus with slow components of constant velocity. (B) Jerk nystagmus with slow components of exponentially increasing velocity. The flat, slow component portions near the intended gaze position follow the fast components and represent extended foveation periods typical of congenital nystagmus. (C) Jerk nystagmus with slow components of exponentially increasing velocity. Extended foveation periods follow slow movements that bring the eye toward the intended gaze position. (D) Pendular nystagmus. Note that foveation periods are brief compared with those in B and C. (E) Jerk nystagmus with slow components of exponentially decreasing velocity.

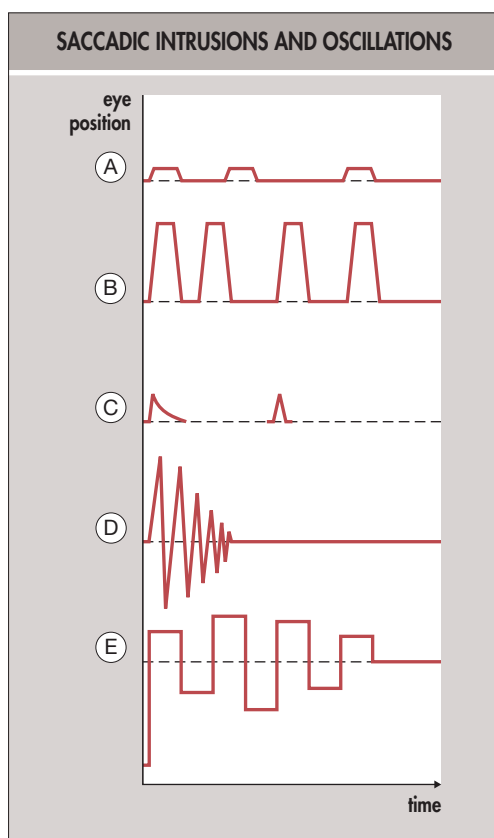
saccades (Fig. 9.19.2). In ocular flutter and opsoclonus, no intersaccadic intervals occur. These are not true nystagmus because these conditions have no slow phase.

Normal visual acuity requires a stationary retinal image on the fovea. If fixation instabilities cause movement of the retinal image across the fovea at speeds of a few degrees per second or greater, visual acuity is diminished. Therefore, many types of nystagmus and saccadic oscillations without intersaccadic intervals cause decreased visual acuity. During volitional saccades, images move across the retina, but there is no sensation of movement of the visual surround. In contrast, most types of nystagmus and saccadic oscillations without intersaccadic intervals cause illusory, back-and-forth movements of the visual surround, called *oscillopsia*.

## DIAGNOSIS

Most types of nystagmus and saccadic instabilities can be detected and identified through careful attention to the characteristics of the oscillations, without the aid of eye movement recordings and other specialized equipment. While the patient fixates on a stationary target at distance and at near, the following questions should be addressed:

- Is the drift away from the target a slow eye movement (nystagmus) or a saccade (saccadic instabilities)?



**Fig. 9.19.2 Saccadic Intrusions and Oscillations.** Dashed lines indicate the intended gaze position. (A) Square-wave jerks with intersaccadic intervals. (B) Macrosquare-wave jerks with intersaccadic intervals. (C) Single saccadic pulse and double saccadic pulses. (D) Ocular flutter with no intersaccadic intervals. (E) Macrosaccadic oscillations following a refixation saccade.

- Do slow movements occur in one direction and fast movements in the opposite direction (jerk nystagmus), or are the opposing movements of equal speed (pendular nystagmus)?
- What is the direction of the instability (horizontal, vertical, oblique, or torsional)?
- What is the effect of blocking fixation? Does it increase the nystagmus intensity (vestibular nystagmus), or does it decrease the intensity (congenital nystagmus)?

Frenzel goggles to block fixation or electronic equipment to record eye movements in the dark are helpful but are usually not readily available. Viewing the fundus of one eye with a direct ophthalmoscope while the patient covers the other eye blocks fixation and magnifies motion of the observed fundus caused by abnormal eye movements. The fundus moves in the direction opposite to that of the eye. The direct ophthalmoscope is an excellent instrument that helps detect small-amplitude oscillations, such as voluntary “nystagmus” and superior oblique myokymia.

Further questions to address are as follows:

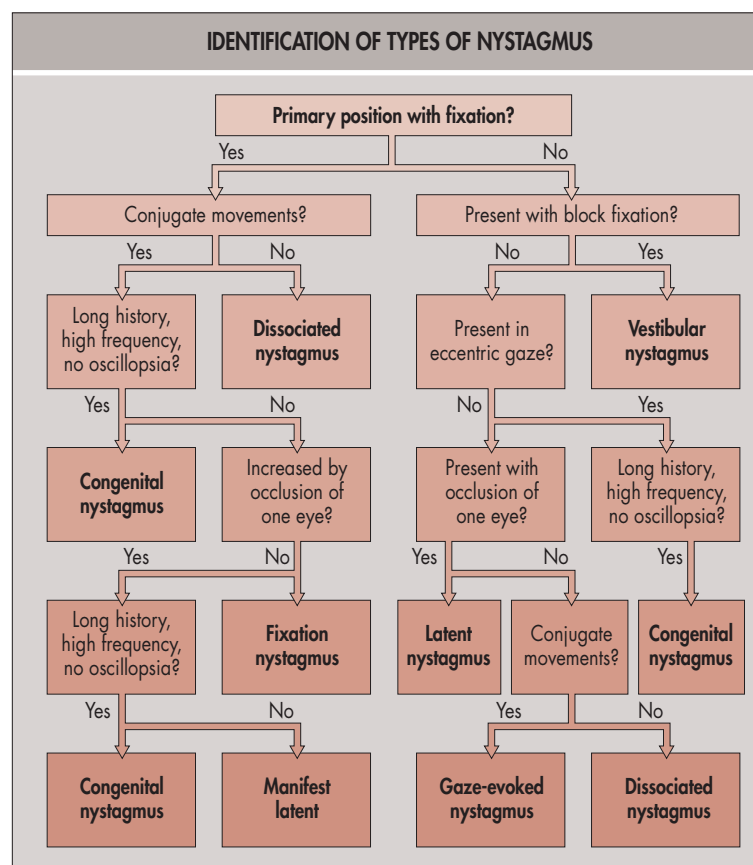
- What is the effect of different gaze positions? Acquired jerk nystagmus generally worsens in the direction of the fast phase.
- Does eccentric gaze change the intensity or the direction of the instability? Congenital nystagmus changes the direction of the fast phase with the position of gaze (i.e., right-beating in right gaze, left-beating in left gaze).
- Is the instability present only in eccentric gaze (gaze-evoked nystagmus)?
- Are the oscillations in both eyes symmetrical, or are they asymmetrical with different amplitudes or directions in each eye (disconjugate nystagmus)?
- If no instability occurs in the sitting upright position, is it present in other positions of the body and head (vestibular nystagmus of benign paroxysmal positional vertigo [BPPV])?

The answers to these questions and information from the patient's history and other physical findings will allow the ophthalmologist to identify the instability. Figs. 9.19.3–9.19.6 are flowcharts that can be used to identify the different types of nystagmus.

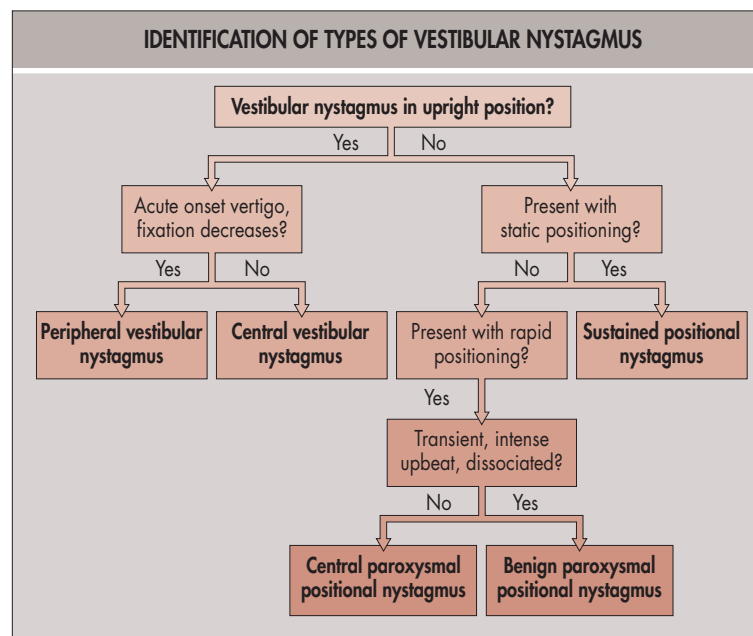
## DIFFERENTIAL DIAGNOSIS

### Congenital Nystagmus

Congenital nystagmus is the most common form of nystagmus, accounting for about 80% of all nystagmus cases. It is also one of several



**Fig. 9.19.3 Identification of Types of Nystagmus.**



**Fig. 9.19.4 Identification of Types of Vestibular Nystagmus.**

common types of nystagmus occurring in children (Table 9.19.1); it is a high-frequency, horizontal nystagmus that begins in the first few months of life (Video 9.19.1). Congenital nystagmus is not pathogenetically associated with other CNS disorders, although it is found frequently in patients who have certain systemic and ocular disorders that impair vision, such as oculocutaneous albinism and ocular albinism (Video 9.19.2). It can be an X-linked recessive, autosomal dominant, or autosomal recessive disorder. The most common genetic cause of X-linked congenital nystagmus is a mutation in the *FMRD7* gene.<sup>2</sup>

The nystagmus waveforms are pendular, jerk, or a combination of the two, and many are complex. Brief intervals often occur when the retinal image is relatively stationary on the fovea, called *extended foveation periods*, which allows better visual acuity. Unlike in vestibular nystagmus, fixation increases the nystagmus intensity, whereas staring and blocking fixation

See clip:  
9.19.1

See clip:  
9.19.2

## IDENTIFICATION OF TYPES OF GAZE-EVOKED NYSTAGMUS

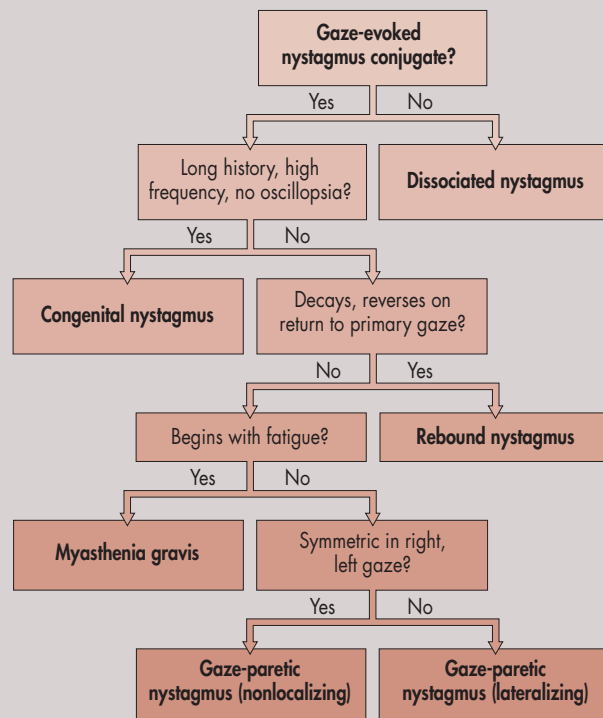


Fig. 9.19.5 Identification of Types of Gaze-Evoked Nystagmus.

## IDENTIFICATION OF TYPES OF DISSOCIATED NYSTAGMUS

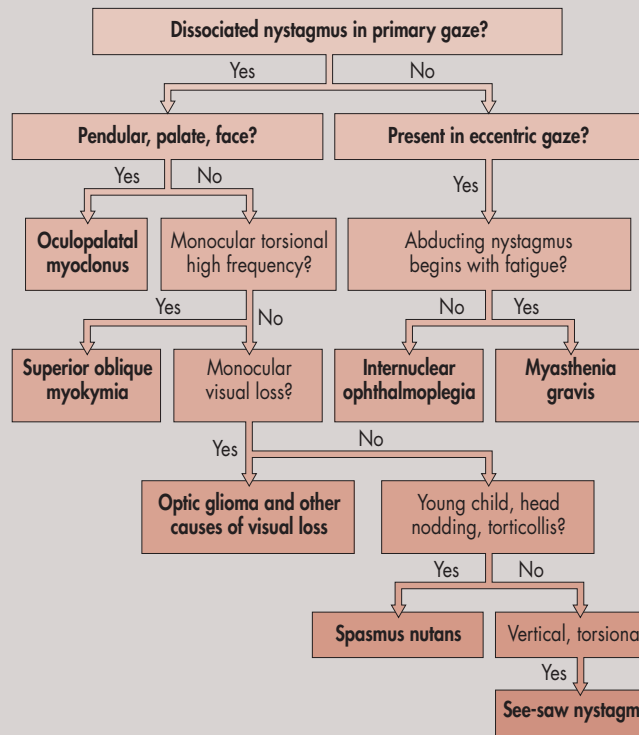


Fig. 9.19.6 Identification of Types of Dissociated Nystagmus.

decrease the nystagmus. In contrast to patients who have acquired types of nystagmus, patients who have congenital nystagmus rarely complain of oscillopsia.

Patients who have congenital nystagmus often exhibit a head turn, which places their eyes into the so-called null point, in which nystagmus intensity is minimized, foveation periods are long, and visual acuity is best. High-frequency, low-amplitude head nodding is seen commonly. The head nodding usually does not improve vision. Congenital nystagmus remains horizontal in vertical gaze and is usually decreased at near with

TABLE 9.19.1 Characteristics and Localizations of Nystagmus in Childhood

Nystagmus	Characteristics	Localization
Idiopathic congenital	Complex waveforms, jerk (increasing velocity slow components), pendular, horizontal, null zone, (face turn, head nodding, no oscillopsia)	Coexisting ocular, visual pathway lesions (not pathogenetic)
Latent/manifest latent	Jerk (decreasing velocity slow components), horizontal, fast components beat toward fixating eye	Coexisting infantile esotropia
Spasmus nutans	Pendular, horizontal, small vertical, torsional, dissociated, high-frequency, (torticollis, head nodding), onset in first year, resolution in 1–2 years	No signs of visual pathway lesions
Monocular visual loss	Pendular, vertical, horizontal, monocular, high-frequency, intermittent, (occasional head nodding)	Gliomas of optic nerve, chiasm or third ventricle, and other causes of visual loss

convergence. The dampening of nystagmus with convergence improves vision, which is one reason why many children who have congenital nystagmus do not need schoolbooks with large-size print. In one form of the nystagmus blockage syndrome, excessive convergence produces an esotropia, fixation of the distant target with the adducted eye, a decrease in nystagmus, and improved vision.<sup>3</sup> In another form, a switch occurs from a congenital nystagmus waveform to a manifest latent nystagmus (MLN) waveform (see the next section) when the adducted eye fixates. In such patients, vision is better with the latter type of nystagmus.

## Latent and Manifest Latent Nystagmus

Latent nystagmus is always associated with strabismus, usually infantile esotropia. In true latent nystagmus, no nystagmus is present with both eyes open (Video 9.19.3). When either eye is occluded, a horizontal jerk nystagmus occurs, the slow components of which are toward the occluded eye and the fast components of which beat toward the uncovered, fixating eye. The shift of fixation is the stimulus for the nystagmus. Electronic eye movement recordings have shown that true latent nystagmus is rare. In most instances, a low-intensity jerk nystagmus (MLN) exists that beats toward the fixating eye without occlusion. Nystagmus intensity increases with occlusion of the nonfixating eye, and the jerk nystagmus reverses direction when the eye that preferentially fixates is occluded. Gaze in the direction of the fast component increases nystagmus intensity, and gaze in the opposite direction decreases the intensity (Alexander's law). Patients who have MLN can have a habitual face turn toward the direction of the fast component, which places the eyes in the opposite direction and improves vision. Congenital nystagmus patients who have jerk nystagmus also can show reversal of the nystagmus direction when each eye is occluded, as a result of a shift in the position of the null point. Rarely, patients who have congenital nystagmus also have MLN.

## Spasmus Nutans

Spasmus nutans occurs in the first year of life and is a triad of pendular nystagmus, head nodding, and torticollis. The nystagmus often is dissociated (both eyes are not beating together), and in individual patients it can vary from conjugate to disconjugate to monocular over a few minutes. Its direction is primarily horizontal, but it can have vertical and torsional components (Video 9.19.4). In most patients, the syndrome seemingly resolves spontaneously over 1–2 years. However, electronic eye movement recordings show that a small-amplitude, intermittent, dissociated, pendular nystagmus can persist at least until age 5–12 years.<sup>4</sup> Characteristically, the nystagmus frequency is higher (3–11 Hz) and its amplitude more variable than in congenital nystagmus.

Head nodding is found in most patients who have spasmus nutans. It induces vestibulo-ocular responses that transform the nystagmus into larger-amplitude, slower, binocularly symmetrical, pendular oscillations with improved vision. Spasmus nutans must be differentiated from other disorders that cause head nodding and nystagmus, such as vision loss in children, intracranial tumors, and congenital nystagmus. Children with impairment of bilateral vision can have rapid, horizontal, pendular head oscillations; horizontal or vertical nystagmus; and intermittent head tilting during attempts to fixate.<sup>5</sup> The nystagmus can be pendular or jerk, with slow components of constant, increasing, or decreasing velocity.<sup>6</sup> The head shaking seems to be a voluntary, learned adaptation that can improve vision. The diagnostic signs from careful examination of eye and head

See clip:  
9.19.3

See clip:  
9.19.4



**TABLE 9.19.2 Characteristics and Localizations of Vestibular Nystagmus**

Nystagmus	Characteristics	Localization
Spontaneous peripheral vestibular	Jerk, horizontal, small torsional, inhibited by fixation	Labyrinth, eighth nerve (acute)
Central vestibular (fixation) nystagmus	Jerk, pendular, horizontal, vertical, torsional, not inhibited by fixation	Brainstem, cerebellum
Sustained positional vestibular	Jerk, horizontal, small torsional, direction fixed, direction changing (static positioning)	Labyrinth, eighth nerve or brainstem, cerebellum
Benign paroxysmal positional	Jerk, dissociated upbeat, latency, not inhibited by fixation, fatigue (Nylen–Barany maneuver)	Posterior vertical canal
Central paroxysmal positional	Jerk, symmetric, upbeat, downbeat	Brainstem, cerebellum

movements, including electronic recordings, can differentiate spasmus nutans from congenital nystagmus but do not reliably separate spasmus nutans from nystagmus and head nodding due to CNS lesions.<sup>7</sup> Visual loss, optic atrophy, abnormal growth and development, signs and symptoms of CNS disorders, or an older age of onset warrants MRI studies.<sup>8</sup> Some clinicians obtain neuroimaging for all patients who have spasmus nutans. Others do not, because the prevalence of CNS tumors in patients without other signs of CNS masses is low.<sup>9</sup>

## Vestibular Nystagmus

Vestibular nystagmus is the most common type of acquired nystagmus. The characteristics and localizations of several types of vestibular nystagmus are shown in [Table 9.19.2](#).

## Peripheral Vestibular Nystagmus

Peripheral vestibular nystagmus is caused by an acute imbalance of tonic innervation to the brainstem from the vestibular labyrinths and the eighth nerves. Destructive disorders, such as labyrinthitis and vestibular neuritis, decrease innervation from the affected ear and produce jerk nystagmus with slow components toward that ear and fast components beating toward the opposite side. Irritative disorders, such as Meniere's disease, increase innervation from the affected ear and generate jerk nystagmus with fast components toward that ear and slow components toward the opposite ear.

Because the vestibular nerve conveys tonic innervation from a horizontal semicircular canal, a pair of vertical canals, and otoliths (sacculi and utricle), the nystagmus is mainly horizontal but has vertical and torsional components as well (rotary nystagmus). The slow component has a constant velocity waveform. Gaze in the direction of the fast component increases the nystagmus intensity (amplitude  $\times$  frequency), and gaze in the direction of the slow component decreases the intensity (Alexander's law). Nausea and vertigo with the sensation of rotation of the environment or self-rotation in the direction of the fast component are usually present. Tinnitus, hearing loss, and ear pain also may be present. The nystagmus intensity is high during the first few days but decreases spontaneously. At this time, fixation might inhibit the nystagmus. However, blocking fixation reveals the nystagmus. Imbalance of tonic inputs from the otoliths can cause a transient skew deviation (hypotropic eye ipsilateral to the damaged ear).

## Central Vestibular Nystagmus

Lesions of the vestibular nuclei, the cerebellum, or the connections between the flocculonodular lobes and the brainstem can cause central vestibular nystagmus. In contrast to peripheral vestibular nystagmus, fixation does not greatly inhibit the nystagmus, which leads to the synonymous term *fixation nystagmus*. Central vestibular nystagmus can be purely horizontal, torsional, or vertical because horizontal and vertical vestibulo-ocular pathways begin to separate in the vestibular nuclei. Jerk nystagmus in primary gaze that is predominantly torsional is associated with lesions of the vestibular nuclei on the side contralateral to the fast component.<sup>10</sup>

## Positional Vestibular Nystagmus

Positional vestibular nystagmus is not present in the sitting upright position but is induced by the supine and lateral positions or by rapid

**TABLE 9.19.3 Characteristics and Localizations of Gaze-Evoked Nystagmus**

Nystagmus	Characteristics	Localization
Physiological, endpoint	Jerk, small-amplitude, intermittent, extremes of horizontal and up gaze	Physiological
Gaze-paretic (symmetric)	Jerk (decreasing velocity slow components) at 30° eccentric gaze	Nonlocalizing (drugs, mental fatigue)
Gaze-paretic (asymmetric)	Jerk (decreasing velocity slow components), horizontal, at 30° eccentric gaze, larger amplitude toward side of lesion	Lesions of brainstem, cerebellum, cerebral hemisphere
Rebound	Jerk, horizontal, decreases and direction can reverse in eccentric gaze, transient jerk nystagmus on return to primary gaze, fast components beating toward eccentric gaze	Cerebellum
Myasthenia gravis	Jerk, horizontal or vertical, gradual onset in prolonged eccentric gaze	Myoneural junction (fatigue—increasing transmission block)

movements of the head and body into head-hanging positions. Fixation suppresses the nystagmus when the cause is a peripheral vestibular lesion but does not suppress it when a central vestibular lesion is present. The nystagmus direction can remain the same in the right and left lateral positions (direction fixated), or it can change (direction changing). The fast components may beat toward the down ear (geotropic) or toward the up ear (apogeotropic). Both peripheral and central vestibular lesions can cause direction fixated and direction changing positional nystagmus.

## Benign Paroxysmal Positional Nystagmus

Rapid positioning of the head and body into the right or left head-hanging position (Nylen–Barany or Dix–Hallpike maneuver) induces benign paroxysmal positional nystagmus (BPPN). After a delay of 1–2 seconds, an intense vertical nystagmus develops. Fixation does not suppress the nystagmus, and the patient usually complains of vertigo after the maneuver. Characteristic binocular asymmetry exists in which the nystagmus primarily beats up in the higher eye (i.e., the eye opposite to the head-hanging position) and is oblique and torsional in the lower eye. The asymmetry is explained by the primary and secondary actions of the vertical extraocular muscles stimulated by the posterior semicircular canals (contralateral inferior rectus and ipsilateral superior oblique muscles). The nystagmus dies away over several seconds. Repetition of the maneuver soon after the initial positioning generates a less intense nystagmus (fatigue).

The cause of BPPN is otoconia that have become dislodged from the otoliths (utricle macula) and either are attached to the cupula of a posterior semicircular canal (cupulolithiasis) or freely move in that canal (canalolithiasis). Endolymph flow in the posterior canal produces an abnormally prolonged deflection of the hair cells in the crista of the canal. Positional exercises, such as Epley's maneuver, can move the granules back into the utricle and eliminate the positional nystagmus and vertigo.<sup>11</sup> Canalolithiasis and paroxysmal positional nystagmus of the horizontal and anterior posterior canals can occur spontaneously or can be produced by repositioning for the posterior canal form of BPPN.<sup>12</sup> The Nylen–Barany maneuver can induce paroxysmal positional nystagmus other than BPPN, such as downbeat nystagmus and other types of central vestibular nystagmus.<sup>13</sup> Therefore, the typical features of BPPN must be present for the diagnosis to be confirmed; it can result from viral labyrinthitis, head injury, and infarction of the inner ear. Most often it is an isolated disorder in older adults.

## Gaze-Evoked Nystagmus

Several types of gaze-evoked nystagmus are present in eccentric gaze but not in primary gaze ([Table 9.19.3](#)). In gaze-paretic nystagmus, no nystagmus occurs in primary gaze, but a jerk nystagmus occurs in about 30° of eccentric gaze. The slow components move the eyes toward primary gaze and have waveforms with exponentially decreasing velocities (see [Fig. 9.19.1](#)). Fast components beat toward the intended eccentric gaze position. The drift toward primary gaze results from impairment of gaze-holding mechanisms that involve the nucleus prepositus hypoglossi and medial vestibular nucleus (the “neural integrator”) and their connections with the flocculonodular lobe of the cerebellum. The eye position signal cannot hold the eyes eccentrically in the orbits, so they drift back toward primary gaze.

Normal, physiological, endpoint nystagmus is present in the extremes of horizontal and upward gazes of about 45°–50°. Therefore, nystagmus at

only 30° is likely to be a pathological finding. Endpoint nystagmus is irregular and might be slightly dissociated (larger amplitude in the abducting eye), which mimics the dissociated nystagmus associated with internuclear ophthalmoplegia. However, the other eye movement abnormalities associated with internuclear ophthalmoplegia are absent. Generally, physiological endgaze nystagmus dampens within 6 seconds.

Symmetrical gaze-paretic nystagmus, in which the nystagmus intensity is the same in right gaze and left gaze, usually is not a localizing sign. It is produced by mental fatigue; CNS depression caused by barbiturates, tranquilizers, anticonvulsants, alcohol, and other drugs; and disorders of the cerebral hemispheres, brainstem, and cerebellum. Asymmetrical, horizontal, gaze-paretic nystagmus often is lateralizing. A lesion of the brainstem or cerebellum is generally on the side of greater nystagmus intensity.

Myasthenia gravis can produce a horizontal or upbeat gaze-paretic nystagmus. Initially, little or no nystagmus exists, but as the extraocular muscles fatigue, nystagmus develops. In horizontal gaze, the amplitude of the fast component in the abducting eye is often larger than that in the adducting eye as a result of the greater fatigue of the medial rectus muscle. Normal subjects can have an endpoint nystagmus of very small amplitude that increases with fatigue.

## Rebound Nystagmus

Rebound nystagmus is a type of horizontal, gaze-paretic nystagmus in which the jerk nystagmus gradually decreases in amplitude as the eyes remain in eccentric gaze for many seconds. In some instances, the nystagmus direction actually reverses (centripetal nystagmus); for example, it becomes left beating in right gaze. On return to primary gaze, a jerk nystagmus occurs that beats in the direction opposite to that of the previous gaze-paretic nystagmus. The secondary nystagmus decreases and disappears after several seconds. Rebound nystagmus usually is associated with disorders of the cerebellum. Vertical rebound nystagmus occurs less often. Normal individuals can experience a few beats of rebound nystagmus after prolonged eccentric gaze if no fixation target is present on return to primary gaze (lights turned off).

## Alternating Nystagmus

The direction of jerk nystagmus changes spontaneously in alternating nystagmus (Table 9.19.4). In periodic alternating nystagmus (PAN), a repetitive cycling of right-beating and left-beating nystagmus occurs in primary gaze. The amplitude of nystagmus gradually increases and decreases over a period of about 90 seconds, followed by a short period of about 10 seconds in which there is no nystagmus, small-amplitude vertical or torsional nystagmus, or square-wave jerks (null period). Nystagmus that beats in the opposite direction then ensues, increasing and decreasing over 90 seconds, and is followed by a null period. The cycle continues and is not affected by other eye movements, except for strong rotational vestibular stimuli, which can reset the cycle. During periods of jerk nystagmus, patients have horizontal oscillopsia and blurred vision. They might spontaneously turn their heads in the direction of the fast component. This moves the eyes to a position of minimal nystagmus and better vision (null position). The null position moves gradually to the right, back to primary gaze, to the left, and back to primary gaze. This type of alternating nystagmus is almost always associated with cerebellar disorders. Ablation of the nodulus and uvula was shown to produce periodic alternating nystagmus in monkeys.<sup>60</sup>

Alternating nystagmus also occurs in congenital nystagmus, in MLN, and in association with severe binocular visual loss from many causes (e.g.,

chronic papilledema, vitreous hemorrhage, cataract). In congenital nystagmus and MLN, the change in nystagmus direction can be caused by a shift of fixation from one eye to the other. However, congenital nystagmus and periodic alternating nystagmus can coexist, for example, in patients with albinism.<sup>14</sup> The periods of alternating nystagmus are not as symmetrical or regular as those in periodic alternating nystagmus associated with cerebellar disorders, although shifting of the null positions also occurs.

## Upbeat Nystagmus

Upbeat nystagmus in primary gaze is caused by lesions that affect the brainstem, especially the lower pontine tegmentum (see Table 9.19.4).<sup>15</sup> Lesions of the medulla, midbrain, thalamus, and cerebellum also can cause upbeat nystagmus. Common causes of these lesions are multiple sclerosis, infarction, intra-axial tumor, Wernicke's encephalopathy, brainstem encephalitis, and cerebellar degeneration. Rarely, upbeat nystagmus can be a form of congenital nystagmus and might be seen as a transient finding in normal infants. Upbeat nystagmus that is present only in upgaze and is associated with symmetrical, horizontal, gaze-paretic nystagmus is usually a type of gaze-paretic nystagmus that might not have a localizing significance. Patients with upbeat nystagmus may have slow components with constant velocity, decreasing velocity, or increasing velocity waveforms. Nicotine can produce a small-amplitude upbeat nystagmus in the dark in normal subjects.

## Downbeat Nystagmus

Downbeat nystagmus in primary gaze usually is caused by a structural lesion in the posterior fossa at the level of the craniocervical junction (see Table 9.19.4). The nystagmus intensity characteristically increases in horizontal eccentric gaze and may be increased by convergence. Convergence also can convert an upbeat nystagmus in primary gaze to a downbeat nystagmus. Lesions of the cerebellum and pons are associated most often with downbeat nystagmus, and the most common causes are infarction, cerebellar degeneration, multiple sclerosis, and congenital malformations.<sup>16</sup> Downbeat nystagmus may be part of an acquired syndrome in adulthood consisting of cerebellar ataxia, lower brainstem dysfunction, or cranial nerve palsies caused by Arnold–Chiari malformations (types 1 and 2). Although such malformations are not the most common cause of downbeat nystagmus, MRI of the posterior fossa should be performed because surgical decompression can diminish the nystagmus and the other abnormalities in the syndrome. Rarely, a variety of other disorders can cause downbeat nystagmus, including lithium toxicity, magnesium deficiency, vitamin B<sub>12</sub> deficiency, midbrain infarction, brainstem encephalitis, Wernicke's encephalopathy, increased intracranial pressure with hydrocephalus, syringobulbia, cerebellar tumor, and anticonvulsant medication. Downbeat nystagmus has been reported to occur as an inherited congenital disorder. The slow components can have constant velocity, increasing velocity, and decreasing velocity waveforms.

## Dissociated Nystagmus

In several types of dissociated nystagmus, eye movements are strikingly disconjugate (Table 9.19.5). Nystagmus might be present in only one eye (spasmus nutans, optic glioma, and uniocular visual loss), larger in one

**TABLE 9.19.4 Characteristics and Localizations of Other Types of Fixation Nystagmus**

Nystagmus	Characteristics	Localization
Periodic alternating	Jerk, horizontal, in primary position, regular phases of right-beating, null, left-beating (shifting null position)	Cerebellar nodulus and uvula
Alternating (irregular)	Jerk, horizontal, in primary position, variable, asymmetric phases	Congenital nystagmus, severe, binocular visual loss
Upbeat	Jerk, fast components beat upward	Only in upgaze—part of symmetric gaze—paretic nystagmus; in primary gaze—lower pons
Downbeat	Jerk, fast components beat downward, vertical intensity increases in horizontal gaze	Cerebellum, lower brainstem

**TABLE 9.19.5 Characteristics and Localizations of Dissociated Nystagmus**

Nystagmus	Characteristics	Localization
Acquired pendular in adults	Pendular, horizontal, vertical, torsional, disconjugate (coexisting palatal myoclonus)	Brainstem, cerebellum
Superior oblique myokymia	Pendular, jerk, torsional, vertical, high-frequency, small-amplitude, monocular	Trochlear nucleus
See-saw	Pendular, vertical, torsional, rising eye intorts, falling eye extorts; rarely jerk	Midbrain (interstitial nucleus of Cajal)
Abducting “nystagmus” of internuclear ophthalmoplegia	Jerk, horizontal, decreasing velocity slow components, larger in abducting eye in horizontal gaze	Medial longitudinal fasciculus in pons, midbrain
Abducting nystagmus of myasthenia gravis	Gaze-paretic nystagmus in horizontal gaze, greater paresis of medial rectus muscle	Myoneural junction—myasthenia gravis

eye than in the other (abduction nystagmus in internuclear ophthalmoplegia), or present in different directions (see-saw nystagmus). Dissociated nystagmus present in the primary position is often pendular and is often jerk nystagmus in eccentric gaze.

### Acquired Pendular Nystagmus in Adults

Acquired pendular nystagmus usually has horizontal, vertical, and torsional components and is often disconjugate. Lesions of the pons, medulla, midbrain, and cerebellum, often caused by multiple sclerosis or infarction, produce oscillations with a typical frequency of 3–4 Hz. MRI studies show large or multiple lesions, which suggests that more than one pathway must be damaged to produce pendular nystagmus.<sup>17</sup> Head tremor may be present. The nystagmus trajectory also can be elliptical or circular. When acquired pendular nystagmus is associated with similar movements of the soft palate, tongue, facial muscles, pharynx, and larynx, it is called *ocular-palatal myoclonus*. The cause usually is an infarction that affects the structures of Mollaret's triangle and their connections (red nucleus in the midbrain, inferior olive in the medulla, and contralateral dentate nucleus of the cerebellum). Hypertrophy of the inferior olive and the pendular oscillations begin several months later. Extensive hemorrhage in the pons can produce a large-amplitude, vertical, pendular nystagmus and bilateral horizontal gaze palsies.

### Monocular Visual Loss and Bilateral Visual Loss

Children who have monocular visual loss from causes other than optic nerve glioma may have monocular, high-frequency, small-amplitude, pendular nystagmus.<sup>18</sup> They do not have intracranial tumors, spasmus nutans, or signs of damage to the optic nerve or optic chiasm. The nystagmus can disappear after successful treatment for the monocular visual loss. Adults who have acquired, severe monocular visual loss (e.g., dense cataract) may have very low-frequency, irregular, vertical drift and jerk nystagmus (Heimann-Bielschowsky phenomenon), which can also be abolished with recovery of vision. Bilateral blindness results from a number of causes and can produce large-amplitude oscillations with small-amplitude ones superimposed. Both oscillations are horizontal and vertical and can have jerk and pendular waveforms. The direction of the jerk nystagmus varies over time (shifting null position). Vestibulo-ocular responses are impaired; volitional saccades and the fast components of vestibular nystagmus may be absent. Head nodding is usually present. Children who have congenital stationary night blindness and rod monochromatism may have small-amplitude, high-frequency, disconjugate, pendular nystagmus, similar to that seen in spasmus nutans.

### See-Saw Nystagmus

See-saw nystagmus is a disconjugate, vertical, pendular nystagmus. In one half of a cycle, the rising eye also intorts and the falling eye extorts. The movements are reversed in the other half cycle. See-saw nystagmus is caused most often by large parasellar tumors that cause bitemporal hemianopsia (optic chiasm) and impinge on the third ventricle. Less often, head trauma and infarction of the upper brainstem are the causes. Congenital forms occur, including those in infants who have albinism. In the congenital forms, the rising eye extorts and the falling eye intorts. See-saw nystagmus may be caused by damage to otolithic pathways involving the interstitial nucleus of Cajal, which participate in the ocular tilt reaction. Stereotactic ablation of the interstitial nucleus of Cajal, clonazepam, and baclofen abolish the nystagmus. Rarely, see-saw nystagmus has a jerk waveform, in which case it arises from a unilateral midbrain lesion. The lesion hypothetically damages the interstitial nucleus of Cajal (torsional eye velocity generator) and spares the adjacent rostral interstitial nucleus of the medial longitudinal fasciculus (MLF; torsional fast component generator).<sup>19</sup>

### Abducting Nystagmus in Internuclear Ophthalmoplegia

In internuclear ophthalmoplegia, horizontal gaze in the direction opposite to the lesion in the MLF in the midbrain or pons induces a jerk nystagmus in the abducting eye and a smaller (or no) nystagmus in the paretic, adducting eye (Video 9.19.5). This abducting nystagmus is the most common type of dissociated nystagmus. It might be simply a gaze-paretic nystagmus with superimposed paresis of the medial rectus muscle ipsilateral to the MLF lesion. However, in many patients, the speed of the exponentially velocity-decreasing waveform of the centripetal slow component is much higher than that found in gaze-paretic nystagmus. The abducting saccade has a characteristic overshooting waveform with a rapid, postsaccadic drift. The hypermetria may be a consequence of an adaptive increase in innervation in response to the weakness of adduction. The saccadic pulse is

increased, but the step is not increased proportionately (pulse-step mismatch) or is absent, which results in a rapid centripetal drift. Therefore, the abducting nystagmus may be caused by a train of hypermetric saccades.<sup>20</sup> Physiological endpoint nystagmus also can be dissociated slightly (larger amplitude in the abducting eye), but the other ocular motor abnormalities that are characteristic of internuclear ophthalmoplegia are absent. These abnormalities consist of limitation of adduction, slow adducting saccades, hypermetric abducting saccades, upbeat nystagmus, and skew deviation.

### Ocular Bobbing

Stupor and coma are associated with several ocular abnormalities, including ocular bobbing. Intermittent, irregular, conjugate, downward saccades are followed by slower, upward drift movements. Patients who have ocular bobbing have extensive damage to the pons from hemorrhage or compression or have toxic or metabolic encephalopathies. Several variants of ocular bobbing exist. In inverse bobbing, or ocular dipping, downward, slow movements are followed by upward saccades and then back toward the primary position. In converse bobbing, or reverse ocular dipping, large-amplitude, upward saccades are followed by downward drifts.

### Saccadic Intrusions

Reflex saccades to objects that enter the visual field are mediated through pathways from the visual association areas of the parietal lobes and temporal lobes and from ocular motor fields in the frontal lobes. They project to the superior colliculi and the saccade-related areas of the brainstem. Normally, reflex saccades to these sites can be inhibited voluntarily. Pathways from the frontal lobes to the basal ganglia (pars reticularis of the substantia nigra) and superior colliculus may be important for the inhibition of reflex saccades. Patients who suffer frontal lobe diseases, including Alzheimer's disease, Huntington's disease, progressive supranuclear palsy, and schizophrenia, have inappropriate saccades that interrupt fixation. These saccadic intrusions have been called the "visual grasp reflex" (see Fig. 9.19.2; Table 9.19.6). Saccadic intrusions do not represent true nystagmus as these disorders do not exhibit a slow phase.

### Superior Oblique Myokymia

Superior oblique myokymia is a very high-frequency, torsional, and oblique oscillation of one eye that causes monocular oscillopsia and, occasionally, vertical diplopia. Careful observation of the conjunctival blood vessels at the slit lamp or of the fundus with an ophthalmoscope reveals the extremely high-frequency, low-amplitude, pendular oscillations, as well as the occasional jerky nystagmoid movements as well as tonic intorsion and infraduction that produce diplopia. Electromyography of the superior oblique muscle has shown abnormal discharges at a frequency of 35 Hz. Superior oblique myokymia usually occurs in otherwise healthy adults, can remit spontaneously, and may recur. Rarely, it is associated with brainstem disorders, such as multiple sclerosis or a pontine tumor.

**TABLE 9.19.6 Characteristics and Localizations of Saccadic Intrusions and Oscillations**

Type	Characteristics	Localization
Square-wave jerks	Horizontal, 1–5°, 200 ms intersaccadic intervals	Not localizing
Macrosquare-wave jerks	Horizontal, 10–40°, 100 ms intersaccadic intervals	Cerebellum
Macrosaccadic oscillations	Horizontal saccadic dysmetria, series of hypermetric saccades, 200 ms intersaccadic intervals	Cerebellum
Voluntary "nystagmus"	Horizontal, high-frequency, low-amplitude, intermittent, no intersaccadic intervals	Volitional
Saccadic pulses	Horizontal, single or double saccades with no steps	Cerebellum, lower brainstem
Ocular flutter	Horizontal, large-amplitude, linear and curvilinear trajectories, no intersaccadic intervals	Cerebellum, lower brainstem
Opsoclonus	Multidirectional, large-amplitude, linear and curvilinear trajectories, no intersaccadic intervals	Cerebellum, lower brainstem
ms, millisecond.		



See clip:  
9.19.5



## Convergence–Retraction Nystagmus and Convergence Nystagmus

Voluntary or reflex upward saccades in Parinaud's syndrome (dorsal mid-brain syndrome) are hypometric and show simultaneous adduction and retraction of both eyes. Simultaneous contraction of antagonist muscles causes the retraction. Optokinetic stimuli that move downward elicit upward, reflex saccades and the pattern of convergence–retraction nystagmus (Video 9.19.6). Convergence nystagmus has been shown to be caused by an Arnold–Chiari malformation type 1, which resolved with surgical decompression of the foramen magnum.<sup>21</sup> It can also be caused by Whipple's disease, which produces contractions of the masticatory muscles (ocular masticatory myorhythmia) and a vertical gaze palsy.<sup>22</sup> Antibiotics can resolve the oculofacial–skeletal myorhythmia.



See clip:  
9.19.6

### Square-Wave Jerks

Normal subjects have infrequent, small-amplitude ( $<1^\circ$  to a few degrees), horizontal saccades that move the eyes away from the fixation target and then back to the target, called *square-wave jerks* (see Fig. 9.19.2). Pause occurs between the to-and-fro saccades (intersaccadic interval) of about 200 milliseconds, and this allows sufficient foveation time for normal visual acuity with no oscillopsia. The frequency of square-wave jerks increases in the dark. Larger ( $1^\circ$ – $5^\circ$ ) and more frequent ( $>2$  Hz) square-wave jerks are abnormal and are associated with cerebellar disorders, progressive supranuclear palsy, Parkinson's disease, Huntington's disease, and schizophrenia. They occur sporadically or in bursts.

### Macrosquare-Wave Jerks

Macrosquare-wave jerks are horizontal and large ( $10^\circ$ – $40^\circ$ ) and have intersaccadic intervals of about 100 milliseconds. They are found in cerebellar disorders (e.g., multiple sclerosis and olivopontocerebellar atrophy) and occur sporadically or in bursts.

### Macrosaccadic Oscillations

Macrosaccadic oscillations are a type of saccadic dysmetria. A hypermetric saccade overshoots the target and is followed by a series of hypermetric, corrective saccades that straddle the target and gradually decrease in size until the target is fixated. The intersaccadic intervals are 200 milliseconds long. Macrosaccadic oscillations are associated with cerebellar disorders.

### Voluntary “Nystagmus”

Normal subjects can voluntarily produce bursts of high-frequency (10–20 Hz), small-amplitude (a few degrees), horizontal, saccadic oscillations, called voluntary “nystagmus.” This is not a true nystagmus because it consists of to-and-fro, back-to-back saccades. Because no intersaccadic intervals occur, visual acuity is poor, and oscillopsia is present during the oscillations. Voluntary “nystagmus” cannot be sustained for more than several seconds; subjects show signs of intense effort, such as squinting, facial muscle contractions, and convergence.

### Saccadic Pulses

Saccadic pulses are saccadic intrusions in which saccades move the eyes away from the fixation target, followed by a rapid drift back to the target (glissade). They represent saccadic pulses without steps; they can occur singly, in a series, or in a train (saccadic pulse train) that mimics nystagmus (abducting nystagmus of internuclear ophthalmoplegia). Saccadic pulses occur in normal subjects, patients who have myoclonus, and patients who have multiple sclerosis. Double saccadic pulses are pairs of saccadic pulses that move in opposing directions and occur back-to-back with no intersaccadic intervals. They are part of a continuum of other saccadic oscillations with no intersaccadic intervals (ocular flutter and opsoclonus).

### Ocular Flutter

Ocular flutter consists of bursts of moderately large-amplitude, horizontal, back-to-back saccades without intersaccadic intervals. Blurred vision and oscillopsia usually are present. Ocular flutter can occur in the primary position and after a refixation saccade (flutter dysmetria); it is associated with the same disorders of the brainstem and cerebellum that produce opsoclonus (see next section). Eyelid blinks induce bursts of large-amplitude flutter in neurodegenerative disorders and a few beats of low-amplitude flutter in normal subjects.

### Opsoclonus

In opsoclonus, a series of large-amplitude, back-to-back, multidirectional saccades interrupt fixation. The directions of the to-and-fro saccades can

be horizontal, vertical, or oblique; their trajectories can be linear or curvilinear, and the frequency is high (10–15 Hz). The chaotic appearance of the oscillations has led to the use of the term “saccadomania.” In its severe form, opsoclonus is nearly continuous and persists even in some stages of sleep. With improvement, or in its milder form, the oscillations are intermittent. During fixation, saccadic burst cells in the pontine paramedian reticular formation (horizontal saccades) and in the rostral interstitial nucleus of the MLF (vertical saccades) are inhibited by tonic activity in pause cells in the nucleus raphe interpositus in the midbrain. Pause cell activity is momentarily inhibited during saccades, and this allows the burst cells to fire and generate the saccadic pulse signal. An abnormal decrease in pause cell activity as a result of direct damage to these cells or abnormal input to them from other neurons might produce opsoclonus and ocular flutter.

Opsoclonus often is associated with cerebellar ataxia and limb myoclonus. The disorders that cause opsoclonus damage the brainstem or cerebellum; they include benign brainstem encephalitis in children and adults following viral illnesses, myoclonic encephalopathy of infants (dancing eyes and dancing feet), paraneoplastic brainstem and cerebellar syndromes in children (neuroblastoma) and adults (small cell lung carcinoma, breast carcinoma, ovarian tumors), and multiple sclerosis.<sup>23,24</sup> Opsoclonus and ocular flutter have been reported in association with drug toxicities, exposure to toxic chemicals, and hyperosmolar coma and as transient findings in normal neonates. Adrenocorticotrophic hormone can diminish the saccadic oscillations of infantile myoclonic encephalopathy and neuroblastoma, and corticosteroids can be effective in paraneoplastic syndromes in adults. Some normal subjects can produce saccadic oscillations volitionally, including many of the characteristics of opsoclonus and ocular flutter.<sup>25</sup>

## TREATMENT

### Drug Treatment

The goal of treating vestibular nystagmus is mainly to diminish the associated vertigo. The large number of medications that are used is an indication that no optimal drug therapy exists for most patients. The classes of drugs include anticholinergics (scopolamine [hyoscine]), antihistamines (meclizine), monoaminergics (ephedrine), benzodiazepines (diazepam), phenothiazines (prochlorperazine), and butyrophenones (droperidol). Unfortunately, drowsiness from many of these drugs limits their efficacy for chronic, recurrent vertigo. An exception is acetazolamide, which is very effective for the treatment of familial periodic ataxia with nystagmus.<sup>26</sup>

The goal in the treatment of nonvestibular forms of nystagmus and saccadic oscillations is to improve vision by alleviating the associated blurring and oscillopsia. As in vestibular nystagmus, many medications have been tried, but few have been found to be consistently effective.<sup>27</sup> Only a few double-blind studies have been carried out: anticholinergics for acquired pendular nystagmus,<sup>28</sup> muscarinic antagonists for acquired pendular and downbeat nystagmus,<sup>29</sup> and 4-aminopyridine for downbeat nystagmus.<sup>30</sup>

Baclofen is an analogue of gamma-aminobutyric acid (GABA) and was developed to treat skeletal muscle spasm. It consistently decreases the symptoms and signs of periodic alternating nystagmus.<sup>31</sup> To diminish drowsiness, the initial dosage is low, 5 mg by mouth three times a day, and is increased gradually. Patients perceive a return of symptoms after a few hours. Baclofen decreases the slow component velocity and oscillopsia in some patients who have upbeat and downbeat nystagmus.<sup>32</sup> Its therapeutic effect might result from augmentation of the physiological inhibitory effect of GABA on the vestibular nuclei in the vestibulocerebellum and on the velocity storage mechanism.

4-Aminopyridine is an inhibitor of voltage-gated potassium channels and improves conduction in demyelinated nerve fibers, leading to benefits in lower extremity strength and walking speed in patients with multiple sclerosis.<sup>33</sup> A randomized, double-blind trial demonstrated that 57% of patients with downbeat nystagmus (idiopathic or related to cerebellar degeneration) treated with 4-aminopyridine experienced improved nystagmus waveform.<sup>30</sup> Near visual acuity and locomotor parameters also improved. The dosages used were 5 and 10 mg by mouth, four times daily.

Clonazepam is an antiepileptic agent that has been shown to decrease downbeat nystagmus in some patients.<sup>34</sup> Its most common side effect is drowsiness. The initial dosage of 0.5 mg by mouth three times a day is increased gradually. Gabapentin (900–1500 mg/day) has been shown to decrease, but not abolish, acquired pendular nystagmus in a few patients.<sup>35</sup> Topical and systemic carbonic anhydrase inhibitors (e.g., brinzolamide) have been found to improve nystagmus waveform and visual acuity in small studies of patients with congenital nystagmus.<sup>36–38</sup>

Adrenocorticotrophic hormone can diminish ocular flutter and opsoclonus in infantile myoclonic encephalopathy and neuroblastoma. Corticosteroids can decrease these saccadic oscillations in paraneoplastic, cerebellar ataxia syndromes in adults. Carbamazepine, baclofen, clonazepam, gabapentin, propranolol, and topical timolol have been used to treat superior oblique myokymia; carbamazepine is generally considered the most effective but has more potential side effects.<sup>39,40</sup>

## Optical Treatment

In congenital nystagmus, convergence and eccentric gaze often decrease the nystagmus and improve vision. To induce convergence, 7 prism diopters (PD) of base-out prism can be placed in each spectacle lens. If the patient is young, -1.00 D can be added to the spherical correction. If the null zone is in horizontal eccentric gaze, the spectacle prism powers can be modified to incorporate a prism effect in which the eyes conjugately rotate toward the null zone (prism apices toward the null zone). Contact lenses have fewer optical aberrations and usually correct the refractive errors in patients who have congenital nystagmus more effectively compared with spectacles. In addition, tactile sensory feedback from the contact lenses might diminish the nystagmus intensity. One congenital nystagmus patient reported transient oscillopsia when contact lenses were removed after a short therapeutic trial.<sup>41</sup>

The combination of a high plus spectacle lens and a high minus contact lens for one eye has been devised to stabilize retinal images in that eye and improve vision.<sup>42</sup> This combination places the image at the eye's center of rotation. However, because vestibulo-ocular eye movements and volitional eye movements do not cause retinal image movement with these lenses, walking is difficult.

In patients who have MLN, spectacle treatment for an accommodative component of their esotropia can transform MLN to latent nystagmus or decrease MLN, each of which leads to an improvement of binocular visual acuity.<sup>43</sup>

## Surgical Treatment

An eccentric null zone in congenital nystagmus often produces a habitual face turn. The face turn, if marked, can cause difficulties when viewing at distance or reading; in addition, it can be a cosmetic and psychosocial problem. Resections and recessions of the four horizontal rectus muscles can move the null zone toward the primary position (Anderson-Kestenbaum procedure), which improves vision in the primary position.<sup>44,45</sup> However, months after the surgery, the null zone may become eccentric again. If convergence decreases congenital nystagmus significantly, surgery to induce a greater convergence effort can be combined with the Anderson-Kestenbaum procedure.<sup>46</sup> Surgical procedures to decrease nystagmus intensity in patients without face turn include retroequatorial recession, myectomy without reattachment, anterior extirpation, and tenotomy with reattachment of all four horizontal rectus muscles.<sup>47-49</sup> Extirpation

and myectomy may induce postoperative strabismus and limitation of ductions.<sup>47</sup> Chin-up or chin-down head positioning may be addressed with vertical rectus muscle resection and/or recession, or oblique muscle surgery.<sup>50</sup> Surgical options for head tilt include transposition of horizontal or vertical rectus muscles, or oblique muscle surgery.<sup>51-53</sup>

In patients who have strabismus and MLN, strabismus surgery can change the MLN to latent nystagmus and improve binocular visual acuity.<sup>43</sup> In Arnold-Chiari malformations, suboccipital decompression can diminish downbeat nystagmus if permanent damage to the midline cerebellum and lower brainstem has not occurred. Procedures to weaken the superior oblique and ipsilateral inferior oblique muscles have been used to treat superior oblique myokymia.

## Other Treatments

A variety of other therapies have been used to treat nystagmus. Of these, Epley's maneuver for BPPN is, by far, the most effective.<sup>11</sup> Tactile stimulation of the face and neck,<sup>54</sup> auditory biofeedback, and acupuncture have been shown by electronic recordings to decrease congenital nystagmus. However, their efficacy outside of the laboratory setting has not been established. Retrobulbar injections or intramuscular injections of botulinum A toxin decrease nystagmus by paralyzing the extraocular muscles. They have been used to treat congenital nystagmus,<sup>55</sup> latent nystagmus,<sup>56</sup> and acquired nystagmus.<sup>57</sup> The paralysis is temporary, requiring repetition of the injection every few months. The side effects are diplopia, ptosis, filamentary keratitis, and increased nystagmus in the noninjected eye from plastic-adaptive changes in response to the paresis of the injected eye.<sup>58,59</sup>

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# Pupillary Signs of Neuro-Ophthalmic Disease

9.20

John J. Chen, Randy H. Kardon

## Definitions:

- **Afferent pupillary disorders** result from interference with light input to the pupillomotor system by dense media opacities or severe deficits in any of the retinal layers, in the optic nerve, chiasm, optic tract, or midbrain pretectal area resulting in a symmetrical decrease in the contraction of both pupils in response to light given to the affected eye.
- **Efferent pupillary disorders** result from damage to the pretectal interneuron or Edinger–Westphal nucleus in the midbrain, in the parasympathetic or sympathetic peripheral nerve that supplies the iris muscles, or in the iris muscles themselves, leading to asymmetrical pupils (anisocoria).

## Key Features

- Relative afferent pupillary defects cause less pupil contraction when one eye is stimulated by light than when the opposite eye is stimulated by light.
- Efferent pupillary defects cause anisocoria, a difference in pupil size between the right and left eyes, the extent of which depends on the condition of lighting or near effort.

## Associated Features

- Relative afferent pupillary defects are typically associated with visual field or electroretinographic asymmetries between the two eyes. Asymmetrical differences in retinal appearance, optic nerve appearance or thickness of the inner or outer retinal layers (as observed by optical coherence tomography) may occur in association with a relative afferent pupillary defect.
- Efferent pupillary defects may be associated with either damage to the parasympathetic or sympathetic nerves that supply the iris or direct damage to the iris sphincter or dilator muscles that results in immobility of the pupil.

## INTRODUCTION

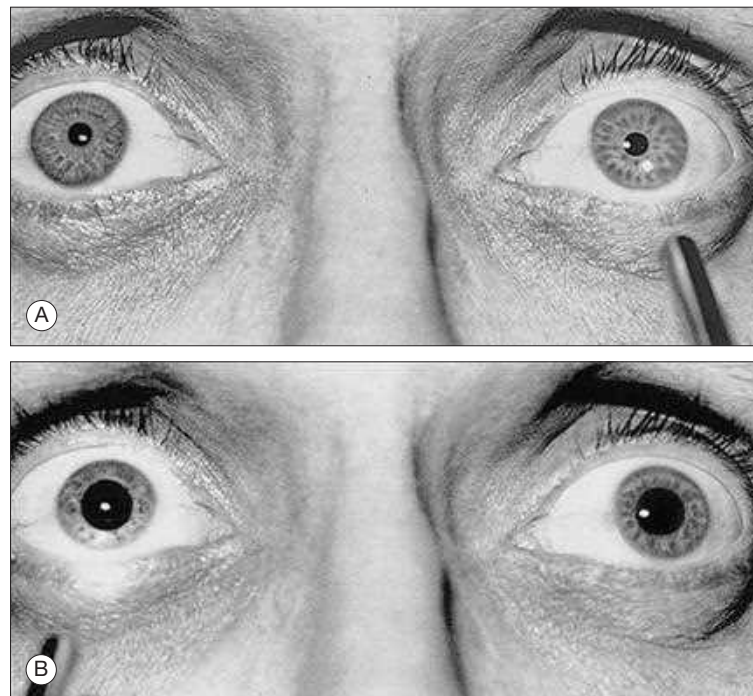
In this chapter, the pupillary appearance and response to light stimulus is discussed from a practical, clinical standpoint. The focus is on features of pupil examination that enable accurate diagnosis and management of diseases of the afferent visual system and those that affect pupil size. The chapter is divided into two parts:

- Pupil examination to assess afferent visual input.
- The diagnostic implications of abnormal integration of the efferent output to the pupils.

Abnormal integration may result in pupils of unequal diameter (anisocoria), pupils that do not dilate well in darkness, or a light–near dissociation, in which pupil contraction to a near reflex greatly exceeds the pupil constriction to a light reflex.

## RELATIVE AFFERENT PUPILLARY DEFECTS

In general, the most important clinical use of the pupil is in the assessment of afferent input from the retina, optic nerve, and subsequent anterior visual pathways (chiasm, optic tract, and midbrain pathways). Because the pupillary light reflex represents the sum of the entire neuronal input (photoreceptors, bipolar cells, ganglion cells, and axons of ganglion cells),



**Fig. 9.20.1 Demonstration of a Large Afferent Defect in the Right Eye.** This is best demonstrated when the light is alternated from eye to eye at a steady rate. The light is kept just below the visual axis and 1–2 inches (3–5 cm) from each eye. Each eye is illuminated for about 2 seconds and then the light switched quickly to the other eye; this allows comparison of the initial direct pupil contraction with light in each eye.

damage anywhere along this portion of the visual pathway reduces the amplitude of pupil movement in response to a light stimulus.<sup>1,2</sup> Thus, the clinician can establish any asymmetrical damage between the two eyes by a simple comparison of how well the pupil contracts to a standard light shone into one eye compared with the same light shone into the other eye.<sup>3</sup> Observation of pupil movement in response to alternating the light back and forth between the two eyes is the basis for the alternating light test, or “swinging flashlight” test, used to assess the relative afferent pupillary defect (rAPD) (Fig. 9.20.1).<sup>4,5</sup> For the swinging flashlight test, each eye is illuminated for 2–3 seconds then the illumination is quickly switched to the other eye to compare the initial direct pupil contraction (velocity and amplitude) and any pupillary dilation/escape.

The pupillary light reflex summates the entire area of the visual field, with some increased weight given to the central 10°.<sup>2</sup> Thus, in general terms, the pupillary light reflex is roughly proportional to the amount of working visual field. Damage to peripheral portions of the retina and visual field defects outside the central field also reduce the amplitude of the pupillary light reflex, and therefore it is not uncommon to have an afferent pupillary defect with normal visual acuity, such as an inferior altitudinal visual field defect from nonarteritic anterior ischemic optic neuropathy that spares the central vision. The rAPD is proportional to the visual field loss and not the visual acuity.

The pupillary light reflex is one of the few objective reflexes that can be used as a clinical test for the detection and quantification of abnormalities of the retina, optic nerve, optic chiasm, or optic tract. Because the amount of the rAPD is correlated, to a large extent, with the amount of asymmetry of visual field deficit between the two eyes, it may be used to help substantiate abnormal results of perimetric testing<sup>6–9</sup>; this often helps the clinician

TABLE 9.20.1 Common Diseases That Produce Relative Afferent Pupillary Defects

Condition	Site	Log Unit Relative Afferent Pupillary Defect	Influencing Factors
Intraocular hemorrhage	Anterior chamber or vitreous	0.0–0.9	Density of hemorrhage
Diffusing media opacity	Cataract or corneal scar	0.0–0.3 in opposite eye	Dispersion of light produces increase in light input
Refractive error	Ocular	0.0	Anisometropic amblyopia may cause a very small relative afferent pupillary defect (rAPD)
Unilateral functional visual field loss	None (non-organic)	0.0	No real visual field loss
Central serous retinopathy or cystoid macular edema	Retina (fovea)	0.3	Area of retina involved, depth of scotoma
Central or branch retinal vein occlusion	Inner retina	0.3–0.6 (nonischemic) ≥ 0.9 (ischemic)	Area of visual field defect and degree of ischemia
Central or branch retinal artery occlusion	Inner retina	0.3–3.0	Area and location of retina involved
Retinal detachment	Outer retina	0.3–2.1	Area and location of detached retina (e.g., 0.6–0.9 log units for macula +0.3 log units for each quadrant)
Anterior ischemic optic neuropathy	Optic nerve head	0.6–2.7	Extent and location of visual field defect
Optic neuritis (acute)	Optic nerve	0.6–3.0	Extent and location of visual field defect
Optic neuritis (recovered)	Optic nerve	0.0–0.6	No visual field defect, residual relative afferent pupillary defect
Compressive optic neuropathy	Optic nerve	0.3–3.0	Extent and location of visual field defect, other eye involvement
Chiasmal compression	Optic chiasm	0.0–1.2	Asymmetry of visual field loss, unilateral central field involvement
Optic tract lesion	Optic tract	0.3–1.2 in the eye with temporal field loss	Incongruity of homonymous field defect, hemi-field pupillomotor input asymmetry
Postgeniculate damage	Visual radiations Visual cortex	0.0	Stimulus light size (no residual relative afferent pupillary defect but definite pupil perimetry defects)
Midbrain tectal damage	Olivary pretectal area of pupil light input region of midbrain	0.3–1.0	Similar to optic tract lesions, but no visual field defect
The expected magnitude of defect is given as well.			

to determine whether a patient's report of visual field defects is believable and trustworthy. Evaluating for an rAPD is very useful in the setting of functional vision loss because it is purely objective, although there is some subjectivity to most other tests, including visual acuity and visual fields. The correlation between visual field asymmetry and rAPD also is a useful monitor of the course of disease for a worsening or improvement in function. rAPDs are, by definition, differences in the input of one eye compared with that of the other. Bilateral symmetrical damage does not produce rAPDs. Thus, a definite rAPD in one eye on the first visit but no rAPD on follow-up may represent improvement in the previously damaged eye or the development of damage in the previously better eye. Therefore, it is always important to remember that the rAPD is, indeed, relative to the other eye.

Estimation of the amount of rAPD in log units (asymmetry between the two eyes) provides an idea of how much asymmetrical visual field damage is present and whether it is consistent with the results of the visual field test. In addition, the amount of rAPD may indicate whether the cause of damage is consistent with the results of the rest of the examination. For example, a patient affected by a small amount of macular degeneration in one eye and not the other is expected to have only a 0.3 log unit rAPD, but if that patient has a 1.2 log unit rAPD, then some additional cause of visual loss is likely, such as a previous branch retinal artery occlusion or optic neuropathy (Table 9.20.1).

The presence of a significant rAPD typically indicates either optic neuropathy or significant retinal disease. Decreased vision from cataract, cornea opacities, and refractive error do not cause a significant rAPD. Large amounts of intraocular hemorrhage can cause a small rAPD (see Table 9.20.1). Knowledge about the expected amount of rAPD can be helpful in this situation. For example, if an eye has light perception with a dense vitreous hemorrhage and has a 2.7 log rAPD (exceeding the expected amount of rAPD from a vitreous hemorrhage), the examiner would know there is significant retina or optic nerve pathology contributing to the vision loss, such as a retinal detachment or traumatic optic neuropathy, despite no view to the posterior pole.

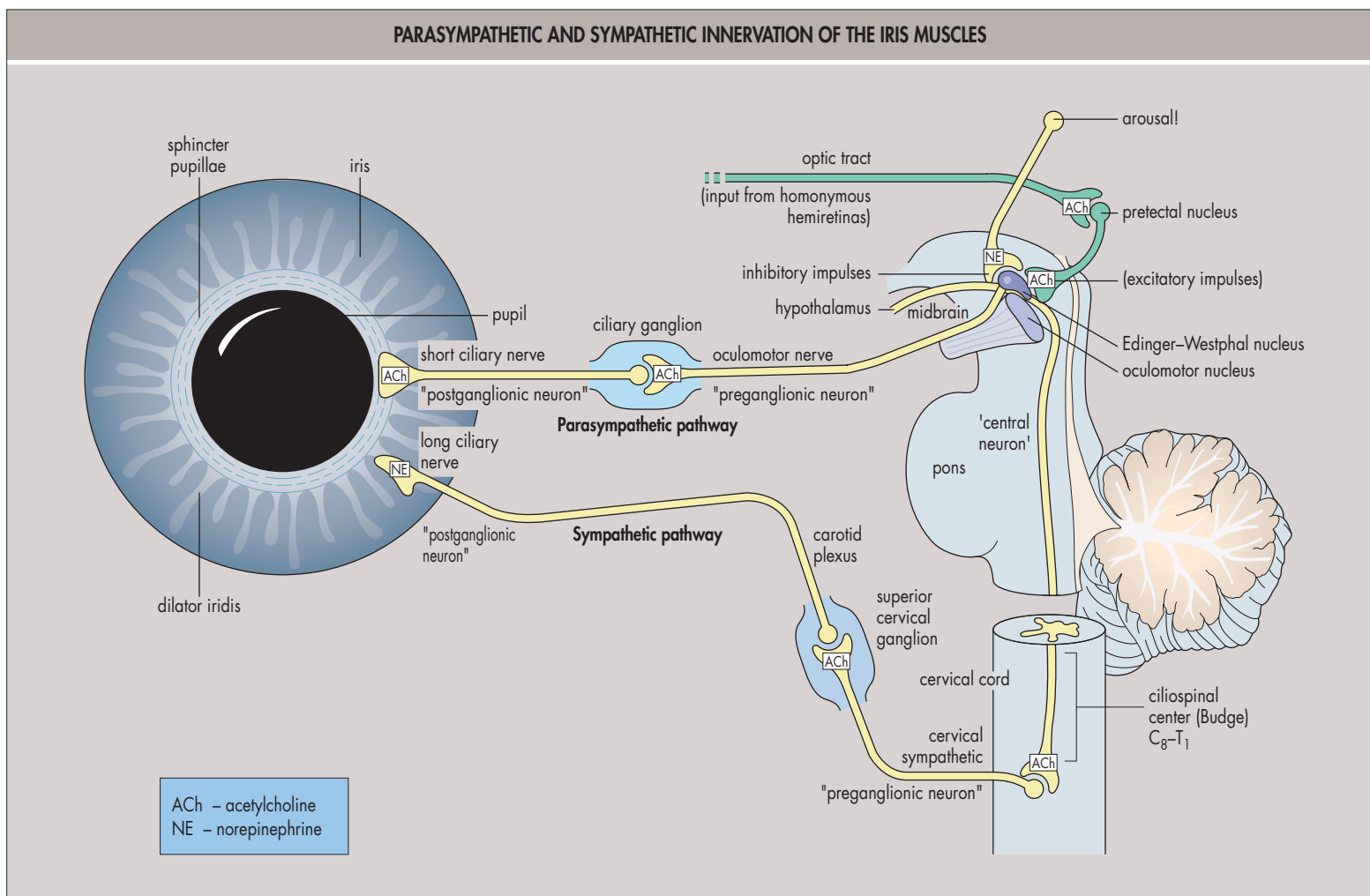
In general, with unilateral visual loss, loss of the central 5° of the visual field results in an rAPD of approximately 0.3 log units. Loss of the entire central area of field (10°) causes an rAPD of 0.6–0.9 log units. Each visual field quadrant outside of the macula accounts for about 0.3 log units, but the temporal field loss results in more loss of pupillary input compared with loss in the nasal field quadrants because the normal temporal visual field extends to approximately 100° compared with 60° for nasal. The correlation between the relative afferent defect and the area and extent of visual field loss, however, is only approximate. Lack of correlation between the two may be important clues as to the cause and extent of damage to the anterior visual system. One example is recovered optic neuritis, where

a 0.3–0.6 log unit rAPD may be present with a normal automated visual field test. Another example is Leber's hereditary optic neuropathy (LHON), where the visual field loss may exceed the expected pupil deficit because of relative sparing of damage to the retinal ganglion cells subserving the pupil light reflex (intrinsically photosensitive retinal ganglion cells containing melanopsin). Studies that used computerized pupillography to quantify the rAPD more precisely showed that some subjects who have normal visual fields and examination results can have a small (0.3 log unit) rAPD.<sup>10–13</sup>

The amount of pupillomotor input asymmetry (the rAPD) may be estimated roughly by using the alternating light test and the subjective grades +1, +2, +3, or +4 (without any neutral density filters) for asymmetry of pupillary response. This subjective grading also may be categorized according to the amount of "pupil escape," or dilation of the pupils, as the light is alternated between the eyes.<sup>14</sup> However, most subjective grading of rAPDs have limitations, such as large-scale errors that arise from age variations in pupil size and pupil mobility. For example, a patient with small pupils and small pupillary contractions to light may have a large rAPD, but the asymmetry in pupil contraction may appear deceptively small on the basis of small differences in pupil excursion with alternating light between the two eyes. However, the amount of neutral density filter needed to dim the better eye until the small contractions are equal represents substantial input damage. More accurate quantification of rAPDs is accomplished by determination of the log unit difference needed to "balance" the pupil reaction between the two eyes<sup>4,5</sup> by using neutral density filters. Use of neutral density filters is more accurate and reproducible and can be used to objectively follow retinal and optic nerve functions.

To quantify the rAPD in log units, the asymmetry in pupil response is balanced by dimming the light shown into the better reacting pupil. A neutral density filter is held over the good eye and the alternating light test repeated. If the input asymmetry is still visible, the density of the filter over the good eye is increased until the amplitudes of the direct light reactions of the two eyes are balanced. To be certain of the measurement, the balance point may be overshoot deliberately and then back titrated. When a dense filter is used, it may be necessary to look behind the filter to see the pupil. Unfortunately, the pupillary response to a repeated light stimulus is far from constant; it changes from moment to moment.<sup>10,11</sup> A common error is to judge the apparent asymmetry of the light reflex too quickly. It is important to alternate the light back and forth at least three times to obtain a mental average of any asymmetry. In this way, moment-to-moment fluctuations in the pupillary response are "averaged out." Despite such efforts, the afferent asymmetry may still fluctuate slightly with time, even when carefully recorded by using computerized pupillography.

Optic neuropathy and retinal disease causing an rAPD will not result in anisocoria. However, the presence of anisocoria can make evaluation of an



**Fig. 9.20.2 Parasympathetic and Sympathetic Innervation of the Iris Muscles.**

rAPD more difficult, and therefore the examiner first needs to check for the presence of anisocoria to ensure that either eye's pupil contraction can be observed during the alternating light test. For example, the presence of an efferent pupil defect and the resulting anisocoria may be mistaken for an apparent rAPD if the pupil response of the eye being illuminated is observed during the rAPD test. If one sphincter is weak, the investigator may still check for an afferent defect by just observing the pupil that still works as the light is alternated between the two eyes, by comparison of its direct and consensual reactions (reverse rAPD technique). While a measurement is made, the good eye is behind the filter, and it may be hard to see the pupil. Sometimes it is necessary to use a side light on the healthy iris to see its consensual pupil reaction. In addition, anisocoria may influence the estimate of pupillary input asymmetry, especially in the case of darkly pigmented irises. A small pupil in one eye will allow less light to pass and will reduce retinal illumination compared with the other eye with the larger pupil, producing an rAPD in the eye with the smaller pupil.

Infants and small children pupils are most easily checked at about 3 ft (1 m) away with a direct ophthalmoscope. In a dark room, the brightest light is used, focus is on the red reflex, and the light is alternated from eye to eye. The baby usually is fascinated by the light, which helps facilitate the pupil examination.

## EFFERENT PUPILLARY DEFECTS

### Anisocoria

As discussed above, a pupillary inequality usually indicates that either the iris muscle or its innervation is damaged (Fig. 9.20.2). To be able to identify the weaker muscle, it is useful to know how the anisocoria is influenced by light. Anisocoria always increases in the direction of action of the paretic iris muscle, just as esotropia increases when gaze is in the direction of action of a weak lateral rectus muscle. Therefore, one of the first important diagnostic approaches to understanding the cause of anisocoria is to observe whether the pupil inequality increases in dark or in light (Fig. 9.20.3).

### Pupillary Inequality That Increases in the Dark

In patients who have a pupillary inequality that increases in dim light (see Fig. 9.20.3), the problem is to differentiate oculosympathetic paresis (Horner's syndrome) from physiological anisocoria (or simple anisocoria)—in which the inequality also is greater in dim light. Patients with a small pupil from functional or mechanical restriction to dilation from synechiae, "little old Adie pupil," cholinergic miosis, or congenital miosis can be easily identified because the pupil will not dilate properly in the dark or with sympathomimetic drops compared with the fellow eye.

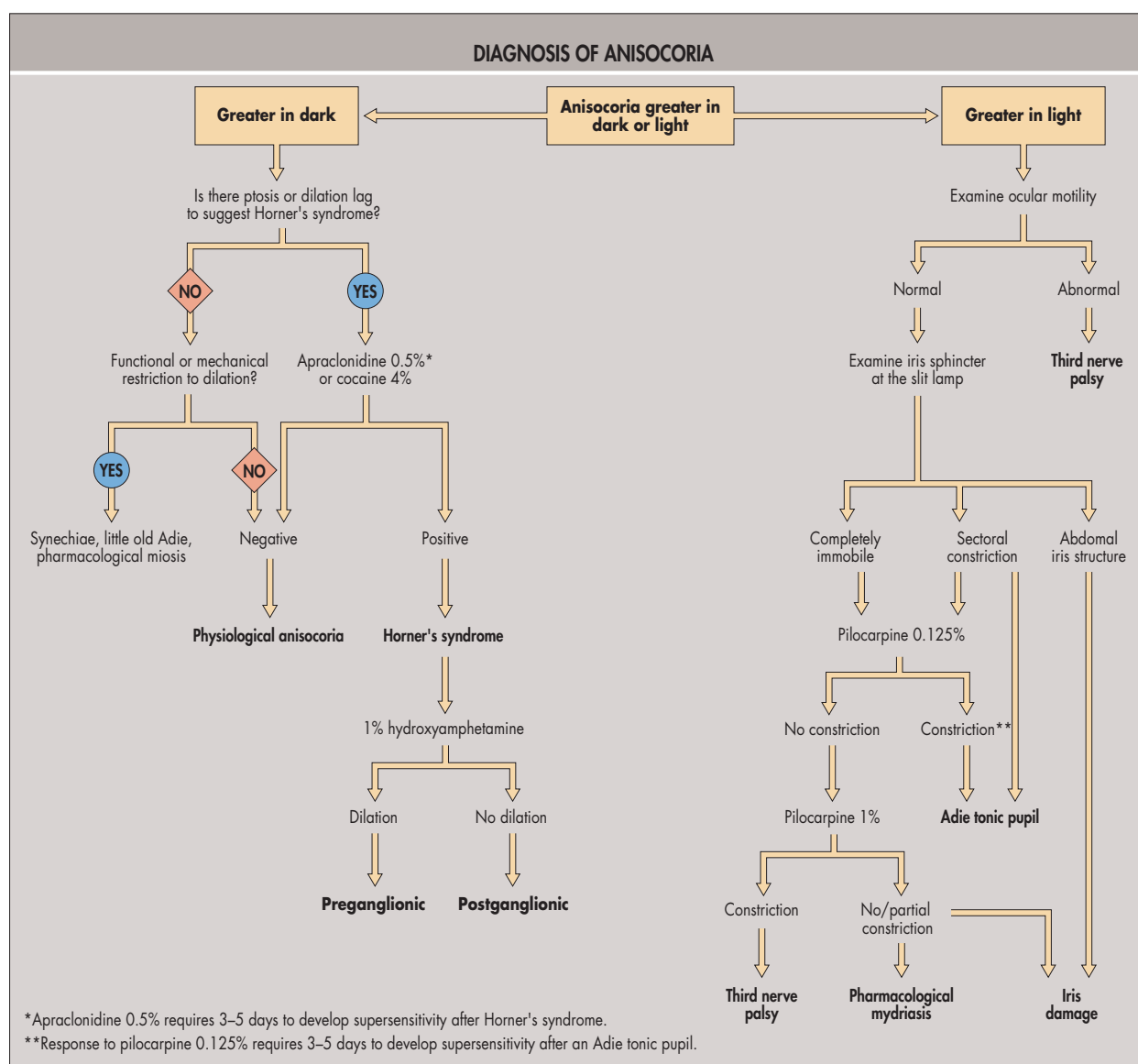
#### Physiological Anisocoria

Physiological anisocoria is common and can be visible in about one fifth of the normal population and is not associated with disease or refractive error. Physiological anisocoria may vary from day to day, or even from hour to hour. About 10% of normal subjects, examined in room light, have an anisocoria of 0.4 mm or more. Physiological anisocoria also, like Horner's syndrome, decreases slightly in light, but it does not show a dilation lag of the smaller pupil and is not accompanied by ptosis or facial anhidrosis. It is believed that physiological anisocoria most likely arises from asymmetrical inhibition at the Edinger-Westphal nucleus in the midbrain. Normally, during wakefulness some inhibition from the reticular activating formation keeps the pupils midsize or larger. During sleep, this inhibition fades and allows the neurons in the Edinger-Westphal nucleus to discharge, which results in miotic pupils. If, during wakefulness, the inhibition is greater to the right Edinger-Westphal nucleus than the left, the right pupil is larger, especially in dim light. When light is added or a near reflex is generated, this inhibition is overcome, the pupils become smaller, and any asymmetrical inhibition diminishes. A reduction of the anisocoria results as the pupils become smaller.

#### Horner's Syndrome

Horner's syndrome is caused by damage to the oculosympathetic pathway, which clinically manifests as ipsilateral miosis, facial anhidrosis, ptosis, "upside-down ptosis" of the lower lid, and, in an acute case, conjunctival





**Fig. 9.20.3 Diagnosis of Anisocoria.** If the anisocoria is greatest in dim light and diminishes in bright light, then the pupillary inequality is usually either physiological (simple anisocoria) or arises from the loss of sympathetic innervation to the dilator muscle (Horner's syndrome). If anisocoria is greater in bright light than in the dark, this indicates that the sphincter of the large pupil is weak or that a parasympathetic lesion is present on that side. A few other conditions need to be considered, but this chart is concerned only with acute damage to a single intraocular muscle or its innervation. (Material adapted and figure created from Focal points: Clinical Modules for Ophthalmologists: Anisocoria, Vol. XXXI, Number 3. American Academy of Ophthalmology; 2013.)



**Fig. 9.20.4 Horner's Syndrome Clearly Acquired in Infancy Must Be Evaluated for Neuroblastoma, a Treatable Tumor.** This baby, with a right ptosis and miosis, developed a flush during cycloplegia that made the vasomotor abnormality very clear—the Horner's syndrome side remained pale. The baby had no sign of Horner's syndrome during her first 8 months, but at 16 months, Horner's syndrome is obvious (ptosis, miosis, and upside-down ptosis). Because the syndrome was acquired, chest radiography was ordered; it showed a mass in the pulmonary apex. Magnetic resonance imaging confirmed the lesion. Surgery revealed a neuroblastoma.

injection and lowered intraocular pressure. The ptosis results from interruption of the sympathetic innervation of Müller's muscle (see Figs. 9.20.2 and 9.20.3; Fig. 9.20.4). The ptosis of Horner's syndrome is mild to moderate and never complete. The pupil is miotic in Horner's syndrome because the sympathetic innervation to the iris dilator muscle is disrupted.

The miotic pupil from Horner's syndrome is more apparent in the dim lighting conditions and has a characteristic "dilation lag," which can be seen in the office by using a handheld light shined from below. The room lights are switched off, and the smaller pupil is examined for an apparent reluctance to dilate. Pupil dilation is normally a combination of sphincter relaxation and dilator contraction, a combination that produces a prompt dilation. The patient who has Horner's syndrome has a weak dilator muscle in one iris as a result of the disruption of sympathetic innervation

and, as a result, that pupil dilates more slowly than the normal pupil. If the sympathetic lesion is complete, the affected pupil dilates only by sphincter relaxation. The resultant asymmetry of pupil dilation produces an anisocoria that is largest 4–5 seconds after the lights have been turned out—the process is much slower than is generally thought. At 10–20 seconds after the lights have been turned off, the anisocoria lessens as the sympathetomized pupil gradually catches up, a process referred to as *dilation lag*. The test is a quick and simple way to differentiate Horner's syndrome from physiological anisocoria. It works well most of the time, particularly in young people who have mobile pupils. Pharmacological testing with either cocaine eyedrops or topical apraclonidine is typically used to confirm the diagnosis of Horner's syndrome.

### Diagnosis of Horner's Syndrome—Cocaine and Apraclonidine Pharmacological Testing

The action of cocaine is to block the reuptake of norepinephrine (noradrenaline) normally released from the nerve endings. If norepinephrine is not released because of an interruption in the sympathetic pathway, cocaine has no adrenergic effect. Therefore, the affected pupil in a patient with Horner's syndrome dilates less with cocaine compared with the normal pupil, regardless of the location of the lesion. Cocaine drops are placed in both eyes. If the anisocoria has increased clearly after 60 minutes, this confirms Horner's syndrome because the normal pupil has dilated more compared with the pupil in Horner's syndrome. If there is at least 0.8 mm of pupillary inequality after cocaine administration, Horner's syndrome is highly likely.<sup>15</sup> If very little dilation of the pupil occurs, even though an oclosympathetic defect is suspected, and the pupil did not dilate well before the cocaine test even after 30 seconds in darkness, then a false-positive cocaine test result must be considered. A false-positive result may occur if the iris is held in a miotic state through either scarring or aberrant

reinnervation of the iris sphincter. If this is suspected, the addition of a direct-acting sympathomimetic agent to both eyes (e.g., 2.5% phenylephrine) at the conclusion of a positive cocaine test should dilate the suspected eye easily and eliminate the cocaine-induced anisocoria after 30 minutes in Horner's syndrome, whereas a structural cause of miosis would not cause the eyes to dilate.

Topical apraclonidine has gained popularity as an alternative to cocaine testing for the diagnosis of Horner's syndrome.<sup>16-21</sup> Unlike cocaine, apraclonidine is not a controlled substance, is easier to obtain and use in a doctor's office, and produces mydriasis in the eye with oculosympathetic paresis from Horner's syndrome as a result of denervation adrenergic supersensitivity. Typically, 45 minutes following topical 0.5% apraclonidine administered to both eyes, the miotic eye with Horner's syndrome dilates and the anisocoria reverses. In most cases, the normal unaffected eye becomes smaller in dim light. This is because apraclonidine is primarily an  $\alpha_2$ -adrenergic agonist, causing inhibition of norepinephrine release at the presynaptic terminus and slight miosis in the normal eye. However, it is also a weak  $\alpha_1$ -adrenergic agonist, and in the presence of adrenergic denervation supersensitivity, it causes mydriasis, as is the case in the eye with Horner's syndrome. In patients with anisocoria of other causes, such as physiological anisocoria, apraclonidine has very little effect on the anisocoria. Apraclonidine has an advantage over cocaine in that it will actively dilate the affected eye and not the normal eye, making its action a positive (mydriatic) one in the affected eye, unlike in the case of cocaine, which causes negative action in the affected eye and positive (mydriatic) action in the unaffected eye. Thus, a positive apraclonidine test result causes a reversal of anisocoria in Horner's syndrome (or significant reduction of anisocoria in milder cases), which is easier to see than an increase in anisocoria expected with a positive cocaine test result. Another advantage of apraclonidine is that it will also reverse the ptosis in Horner's syndrome within minutes because of its activity on Müller's muscle, which is also innervated by the sympathetic pathway and becomes supersensitive in Horner's syndrome. After lack of sympathetic activity, adrenergic supersensitivity usually occurs between 2 and 5 days. Therefore, in very acute cases, cocaine is still preferred for pharmacological confirmation of Horner's syndrome. On a cautionary note, there have been a small number of reports of respiratory depression in infants exposed to topical apraclonidine because of its ability to cross the blood-brain barrier, similar to bromonidine, and is therefore contraindicated in infants unless the infant can be monitored for 4-5 hours after testing. Therefore, testing in children is more commonly performed with cocaine because of this possible serious side effect of apraclonidine.

### Location of Damage to the Sympathetic Pathway

After the diagnosis of Horner's syndrome is made, localizing whether the damage is along the preganglionic or postganglionic sympathetic pathway helps direct imaging, if indicated. Horner's syndrome sometimes manifests so characteristically that further efforts to localize the lesion are superfluous, as with patients with cluster headaches or patients with a history of surgery or trauma along the sympathetic pathway. Localization of a sympathetic lesion is a question of considerable clinical importance because many postganglionic defects are caused by vascular headache syndromes, cavernous sinus pathology, or carotid dissections, and preganglionic lesions sometimes result from malignant tumors or strokes to the central sympathetic location in the brain. These findings can assist the radiologist in interpretation of any diagnostic imaging. Pharmacological testing with hydroxyamphetamine drops can be helpful in localizing the lesion as well.

Hydroxyamphetamine releases norepinephrine from storage vesicles in the postganglionic sympathetic nerve endings at the iris dilator muscle. When the lesion is postganglionic, the third order nerve is dead, and no norepinephrine stores are available for release at the iris. When the lesion is complete, the pupil does not dilate at all. However, the dying neurons and their stores of norepinephrine may last for almost 1 week from the onset of damage. Therefore, a hydroxyamphetamine test administered within 1 week of a postganglionic lesion may give a false preganglionic localization if some of the norepinephrine stores remain. When Horner's syndrome is caused by preganglionic or central lesions, the pupils dilate normally because the postganglionic third order neuron and its stores of norepinephrine, although disconnected, are still intact.

To perform the hydroxyamphetamine test, the pupil diameters are measured before and 60 minutes after hydroxyamphetamine drops have been placed in both eyes. The change in anisocoria in room light is noted. If the affected pupil—the smaller one—dilates less compared with the normal pupil, an increase in anisocoria occurs, and the lesion is in the

postganglionic neuron. If the smaller pupil now dilates so much that it becomes the larger pupil, the lesion is preganglionic and the postganglionic neuron is intact. The examiner must wait at least 48 hours after cocaine has been used before the administration of hydroxyamphetamine; cocaine inhibits the uptake of hydroxyamphetamine into the presynaptic sympathetic nerve terminal and seems to block its effectiveness. In general, if the anisocoria increases by at least 0.5 mm after hydroxyamphetamine administration, the lesion is most likely postganglionic. A decrease in anisocoria points toward a preganglionic location of the lesion. However, hydroxyamphetamine is no longer commercially available, and there are rare reports of false localization with hydroxyamphetamine. For these reasons, many clinicians forgo further localizing with hydroxyamphetamine and image the entire sympathetic pathway unless history or associated signs and symptoms clearly localize the lesion. For instance, acute Horner's syndrome with associated ipsilateral neck or facial pain requires urgent imaging of the neck for evaluation of a carotid dissection.

### Horner's Syndrome in Children and Infants

When a child is observed to have a unilateral ptosis and miosis, the first question is to ascertain whether Horner's syndrome is present and, if present, whether it was acquired or was present at birth. A child who has congenital Horner's syndrome and naturally curly hair has, on the affected side of the head, hair that seems limp and lank. The shape of the hair follicles depends on intact sympathetic innervation, as does the iris pigment. Iris melanocytes, derived from the neuroectoderm, require sympathetic innervation to produce melanin, and if the innervation is not present at birth or interrupted during the first year of life, a lighter iris will occur, resulting in heterochromia. However, a child with Horner's syndrome who has blond, straight hair and very pale, blue eyes will not have any visible asymmetry of hair straightness or iris heterochromia. These signs are typically seen in congenital Horner's syndrome but can be rarely seen in acquired Horner's syndrome.

The most telling symptom is the hemifacial flush (blanch on the affected side) that occurs with nursing or crying. Generally, the affected side is pale. In an air-conditioned office, it may be hard to decide whether sweating is decreased on the affected side. A cycloplegic refraction sometimes produces an atropinic flush everywhere except on the affected face and forehead and, thus, provides additional evidence toward diagnosis because of lack of sympathetic innervation to the skin vasculature. When the pupil, eyelid, and skin signs of Horner's syndrome are equivocal, pharmacological testing is needed to make the diagnosis with more certainty. Because of the possible central nervous system depression that can occur with apraclonidine, cocaine testing is generally used (see above section on cocaine testing) and occlusion of the punctae of the tear ducts after cocaine drops will reduce the low risk of systemic side effects even further.

Making a diagnosis of Horner's syndrome in infancy or childhood is important because these patients must be evaluated for neuroblastoma—a treatable tumor (see Fig. 9.20.4), unless there is a known history of surgery in the area of the sympathetic chain to explain Horner's syndrome.

### Pupillary Inequality That Increases With Light

For a patient who has pupillary inequality that increases with light, several problems must be addressed (see Fig. 9.20.3). The diagnostic evaluation is usually focused on whether the efferent pupil defect is caused by denervation, direct damage to the iris sphincter muscle, or pharmacological mydriasis.

### Slit-Lamp Examination of the Iris

Trauma to the globe usually results in a torn sphincter and an iris border that transilluminates at the slit lamp, showing small divots. The pupil is often not round and may show segmental areas of sphincter immobility, similar to an Adie's pupil (see below); other evidence of ocular injury may also be present. Naturally, such a pupil does not constrict well to light. An atrophic sphincter caused by previous herpes zoster iritis also may reveal transillumination defects, as seen with the slit lamp, that arise from previous ischemic insults to the iris. An irregular pupil with a sectoral immobility may also be a sign of iridocorneal endothelial (ICE) syndrome. If, however, the iris looks normal, further investigation is required, as outlined below.

### No or Little Residual Light Reaction

If no residual light reaction is present, the possibility of pharmacological mydriasis must be explored.<sup>22</sup> However, a completely blocked light reaction sometimes may occur when the sphincter is denervated by either a

preganglionic lesion (third nerve palsy) or a postganglionic lesion (acute, complete tonic pupil), in acute angle closure (iris ischemia), or with an intraocular iron foreign body (iron mydriasis). If the dilated pupil still has some response to light, the dilation may result from partial denervation of the sphincter, incomplete atropinization, or adrenergic mydriasis. When the light reaction is poor because the dilator muscle is in spasm (as a consequence of adrenergic mydriatics, such as phenylephrine, or in some patients with acute migraine), then the pupil is very large, the conjunctiva is blanching, and the lid is retracted. In such cases, any decrease in the amplitude of accommodation is minor.

### Segmental Paralysis of the Iris Sphincter

When some residual light reaction occurs, the iris sphincter is examined for sector palsy by using the slit lamp. When the dilator is in a drug-induced adrenergic spasm or when an atropine-like drug blocks the cholinergic receptors in the iris sphincter, the entire sphincter muscle (all 360°) is affected. This usually does not happen when postganglionic parasympathetic nerve fibers have been interrupted in Adie's syndrome. In patients with Adie's syndrome, there is usually at least one sector of the iris sphincter showing a residual light reaction at the slit lamp, causing the so-called *vermiform movement*. Thus, a pupil that has a weak light reaction and no segmental palsy usually indicates a drug-induced mydriasis, or resulting from a third cranial nerve paresis (preganglionic parasympathetic nerve), which may require more extensive investigations.

### Pupillary Supersensitivity to Cholinergic Drugs

If weak pilocarpine (about 0.1%) is applied to both eyes (with both corneas healthy and untouched), and the affected (mydriatic) pupil constricts more than the normal pupil to become the smaller pupil in dim light after 30 minutes, it can be concluded that the iris sphincter is showing denervation cholinergic supersensitivity. Cholinergic supersensitivity can occur within days of denervation. It seems likely that with a postganglionic denervation (ciliary ganglion to the eye), the sphincter will show a little more supersensitivity than in the preganglionic case (third nerve palsy); however, the differences are not great and therefore cannot be used to differentiate Adie's syndrome from a pupil involving third nerve palsy. Cholinergic supersensitivity of the iris sphincter is considered now to be only a weak sign of Adie's syndrome. As the iris sphincter is reinnervated by cholinergic accommodative fibers and becomes smaller over time, supersensitivity can be lost.<sup>23</sup>

It is very rare for an ambulatory patient to have an isolated sphincter palsy caused by damage to the intracranial third nerve without ptosis or diplopia. However, a patient should be warned that if ptosis or double vision does develop, a prompt re-evaluation should be undertaken for compression of the oculomotor nerve. If the normal pupil constricts a little to dilute pilocarpine and the dilated pupil does not constrict at all, the mydriasis may be the result of a local dose of an anticholinergic drug, such as atropine. A stronger concentration of pilocarpine showing no or little pupil constriction would confirm this.

### Pupillary Undersensitivity to a Miotic Dose of Pilocarpine

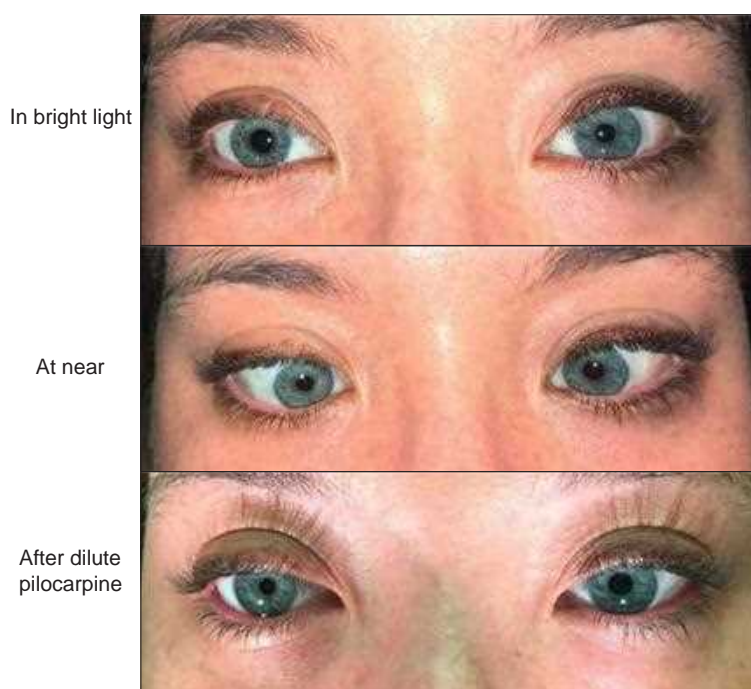
If the affected pupil reacts little or not at all and the unaffected pupil constricts normally on application of pilocarpine 1% in each eye, then the mydriasis is likely caused by a problem with the sphincter muscle itself and not because of denervation. Non-neuronal causes of mydriasis are as follows:

- Anticholinergic mydriasis (e.g., scopolamine (hyoscine), cyclopentolate, atropine).
- Traumatic iridoplegia (sphincter rupture, pigment dispersion, angle recession).
- Angle-closure glaucoma (ischemia of the iris sphincter).
- Fixed pupil after anterior segment surgery.
- Bound down iris (synechia) after iritis or as a result of ICE syndrome.

The cause for complete loss of function of the iris muscles after anterior segment surgery is unknown. An excessive rise in intraocular pressure during or after surgery can sometimes cause ischemic damage to the iris sphincter.

### Tonic Pupil of Adie's Syndrome

Young adults (more women than men) may present with one pupil that is large or with a complaint that they are not able to focus up close with one eye because of Adie's syndrome, which results from an injury, often idiopathic, to the ciliary ganglion or short ciliary nerves. Slit-lamp examination



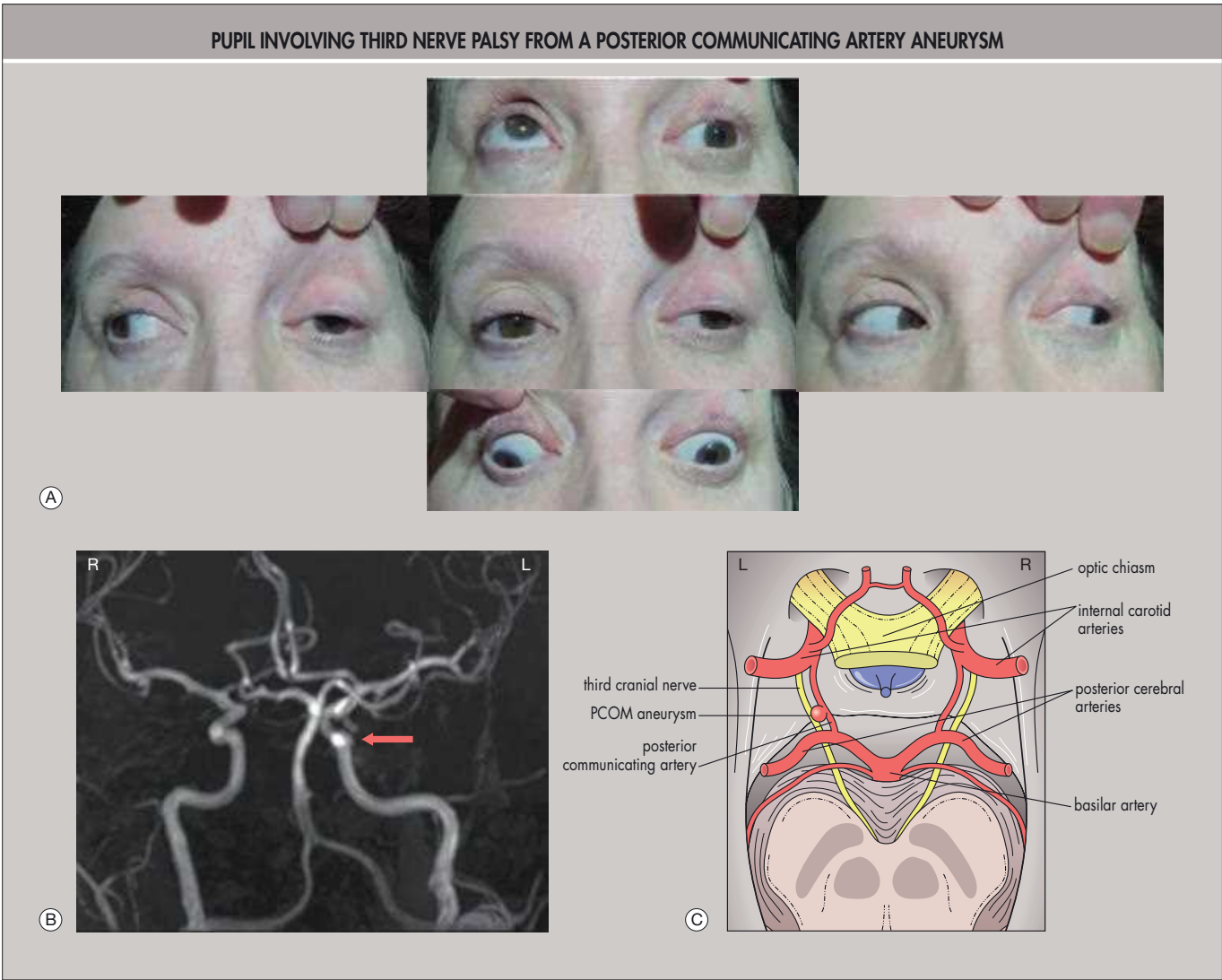
**Fig. 9.20.5 Adie's Syndrome.** This patient has a right Adie's syndrome that has been present for 1 year. With time, there has been aberrant regeneration of the accommodative post-ganglionic parasympathetic fibers to the iris sphincter, in addition to re-innervation to the ciliary muscle, causing a tonic pupil contraction to a near effort without return of the light reflex, resulting in a light-near dissociation of the pupil. Dilute pilocarpine results in reversal of the anisocoria because of the hypersensitivity.

usually shows segmental denervation of the iris sphincter. Within the first week, supersensitivity to cholinergic substances may be demonstrated. After about 2 months, nerve regrowth is active and fibers originally bound for the ciliary muscle (they outnumber the sphincter fibers by 30:1) start to arrive (aberrantly) at the iris sphincter, and this produces the characteristic light-near dissociation of Adie's syndrome (Fig. 9.20.5). Eventually, the affected pupil becomes the smaller of the two pupils, especially in dim light, because of the aberrant reinnervation by accommodative fibers ("little old Adie pupil"). The segmental palsy of the iris sphincter is seen particularly well by using infrared video recording of transillumination of the iris.<sup>23</sup> Patients with Adie's syndrome also often have impaired deep tendon reflexes.

### Third Nerve Palsy

A pupil involving third nerve palsy is considered a neurological emergency because a small percentage of these are caused by life-threatening aneurysms (Fig. 9.20.6). An old clinical rule of thumb is that if the pupillary light reaction is spared, the third nerve palsy probably does not result from compression or injury, but more likely from small vessel disease, as may be seen in diabetes. It would be exceedingly rare for compression, especially from a posterior communicating artery aneurysm, to cause complete external dysfunction with pupil sparing because the pupillary fibers run along the dorsomedial surface of the nerve. However, there are multiple reports of aneurysms causing a partial pupil sparing third nerve palsy initially, which later worsen to involve the pupil and have the risk for potential catastrophic rupture. Therefore patients with a partial pupil-sparing third nerve palsy require urgent neuroimaging to rule out an aneurysm.<sup>24</sup> Approximately 16% of microvascular third nerve palsies have visible anisocoria, so pupil involvement does not necessarily mean a compressive lesion.<sup>25</sup> Finally, a very small number of pupil-sparing third cranial nerve palsies arise from midbrain infarcts, although these are typically accompanied by other neurological signs or symptoms, such as contralateral weakness. It is extraordinarily rare for an acute pupil involving third nerve palsy to show segmental palsy; acute cases show partial to complete efferent pupil defects that are symmetrically palsied around the circumference of the sphincter muscle. In addition, almost all cases of pupil involving third nerve palsy will have other elements of oculomotor dysfunction, including ptosis or extraocular motility deficits. Therefore, patients with isolated pupillary dilation do not require neuroimaging for aneurysms.<sup>24</sup>





**Fig. 9.20.6 Pupil Involving Third Nerve Palsy From a Posterior Communicating Artery Aneurysm.** This patient had an acute painful left pupil involving third nerve palsy with pupil dilation, ptosis, and deficits in elevation, adduction, and depression from a posterior communicating artery aneurysm (red arrow). The diagram demonstrates the close relationship between the posterior communicating artery aneurysm and the third cranial nerve. A pupil-involving third nerve palsy is compression, until proven otherwise.

### Aberrant Regeneration of the Third Cranial Nerve

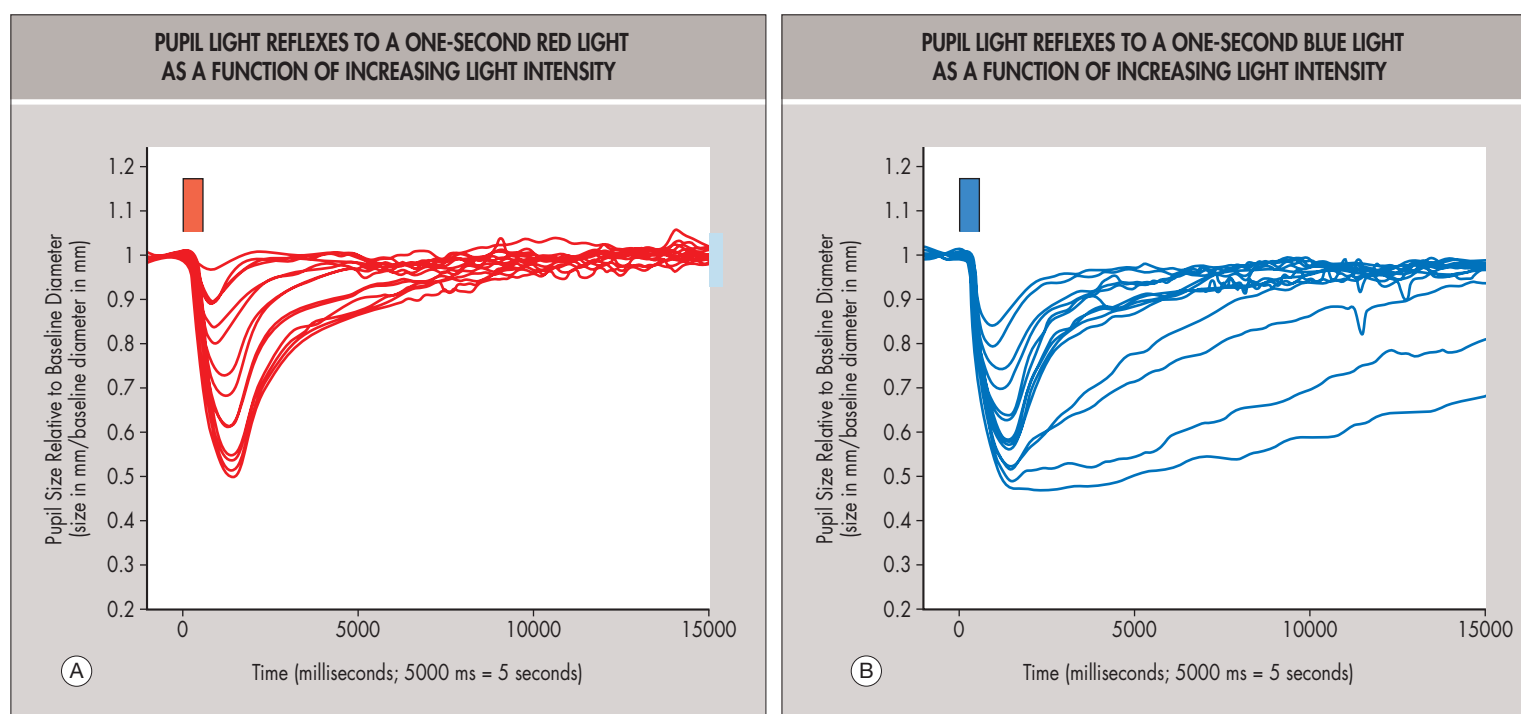
The third cranial nerve carries instructions to several different muscles, so when the nerve is injured and the fibers regrow, they may grow into the wrong location. This most commonly occurs when the glial scaffolding, which normally segregates nerve bundles, is disrupted by trauma or external compression by a tumor. For example, the eye may inappropriately turn in when the patient is trying to look down or up, or the pupil may inappropriately constrict with depression, adduction, or supraduction of the globe. This does not occur with microvascular third nerve palsies, and therefore, aberrant regeneration outside of trauma is compression until proven otherwise.

### POOR PUPIL DILATION

When one or both pupils stay small and miotic, even in darkness, a number of factors may be responsible (Table 9.20.2). To better understand the different possible mechanisms, it is important to understand the normal process that allows the pupil to dilate in darkness. When a light stimulus is terminated, two mechanisms cause the pupil to dilate. The greater part of pupil dilation arises from inhibition to the Edinger–Westphal nucleus in the midbrain, which reduces the firing of the preganglionic parasympathetic neurons in the Edinger–Westphal nucleus and results in relaxation of the iris sphincter. Within a few seconds, sympathetic nerve firing increases, which augments the pupil dilation by active contraction of the dilator muscle. The combined inhibition of the iris sphincter and stimulation of the iris dilator is a carefully integrated neuronal reflex. Therefore, inability of the pupil to dilate in darkness may occur because of a sympathetic nerve palsy, mechanical limitations of the pupil (scarring),

**TABLE 9.20.2 Causes of Poor Pupil Dilation in Darkness**

Cause	Location	Mechanism
Past inflammation or surgical trauma	Posterior iris surface or sphincter	Scarring or synechiae of the iris because of past iritis
Acute trauma	Sphincter	Prostaglandin release causes sphincter spasm
Adie's syndrome tonic pupil Third cranial nerve aberrant reinnervation	Sphincter	Aberrant regeneration of iris sphincter by accommodative or extraocular motor neurons that are not inhibited in darkness
Pharmacological miosis	Iris sphincter	Cholinergic influence
Unilateral episodic spasm of miosis	Postganglionic parasympathetic neuron	Uninhibited episodic activation of postganglionic neurons
Congenital miosis (bilateral)	Sphincter	Developmental abnormality
Fatigue, sleepiness	Edinger–Westphal nucleus	Loss of inhibition at midbrain from reticular activating formation
Lymphoma, inflammation, infection	Periaqueductal gray matter	Interruption of inhibitory fibers to the Edinger–Westphal nucleus
Central-acting drugs	Reticular activating formation, midbrain	Narcotics, general anesthetics
Old age (bilateral miosis)	Reticular activating formation, midbrain	Loss of inhibition at midbrain from reticular activating formation
Oculosympathetic defect	Sympathetic neuron interruption	Horner's syndrome



**Fig. 9.20.7 Pupil Light Reflexes to Red and Blue Lights as a Function of Light Intensity—The Melanopsin-Mediated Sustained Response to Blue Light.** Pupil tracings are shown for pupil light reflexes in response to a one-second duration red light (red tracings) or blue light (blue tracings) that increases in intensity. As the light intensity increases, the pupil contraction increases in amplitude. At the brightest light intensity, the pupil contraction becomes very sustained with blue light but not with red light, representing a signature of intrinsic activation of a melanopsin-mediated pupil response.

pharmacological miosis, aberrant reinnervation of cholinergic neurons to the iris sphincter that are not normally inhibited in darkness (accommodative or extraocular motor neurons), or inhibitory input signal not received by the Edinger–Westphal nucleus.

## RETINAL ORIGIN OF THE PUPIL LIGHT REFLEX—THE MELANOPSIN-CONTAINING RETINAL GANGLION CELL

Recent evidence has shown that almost all of the rod and cone input to the pupil light reflex is mediated by a special class of retinal ganglion cells containing the primitive visual pigment melanopsin found in the retina of lower animals.<sup>26–47</sup> Besides being activated by rod and cone input causing a transient pupil response, the melanopsin retinal ganglion cell is itself also directly sensitive to light (peak sensitivity is in the blue wavelength range), providing a sustained steady-state pupil constriction to light (Fig. 9.20.7). This intrinsic, direct activation pathway of the melanopsin-containing retinal ganglion cells causes the cell to discharge in a sustained way and is directly proportional to steady-state light input, similar to a direct-current light meter, which does not show the classic light adaptation properties.

In genetically altered mice that completely lack functional rods and cones, it was discovered that a rather robust pupil light reflex was still present. This unexpected finding was followed by a series of studies to identify what retinal element could be contributing to the pupil light reflex in the absence of rod and cone input. Through clever labeling experiments, a specific ganglion cell was identified as containing melanopsin, which was itself photosensitive, with a broad spectral peak centering on about 490 nm. Elegant electrophysiological recordings coupled with the study of response properties of these ganglion cells have revealed that the melanopsin-containing retinal ganglion cells project to the pretectal nucleus (the site of the first midbrain interneuron synapse for the pupil light reflex pathway) and also provide light sensing information for the diurnal regulating areas of the hypothalamus (suprachiasmatic nucleus) that modulate the circadian rhythm and other important light-modulated biological functions. More recently, a number of subtypes of melanopsin-containing retinal ganglion cells, which appear to have preferential activating properties and projections to the brain, have been identified. Studies have recently shown that patients with Alzheimer's disease have significant loss of melanopsin-containing retinal ganglion cells, and this factor may be a large contributor to the circadian rhythm dysfunction seen in Alzheimer's disease.<sup>38</sup> In addition, patients with multiple sclerosis were shown to have a decrease in the melanopsin-mediated pupillary

light reflex that correlates with ganglion cell layer thinning, which could put patients at risk for retinohypothalamic dysfunction.<sup>39</sup> Other conditions, such as mitochondrial optic neuropathies have a selective sparing of the melanopsin ganglion cells, which can explain the preserved pupillary light reflex in some patients with LHON and dominant optic atrophy.<sup>40</sup>

In addition to receiving rod and cone input to the pupil light reflex, melanopsin ganglion cells are capable of transduction of light directly, without photoreceptor input, and are likely responsible for providing more steady-state light input information to the brain. This helps explain why some patients blind because of photoreceptor loss still exhibit both a pupil light reaction to bright blue light and also maintain a circadian rhythm, whereas patients blind because of optic nerve lesions (loss of melanopsin ganglion cell input) are often lacking a normal circadian rhythm. By adjusting the state of adaptation (dark adaptation versus light adaptation), the light intensity, the duration of the light stimulus (i.e., 1 second) and the peak wavelength of the light stimulus (i.e., red versus blue light), one can record pupil contractions that are primarily rod mediated, cone mediated, and melanopsin mediated, which can be useful in detecting disorders of different classes of photoreceptors<sup>41–46</sup> or more distal disorders<sup>47</sup> in a clinical setting.

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# Presbyopia and Loss of Accommodation

# 9.21

Sean P. Donahue, Reid A. Longmuir

**Definition:** Loss of accommodation, the ability of the eye to increase its refractive power, may occur as a result of the age-associated decrease in elasticity of the natural lens (presbyopia), or from other less common causes.

**Key Feature**

- Blurred vision at near.

**Associated Features**

- Advanced age.
- Drug use (cholinergics, botulism).
- Other rare causes.

**INTRODUCTION**

Accommodation is the ability to increase the refractive power of the optical system of the eye. It is necessary to produce a clear retinal image of objects that are near. For accommodation to occur, the ciliary body contracts, the lens zonules relax, and the crystalline lens assumes a more spherical shape, which increases its refractive power.

Presbyopia is by far the most common cause of loss of accommodation. Although age-associated loss of elasticity of the lens and lens capsule has been implicated, the true pathogenesis remains obscure. Disorders other than presbyopia can affect accommodation but are, for the most part, relatively rare.<sup>1</sup>

**EPIDEMIOLOGY AND PATHOGENESIS**

The neural pathway for accommodation probably begins in the midbrain. Attempts at accommodation are associated with convergence and pupillary miosis (the “near triad”), so the areas responsible for accommodation are probably related closely to those that produce convergence. These areas receive input from the cerebral cortex and pretectum; complex pathways project symmetrically to the portion of the third cranial nerve nucleus responsible for accommodation, probably in the caudal segment of the Edinger–Westphal parasympathetic nucleus.<sup>2,3</sup> These fibers then travel from the third cranial nerve nucleus to the ciliary ganglion, where they synapse with postganglionic parasympathetic fibers destined for the ciliary body and iris sphincter. They reach the intrinsic muscles of the eye via the short ciliary nerves. It is possible that a direct (nonsynapsing) pathway from the midbrain to the ciliary body also exists.

The ciliary body also receives sympathetic input, as evidenced clinically by the increased accommodative amplitude seen in the affected eye of patients with Horner’s syndrome. However, parasympathetic control is of much greater clinical importance.<sup>3</sup>

Because accommodation is mediated almost exclusively via parasympathetic pathways, it is antagonized best with muscarinic blockers. Five muscarinic antagonists are commonly used in ophthalmology (Table 9.21.1). Tropicamide (Mydracil®) has a very short half-life and should not be used to determine the cycloplegic refraction. Cyclopentolate is effective and has sufficient half-life to be the standard in pediatric ophthalmology. Phenylephrine (adrenaline), a sympathomimetic, causes mydriasis but has no significant effect on accommodation.

Accommodative ability decreases with age. Although a great deal of variability occurs in the normal levels of accommodation, children have remarkable accommodative abilities and presbyopia is rare prior to age

TABLE 9.21.1 Standard Cycloplegic Agents

Agent	Available Concentrations (%)	Maximum Effect for Cycloplegia (minutes)	Duration of Cycloplegia (hours)
Tropicamide	1, 2	15	4–6
Cyclopentolate	0.5, 1, 5	20–45	24
Homatropine	2, 5	45–60	72
Scopolamine	0.25	30–60	168 (7 days)
Atropine	0.25, 0.5, 1	120	360 (15 days)

TABLE 9.21.2 Accommodative Amplitudes at Given Ages

Age (years)	Amplitude of Accommodation (D)	Near Point When Emmetropic (cm)
20	+11.00	9.1
32	+8.00	12.5
40	+6.00	16.7
44	+4.00	25.0
48	+3.00	33.3
56	+2.00	50.0
64	+1.00	100.0

35 years. Normal values for accommodative amplitudes are given in Table 9.21.2.

**OCULAR MANIFESTATIONS**

Because accommodation is part of the near reflex, it is linked closely with convergence and pupillary miosis. Clinically, it is very difficult to separate these components, and the presence of pupillary miosis is a good indicator of accommodative effort.

Disorders of accommodation present with blurred vision at near. Patients who have latent hyperopia must use a portion of their accommodative reserve to focus at distance and may present with premature presbyopia. Mild myopia, in contrast, may delay symptoms of presbyopia.

Most disorders of accommodation are bilateral. Thus, if the patient is corrected to emmetropia, the amount of near blurring should be similar in each eye. Disorders that present as a unilateral loss of accommodation localize to the infranuclear third cranial nerve, the ciliary ganglion (Adie’s syndrome), or the effector organ (ciliary body) itself (pharmacological cycloplegia).<sup>3</sup>

**DIAGNOSIS**

Accommodation can be measured by determining the accommodative amplitude or the accommodative range.<sup>4,5</sup> In all tests, it is important that refractive error be corrected properly to put the far point at infinity and render the ocular system emmetropic at distance.

Three methods are typically used to determine accommodative amplitude:

- A small target is brought forward toward the eye until the patient reports blurring. This distance is called the *near point of accommodation*. The reciprocal of the distance at which the target blurs is the accommodative amplitude. For example, if the target blurs at 25 cm distance, the subject has +4.00 diopter (D) of accommodative amplitude.
- The Prince rule—to determine accommodative amplitude, a scaled ruler combined with a near add of +3.00 D, which puts the far point of a person with emmetropia at 33 cm. The target on the Prince rule is

brought forward until the patient reports blurring; this distance is then converted into the diopters of accommodative amplitude, taking into account the +3.00 D addition.

- A distance target and lenses of increased minus sphere to induce accommodation are used. More minus sphere is added until the subject can no longer overcome the minus lenses with accommodation. The amount of minus sphere that can be overcome represents the accommodative amplitude.

The accommodative range refers to the range of distances that can be viewed clearly by using accommodation. Typically, it is expressed without correction for emmetropia. A person with +2.00 D hyperopia with +4.00 D of accommodation would have an uncorrected accommodative range of infinity to 50 cm, whereas one with −2.00 D myopia with a similar accommodative amplitude would have an accommodative range of 50 cm–17 cm.

## DIFFERENTIAL DIAGNOSIS

The most common cause of accommodative dysfunction is presbyopia. Symptoms of bilateral, progressive blurred vision at near with eye strain, in a patient of appropriate age, are usually enough to make the diagnosis. When presbyopic symptoms or decreased accommodative amplitudes are seen in an individual younger than age 40 years, the patient most likely has latent hyperopia; a cycloplegic refraction confirms the diagnosis.

Accommodative problems also can be caused by lesions anywhere along the neuroanatomical pathway that subserves accommodation.<sup>6</sup> These, however, are relatively rare. Trauma to the parasympathetic nuclei in the midbrain, to supranuclear structures, or to the third cranial nerve can produce asthenopic symptoms. Concussion in adolescents is associated with accommodative and convergence dysfunction in approximately 50% of cases.<sup>7</sup>

Adie's tonic pupil is typically associated with decreased accommodation, which resolves over time as accommodative fibers reinnervate the pupil. Pharmacological cycloplegia also produces temporary accommodative dysfunction. Systemic medications, especially anticholinergics, can cause decreases in accommodation. A number of systemic diseases can cause either temporary or permanent loss of accommodation,<sup>6</sup> though these diseases typically do not present with loss of accommodation as a chief complaint.

Whether accommodative dysfunction occurs in otherwise healthy children is a subject of controversy in the optometry and pediatric ophthalmology literature. Some authorities believe that decreased accommodative amplitudes in children are effort related (as evidenced by lack of pupillary

constriction to an attempted near target); others believe that such an entity is real and can be treated successfully with orthoptic exercises.<sup>8,9</sup>

Increased accommodation occurs rarely. Patients with acute Horner's syndrome may notice an increased accommodative range on the affected side. An abnormally proximal near point of accommodation is caused by miotic agents, such as pilocarpine. When seen in isolation, accommodative spasm is usually a functional disorder associated with episodic esotropia, diplopia, blurred vision at distance, miosis, and an abnormal near point of accommodation. It has been reported as a persistent condition, but this is rare, and may respond to cycloplegia.<sup>10</sup> Accommodative spasm has been associated with numerous other systemic conditions, including head trauma.<sup>6</sup>

## TREATMENT

Once any latent hyperopia has been addressed, the treatment of presbyopia involves the use of plus lenses for near work either in a bifocal or as reading glasses. Several methods can be used to determine the proper addition. Most problems with reading additions result from overcorrection for the near distance. Correction to emmetropia and the use of trial frames (rather than the phoropter) to determine the proper addition yield the best results. Multifocal intraocular lenses and monovision correction are also used as treatment for presbyopia. Acquired causes of loss of accommodation can be treated similarly.

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# Headache and Facial Pain

Joel M. Weinstein, Michelle Y. Wang

9.22

**Definition:** Chronic, intermittent, or episodic pain that involves the head, skull, scalp, or face.

### Key Features

- Most headaches fall into specific rubrics (e.g., migraine, tension-type headache) that involve fairly common patterns of symptoms.
- Most headaches do not reflect serious organic disease, but a thorough history is critical to identify certain red flags.

### Associated Feature

- Although usually benign, the pain from headaches can be devastating and interferes with routine activities.

## INTRODUCTION

Headache and facial pain are among the most common complaints seen in medical practice. In this chapter, a working approach to facilitate the diagnosis of patients with headache is elucidated. This requires both knowledge of various nonophthalmological disorders and a methodology with which to elicit the relevant clinical history.

### The Art and Science of Taking a Headache History

To sort out the multitude of factors that can contribute to or cause headaches, it is essential to obtain a relevant past medical history, a basic neurological review of systems, and a directed headache history (outlined in the next section and in [Box 9.22.1](#)).

### Basic Outline of the Headache History

#### *Date of Onset, Age at Onset, and Frequency of Symptoms*

The length of time that a patient has suffered from headaches is the first guidepost in differentiating benign headaches from those that signify a progressive neurological or systemic disorder. At one end of the spectrum, a pattern of long-standing intermittent headaches with headache-free intervals recurring over months to years is rarely indicative of serious intracranial or systemic pathology. Most of these patients have vascular or tension-type headaches. Conversely, the sudden onset of severe and persistent headaches in an otherwise headache-free individual, especially when accompanied by focal neurological signs or symptoms, is clearly a cause for concern. Patients experiencing their first attack of migraine may

cause confusion in this regard, however, because the initial episode may be accompanied by focal deficits (e.g., hemianopia) but not by the typical signs and symptoms that characterize most recurrent vascular headache episodes.

Some headaches develop, and perhaps progress, over weeks to months. Although most headaches in this category have a benign cause, this is the group of patients in which serious intracranial or systemic pathology should be carefully ruled out. Headaches that result from intracranial masses or increased intracranial pressure usually have an insidious onset and occur daily, and there are rarely prolonged headache-free intervals.

### Location

Tension-type headaches are often occipital in location and extend to the posterior neck and shoulders ([Fig. 9.22.1](#)). However, intracranial processes, especially in the posterior fossa, can cause a similar distribution of pain. A band-like distribution of pain, which presumably reflects occipitofrontalis tension, also is quite common in patients who have tension-type headache. Hemicranial headaches that become holocephalic are generally vascular (i.e., migrainous) in nature. Headaches of dental or sinus origin frequently cause frontal, periorbital, or malar pain.

### Duration

Persistent and unrelenting pain that lasts for days at a time rarely results from vascular or tension headaches; it should arouse suspicion of intracranial disease, sinus inflammation, cranial arteritis, or carotid dissection.

### Predisposing Factors

For a minority of patients with vascular headache syndromes, foods or allergens have been identified that precipitate headaches.<sup>1</sup> These include chocolate, red wine, oranges, and fatty foods. In other vascular headache patients, stress—or, more commonly, relief of prolonged stress—triggers a headache episode. Other triggers for vascular headache include bright lights, exercise, sexual intercourse, and alcohol.

### Preceding Symptoms

Many patients with vascular headaches have some form of premonitory symptoms that precedes their headache by as much as 24 hours or more.<sup>2</sup> This may include drowsiness, irritability, insomnia, depression, or hypomania. Unformed visual hallucinations occur in 10%–15% of migraineurs; typically, these last 10–40 minutes and are followed almost immediately by headache. It is important to differentiate the migrainous visual prodrome from the hallucinations that may occur as epileptiform phenomena in patients who have more serious intracranial disease (see later).

### Quality and Severity of Pain

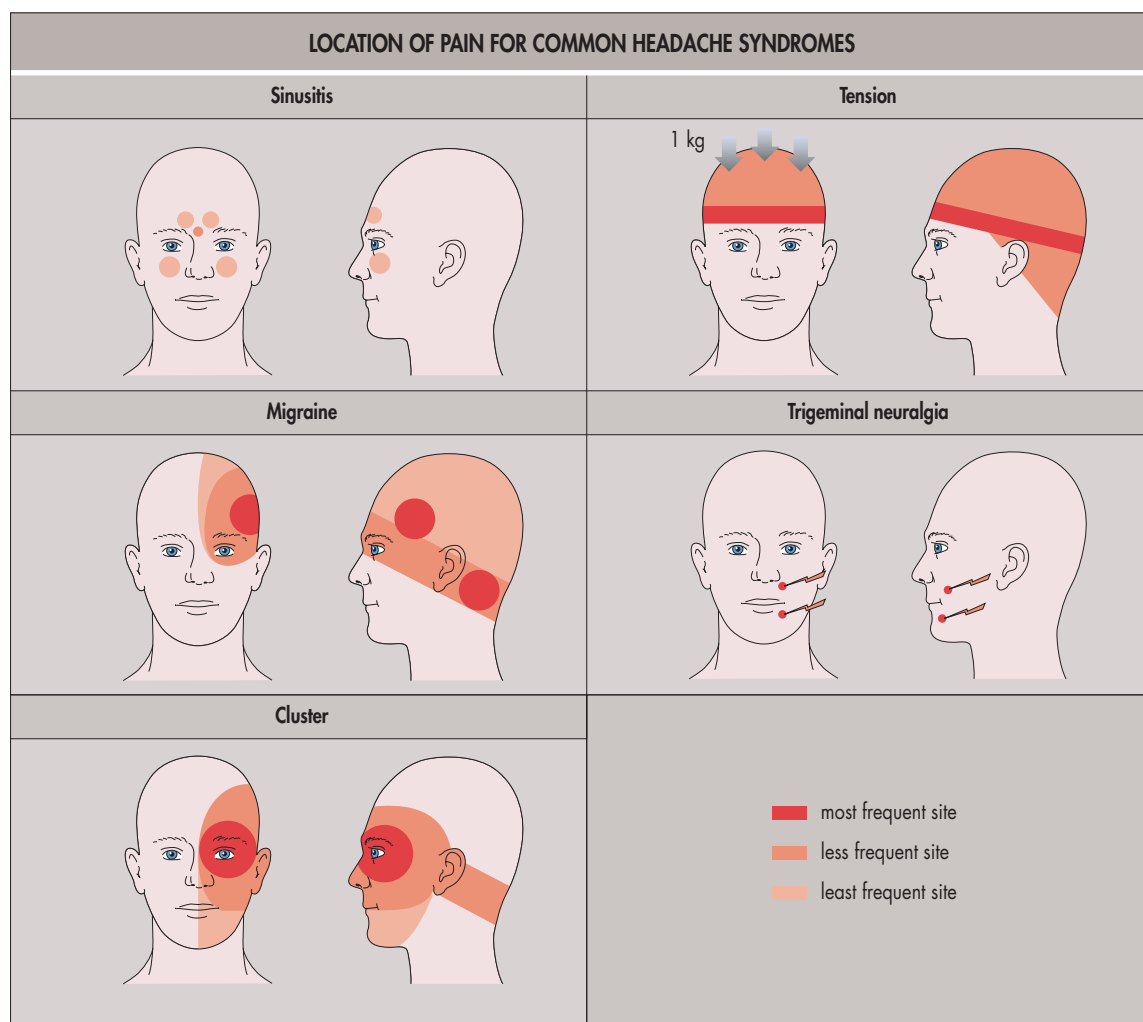
Both vascular headaches and headaches that result from intracranial masses may vary widely in severity, from mild to excruciating. Pain from vascular headache starts out as a dull ache but frequently becomes pulsatile and often is described as “throbbing.” It may be alleviated by compression or massage of the external carotid artery; usually, it is exacerbated by physical activity. Cluster headaches characteristically are extremely severe. Tension-type headaches are seldom severe enough to require bed rest and rarely are described as “throbbing.” Headache from intracranial hemorrhage typically is quite severe and usually is accompanied by focal signs or other neurological symptoms.

### Accompanying Symptoms

Nausea, photophobia, phonophobia (e.g., aversion to sound, especially loud noises), and drowsiness frequently occur during acute migraine headaches and are useful in differentiating vascular from nonvascular paroxysmal headache syndromes. These symptoms also may occur in acute

#### **BOX 9.22.1 Basic Outline of the Headache History**

Date of onset/age at onset  
Frequency of symptoms  
Location  
Duration  
Predisposing factors  
Preceding symptoms  
Quality and severity of pain  
Accompanying symptoms



**Fig. 9.22.1 Location of Pain for Common Headache Syndromes.** Tension headache often is described as a feeling of weight in the head or a band-like sensation around the head. The stabbing nature of trigeminal neuralgia is depicted by zigzag lines.

intracranial processes, however, which must be distinguished on the basis of other signs and symptoms. A detailed review of neurological symptoms must be elicited from all patients with headache, and this greatly aids in identifying patients who have intracranial inflammation, hemorrhage, or space-occupying lesions.

## DIFFERENTIAL DIAGNOSIS OF HEADACHE SYNDROMES

The International Headache Society (IHS) has classified headache and facial pain disorders and has provided diagnostic criteria by which various syndromes can be distinguished (a partial listing is given in [Box 9.22.2](#)). At this time, however, no specific diagnostic tests exist for the three most common headache disorders:

- Migraine.
- Tension-type headache.
- Cluster headache.

The diagnostic criteria, therefore, are highly dependent on an accurate and reliable history.

### Migraine

The IHS classification separates patients with migraine into those without focal neurological symptoms, or “aura,” preceding or accompanying the headache and those with such symptoms (subtypes 1.1 and 1.2, respectively). Subtype 1.3 describes frequent and chronic headache that could be either tension-like and/or migraine-like. Prolonged attacks or attacks that result in permanent ischemic damage to the central nervous system are defined as complications of migraine under subtype 1.4. Subtype 1.5 describes migraine-like attacks but excludes one of the diagnostic features, and this type was previously termed *migrainous disorder* and now termed *probable migraine*. Subtype 1.6 includes several well-recognized but uncommon clinical syndromes associated with migraine with or without aura. This subtype was previously noted to occur in childhood and termed

*childhood periodic syndromes* or *abdominal migraine*; however, it can occur in adulthood as well.

### Epidemiology of Migraine

Migraine has been a major public health issue, costing significant disability and medical expenses. Data from National Ambulatory Medical Care Survey/National Hospital Ambulatory Medical Care Survey showed that headache was the fifth leading cause of emergency room visits. In the United States, large-scale surveillance studies, including the National Health Interview Survey and the National Health and Nutrition Examination Survey, found that the 3-month prevalence rates of migraine ranged from 16.6% to 22.7%.<sup>3</sup> The American Migraine Prevalence and Prevention found prevalence rates of 11.7% for migraine and 4.5% for probable migraine.

Migraine is more common in women, affecting one in every four women. The prevalence is lower in children but is still substantial,<sup>4</sup> with an equal prevalence of about 3% for boys and girls at age 7 years, increasing to 15% at age 15 years. The first attack of migraine occurs before age 10 years in about 25% of patients, by age 25 years in about 65%, and by age 40 years in more than 90%.<sup>4</sup> Onset in later life does occur, however, and may be confused with transient cerebral ischemia. The criteria used to differentiate migraine equivalents in older patients from transient cerebral ischemic episodes have been discussed at length by Fisher.<sup>5</sup> Of all features, visual symptoms are the most common presentation in late-life migraine.<sup>6</sup>

No consistent relationship to ethnic group, socioeconomic status, or personality profile has been found. However, a familial predisposition for migraine clearly exists. One genetic study found a risk of 70% if both parents were affected and 45% if only one parent was affected.<sup>7</sup> The pattern of inheritance appears to be complex and multifactorial. More genetics studies are underway, which may provide more insights into the pathophysiology of migraine.<sup>8</sup>

### Clinical Features of Various Migraine Syndromes

#### Migraine Without Aura (Previously Termed Common Migraine)

The IHS published its third edition of *Classification of Headache Disorders* in 2013.<sup>9</sup> Migraine without aura is defined by the IHS as at least five attacks

### BOX 9.22.2 Partial Listing of the IHS Classification of Headaches (2013)

1. Migraine
  - 1.1 Migraine without aura
  - 1.2 Migraine with aura
    - 1.2.1 Migraine with typical aura
      - 1.2.1.1 Typical aura with headache
      - 1.2.1.2 Typical aura without headache
    - 1.2.2 Migraine with brainstem aura
    - 1.2.3 Hemiplegic migraine
    - 1.2.4 Retinal migraine
  - 1.3 Chronic migraine
  - 1.4 Complications of migraine
    - 1.4.1 Status migrainosus
    - 1.4.2 Persistent aura without infarction
    - 1.4.3 Migrainous infarction
    - 1.4.4 Migraine aura-triggered seizure
  - 1.5 Probable migraine
  - 1.6 Episodic syndromes that may be associated with migraine
2. Tension-type headache
3. Trigeminal-autonomic cephalalgias (TACs)
  - 3.1 Cluster headache
  - 3.2 Paroxysmal hemicrania
4. Other primary headache disorders
  - 4.7 Primary stabbing headache
6. Headache attributed to cranial or cervical vascular disorder
  - 6.4.1 Headache attributed to giant cell arteritis (GCA)
11. Headache or facial pain attributed to disorder of the cranium, neck, eyes, ears, nose, sinuses, teeth, mouth or other facial or cervical structure
  - 11.5 Headache attributed to disorder of the nose or paranasal sinuses
13. Painful cranial neuropathies and other facial pains
  - 13.1 Trigeminal neuralgia
  - 13.8 Paratrigeminal oculosympathetic (Raeder's) syndrome

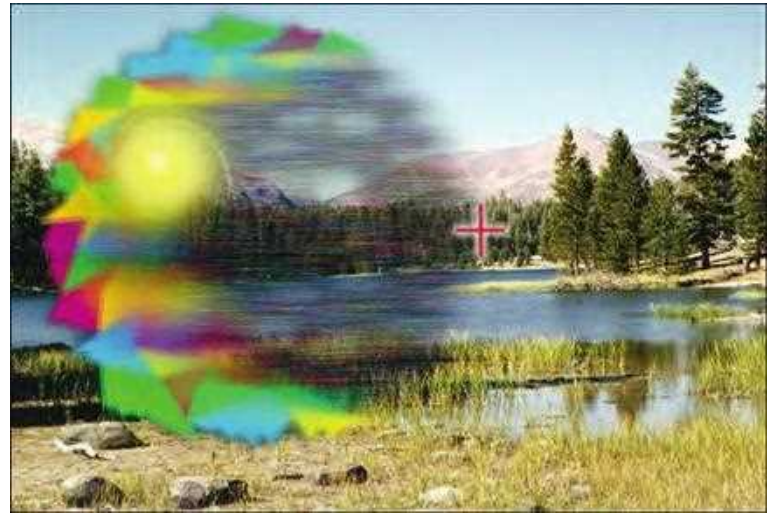
For the complete classification, see Headache Classification Committee of the International Headache Society. The International Classification of Headache Disorders, 3rd ed. (beta version). Cephalalgia 2013 Jul;33(9):629–808.

of headache lasting 4–72 hours, which has at least two of the following characteristics: (1) unilateral, (2) pulsating, (3) moderate or severe intensity, and (4) aggravation by physical activity. The headache is associated with (1) nausea, and/or vomiting; or (2) photophobia and phonophobia. Migraine headache in children and adolescents is more commonly bilateral. Although migraine without aura is not preceded by focal neurological symptoms (by definition),<sup>10</sup> many patients notice autonomic or mood disturbances as long as 24 hours before an impending attack.<sup>2</sup> These include irritability, depression, drowsiness, and hunger (sometimes with a craving for specific foods). Other patients may experience hypomania or elation. These premonitory symptoms presumably arise in the hypothalamus; it is interesting, in this regard, that similar symptoms may be induced by certain 5-hydroxytryptamine (5-HT) antagonists.<sup>11</sup>

The headache phase of migraine without aura usually begins unilaterally, often in the periorbital area, and may or may not progress to become holocephalic. The pain may begin anywhere on the head or face. Although many migraineurs report a strong predilection for episodes to occur repeatedly on the same side, most report occasional episodes on the other side as well. Frequent episodes that involve only one side should arouse suspicion of a space-occupying lesion. The pain often is described as “throbbing,” usually builds over 1–2 hours and typically lasts 4–8 hours; however, attacks that last up to 24 hours are not uncommon. The pain usually is exacerbated by routine physical activity, such as bending or minor exertion. Nausea is a prominent feature in 80%–90% of migraineurs, but vomiting is relatively uncommon. Photophobia and phonophobia are relatively common, and most patients withdraw to a dark, quiet room and lie still during severe attacks. Drowsiness is common, and many patients find that sleep provides substantial relief.

#### Migraine With Aura (Previously Termed *Classic Migraine*)

The IHS defined migraine with aura as having at least two attacks of one or more reversible aura with at least two of the following characteristics: (1) at least one aura symptom occurring gradually over  $\geq 5$  minutes; (2) aura symptom lasting 5–60 minutes; (3) at least one aura being unilateral,



**Fig. 9.22.2 Scintillating Scotoma in Migraine With Aura.** The leading edge of the scotoma is “positive” (i.e., it consists of bright flickering imagery that obscures or replaces the normal visual field), whereas the trailing edge of the scotoma often is “negative” (i.e., it displays a relatively dark area that fully or partially obscures the visual surround). The illustration depicts a typical fortification scotoma with sharply angulated borders; many other variants of the migraine scotoma may occur (see text).

and (4) aura accompanied or followed by headache within 60 minutes. Aura symptoms are most often visual symptoms but can also be sensory, speech, motor, or brainstem symptoms.

Migraine with aura is characterized by a prodrome consisting of a completely reversible focal neurological symptom that typically lasts 15–45 minutes.<sup>7,11–13</sup> This prodrome is followed by a headache with a duration and quality similar to that of migraine without aura. The most common prodrome is, of course, the homonymous scintillating scotoma. Less frequently, the aura may consist of a hemi-sensory disturbance (paresthesia or numbness that involves one side of the body or face), hemiparesis, or dysphasia.<sup>10,12</sup> With the exception of the typical homonymous visual aura (described later), patients who have focal neurological defects require neurological consultation to differentiate migraine from more serious transient cerebral ischemia.

The most common description of the visual aura is the perception of multicolored shimmering (scintillating) lights, beginning in the paracentral area and expanding in a crescent-shaped fashion to obscure a large portion of a homonymous hemi-field of both eyes (Fig. 9.22.2). The borders of the scotoma often have jagged edges (teichopsia, or fortification scotoma, analogous to a medieval fortress). Although the leading edge of the scotoma may be “positive” (i.e., may have flickering imagery that obscures or replaces the normal visual field), the trailing edge of the scotoma is often “negative” (i.e., displays a relatively dark area that fully or partially obscures the visual surround, as illustrated in Fig. 9.22.2). Other variants include a gray, black, or colored haze; the perception of a swirling pool of water; and “television interference” or “snow.”<sup>13</sup>

It is quite common for patients who have homonymous visual loss of any cause to perceive their deficit incorrectly as monocular and ipsilateral to the visual field defect. In patients who report monocular loss, it is imperative to determine whether each eye was checked separately. In most instances, the patient’s report of a negative scotoma with both eyes open is an indication that the episode of visual loss was homonymous rather than monocular.

#### Structural Lesions That Mimic Migraine With Aura

Rarely, structural disease that involves the occipital region will mimic migraine with visual aura. In particular, arteriovenous malformations (AVMs) of the occipital lobe are examples, which may cause transient homonymous visual loss with scintillating scotoma and headache. In the vast majority of cases, however, these two syndromes may be differentiated on clinical grounds alone. In two large series on occipital AVMs,<sup>14,15</sup> none of the patients had the 15- to 20-minute visual episodes that are characteristic of classic migraine. The headaches in patients with AVMs were consistently localized to the same side. In addition, the visual phenomena often persist intermittently throughout the headache, unlike in classic migraine, in which the visual aura is usually complete before the onset of headache.



### Recurrent Painful Ophthalmoplegic Neuropathy (Previously Termed *Ophthalmoplegic Migraine*)

The IHS defined recurrent painful ophthalmoplegic neuropathy as at least two attacks of unilateral headache accompanied by ipsilateral paresis of at least one ocular motor nerve. The vast majority of patients experienced their first attack in early childhood.<sup>16</sup> Recurrent painful ophthalmoplegic neuropathy almost always involves the third cranial nerve. Rare cases of sixth cranial nerve involvement, and even rarer cases that involve the fourth cranial nerve, have been reported. It is important to exclude other reasonable causes by clinical and radiological studies.

In addition to these criteria, Daroff<sup>17</sup> pointed out that a characteristic abnormality has been demonstrated in all cases involving the third nerve in which magnetic resonance imaging (MRI) has been performed: thickening and contrast enhancement of the nerve root as it exits the midbrain. This and other clinical findings led Lance and Zagami<sup>18</sup> to postulate that recurrent painful ophthalmoplegic neuropathy is a recurrent demyelinating, inflammatory cranial neuropathy.

The headache that occurs in recurrent painful ophthalmoplegic neuropathy is not always severe. It usually begins ipsilaterally but may become bilateral; it lasts from several hours to days. Rarely, the pupil is spared. The ophthalmoplegia usually resolves completely, but residual ptosis and ophthalmoplegia may be present after repeated attacks. Resolution usually requires several weeks or, less commonly, several months.

The differential diagnosis of painful ophthalmoplegia is discussed at length in Chapter 9.16. In practice, when presented with a patient who is undergoing a first episode of pupil-involving third nerve palsy, it is almost always necessary to rule out an aneurysm or other compressive lesion via neuroimaging studies.

The etiology of recurrent painful ophthalmoplegic neuropathy is uncertain and multiple mechanisms may be involved. The evidence for these disparate, but perhaps complementary, mechanisms has been discussed at length by various authors.<sup>16-18</sup>

### Retinal Migraine

The IHS defined retinal migraine as having at least two attacks of fully reversible monocular positive and/or negative aura with at least two of the following characteristics: (1) aura spreading gradually over  $\geq 5$  minutes; (2) aura lasting 5–60 minutes; and (3) aura accompanied by or followed by headache within 60 minutes. Although most visual symptoms in migraine are hemianopic and cortical in origin, transient (rarely permanent) monocular visual loss is well documented.<sup>19-21</sup> Both optic nerve<sup>21</sup> and retinal<sup>19,20</sup> ischemic episodes have been reported in migraine. In some cases, the amaurosis may occur during, rather than before, the headache phase. Retinal vasospasm has been observed ophthalmoscopically during the attack in several patients.

There appears to be two categories of young patients who experience amaurosis fugax secondary to presumed or observed vasospasm. The first group includes individuals who have well-established migraine, with or without hemianopic auras, who develop migraine headaches associated with episodes of amaurosis fugax.<sup>19,22,23</sup> The second group consists of young patients with no history of migraine who experience episodes of amaurosis fugax.<sup>19</sup> The mechanism of visual loss in this second group is less clear, and its relationship to the dynamics of migraine is less certain than for the first group. Many of the patients in the second group have antiphospholipid antibodies or other evidence of autoimmune disturbance. Nevertheless, patients in this group, like those in the first, tend to respond well to calcium channel blockers or sometimes to aspirin.<sup>22,23</sup> It has been suggested that retinal vasomotor instability, as a result of a migraine-like mechanism, may be compounded by interference with prostacyclin release at the endothelial cell level (in some cases because of antiphospholipid antibodies).<sup>24</sup> This would account for the beneficial effect of both aspirin and calcium channel blockers. However, nonmigraine diagnoses should be excluded in all patients (young and old) who have amaurosis fugax. These diagnoses include embolic disease from the heart and carotid-ophthalmic system, hypercoagulability and hyperviscosity of various causes, and systemic vasculitides (for a detailed discussion of the differential diagnosis of amaurosis fugax, see Chapter 9.26).

### Pathogenesis of Migraine

Although the pathogenesis of migraine remains uncertain, most researchers believe that the vascular alterations are not primary but result from a complex interplay of neuronal, hormonal, hematological, biochemical, and myogenic factors. The major controversies revolve around the mechanisms by which the prodrome, aura, and headache phases are triggered by the following:

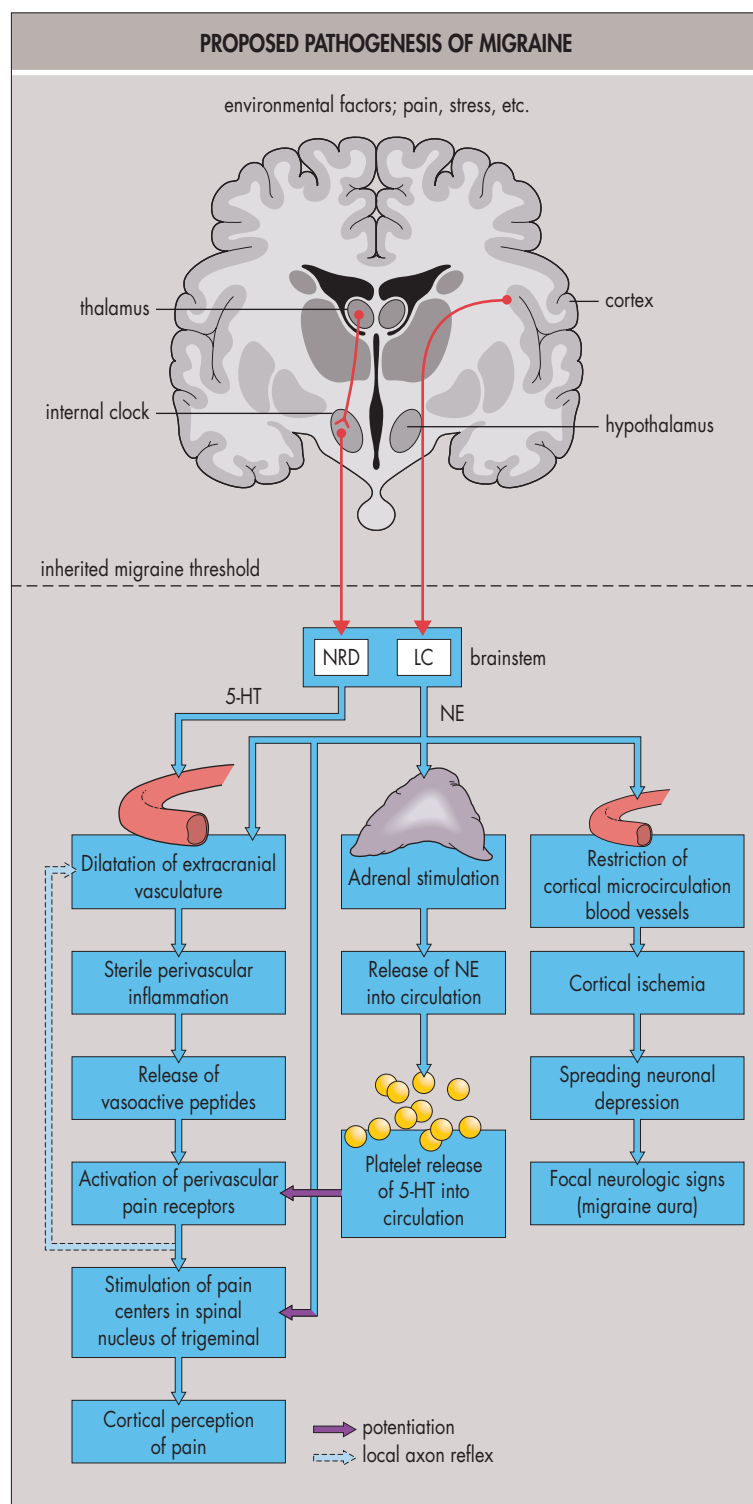


Fig. 9.22.3 Proposed Pathogenesis of Migraine.

- Primary aberrant neuronal activity.
- Various neuropeptides and vasoactive substances.
- Primary alterations in extra- and intracerebral blood flow.

Although an exhaustive discussion of migraine pathogenesis and the interplay of these mechanisms is beyond the scope of this chapter, the major theories are outlined briefly and illustrated in Fig. 9.22.3. The interested reader is referred to a thorough account in two reviews.<sup>25,26</sup>

On the basis of epidemiological evidence, there is general agreement that migraineurs have a genetically determined lower threshold for certain environmental (or internal) triggers that can initiate a peculiar cascade of vascular and neurogenic events and lead to a migraine episode. Migraineurs differ from headache-free controls in several aspects of pain control and cerebrovascular reactivity, including the following:

- Altered hypothalamic and brainstem responses to various stimuli, including dopaminergic agonists.

- Altered intra- and extracranial vascular reactivity to stress, exercise, carbon dioxide, and cold stimuli (e.g., brief headache induced by ice cream is much more common in migraineurs).
- Diminished responses at various central nervous system sites to dopaminergic agents.
- Altered platelet function, especially with regard to 5-HT (or serotonin) release.

On the basis of data from both human study and an experimental model, Lance et al.<sup>11</sup> proposed the mechanism for the development of migraine outlined here and illustrated in Fig. 9.22.3. An inherited migraine threshold renders the migraineur unusually susceptible to fluctuations in cortical or hypothalamic function (signaled by mood changes, excessive thirst, hunger, etc.). Once this threshold is reached, the following sequence of events is activated (see Fig. 9.22.3).

Brainstem nuclei, including the nucleus raphe dorsalis (NRD) and the locus ceruleus (LC), are activated by cortical and hypothalamic events. These pathways employ 5-HT and norepinephrine (NE; noradrenaline), respectively, as neurotransmitters. Stimulation of the LC causes constriction of the cortical microcirculation blood vessels via release of the neurotransmitter NE. Stimulation of the LC, NRD, or trigeminal nerve may cause dilatation of the extracranial vasculature.

Cortical ischemia produced by microvascular changes may be accompanied by spreading neuronal depression, associated with focal neurological symptoms (e.g., homonymous hemianopia). This accounts for the migrainous aura, which may occur independently of the headache.

Release of 5-HT and vasoactive peptides at nerve endings on blood vessels may induce a sterile inflammatory response, which results in pain. This response may be perpetuated by local axon reflexes or by a central reflex pathway.

Stimulation of the LC also causes release of NE from the adrenals; NE, or an unknown 5-HT-releasing factor, causes platelets to release 5-HT into the circulation. Free 5-HT causes increased sensitivity of vascular receptors, which potentiates both abnormal vascular reactivity and the painful inflammatory response.

Pain afferents from intra- and extracranial vascular structures synapse on second-order neurons in the spinal nucleus of the trigeminal nerve. Transmission at these neurons is regulated, in part, by the LC, as well as by other brainstem nuclei. Improper activity of the LC may potentiate transmission of pain impulses at these synapses.

### Treatment of Migraine With Aura and Migraine Without Aura

The management of migraine should include patient education and reassurance, avoidance of triggers, and both nonpharmacological and pharmacological therapy.<sup>27</sup> Lifestyle modifications, including regular exercise, maintaining a regular sleep pattern, and smoking cessation, are an important part of headache management. Others may find relaxation training and biofeedback helpful. Pharmacological therapy consists of acute (abortive) treatment to terminate an attack and relieve pain and preventive (prophylactic) treatment to reduce attack frequency, severity, and duration. Medication should be selected on the basis of side-effect profiles, comorbidities, and personal considerations and tailored to each patient.

Acute migraine treatment consists of nonspecific and specific agents. Nonspecific medications, such as analgesics, opioids, antiemetics, corticosteroids, and dopamine antagonists, may be able to control acute pain caused by migraine as well as other pain disorders. More specific medications, including ergotamine, dihydroergotamine (DHE), and triptans can better control migraine attacks but not pain associated with other causes. Patients should be educated to take medications at the first sign of an attack to achieve maximal therapeutic benefits. It is important to avoid medication overuse headache by limiting acute medications to <10 days per month.

Patients with mild to moderate nondebilitating migraine may be relieved by nonsteroidal anti-inflammatory drugs, nonopioid analgesics, combination aspirin-acetaminophen-caffeine, or isometheptene muate-dichloralphenazone-acetaminophen.

For patients who have more severe migraines, use of specific medications, such as triptans or DHE, is the preferred treatment.<sup>28</sup> Several triptans are available for oral use. Patients with nausea and vomiting may be given intranasal sumatriptan or zolmitriptan or subcutaneous sumatriptan. Triptans should not be used again within 24 hours or within 24 hours after the use of ergotamine. Given concern for cardiovascular risks, triptans should also not be used in patients with ischemic heart disease, Prinzmetal's angina, uncontrolled hypertension, or vertebrobasilar migraine. Most triptans should not be used in combination with monoamine oxidase

inhibitors. When triptans are used in combination with selective serotonin reuptake inhibitor, the concern for added risk of serotonin syndrome has been raised but is likely low.<sup>29</sup> Nevertheless, risks and benefits must be considered on an individual basis.

If triptans or DHE fail, parenteral ketorolac can be tried. A single dose of parenteral dexamethasone added to abortive therapy for severe migraine headache was found to be associated with a 26% reduction in recurrence rate within 72 hours.<sup>30</sup> Opioids or butalbital should only be used as the last resort.

For patients who have frequent attacks or who do not respond to acute treatment, daily treatment for prophylaxis of headache is warranted. Preventive treatment can reduce the frequency and severity of migraine attacks, improve responsiveness to acute attacks, and prevent progression to chronic migraine. Treatment is highly individualized and may be selected based on the comorbidities. The American Academy of Neurology and the American Headache Society published a guideline for episodic migraine prevention in adults.<sup>31</sup> Beta-blockers (metoprolol, propranolol, or timolol), antiepileptic drugs (divalproex sodium, sodium valproate, topiramate), and triptans (frovatriptan) are effective agents and should be offered to patients for migraine prevention. Antidepressants (amitriptyline, venlafaxine), other beta-blockers (atenolol, nadolol), and other triptans (naratriptan, zolmitriptan) are probably effective and should be considered.

Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers are possibly effective. Calcium channel blockers are frequently used, but data are conflicting. Botulinum toxin injection has been effectively used for chronic migraine.

Controversies in the treatment of migraine are thoroughly discussed in the review by Evans and Lipton.<sup>32</sup> Topics covered include prophylaxis for recurrent or chronic migraine, treatment of basilar or complicated migraine, and use of oral contraceptives in migraine.

## Tension-Type Headache

Episodic tension-type headache is the most common form of headache seen in medical practice.<sup>33</sup> Most patients describe their tension headaches as a mild to moderate "pressing" or "squeezing" sensation, or they may compare the pain to a tight band that encircles the scalp. The pain is generally nonpulsatile and almost always bilateral. It may be bifrontal, bioccipital, or "band-like." Pain radiating to the posterior neck is common, as is tightness of jaw muscles. Nausea, photophobia, and phonophobia are absent or minimal. Unlike migraine, tension headaches are not exacerbated by routine physical activity. In addition, unlike migraine, tension headaches are not preceded by the prodromal constitutional or focal neurological symptoms noted earlier.<sup>33</sup>

Tension headaches may occur as infrequently as once a year and last only 30 minutes, or they may last all day and occur daily in an unrelenting fashion. Most patients who seek medical attention for their tension headaches have episodes that occur several times weekly or monthly, punctuated by headache-free intervals. The presence of headache-free intervals helps differentiate these headaches from more serious pathological processes, also taking into account the absence of other systemic or neurological symptoms. These patients are often aware of stressful emotional triggers that precipitate their tension headaches; therefore, they can readily identify, if not control, the exacerbating factors. Depression is present in up to one third of patients who experience persistent tension headaches.<sup>33</sup> Many patients with tension headaches also have migraines, but usually they can differentiate the two types of headache on the basis of severity, duration, and associated symptoms.

There is some controversy about the role of the pericranial musculature in the production of tension headache.<sup>33</sup> Although muscle spasm and tenderness may be the result, rather than the primary cause, of chronic tension headaches in many patients, it appears that distinct myofascial trigger points can be a source of pain in some patients. The myofascial pain syndrome is characterized by reproducible pain on palpation of trigger points.<sup>33</sup> The pain generally is referred to a location somewhere along the band of taut muscle that includes the trigger point, although it may be at some distance from the trigger point itself. According to Jay,<sup>34</sup> the syndromes of tension headache, myofascial pain syndrome, and fibromyalgia represent a spectrum of severity of the same underlying disorder.

## Cluster Headache

Cluster headaches are perhaps the most painful type of "benign" headache. The pain can be so severe that some patients with this disorder report experiencing suicidal thoughts. The pain typically is unilateral and

periorbital in location and tends to occur on the same side during each attack; rarely is the opposite side involved. Unlike migraines, cluster headaches are more common in men than in women. In addition, patients with cluster headaches, unlike migraineurs, generally are hyperactive during an attack—they often pace the room or rock fitfully in a chair. Sympathetic dysfunction ipsilateral to the pain is common.<sup>35</sup> Horner's syndrome may be present during the attack, along with lacrimation, conjunctival injection, nasal congestion, rhinorrhea, and eyelid edema. Horner's syndrome may persist, especially after repeated attacks; pharmacological testing reveals a postganglionic localization. Attacks are usually shorter than in migraine and last 15–180 minutes, with an average of about 45 minutes. The attacks cluster in time; characteristically, they occur at least once daily, usually at the same time of day. Nocturnal occurrence is common, and the headache often wakes the patient from sleep. Some patients also find that attacks can be precipitated by alcohol, histamine, or nitroglycerin ingestion. As the cluster period progresses, the frequency of episodes may increase to eight per day. The cluster period typically lasts for 4–12 weeks. The patient is then asymptomatic until the next cluster period, which typically occurs a year or more later, usually at the same time of year.

The treatment of cluster headaches is highly individualized and has been reviewed at length elsewhere.<sup>35</sup> Some of the same agents used for migraine may be used for cluster headache as well and include sumatriptan for acute attacks and methysergide for short-term use (<6 months). In addition, prednisone is often effective in halting bouts of cluster headaches. For more resistant cases, lithium is often useful.

## Paroxysmal Hemicrania

Normally classified as a cluster headache variant, this unusual syndrome is characterized by multiple brief episodes of “stabbing” pain, typically in the periorbital region.<sup>36</sup> The pain usually is quite severe and lasts for 2–30 minutes. Repeated series tend to occur throughout the day, as often as 10–15 times. Episodes are accompanied by hemicranial autonomic dysfunction similar to that seen with cluster headaches. Unlike cluster headache, men and women are equally affected. The syndrome often responds to indomethacin 50 mg three times daily.

## Temporal Arteritis

Headache is the most common symptom in temporal arteritis<sup>37,38</sup>; this diagnosis should be considered in all adults age >50 years and have headache or facial pain. The headache of temporal arteritis classically is located over a branch of the superficial temporal artery and is described as a “dull ache” that persists throughout the day. It may be accompanied by tenderness of the artery and overlying scalp.<sup>37,38</sup> The artery, if severely affected, may be indurated and nonpulsatile. Many patients, however, present with a nonspecific unilateral or bilateral headache.

All patients in this age group should be asked specifically about symptoms of vasculitis and vascular insufficiency that involve the extracranial carotid circulation. These include the following:

- Presence of pain or tenderness around the temporal arteries.
- Scalp tenderness.
- Pain or fatigue with chewing (i.e., jaw or tongue claudication).
- Diplopia, which is generally thought to result from extraocular muscle ischemia rather than from cranial neuropathy.
- Transient visual loss as a result of optic nerve or retinal ischemia.

In addition, many but not all patients with temporal arteritis have symptoms of more widespread rheumatological involvement (i.e., polymyalgia rheumatica).<sup>37</sup> These symptoms may be nonspecific and include malaise and easy fatigability, weight loss, anorexia, proximal myalgias, and unexplained fevers.

A sedimentation rate should be obtained to rule out temporal arteritis in all patients a >60 years complaining of headache or facial pain, unless the pain obviously results from another cause. The test is simple, noninvasive and identifies about 90% of patients who have this disorder.<sup>37</sup> Unless otherwise contraindicated, corticosteroid therapy should be instituted, pending results of a temporal artery biopsy. A thorough discussion of the issues that surround diagnosis and therapy of temporal arteritis can be found in Chapter 9.8.

## Headache as a Result of Intracranial Processes

Ruling out intracranial pathology should be one of the primary goals of the ophthalmologist when evaluating a patient with headache. Although

### BOX 9.22.3 Warning Signs for Headaches Caused by Serious Intracranial or Systemic Pathology

New onset headache in a previously headache-free patient  
New pattern or new type of headache  
“The worst headache I’ve ever had.”  
Change in personality or mental status  
Focal neurological deficit  
Signs of meningeal irritation  
Unexplained fever  
Recent head trauma

myriad intracranial processes can cause headache, most intracranial pain is caused by inflammation or stretching of pain-sensitive structures in the dura and blood vessels. Although the complete differential diagnosis of intracranial headache is beyond the scope of this chapter, several warning signs should alert the ophthalmologist to the possibility of a serious neurological problem (Box 9.22.3):

- A change in the usual pattern of headache. An acute or subacute increase in the intensity and frequency of a well-established headache pattern should arouse suspicion, as should the onset of a new type of headache.
- Headache described as “the worst headache I’ve ever had.”
- Headache triggered by exertion, by coughing or sneezing, or by postural changes, such as bending over. These features often signal irritation or stretching of pain-sensitive intracranial structures.
- Headache accompanied by signs of meningeal irritation, such as stiff neck, nausea, vomiting, or fever.
- Headache accompanied by focal or nonfocal neurological signs (e.g., focal weakness or numbness, aphasia, impaired cognitive function, change in personality).

Negative responses to questions about these “red flags” help rule out intracranial pathology.

## DIFFERENTIAL DIAGNOSIS OF FACIAL PAIN

Facial pain may arise from a variety of structures of the face and neck, including the sinuses, nasopharynx, teeth and gums, facial muscles, orbit, middle ear, trigeminal nerve, muscles of mastication, and carotid artery and its tributaries.

### Headache Attributed to Disorders of the Nose or Paranasal Sinuses (Previously Termed *Sinus Headache*)

The diagnosis of pain that results from acute sinus inflammation is rarely difficult. A prior history of sinus inflammation or respiratory allergies is often elicited. In general, the pain is of low to moderate intensity and is present on a daily basis. The pain usually is localized to the frontal or maxillary area, and there is tenderness to percussion over the affected sinus. The pain is often worsened by bending forward and may be accentuated by blowing the nose or sneezing. Symptoms of nasal “stuffiness” are usually present, and mucopurulent drainage from the nostrils may be seen. If the nasal passages are blocked, use of a nasal decongestant can be useful diagnostically and often results in discharge. In doubtful cases, a simple plain film of the sinuses or an opinion from an otolaryngologist should be obtained.

Sphenoid mucocoeles may invade the orbital apex, resulting in ocular motility disturbances or optic neuropathy. Nasopharyngeal carcinoma has a propensity to invade the base of the skull by traveling along neural foramina.<sup>39</sup> These tumors may cause ocular motility disturbances, most commonly sixth cranial nerve palsy, facial numbness or pain, or decreased hearing as a result of closure of the eustachian tube. These tumors can be missed easily on plain films and require computed tomography (CT) or MRI for early detection.

## Orbital Inflammation and Neoplasia

Although the physical examination and differential diagnosis of orbital disease is beyond the scope of this chapter, the classic signs and symptoms should be elicited meticulously in all suspicious patients (see Chapter



12.10). Small posterior orbital masses, such as optic nerve sheath meningiomas, may cause little exophthalmos, but will be detected by careful testing of visual function, including color vision and pupillary function, and visual fields. Orbital myositis and inflammatory orbital pseudo-tumor ordinarily cause persistent unilateral pain of moderate to severe intensity, and signs of proptosis or dysmotility usually are present.

Posterior scleritis may be difficult to diagnose.<sup>40</sup> The pain is persistent, often moderately severe, and may be accentuated by eye movement. CT or MRI generally shows thickening and enhancement of the affected posterior sclera.

### Classic Trigeminal Neuralgia (Previously Termed *Tic Douloureux*)

Trigeminal neuralgia is characterized by sudden, intense jabs of pain that last only a fraction of a second to 2 minutes.<sup>41</sup> The pain generally is limited to one of the three divisions of the trigeminal nerve, with the second and third divisions involved most frequently. The pain usually is described as lancinating or “stabbing” in quality; it often recurs in a series of paroxysms that extend over several minutes. Most patients can identify a triggering activity, such as chewing, swallowing, or light touch to a part of the face, which initiates a paroxysm. Classic trigeminal neuralgia is usually caused by neurovascular compression of trigeminal nerve by the superior cerebellar artery. MRI is indicated to demonstrate the compression and rule out other secondary causes.

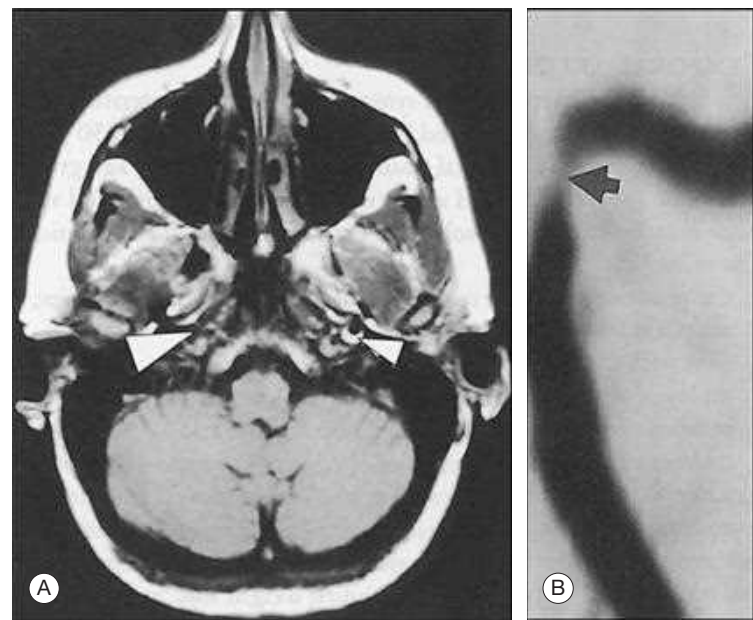
### Paratrigeminal Oculosympathetic (Raeder's) Syndrome

In 1924, Raeder described a series of patients with headache. The first group had episodic headaches caused by what is now known as the *cluster headache syndrome*. The second group had chronic pain in the trigeminal distribution caused by a variety of space-occupying lesions. The term “Raeder's paratrigeminal syndrome” generally should not be used, to avoid confusion between the benign cluster headache syndrome, on the one hand, and potentially lethal skull base tumors or aneurysms, on the other.

Paratrigeminal oculosympathetic syndrome is characterized by constant unilateral pain in the distribution of ophthalmic division of the trigeminal nerve and ipsilateral Horner's syndrome. All patients with suspected oculosympathetic paresis should undergo a cocaine test or apraclonidine test for confirmation and a hydroxyamphetamine test for localization (see Chapter 9.20). These tests should be followed by appropriate neuroimaging of either the base of the skull and upper neck (for postganglionic lesions) or the chest and neck (for preganglionic lesions). Trigeminal sensation should be checked in all three divisions. In patients who have facial pain and postganglionic Horner's syndrome, the clinician should be particularly aware of the signs and symptoms of dissection of the internal carotid artery.<sup>42</sup> Dysesthesia of the scalp and dysgeusia, or unpleasant taste, are common, along with postganglionic Horner's syndrome. Although spontaneous dissections occur, most middle-aged or older patients have hypertension, and most younger patients have had significant neck trauma. The condition usually is diagnosed readily with MRI (Fig. 9.22.4).

### Primary Stabbing Headache (Ice-Pick Headaches, Jabs and Jolts Syndrome)

This syndrome consists of intense stabbing pain that lasts only a few seconds and can occur in the periorbital region, forehead, or frontal area,<sup>43</sup> but extratrigeminal involvement is common. The pain can recur with irregular frequency and move from one area to another. There is no



**Fig. 9.22.4 Magnetic Resonance Imaging (MRI) of Spontaneous Carotid Dissection.** (A) T2-weighted MRI through the base of the skull demonstrates normal flow void in the right internal carotid (large arrow) and curvilinear high signal intensity in the left internal carotid (small arrow) caused by spontaneous dissection in a 52-year-old man with hypertension. (B) Magnetic resonance angiogram in the anterior oblique projection demonstrates an area of narrowing of the internal carotid artery caused by dissection (arrow) just distal to the bifurcation.

associated autonomic symptom. This type of pain is seen in about one third of migraineurs and may accompany a migraine episode or occur independently. When this type of headache occurs independently of migraine episodes, it usually is quite responsive to indomethacin.

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# Tumors, Infections, Inflammations, and Neurodegenerations

9.23

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## Definitions:

- Tumors may compromise the function of adjacent tissues through mechanical compression.
- Infections damage tissue via direct invasion by microorganisms (bacterial, fungal, or viral) and host immunological inflammatory response.
- Inflammations reflect intrinsic responses by various tissues related to the immune system and may compromise tissue function.
- Neurodegenerations of the central nervous system often involve premature dysfunction consequent to genetic factors.

## Key Features

- Tumors, infections, and inflammations of the central nervous system may involve the meninges, the brain substance (parenchyma), or the surface of the brain (extraparenchymal).
- Neurodegenerations may be specific for certain regions of the brain (e.g., Huntington's chorea) or involve the brain diffusely (e.g., Alzheimer's disease).

## Associated Features

- Tumors may be benign or malignant and primary or metastatic.
- Inflammatory and infectious responses may be acute or chronic, according to the cadence of development.

## TUMORS

### Introduction

Brain tumors produce symptoms depending on their size, location, cell of origin, or nonspecific mechanical effects (e.g., blockage of the cerebrospinal circulation). Tumors may present with either localizing or nonlocalizing signs and symptoms. In adults with new-onset seizures, up to one third will harbor an intracranial tumor.<sup>1</sup> Nonlocalizing signs of increased intracranial pressure (papilledema and sixth nerve palsies) may be caused by an intracranial tumor.

Several tumors mimicking infections or inflammations at the base of the brain with neuro-ophthalmic symptoms will be discussed.

### Epidemiology and Pathogenesis

Tumors tend to develop in the posterior fossa in children and in the cerebral hemispheres in adults. Medulloblastomas are most common in male children age 4–8 years. Neuroblastomas, ependymomas, and papillomas of the choroid also are more common in the young.

### Ocular Manifestations

Papilledema and diplopia may be produced by intracranial tumors in any location. Tumors of the optic nerve (meningiomas or gliomas) often produce slowly progressive, painless visual loss, loss of optic nerve functions, visual field defects, and disc edema in the early stage. Eventually, optic atrophy develops. Intraorbital tumors may produce proptosis, resistance to retropulsion, orbital congestion, and diplopia.

Metastatic tumors, or malignant invasive tumors, may produce inflammation and tissue necrosis and may even simulate orbital cellulitis.

Cavernous sinus involvement may produce ophthalmoplegia with or without pain. The signs and symptoms may be quite similar to those of orbital apex syndrome. Numbness or pain in the distribution of the first division of the fifth cranial nerve is common.

Tumors near the optic chiasm, including pituitary adenoma, gliomas, meningiomas, craniopharyngiomas, tumors from the sphenoidal sinus or clivus, may involve the optic chiasm and produce a chiasmal syndrome (bitemporal visual field defects). Pituitary adenomas rarely expand suddenly when affected by necrosis and hemorrhage (pituitary apoplexy).

Tumors in the parietal and temporal lobes may involve the visual pathways and produce corresponding visual field defects. Occipital lobe tumors produce congruous visual field defects but spare visual fixation.

## Pathology

Histopathological features of tumors and immunohistochemistry are useful in the differentiation of subsets of tumor types. Biopsy specimens could be used for frozen section or permanent section or be preserved in mixed buffered aldehydes for possible electron microscopy.

## Treatment

Treatment should address the primary brain tumor, malignant cells in cerebrospinal fluid (CSF), base of the brain syndrome, paraneoplastic syndrome, or possible immune responses. At times, immunosuppressive therapy is of temporary benefit (e.g., corticosteroids for cancer-associated retinopathy or in CSF paraneoplastic disease). Radiation therapy often may be necessary.

### Course and Outcome

Responses to chemotherapy or radiation therapy are extremely variable and depend largely on the type of neoplasm. However, the long-term visual prognosis is guarded.

## INFECTIONS

### Introduction

Infections of the central nervous system (CNS) have a diverse presentation; however, most share four cardinal manifestations:

- Headache.
- Altered mental status.
- Focal neurological signs.
- Fever.

Other characteristics are important in the evaluation of affected patients (time course and natural history of the disease). *Chronic meningitis* is defined as meningitis that fails to improve or progresses over at least 4 weeks of observation.<sup>2</sup> Basilar meningitis usually runs a subacute or chronic course with moderate to high rate of mortality. Focal neurological findings are more common than in acute meningitis. Diagnosis of the causative agent is of utmost importance.

### Epidemiology and Pathogenesis

Meningitis can present with a variety of clinical syndromes. The clinical expression depends on the patient's underlying medical condition and



immune status.<sup>3</sup> *Meningococcus* infection accounts for 20% of all cases in the United States. Interestingly, serogroup B is present in 50% of such cases. In the cases of acute fulminant infectious meningitis, a severe inflammatory process occurs in the meninges, primarily in the subarachnoid spaces over the brain convexity, around the cisterns, and at the base of the brain; the reaction rarely breaks into the parenchyma. As the inflammation continues, adhesions form and interfere with CSF flow and cause meningeal fibrosis along the roots of the cranial nerves. Toxins from the infectious organism also contribute to the inflammatory process via the release of various cytokines.

## Ocular Manifestations

The systemic symptoms of fever, chills, nausea, and vomiting are often accompanied by headache, stiff neck, seizures, and cranial nerve palsies. In viral and bacterial infections, symptoms manifest acutely but are more insidious in the basilar meningitis caused by fungal infection, tuberculosis, syphilis, or other similar causes.

Basilar meningitis may produce diplopia by involving the third, fourth, and sixth cranial nerves. More rarely, an optic neuritis or chiasmatis may develop, leading to loss of vision and visual field. More often, increased intracranial pressure results in papilledema and its associated signs and symptoms.

## Diagnosis and Testing

The hallmark signs for most forms of meningitis are the meningeal signs of Kernig and Brudzinski. The key finding is an abnormal CSF analysis showing increased intracranial pressure, increased white blood cell count, cloudy CSF, increased protein, decreased sugar level, and identification of the microorganism on Gram staining with growth on the appropriate culture media. However, persistent signs and symptoms of acute meningitis with sterile CSF could be seen in patients treated partially. Negative results of Gram staining or culture and sensitivities also may reflect fungal, tuberculous, and parameningeal infections.

## Pathology

Generally, infections are identified by Gram staining or culture and sensitivities. However, on occasion, histopathology may be helpful, particularly in cases of fungal, protozoan, or atypical bacterial infections.

## Treatment

Appropriate antibiotic therapy is essential in cases of bacterial meningitis; delay can result in life-threatening consequences. It is important that the antibiotic crosses the blood–CSF barrier in sufficient concentrations to achieve therapeutic values in CSF. Maintenance of adequate fluid and electrolyte balance is important for control of cerebral edema. Administration of corticosteroids in conjunction with antibiotics has been advocated by some investigators because it is beneficial in reducing neurological sequelae in children.

## Course and Outcome

The outcome may be only minimal neurological sequelae if bacterial meningitis is treated on time and effectively. About 20%–25% of patients may experience variable sequelae ranging from minimal facial weakness and hearing loss to severe intellectual or other physical ailments, such as hemiplegia, paraplegia, seizures, cranial nerve palsies with diplopia, blindness, chronic increased intracranial pressure, syndrome of inappropriate antidiuretic hormone, and subdural effusion. In association with the human immunodeficiency virus (HIV) epidemic, infectious meningitis may become more resistant to therapy, and the process may be chronic and indolent with a poorer response to treatment.<sup>4</sup>

# INFLAMMATIONS

## Introduction

Inflammations of the brain mainly involve blood vessels with or without wall necrosis. Systemic vasculitis may be present with predominant CNS manifestations. Primary CNS vasculitis exists as well.

## Epidemiology and Pathogenesis

Vasculitis is an idiopathic disorder involving the small and medium blood vessels of the brain and spinal cord, and usually presents with multiple bilateral cortical and subcortical, either caused by ischemia or directly from the effects of inflammation. Vasculitis is most common in young adults. Granulocytes and macrophages directly destroy oligodendrocytes, neurons, and axons, either through the release of cytotoxic agents or through phagocytosis.

The specific pathogenesis varies with the type of systemic vasculitis. Polyarteritis nodosa (PAN) is rare, with a male/female ratio of 2.5:1. In systemic lupus erythematosus (SLE), most cases begin in the age range of 20–40 years, and 95% of patients are women. Giant cell arteritis (GCA) is a relatively common form of vasculitis, with a 5-year incidence as high as 24 per 100 000 in individuals of northern European ancestry who are older than 50 years. Wegener's granulomatosis is a rare entity with unknown cause and a male/female ratio of 2:1. The pathogenesis includes the evolution of necrotizing granulomas.

Sjögren's syndrome is a chronic condition with a prevalence of 2%–3% in the general population. It is caused predominantly by lymphocytic infiltration of lacrimal and salivary glands. Several cases have been reported in young adults, adolescents, and even children, although it is traditionally considered a disease of middle-aged to older women. Behçet's syndrome occurs more frequently in those of Middle Eastern, Mediterranean, or Japanese descent and has a male preponderance. Its pathogenesis remains elusive, but an association with the HLA-B5 antigen occurs in some geographical regions.

Miller–Fisher syndrome, with a mean age at onset of 43.6 years, has a male/female ratio of 2:1. Neurological symptoms are preceded by viral infection in more than 70% of cases. Vogt–Koyanagi–Harada (VKH) syndrome is a granulomatous inflammatory disorder occurring more commonly in dark-pigmented races, such as Asians, Hispanics, American Indians, and Asian Indians. It accounts for 6.8%–9.2% of all cases of uveitis in Japan. Most patients are in the second to fifth decades of life. The pathogenesis may be the selective damage of melanocytes as part of an autoimmune process.

## Ocular Manifestations

Ophthalmoplegia or optic neuropathy characterizes involvement of cranial nerves and/or posterior visual pathways with characteristic visual field defects.

The clinical manifestations vary widely as diffuse or focal neurological dysfunction. Typical symptoms of diffuse involvement include headache, seizures, confusion, hallucination, and generalized lethargy. Focal involvement may manifest as a cerebrovascular accident.

## Systemic Necrotizing Vasculitides

Systemic necrotizing vasculitides are listed in [Table 9.23.1](#). In PAN, the visual loss rarely results from retinal vasculitis, or cortical blindness. The CNS becomes involved with variable frequency, usually after the initial diagnosis of PAN. Presentation is variable and may include diffuse encephalopathy or seizures. Focal neurological deficits appear to be secondary to cerebral infarction and hemorrhage. Peripheral neuropathy (mononeuritis multiplex) is frequently the presenting manifestation; seen less commonly is a diffuse, sensorimotor type. These forms of neuropathy are attributed to ischemia or arteritis of nutrient vessels.<sup>5</sup>

In SLE, visual sensory disturbances may result from optic neuritis (inflammatory or ischemic) or papilledema. Retrochiasmatic involvement may present as transient visual phenomena (which may be mistaken for migraine) or as permanent homonymous field defects (acute or subacute). CNS involvement occurs in 35%–60% of patients with SLE. The neurological manifestations may be of diffuse or focal type.<sup>6</sup> The ocular motor pathway may be involved from the cerebral cortex to the extraocular muscles; the most common locus of involvement is a brainstem infarction.<sup>7</sup>

GCA is a common vasculitis with the most serious clinical manifestations largely being ophthalmic. One of the most devastating complications is irreversible blindness, occurring in 36% of cases. The incidence of second eye involvement is about 65% if the condition is left untreated. The most common ocular presentation is anterior ischemic optic neuropathy. Visual loss may also result from posterior optic neuropathy, severe choroidal ischemia, central retinal artery or ophthalmic artery occlusion, ischemia of anterior segment, chiasm, or visual cortex. Diplopia is related to ophthalmoplegia.

**TABLE 9.23.1 Primary Central Nervous System and Systemic Vasculitides**

Vasculitic Type	Name	Age (Years)	Central Nervous System Sign (Most Common)
Primary central nervous system	Granulomatous angiitis of the central nervous system	20–50	Headache
	Cogan's syndrome	20–30	Encephalitis
	Eale's disease	20–40	Retinal phlebitis
	Acute posterior multifocal placoid pigment epitheliopathy	15–30	Retinal inflammation
	Microangiopathy of the brain	20–40	Stroke
Systemic	Polyarteritis nodosa	40–70	Stroke
	Wegener's granulomatosis	25–50	Cranial palsy
	Giant cell arteritis	55–85	Cranial palsy
	Systemic lupus erythematosus	20–40	Organic brain
	Sjögren's syndrome	40–50	Encephalitis
	Behçet's syndrome	15–30	Cranial palsy
	Relapsing polychondritis		
	Allergic angiitis		
	Scleroderma		
	Polymyositis and dermatomyositis		
	Hypersensitivity vasculitis		
	Henoch–Schönlein purpura		
	Mixed cryoglobulinemia		
	Lymphomatoid granulomatosis		
	Takayasu's arteritis		
	Lethal midline granuloma		

In GCA, headache and pain often occur in the temples, occipital region, ear, or tongue. Jaw claudication is classic and highly specific symptom but, unfortunately, is not consistently present (found in 30% of patients). Other neurological manifestations occur in 30% of patients and include transient ischemic attacks involving the posterior circulation, infarcts of the vertebral-basilar system that produce ataxia, lateral medullary syndrome, homonymous hemianopia, dementia, otological manifestations, loss of taste, and gangrene of the tongue.<sup>8</sup>

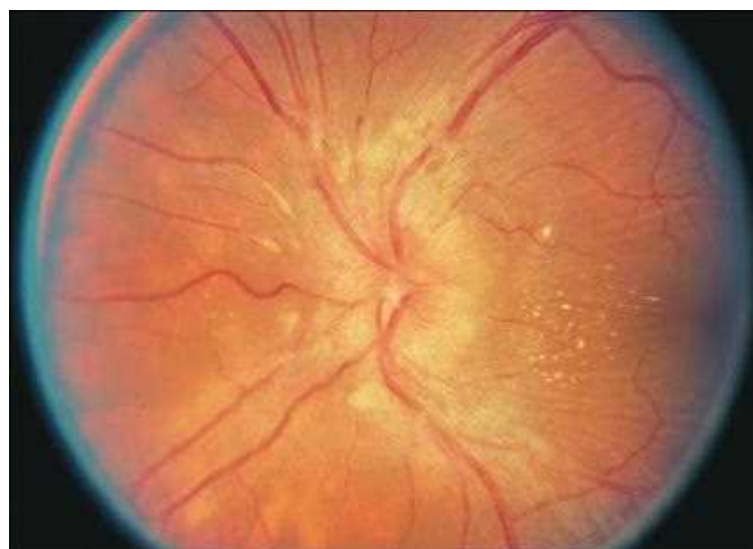
Wegener's granulomatosis may simulate the appearance of orbital pseudo-tumor or lymphoma. Orbital involvement occurs in 20% of patients. Necrotizing scleritis and uveitis may be the initial manifestations. Involvement of the CNS occurs in 25%–50% of cases and usually presents as cranial neuropathies, hypertensive encephalopathy, and cerebral vasculitis.<sup>9,10</sup>

In Sjögren's syndrome, the cardinal ocular manifestation is dry eyes, which may result in corneal ulceration and even perforation. Optic neuropathy may occur alone but more commonly is associated with multifocal CNS disease. Presentations include acute retrobulbar optic neuritis, ischemic optic neuropathy, and insidious visual loss with optic atrophy. Cranial neuropathies may be peripheral or central. The best recognized is a trigeminal sensory neuropathy. Facial nerve involvement may compromise autonomic secretory function and exacerbate the sicca syndrome. Acute and chronic subarachnoid hemorrhages with microhemorrhages within the meninges are very common in CNS antibody-positive individuals (SS-A). Less common CNS manifestations are parkinsonism, cerebellar syndromes, and aseptic meningitis.<sup>11</sup>

In Behçet's syndrome, ocular involvement is seen in 83%–95% of men and 67%–73% of women. Bilaterality is the usual presentation, although delayed, and asymmetrical involvement of the fellow eye is common. Loss of vision as a late complication may result from chronic anterior segment inflammation, neovascular glaucoma, or occlusive vasculitis. Neovascularization, retinal detachment, and optic atrophy are common sequelae. In patients with ocular disease, 10%–30% present with meningoencephalitis, brainstem syndrome, and organic brain syndrome.<sup>12</sup>

In sarcoidosis, the most commonly affected organs are the eyes, lacrimal glands, lungs, lymph nodes, and salivary glands. Ocular manifestations include granulomatous uveitis, inflammatory glaucoma, optic neuropathy (Fig. 9.23.1), and enlarged lacrimal glands. About 5% of patients present with either central or peripheral nervous system disease within 2 years of onset. Meninges at the base of the brain are most affected; secondary infiltration of cranial nerves (37%–73%) and obstruction of CSF flow (7%) also occur. CNS parenchymal disease is common (8%–40%).

Miller–Fisher syndrome is a variant of Guillain–Barré syndrome. It consists of the triad of ataxia, ophthalmoplegia, and areflexia. The initial presentation is commonly diplopia (39%). A complete external and internal ophthalmoplegia, which may be bilateral, is seen in about 50%. Other manifestations are supranuclear gaze paresis with internuclear ophthalmoplegia, Parinaud's syndrome, and occasional facial palsy. Ataxia is



**Fig. 9.23.1 Fundus View of Optic Nerve Head in Sarcoidosis.** Note the sheathing of vessels and exudates (neuroretinitis), as well as pallid edema of the optic disc.

cerebellar in most cases. Areflexia was present in 81% of the 223 cases reviewed.<sup>13</sup>

VKH syndrome is a bilateral, diffuse, granulomatous panuveitis associated with vitiligo, alopecia, poliosis, and CNS signs. It may clinically be categorized into four phases:

- Prodrromal—characterized by headache, nausea, vertigo, fever, meningismus, and orbital pain.
- Uveitic—70% of patients present with unilateral or bilateral posterior uveitis.
- Convalescent—follows after several weeks and is characterized by depigmentation of the skin and choroid.
- Chronic recurrent—characterized by smoldering panuveitis with acute exacerbations of granulomatous anterior uveitis.

The neurological manifestations are more common during the prodromal phase. Focal neurological signs, such as cranial neuropathies, hemiparesis, aphasia, transverse myelitis, and ciliary ganglionitis, may be found but are uncommon. Lumbar puncture may reveal lymphocytic pleocytosis and elevated protein.

## Diagnosis and Testing

Angiography generally is not very sensitive for CNS vasculitis. The gold standard for such diagnosis is biopsy of the leptomeninges.<sup>14</sup>

In PAN, the common but nonspecific laboratory findings include decreased serum complement and circulating immune complexes. The diagnosis often is established by biopsy of the sural nerve or muscle. In SLE, an important laboratory test is antinuclear antibody titers (double stranded). For CNS lupus, the following laboratory tests are helpful:

- Elevated CSF immunoglobulin index or oligoclonal band.
- CSF antineuronal antibodies.
- Serum antiribosomal antibodies.

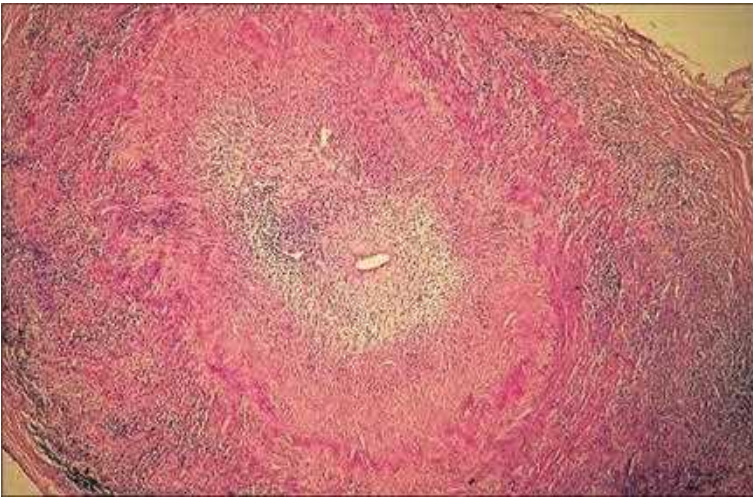
Together, these tests have a sensitivity of 100% and a specificity of 86%. Furthermore, patients who show focal presentations have evidence of antiphospholipid antibodies, abnormal results of brain magnetic resonance imaging (MRI) with multiple lesions, and peripheral vasculitis.

In GCA, the diagnosis is primarily clinical. However, more than 80% of patients have markedly elevated Westergren's erythrocyte sedimentation rate. Other helpful laboratory tests include complete blood count (for anemia), serum fibrinogen levels, C-reactive protein, and plasma activating factor. Biopsy of the temporal artery is used for definitive diagnosis.

For Wegener's granulomatosis, clinical diagnosis requires the finding of at least two of the following four criteria established by the American Academy of Rheumatology:

- Oral ulcers or purulent bloody nasal discharge.
- Abnormal chest radiographs that show nodules, fixed infiltrates, or cavities.
- Microhematuria that signals kidney involvement.
- Biopsy-proven granulomatous inflammation within the arterial wall.





**Fig. 9.23.2 Temporal Artery Almost Obliterated by Vasculitis.** In this case of giant cell arteritis, the media is filled with granulomatous infiltration (with giant cells and epithelioid cells). Also, note that the elastica has been fragmented (periodic acid–Schiff staining).

For histological diagnosis, the nasal mucosa is the best biopsy source. Another useful laboratory test is that for antineutrophilic cytoplasmic antibodies type C, a specific marker found in 90% of patients with systemic involvement.

In Sjögren's syndrome, the electroencephalography result is abnormal in more than 50% of patients. Cerebral angiography shows changes consistent with vasculitis of small to medium vessels in 20%. Brain MRI results are abnormal in about 80% of patients affected by progressive focal neurological symptoms, but these MRI changes are not distinguishable from those found in multiple sclerosis. Studies of CSF show an elevated immunoglobulin G index in 50% of cases with oligoclonal bands present. Other laboratory tests include anti-Ro (SS-A) and anti-La (SS-B) antibodies; however, a definitive diagnosis may require a salivary gland biopsy.

In Behçet's syndrome, fluorescein angiography is of major importance as an early diagnostic tool because leakage from the vessels may be found even in the absence of fundoscopic abnormalities. In sarcoidosis, the serum angiotensin-converting enzyme levels and gallium-67 scans of the head and chest are useful but biopsy of affected tissue can be diagnostic.

## Pathology

The cellular infiltrate is composed of lymphocytes, macrophages, and giant cells in all layers of the vessel wall. In PAN, a widespread panarteritis is found. The necrosis of the media and elastic membranes results, in some cases, in the formation of small aneurysms, which may thrombose or rupture. In SLE, immune complex deposits in the walls of small blood vessels; the primary damage occurs in the subendothelial connective tissues of capillaries, small arteries, veins, and endocardium. In GCA, the granulomatous inflammation results in vessel obstruction, embolism, or thrombosis (Fig. 9.23.2). The characteristic is the intimal proliferation and destruction of the internal elastic lamina.

In Wegener's granulomatosis, the granuloma formation or vasculitis involves the small arteries and veins, and a fibrinoid necrosis of the vessel wall with infiltration by neutrophils and histiocytes. In Sjögren's syndrome, the inflammatory infiltrates are predominantly lymphocytes (T cell type), macrophages, and plasma cells. Small blood vessels of the venous as well as arterial system are invariably involved. In the CNS, blood vessels within the white matter, in subcortical and periventricular locations, are mainly involved. In Behçet's syndrome, an occlusive, necrotizing, nongranulomatous vasculitis and perivasculitis are found in the uvea and retina. In sarcoidosis, noncaseating granulomas in the lacrimal glands, lymph nodes, conjunctiva nodules, or even the liver may be seen.

## Treatment

The treatment of CNS vasculitis with prednisone or cyclophosphamide may produce remission or cure.<sup>15</sup> Certain inflammations require a more specified approach. For example, in Wegener's granulomatosis, treatment involves cytotoxic therapy with cyclophosphamide and, less commonly, with methotrexate, azathioprine, and chlorambucil. The response to therapy is measured by clinical improvement and reduction of the antineutrophil

cytoplasmic antibody titer over time. Sjögren's syndrome requires pulse cyclophosphamide therapy in conjunction with corticosteroids for at least 12 months until stabilization of disease course or improvement occurs.

Treatment of sarcoidosis consists of systemic corticosteroids for several weeks. If this fails, immunosuppressive agents are used.

## Course and Outcome

The chronic course for CNS vasculitis is usually characterized by cognitive deficits and focal findings. Without treatment, patients often suffer recurrent strokes and die within a few years.<sup>15</sup> The prognosis is poor in PAN; patients die as a result of lesions in the kidneys, heart, or other viscera. Cerebral SLE may be catastrophic and generally has a poor prognosis; death may result from renal failure, infection, or CNS involvement. Wegener's granulomatosis was once regarded as fatal, but survival rates have improved with the use of cytotoxic drugs, predominantly cyclophosphamide.

The prognosis for Miller–Fisher syndrome is good, with complete recovery, on average, within 10 weeks of treatment. Secondary infections, such as pneumonia or sepsis, may cause morbidity and mortality. In VKH syndrome, the prognosis is fair, but ocular complications, including cataracts, glaucoma, and subretinal neovascular membranes, are common. The major risk for the development of complications is recurrence of the intraocular inflammation.<sup>16</sup>

## NEURODEGENERATIONS

### Introduction

Despite the specific denotation and vague negative connotation of “degeneration,” the term *neurodegeneration* continues to be used to imply a decline to a lower level of CNS function. We consider the term synonymous with *heredodegeneration*. This, as well as the older term *abiotrophy*, suggests a genetic cause for premature neuronal disease and death. Neuronal injury can be a result of metabolic, toxic, or nutritional problems; however, not surprisingly, the clinical manifestations of these two categories of disease are quite similar. Recent advances in genetics and molecular biology have elucidated inborn errors in metabolism.

### Epidemiology and Pathogenesis

Each of the neurodegenerative diseases has a different epidemiology and pathogenesis. Alzheimer's disease is the most common form of dementia (60%–70%), with a prevalence of 11% at age 65 years and 32% for those older than 80 years.<sup>17</sup> A genetic basis is strongly suspected; however, a number of environmental risk factors and even viral infections have been implicated. The pathology involves marked atrophy of the cerebral cortex. Histopathology reveals nonspecific plaques and tangles. Selective loss of large retinal ganglion cells and their axons that underlie the M-cell pathway may contribute to the visuospatial abnormalities.<sup>18,19</sup>

### Ocular Manifestations

Each neurodegenerative syndrome has its own constellations of signs and symptoms. An outline of such degenerations is given in Box 9.23.1, and a brief description of some of the more characteristic ophthalmic features is given below.

Dystonic movements are sustained contractions or spasms that may be twisting or postural and tend to increase with physical activity. In children with dystonia, involvement of the arms and legs often occurs. Dystonic tremor includes both action and postural tremor. Dystonia tends to progress from focal to segmental to generalized. In advanced cases, the affected body part remains in a fixed dystonic posture. In adults, dystonia may begin with the arms (writer's cramp), neck (torticollis), face (blepharospasm), jaw (oromandibular), tongue (lingual), or vocal cords (spastic).

Blepharospasm is a form of focal dystonia caused by contraction of the orbicularis muscles; it begins with increased blinking followed by involuntary eyelid closure.<sup>20,21</sup> In Meige's syndrome, blepharospasm is combined with oromandibular dystonia. Hemifacial spasm is considered to be a form of segmental (branchial) myoclonus.<sup>20</sup>

### Cerebellar Neurodegenerative Diseases

When the cerebellum and its connections are affected in a familial or hereditary pattern, the cardinal clinical feature is ataxia. The inherited ataxias may have an early onset; for example, Friedreich's ataxia, an autosomal recessive disorder, starts before age 30 years and presents with



**BOX 9.23.1 Neurodegenerations**

Dystonia	Drug-induced
Cerebellar	• Levodopa
Friedreich's ataxia	• Anticonvulsants
Marinesco–Sjögren syndrome	• Anticholinergics
Ramsay Hunt's syndrome	• Antipsychotics
X-Linked inherited ataxia	Metabolic and endocrine
Charcot–Marie–Tooth disease	• Chorea gravidarum
Parkinson's Disease	• Hyperthyroidism
Progressive supranuclear palsy	• Birth control pills
Shy–Drager syndrome	• Hyperglycemic nonketotic encephalopathy
Hallervorden–Spatz disease	Vascular
Chorea	• Hemichorea/hemiballismus with subthalamic nucleus lesion
	• Periarthritis nodosa
	Dementias
	• Alzheimer's disease
	• Pick's disease
	• Creutzfeldt–Jakob disease
	• Dyke–Davidoff–Masson disease
	• Charles Bonnet's disease
	Mitochondria-related diseases
	• Mitochondrial encephalopathies—DNA related
	• Leber's hereditary optic atrophy
	• Mitochondrial disease with mutations of nuclear DNA

progressive ataxia of gait, limbs, absent deep tendon reflexes, and extensor plantar responses. Patients also have dysarthria, clumsiness, and cardiopathy (91%). Less common features of Friedreich's ataxia include nystagmus (25%), pes cavus (50%), diabetes (10%–20%), deafness, and optic atrophy (25%). Posterior column disorder is seen in almost all patients. Loss of appreciation of vibration is an early sign. Results of computed tomography (CT) and MRI of the brain are usually normal, except with cerebellar atrophy. Cervical spinal cord atrophy with normal CSF is present. The course is progressive, although variability exists, and treatment is only palliative.

Ramsay Hunt's syndrome is an early-onset progressive myoclonic ataxia. The most common cause is mitochondrial encephalomyopathy. Marinesco–Sjögren syndrome is another recessive ataxia characterized by young age at onset, congenital cataracts, mental retardation, and short stature.

Autosomal dominant cerebellar ataxia (ADCA) is a form of spinocerebellar ataxia which begins during adulthood. Ataxias are categorized according to clinical characteristics and gene loci, designated as SCA1, SCA2, and so on. The most common clinical form of ADCA is SCA1, which usually begins in patients between ages 20 and 40 years, with gait ataxia, early hyperreflexia, abnormal evoked potentials, peripheral neuropathy, and pseudobulbar dysarthria. Early nystagmus and ophthalmoparesis is common. MRI shows cerebellar and brainstem atrophy, which particularly affects the pons and middle cerebellar peduncle.

Azorean disease (SCA3) presents with gait and limb ataxia, leg spasticity, dysarthria, pyramidal signs, dystonia, rigidity, amyotrophy, and facial and lingual fasciculations. The ocular manifestations are pseudo-proptosis with lid retraction, decreased blinking, and ophthalmoplegia, in which saccades are slow; also found are nystagmus and ocular dysmetria, followed by supranuclear ophthalmoplegia with spared downgaze. Ataxia SCA2 is characterized by ataxia, slow saccades without nystagmus and early loss of tendon reflexes in the arms. Other ADCAs are defined by different combinations of cerebellar ataxia and retinal degeneration.

Ataxia telangiectasia, or Louis–Bar syndrome, an autosomal recessive disorder linked to a metabolic error. Oculomotor apraxia is prominent (pseudo-oculomotor apraxia). Telangiectasias of the skin and conjunctiva are often seen.

**Parkinsonism**

The parkinsonism symptom complex is characterized by six cardinal features:

- Tremor at rest.
- Rigidity.
- Bradykinesia–hypokinesia (slow and delayed movements).
- Flexed posture.
- Loss of postural reflexes.
- Freezing phenomenon (motionlessness).

Two of these features, which must include either tremor or bradykinesia, are required for definitive diagnosis of parkinsonism. Resting tremors with the “rolling pill sign” is common. Additionally, patients have decreased attention span and visuospatial impairments. Depression develops at a rate of 2% of cases per year. Cognitive impairment may occur without memory problems.

**Progressive Supranuclear Palsy**

This is a neurodegenerative disease characterized by pseudobulbar palsy, supranuclear vertical gaze palsy (primarily downgaze), extrapyramidal rigidity, gait ataxia, and dementia. The course is evolution to bed confinement in about 5 years and death a few years later.<sup>21</sup>

**Chorea**

Choreas may be hereditary, secondary, drug-induced, metabolic, endocrine, vascular, or miscellaneous (senile, or essential).

Huntington's disease, a progressive hereditary disorder that manifests only in adult life, is characterized by chorea, personality disorder, and dementia. Sydenham's chorea is seen in children and is characterized by rapid, irregular, aimless, involuntary movements of the muscles of the limbs, face, and trunk. Patients also show emotional lability, hypotonia, and muscular weakness.

**Dementias With Eye Findings****Alzheimer's Disease**

A progressive neurological disorder may present with visual disturbances, such as anomalies of color vision, spatial contrast sensitivity disturbance, fixation instability, saccadic latency prolongation with hypometric saccades, and saccadic intrusions during smooth-pursuit eye movements.<sup>18,19</sup>

The vestibular ocular reflex is normal in most patients. Some patients may show disorders of higher cortical dysfunction, such as visual agnosia and optic ataxia. Other dementias that accompany inherited metabolic disease with eye findings include Wilson's disease, Fahr's syndrome, metachromatic leukodystrophy, mitochondrial encephalopathy with lactic acidosis and stroke-like (MELAS) syndrome, myoclonic epilepsy with ragged red fibers (MERRF) syndrome, and Hallervorden–Spatz disease.

**Charles Bonnet's Syndrome**

This is more than a type of dementia. Classically, it has been regarded as such because this condition is often an early marker for various dementias.<sup>22</sup> This syndrome involves the onset of complex and vivid visual hallucinations in the absence of clouded consciousness, medical illness, psychopathology, or intellectual impairment. Classically, the visual hallucinations may be formed or unformed and probably represent a release phenomenon in the setting of deafferentation. It may occur after a stroke or other causes of diminished vision in both eyes.

**Cerebrovascular Diseases**

In addition to the focal deficit, an acquired intellectual impairment results from multiple small brain injuries caused by stroke. Loss of memory, cognitive impairments involving attention, orientation, visuospatial abilities, calculation, and motor control are present. Cortical syndrome caused by repeated atherothrombotic or cardioembolic strokes, is characterized by obvious, focal, sensorimotor signs with abrupt onset of cognitive failure. In contrast, subcortical syndrome is notable for pseudobulbar signs, isolated pyramidal signs, depression, emotional lability, frontal behavior, mild memory impairment, disorientation, inattention, and perseveration.<sup>23</sup>

**Dementia Complex Associated With HIV**

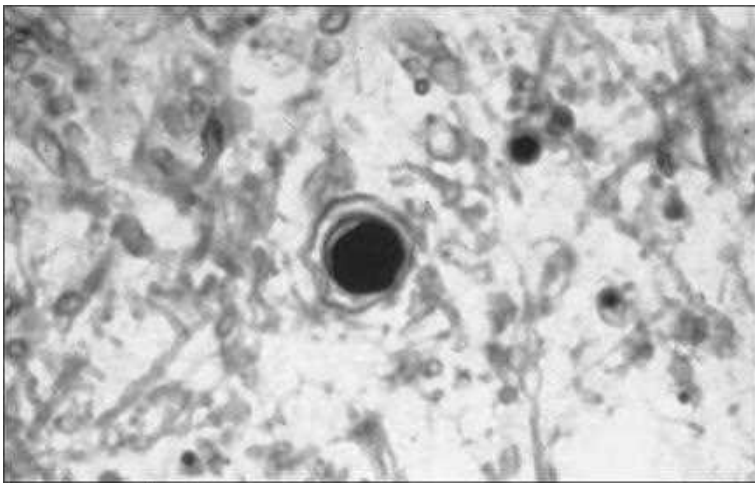
This sequela includes several CNS problems, such as apathy, cognitive slowing, memory loss, and the more focal neurological abnormalities. The eye findings include subtle deficits of color vision and contrast sensitivity, especially in the midspatial frequencies.<sup>24</sup>

**Prion Diseases**

Prion diseases include kuru, Creutzfeldt–Jakob disease, fatal familial insomnia, and Gerstmann–Sträussler–Scheinker disease. These diseases cause rapidly progressive dementia that may include visual agnosias.<sup>25</sup>

**Diagnosis and Testing**

In Huntington's chorea, neuroimaging often shows enlarged ventricles with a butterfly appearance because of atrophy of the caudate nuclei. Prenatal testing for genetic counseling is available. The Huntington's disease gene is located near the tip of the short arm of chromosome 4.



**Fig. 9.23.3 Degenerating Axons in the Human Optic Nerve in Alzheimer's Disease.** Note several dark profiles, the largest of which has an extra myelin sheath about it (paraphenylenediamine staining, epon embedded section).

In Alzheimer's disease, aside from extensive neurological workup (psychometric testing, ophthalmological testing), a visual evoked potential test may be of diagnostic significance because these patients often show a normal-pattern visual evoked potential yet an abnormal flash visual evoked potential. Further, the electroretinograms of these patients show a lower-amplitude pattern compared with normal flash electroretinograms. Ocular motility may also be abnormal.

In prion diseases, electroencephalography shows diffuse slowing, with pseudo-periodic, biphasic, and triphasic spike and wave complexes that are time locked to myoclonic jerks. Elevated level of CSF marker, a protein designated 14-3-3 that is detected by immunoassay, is found in patients with Creutzfeldt-Jakob diseases. This test has about 96% sensitivity and specificity. However, biopsy of brain tissue remains the diagnostic gold standard.

## Pathology

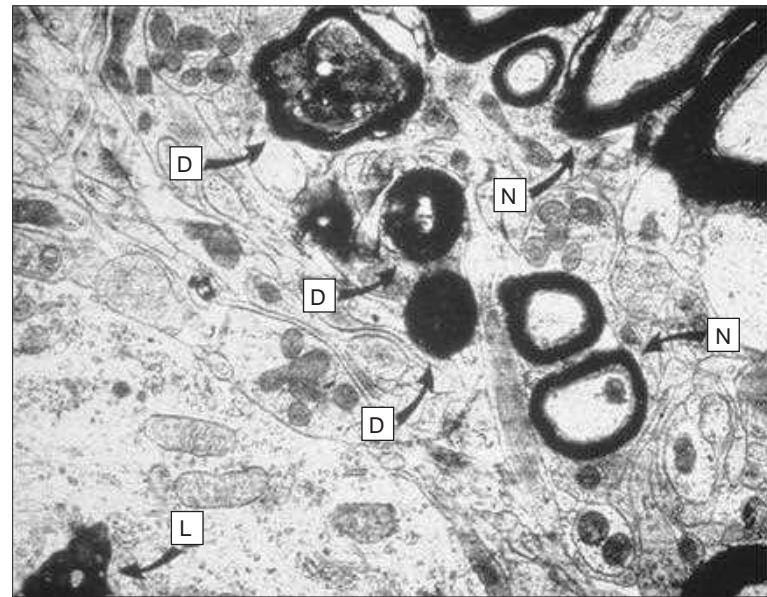
The pathophysiological problem of Parkinson's disease relates to decreased dopaminergic neurotransmission in the basal ganglia with loss of dopamine receptors. The multiple causes include drug-induced, postinfection, posttraumatic, tumor-related, metabolic, hypoxic, postencephalitic, toxic, multi-infarct, and idiopathic. The pathological markers in Parkinson's disease are the so-called Lewy bodies. In Alzheimer's disease, in addition to the amyloid plaques and tangles in the cerebral hemispheres, there is degeneration of retinal ganglion cells and their axons (Figs. 9.23.3 and 9.23.4). This can also be detected by optical coherence tomography for retinal nerve fiber layer thickness.<sup>26</sup>

## Treatment

Stereotaxic thalamotomy may be useful in unilateral dystonia, but bilateral ablations carry a 20% risk of dysarthria.

Medical treatment of hemifacial spasm has been attempted but botulinum toxin injection has been proven effective though multiple reinjection is necessary. Cerebellar neurodegenerative diseases with paroxysmal (or periodic) cerebellar ataxia may be amenable to treatment with acetazolamide in doses of 250–1000 mg/day, which reduces or abolishes the attacks.

In Parkinson's disease, treatment options include dopamine precursors, carbidopa, dopamine agonist, dopamine releasers, anticholinergics, antidepressants, muscle relaxants, and surgery by using such techniques as thalamotomy, pallidotomy, subthalamic stimulation, or implants of embryonic tissues. Levodopa is the most widely used drug but the response is variable, and after 5 years of therapy, up to 75% of patients have serious complications.<sup>27</sup>



**Fig. 9.23.4 Electron Microscopy of the Optic Nerve in Alzheimer's Disease.** Demonstrated are degenerating axons (D) and glial cells with lipofuscin (L), part of the process of degeneration. Normal myelinated axons (N) are also seen.

Huntington's chorea may be treated with tricyclic antidepressants and antipsychotics.<sup>1</sup> No specific treatment exists for Sydenham's chorea, but sedatives and antidopaminergic drugs may be used.

Cholinesterase inhibitors have been used for treatment of cognitive symptoms of Alzheimer's disease with minimal success. Currently, no treatment for prion diseases exists; care must be taken to avoid iatrogenic spread from organ donation or accidental inoculation.

## Course and Outcome

Most neurodegenerative diseases have a long and relentless downward course. However, in many cases, the process may proceed very slowly. In Parkinson's disease the initial response to therapy is often excellent and may last 5–10 years. For hemifacial spasm or blepharospasm, injections of botulinum toxin show excellent control of the disorder.

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# Urgent Neuro-Ophthalmic Disorders

9.24

Peter A. Quiros

**Definition:** Neuro-ophthalmic emergencies are vision-threatening and sometimes life-threatening conditions, requiring prompt diagnosis and management.

## Key Features

- Giant cell arteritis typically causes generalized symptoms, such as jaw claudication, scalp tenderness, headaches, myalgias, fatigue, and weight loss, along with visual loss.
- The majority of intracranial aneurysms arise at the levels of carotid artery, posterior communicating artery, ophthalmic artery, and the cavernous sinus.
- Cavernous sinus thrombosis usually causes eye pain, proptosis, and multiple cranial nerve palsies.
- Orbital apex syndrome shares many similar features as cavernous sinus thrombosis, with the addition of optic nerve signs.
- Painful ophthalmoplegia and vision loss are key features of pituitary apoplexy.

## INTRODUCTION

There are few true ophthalmological emergencies. Although rare, the outcomes of neuro-ophthalmic emergencies<sup>1,2</sup> can be associated with high morbidity and even mortality. The ocular manifestations of neuro-ophthalmic emergencies are but portents of more dangerous central nervous system or systemic pathology. The vision-threatening and potentially life-threatening nature of these disorders requires prompt recognition and diagnosis on the physician's part. A delay of even a few hours could result in a dire outcome.

There are five neuro-ophthalmic emergencies:

- Giant cell arteritis (GCA).
- Orbital apex syndrome.
- Intracranial aneurysm.
- Cavernous sinus thrombosis.
- Pituitary apoplexy.

These may be grouped together by initial symptoms into three categories, for ease of diagnosis:

- Entities resulting in vision loss—GCA.
- Those causing ophthalmoplegia—cavernous sinus thrombosis and intracranial aneurysm.
- Those causing both vision loss and ophthalmoplegia—orbital apex syndrome and pituitary apoplexy.

## EPIDEMIOLOGY AND PATHOGENESIS

### Giant Cell Arteritis

The incidence of GCA (in the United States) is approximately 1 in 150 000 per annum in patients age greater than 60 years.<sup>3</sup> The incidence increases sharply with age and can be as high as 44 per 100 000 among patients in their 90s.<sup>3</sup> The disease occurs three times as often in women as in men.<sup>3</sup> Caucasians are affected much more often than Blacks and Hispanics.<sup>2,3,5</sup> The mean age of onset is the seventh decade.<sup>5</sup>

GCA is a systemic disease that affects primarily medium-sized to large-sized arteries, particularly the temporal, ophthalmic, and short

posterior ciliary arteries.<sup>6</sup> Segments of these latter vessels become occluded, which leads to choroidal ischemia or ischemic optic neuropathy.<sup>7</sup> The arterial thrombosis of GCA may be demonstrated by delayed choroidal and disc filling on fluorescein angiography.<sup>8</sup>

### Aneurysm

The incidence of intracranial saccular aneurysms is approximately 9 per 100 000. The incidence of rupture of asymptomatic aneurysms increases with age, peaking during the sixth and seventh decades. They are somewhat more frequent in women than in men.<sup>9</sup> The vast majority of intracranial aneurysms arise from the carotid artery's main trunk (40%), at the level of the posterior communicating (PCOM) artery, the ophthalmic artery, and the cavernous sinus.<sup>10,11</sup> Rupture of PCOM artery aneurysms has been reported to be as high as 85%.<sup>12</sup> In addition, the PCOM artery is, by far, the most frequent location to cause a third nerve palsy prior to rupture.<sup>13</sup>

PCOM artery aneurysms generally cause pupil-involving third cranial nerve palsies. These occur either as a result of subarachnoid hemorrhage or by external compression of the third cranial nerve caused by aneurysmal expansion prior to rupture.<sup>14</sup>

### Cavernous Sinus Thrombosis

The incidence of cavernous sinus thrombosis (CST), which is a rare disorder, has not been estimated. It may be classified as septic or aseptic, the latter being the rarer of the two forms. The mortality from septic CST was nearly 100% in the preantibiotic era. Although now lower, the mortality rate remains at about 30%.<sup>4</sup>

Most septic thromboses of the cavernous sinus arise from the sphenoid or ethmoid sinuses. Dental infections, facial cellulitis, and otitis rarely lead to CST because of the advent of antibiotics.<sup>4</sup> Acute infections of the sinuses are usually caused by Gram-positive bacteria, whereas chronic infections are more often associated with Gram-negative bacteria and fungi.

Aseptic thrombosis of the cavernous sinus is associated with conditions that lead to venous thrombosis. These may include polycythemias, sickle cell disease (vasculidities), trauma, neurosurgery, pregnancy, and oral contraceptive use.

### Orbital Apex Syndrome

Less than 1% of all orbital cellulites result in an orbital apex syndrome.<sup>15</sup> However, over 50% of these occurs in patients with diabetes mellitus.<sup>16</sup> In these patients, rhinocerebral mucormycosis is, by far, the most frequent cause of orbital apex syndrome.

Even though ketoacidosis is not always present,<sup>17,18</sup> it is the most important risk factor.<sup>19</sup> Studies have demonstrated a lack of inhibitory activity against *Rhizopus* in serum from patients with ketoacidosis. It appears that this inhibitory activity is restored with correction of the acidosis.

### Pituitary Apoplexy

This life-threatening condition is rare and its incidence is difficult to establish. It is thought to occur in 0.6%–9.1% of all surgically managed cases of pituitary adenoma.<sup>20</sup>

The age range is broad, ranging from the first decade to the ninth decade.<sup>20</sup> One study estimated the peak incidence to occur during the fifth decade.<sup>21</sup> There appears to be no gender predominance.

Pituitary apoplexy occurs with sudden enlargement of a tumorous pituitary gland, usually caused by adenoma. The sudden enlargement damages surrounding structures, such as the optic chiasm and the hypothalamus.

Rapid expansion into the cavernous sinus is also not uncommon. The expansion may be caused by hemorrhage or infarction. Precipitating factors include reduced blood flow as in hypotension; stimulation of the gland in increased estrogen states, such as pregnancy; anticoagulation; and increased blood flow.<sup>21</sup>

## OCULAR MANIFESTATIONS

### Giant Cell Arteritis

Sudden visual loss is, by far, the most common manifestation of GCA, occurring in approximately 50% of these patients.<sup>22</sup> Vision loss occurs overwhelmingly as a result of arteritic anterior ischemic optic neuropathy. The permanent vision loss often is preceded by transient loss of vision, such as amaurosis fugax.<sup>23</sup>

Other causes of vision loss also associated with GCA, although occurring less frequently, include central retinal artery occlusion, choroidal ischemia, and posterior ischemic optic neuropathy. GCA should be suspected in the older patient who has central retinal artery occlusion but no history of valvular disorders or visible emboli.<sup>24</sup>

Even though vision loss is the primary ophthalmic problem found in GCA, patients may also experience diplopia. This problem may occur as a result of infarction of the extraocular muscles, their associated cranial nerves, or the brainstem nuclei. In fact, GCA may cause a greater stroke syndrome.

### Aneurysm

Ophthalmic manifestations are determined by the position of the aneurysm. These may range from vision loss resulting from ophthalmic artery aneurysms, cortical blindness resulting from basilar aneurysms, or ophthalmoplegia resulting from aneurysms of the circle of Willis or the cavernous sinus. The most common manifestation, however, is ophthalmoplegia.

Patients will have complete unilateral ptosis. Upon lifting the lid, the examiner will find an abducted eye that cannot adduct, infraduct, or supraduct. These patients usually have 1–2 mm of proptosis. This phenomenon is thought to result from laxity of the palsied musculature and not from aneurysmal displacement. Anisocoria is usually present as a result of disruption of the parasympathetic fibers that travel on the outside of the nerve. The anisocoria will be accentuated in bright light. That is, the pupil will appear dilated and unable to constrict in bright light.

Suspicion of intracranial aneurysm should be raised in all patients without diabetes but who have third cranial nerve palsies, especially those with pupillary involvement.

### Cavernous Sinus Thrombosis

In patients with septic CST, a host of ocular abnormalities will manifest. Those with infections entering the cavernous sinus anteriorly usually will have eye pain, orbital congestion, proptosis, adnexal edema, ptosis, and ophthalmoplegia. The ophthalmoplegia may involve the third, fourth, and sixth cranial nerves. In addition, there may also be involvement of the first and second branches of the trigeminal nerve.

Symptoms are initially unilateral but often become bilateral as the infection and thrombosis spread to the contralateral side through the circular sinus. This sinus connects the right and left cavernous sinuses posteriorly. In addition, these patients are usually febrile. Nausea, vomiting, and somnolence are not uncommon.

### Orbital Apex Syndrome

In patients with an orbital apex syndrome, complete ophthalmoplegia, ptosis, decreased corneal sensation, and vision loss are manifested. Unlike CST, the vision loss is present early on. Patients usually develop optic nerve signs, such as a relative afferent pupillary defect. There is little adnexal edema and orbital congestion, which are present in the early stages but develop as the disease progresses. Proptosis is often present, but patients do not always complain of pain.

Eschars rarely are seen initially but usually develop around the orbit if the disease goes untreated (Fig. 9.24.1).

### Pituitary Apoplexy

Patients usually suffer painful ophthalmoplegia and vision loss. Damage to the visual pathways occurs most frequently at the level of the chiasm.



**Fig. 9.24.1** (A) Patient with mucormycosis of the right orbit, resulting in an orbital apex syndrome. (B) Axial view from orbital magnetic resonance imaging demonstrating mucormycosis of the ethmoid sinuses with extension into orbit.

Therefore, visual field defects are common. Vision loss is variable, however, and may not always produce a relative afferent pupillary defect. The degree of ophthalmoplegia may also be variable and asymmetrical, depending on the extent of involvement of each cavernous sinus.

## DIAGNOSIS AND ANCILLARY TESTING

### Giant Cell Arteritis

The diagnosis of temporal arteritis is based on clinical signs and symptoms. Laboratory findings are helpful, and temporal artery biopsy is the confirmatory gold standard.

Systemic review results in older patients with vision loss and/or transient vision loss are usually positive. Therefore, a thorough review of systems for GCA should be performed. A diagnosis can be arrived at with great certainty if several systems show positive results for symptoms.<sup>25</sup>

Most patients complain of headache, usually unilateral headache. In addition, there is usually scalp tenderness, as well as tenderness over the affected artery. Jaw claudication is often present. Although its absence does not rule out GCA, this sign is quite characteristic of GCA, as it is seen rarely in other disorders. Finally, myalgias, fatigue, weight loss, and decreased appetite are seen frequently. Positive findings in three or more systems in the older patient should raise a high level of suspicion.

Laboratory testing usually consists of erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) level, and complete blood count. The ESR and CRP level usually are elevated markedly. The ESR should be adjusted for age and gender. The upper limit of normal is considered to be age divided by two in men and age plus 20 divided by two in women.<sup>26</sup>

The complete blood count often will reveal a normocytic anemia as well as thrombocytosis.<sup>27</sup>

Temporal artery biopsy is the gold standard for diagnosis. A 2-cm segment of temporal artery should be obtained and several sections

sampled because “skip lesions” may occur; that is, sections of the affected artery may be interspersed with nonaffected sections. A single negative biopsy meeting the above criteria is usually enough to rule out GCA. However, despite low statistical yield,<sup>28</sup> if suspicion is high, a second biopsy may be performed, given that a missed diagnosis would result in dire consequences.

## Aneurysm

Frontal head pain is usually present in both ruptured and unruptured aneurysms. In an unruptured aneurysm, the pain is referred from the adjacent tentorium. Like the eye and the forehead, the tentorium is supplied by the first branch of the trigeminal nerve. A pupil-involving oculomotor nerve palsy is nearly invariably present. If such is the case, the aneurysm should be detectable by magnetic resonance angiography (MRA) or spiral computed tomography angiography (CTA).<sup>29</sup> These modalities, however, may miss intracranial aneurysms of 3 mm or less.<sup>30,31</sup> Therefore, digital subtraction cerebral angiography remains the gold standard. A saccular aneurysm of 4 mm or greater usually is seen at the junction of the internal carotid and the posterior communicating arteries (Fig. 9.24.2).

## Cavernous Sinus Thrombosis and Orbital Apex Syndrome

Apart from the ocular signs that distinguish these two entities, neuroimaging is necessary to make the diagnosis. Orbital CT without contrast and magnetic resonance imaging (MRI) with fat suppression will locate the site of involvement. In the case of orbital MRI, fat suppression is necessary to visualize involved orbital structures. The “noise” created by the fat may mask inflammation otherwise. Sinus disease is nearly always present.<sup>32</sup> In fact, orbital apex syndrome rarely occurs without adjacent ethmoid sinusitis. Sphenoid and maxillary sinus disease is also common. In either case, contrast-enhanced scans should be ordered with coronal and axial views that extend as far back as the posterior and inferior cavernous sinus.

## Pituitary Apoplexy

In addition to ocular manifestations, most patients exhibit meningeal irritation. Following the apoplexy, hypofunction of the gland is common.<sup>33</sup> Patients may, therefore, exhibit irregular menses, decreased libido, hyponatremia, hypothyroidism, or hypercortisolism.

MRI is the gold standard for neuroimaging because it will delineate both the tumor and any hemorrhage (Fig. 9.24.3). It is much more sensitive than CT.<sup>34</sup>

## DIFFERENTIAL DIAGNOSIS

### Giant Cell Arteritis

The differential of GCA is extensive. GCA is confused often with nonarteritic anterior ischemic optic neuropathy. Patients with nonarteritic ischemic optic neuropathy tend to be younger, have less severe vision loss, and have a negative review of systems as well as normal laboratory test results.

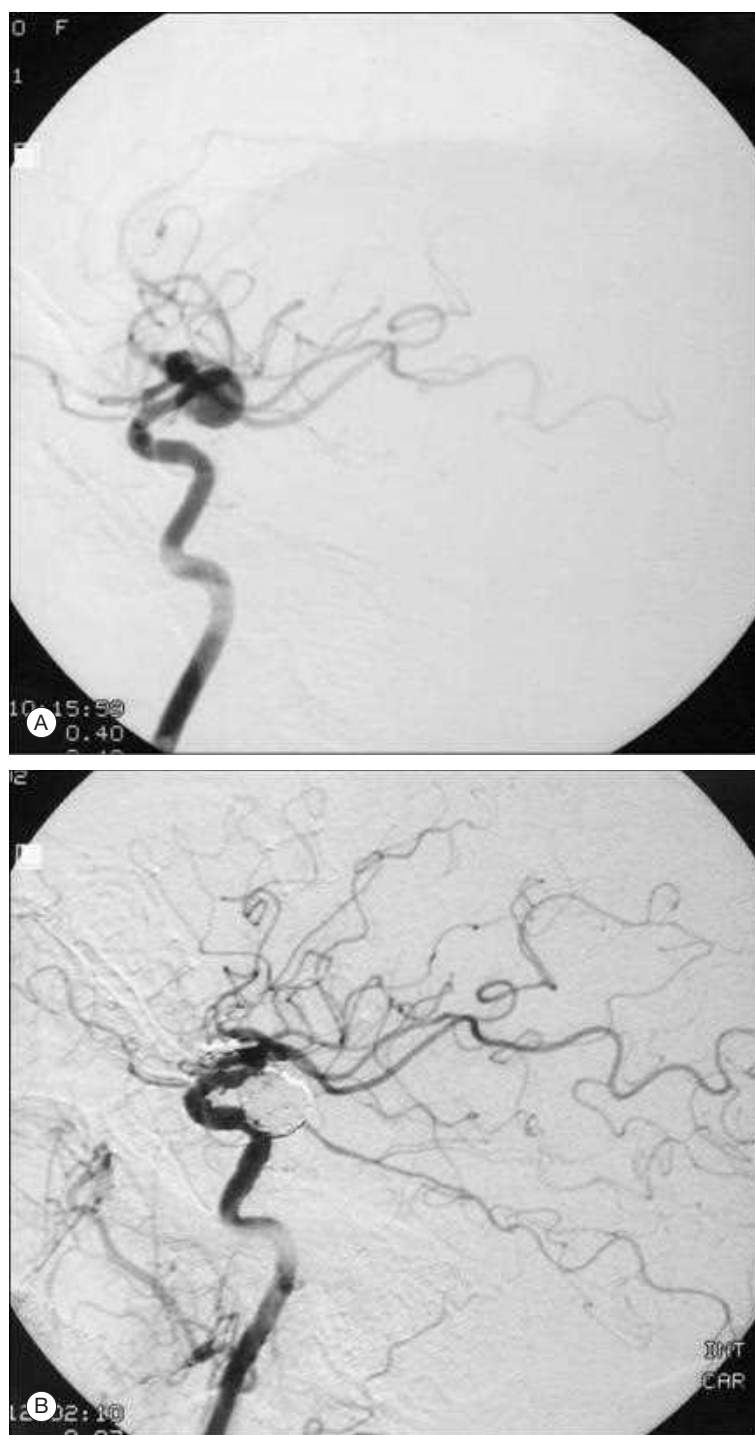
The differential may also include the following:

- Inflammatory optic neuritis—patients, usually in their 20s and 30s, have pain with eye movements, optic nerve swelling, and a negative review of systems.
- Compressive tumor—very slowly progressive vision loss, negative review of systems.
- Diabetic papillophlebitis—younger patients with diabetes, optic nerve swelling with hemorrhages, negative review of systems, mildly elevated ESR.
- Central retinal artery or vein occlusion.

## Aneurysm

If angiography findings are negative, the following entities may produce a similar clinical picture:

- Microvascular or ischemic lesions—patients usually have diabetes; pupil nearly always spared.
- Epidural or subdural hematoma—a history of trauma in most cases, mental status changes common.



**Fig. 9.24.2** (A) Digital subtraction angiography (DSA) scan of PCOM artery aneurysm resulting in third nerve palsy. (B) DSA scan of the same aneurysm after endovascular coiling.

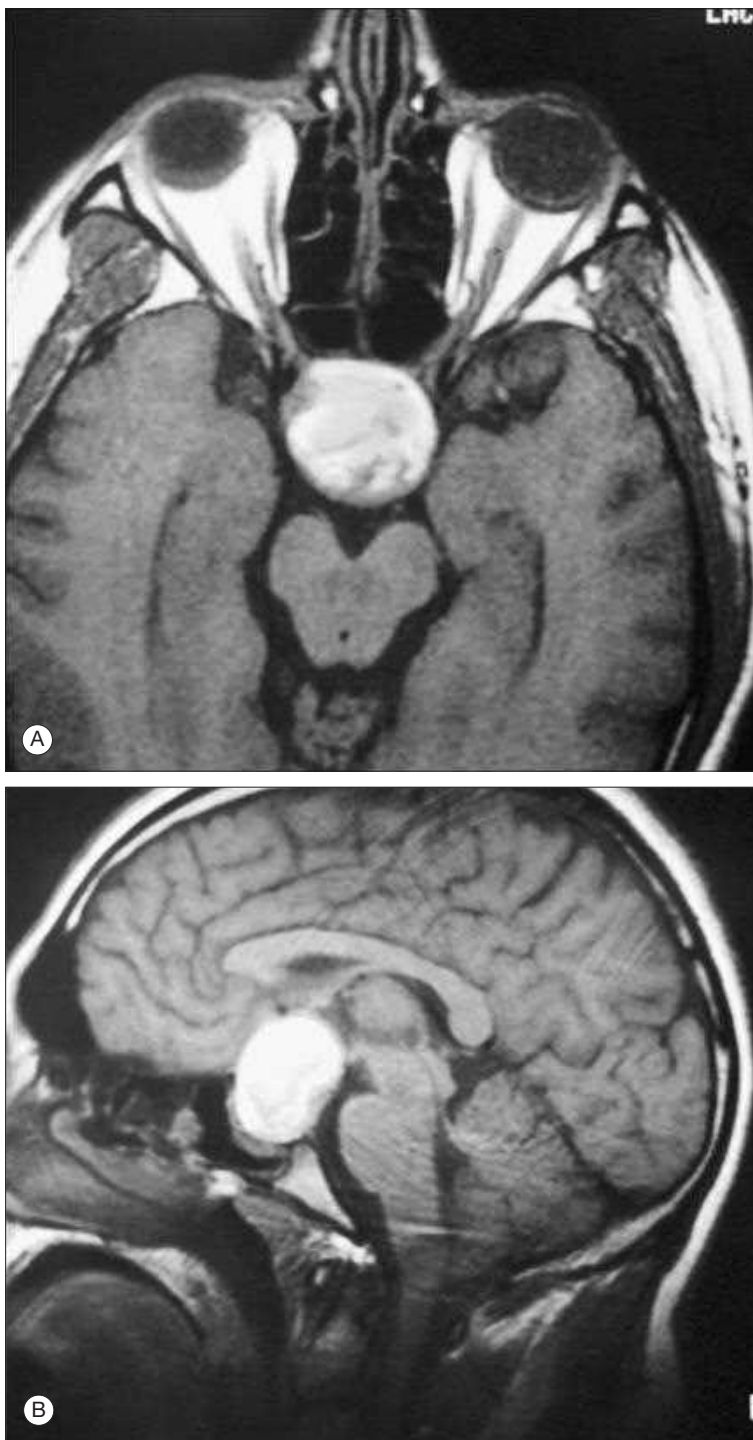
- Meningitis or encephalitis—fever and nuchal rigidity, often accompanied by mental status changes and seizures.
- Hypertensive crisis—flame-shaped retinal hemorrhages usually present, as well as optic nerve edema.
- Migraine—a relapsing and remitting course often accompanied by nausea, photophobia, visual auras, and transient hemiplegia, ophthalmoplegia, or ataxia.

## Cavernous Sinus Thrombosis and Orbital Apex Syndrome

These entities have similar differential diagnoses because most problems arise from adjacent structures.

- Tolosa–Hunt syndrome—otherwise healthy patients, severe pain, vision loss rare, inflammatory “pseudo-tumor” seen on neuroimaging.
- Arteriovenous fistula—often with antecedent trauma, bruit may be auscultated, arterialized conjunctival vessels.





**Fig. 9.24.3** (A) Axial magnetic resonance imaging (MRI) view of enlarged apoplectic pituitary gland involving chiasm. (B) Sagittal MRI view from the same patient.

- Thyroid eye disease—rarely seen without lid retraction and lid lag, positive forced ductions, thickened extraocular muscles on CT scan with little to no sinus disease.

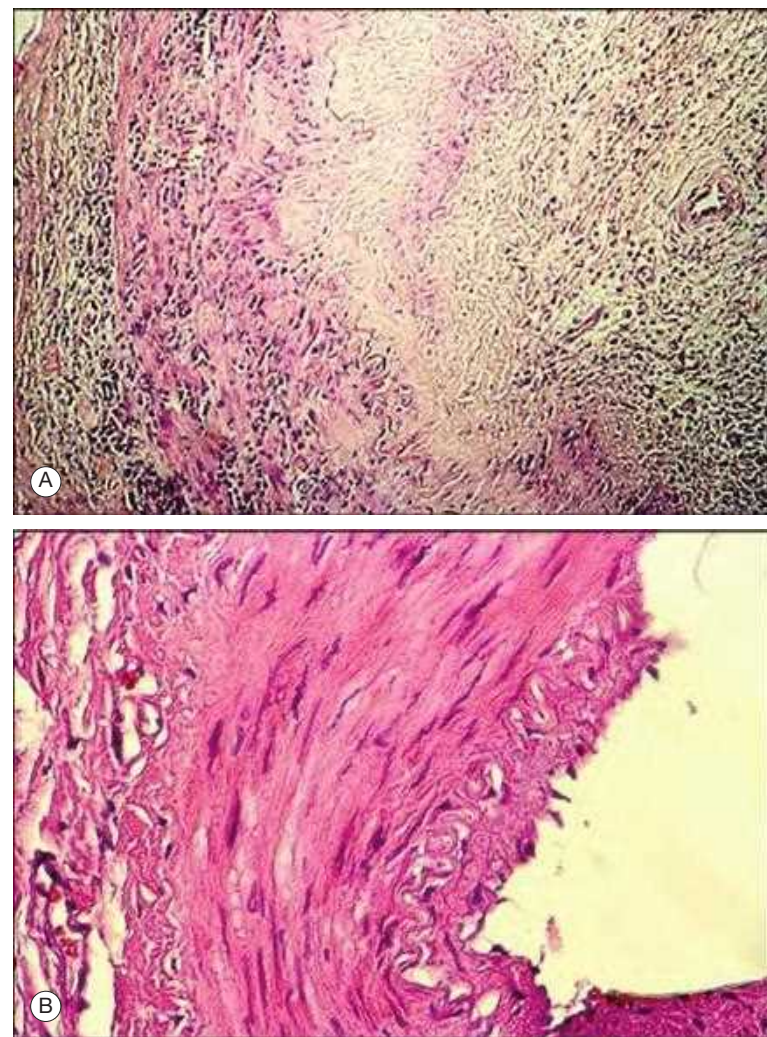
### Pituitary Apoplexy

Intracranial aneurysm, both expanding and ruptured, should be considered if MRI fails to reveal pituitary hemorrhage. MRA should then be performed.

## PATHOLOGY

### Giant Cell Arteritis

Biopsy specimens will reveal an overwhelming inflammatory mononuclear cellular infiltrate. There is destruction of the internal elastic lamina and necrosis of the media is seen often. Vessel lumens often are completely occluded. Multinucleated giant cells may be present (Fig. 9.24.4) but disappear within days after corticosteroid therapy is initiated.



**Fig. 9.24.4** (A) Temporal artery biopsy positive for giant cell arteritis. Note destruction of elastic lamina and almost complete luminal occlusion. (B) Normal temporal artery specimen.

### Aneurysm

Histologically, aneurysmal vessels exhibit markedly thinned media and adventitia. There is generalized disruption of the internal elastic lamina, with areas of thinning, fragmentation, and even absence. Some investigators have found a deficiency or defect in type III collagen formation, as well as a decrease in the ratio of type III to type I collagen.<sup>35</sup>

### Cavernous Sinus Thrombosis and Orbital Apex Syndrome

Sinus specimens often will reveal infectious organisms. Bacterial Gram staining should be performed to ascertain the presence of Gram-positive or Gram-negative bacteria, or both. In addition, staining with India ink and special stains for fungi should be performed to evaluate for mucormycosis. Nonseptate, large, branching hyphae that stain easily with hematoxylin and eosin are indicative of *Mucor* and *Rhizopus* species.

### Pituitary Apoplexy

This condition is marked by pituitary hemorrhage, often accompanied by necrosis, and thrombosis. Most specimens have a high degree of necrosis, making cell type identification difficult. One study, however, found null cells to be the most frequent (61%), followed by somatotroph (17%), corticotroph (11%), lactotroph (5.5%), and gonadotroph (5.5%).<sup>36</sup>

## TREATMENT

### Giant Cell Arteritis

The well-accepted management for GCA is systemic corticosteroids. Generally, the ophthalmic literature favors higher doses than the

rheumatological literature. There is no clear agreement on starting dosage.<sup>37</sup> Neuro-ophthalmologists usually start at dosages of 80–100 mg of oral methylprednisolone daily. Rheumatologists may advocate lower dosages of 40–60 mg daily. Some clinicians employ initial intravenous corticosteroid therapy. Retrospective series have indicated increased likelihood of improvement in vision in those managed initially with intravenous corticosteroids.<sup>38</sup>

ESR as a therapeutic endpoint should be tested every 4–6 weeks and therapy titrated accordingly. There is general consensus that the duration of therapy should extend for many months, often up to 1–2 years, and that the use of interleukin-6 inhibitors may help decrease the length of corticosteroid therapy.

## Aneurysm

Management of unruptured intracranial aneurysms depends, in part, on their size and position, as well as the age and health of the patient. Unruptured aneurysms may be managed via a direct or “open” surgical approach or with an endovascular approach.

The direct surgical approach aims to apply metal clips at the base of the aneurysm to close it off. This approach is quite successful but poses the same risks associated with open craniotomy. Damage to adjacent structures (oculomotor nerve) may occur.

The endovascular approach uses catheters to introduce balloons or thromboembolic coils into the aneurysm, thereby mechanically occluding it or thrombosing it. This approach carries a lower risk of mortality and morbidity but can be complicated by incomplete closure of the aneurysm or displacement of the endovascular balloon, as well as rupture caused by catheter penetration of the thin aneurysm wall.

## Cavernous Sinus Thrombosis and Orbital Apex Syndrome

Septic thrombosis of the cavernous sinus is usually managed with a combination of antibiotics and anticoagulation. Corticosteroids may also play a role in reducing inflammation. If sinus disease is present, debridement of the sinuses should also take place. If there is clinical evidence or suspicion of *Mucor*, treatment with amphotericin B should be initiated. Correction of underlying metabolic acidosis greatly increases the chances of survival.<sup>15</sup>

Orbital apex syndrome is managed in much the same way, except that in cases of *Mucor*, sinus exenteration as well as orbital exenteration may be necessary to improve survival.

Aseptic thrombosis of the cavernous sinus is managed primarily by managing the underlying condition. Adjuvant anticoagulation may stop the spread of thrombosis.<sup>39</sup>

## Pituitary Apoplexy

Most patients are managed with decompression of the sella transsphenoidally. In general, these patients have a neuro-ophthalmic abnormality prompting surgery. Some groups advocate the use of bromocriptine in cases with little or no neuro-ophthalmic deficit.

Supplementation of pituitary hormones is often necessary for prolonged periods after the apoplectic event.

## COURSE AND OUTCOMES

### Giant Cell Arteritis

The primary goal of therapy is to avert vision loss in the fellow eye. Restoration of vision in the affected eye is rare. However, if left untreated, nearly 90% of patients will suffer vision loss in the fellow eye.<sup>40</sup>

## Aneurysm

The results of surgery on unruptured aneurysms are excellent. Mortality rates with these procedures are as low as 1%–5%.<sup>41</sup> Morbidity is somewhat higher at 10%–15%, which usually manifests in the form of incomplete recovery of oculomotor nerve function or aberrant regeneration.

## Cavernous Sinus Thrombosis

The mortality rate for patients with septic cavernous sinus thrombosis is about 30%. Morbidity is very high. Nearly all survivors have some neurological deficit. These usually result from damage to the cranial nerves of the cavernous sinus. Therefore, ophthalmoplegias, sensory neuropathies, and even retinal vein or artery occlusions may be seen.

Aseptic thrombosis has a much lower mortality compared with septic thrombosis. Morbidity, nonetheless, remains high, with damage to the intracavernous cranial nerves being common.

## Orbital Apex Syndrome

The mortality from *Mucor*-induced orbital apex syndrome is reported to be between 46% and 52%<sup>42</sup> despite amphotericin B therapy. Morbidity remains high because many patients require exenteration of the sinuses and orbit. Permanent neurological deficits are common.

## Pituitary Apoplexy

Surgical decompression of the sella appears to have good neuro-ophthalmic outcomes. Improvements in visual acuity, field deficits, and ophthalmoplegia have been reported to be as high as 76%–91%.<sup>36</sup> Endocrine abnormalities, however, have remained high, with 43%–58% requiring some form of hormonal supplementation. Mortality with surgical management has remained low.

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# Trauma, Drugs, and Toxins

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9.25

**Definition:** Visual abnormalities caused by brain dysfunction and injury resulting from extrinsic damage by head trauma or exposure to medications, hallucinogens, or toxins.

### Key Features

- Motility disorders, saccadic abnormalities, nystagmus, convergence insufficiency.
- Visual perceptual-motor dysfunction.
- Positive visual phenomena.
- Formed and unformed visual hallucinations.
- Dyschromatopsia.
- Visual field defects.
- Blurred vision or visual loss.
- Cerebral (cortical) blindness.

### Associated Features

- Headaches.
- Short-term memory loss.
- Impaired concentration.
- Behavioral changes.
- Other physical neurological deficits.

## TRAUMA AND THE BRAIN

### Introduction

Visual abnormalities that follow closed head trauma occur commonly and can involve any part of the visual pathway. Prompt recognition and treatment of these conditions enhance the potential for the patient's rehabilitation.

### Epidemiology and Pathogenesis

Head trauma is an important public health problem. Approximately 900 000 patients are hospitalized yearly in the United States for the consequences of closed head trauma. The most common cause of head injury in the United States is motor vehicle accident, and the severity of head injury is correlated directly with the lack of proper seatbelt and helmet use.<sup>1</sup> Of all persons injured in motor vehicle accidents, 70% incur head injuries. Men are injured twice as frequently as women, and alcohol is a significant contributing factor in men. About one half of all patients are age 15–34 years. Assault, including child and spousal abuse, accidents in the home or at the workplace, and sports injuries contribute to traumatic brain injury (TBI).

Unfortunately, few studies characterize the incidence of the visual sequelae of head trauma. After a brain injury, the visual system often is not evaluated comprehensively. This may reflect the lack of articulated complaints from patients with head injury, either because of lack of subjective experience or because of reduced cognition. Family members or rehabilitative personnel often identify the deficits and bring the patients' visual problems to medical attention. In one report, 50%–65% of patients who attended a rehabilitation facility had experienced visual disturbances after TBI.<sup>2</sup> No apparent correlation exists between the severity of the trauma and the presence of visual disorders. Indeed, a study of acute mild TBI in a pediatric trauma center emergency department found photophobia and blurred or double vision in 15%–39% of children.<sup>3</sup>

### Ocular Manifestations

Visual deficits after head injury may be monocular or binocular (Box 9.25.1). Cortical injury causes changes in refraction, saccades, and other sensory-motor relationships. The most common visual complaint after head trauma is blurred vision because of convergence insufficiency. Patients who have convergence insufficiency also may have difficulty reading, diplopia at near, eye strain, tearing, photosensitivity, and headaches. Control of saccadic eye movements can be disrupted after damage to either brain hemisphere. Esophoria and exotropia are common sequelae of head trauma. Binocular single vision may be lost after a head injury, with the breakdown of a latent phoria or loss of the normal physiological fusion of the image presented to each eye. Visual field defects after closed head trauma are not uncommon. In one report, tunnel fields that suggested functional visual loss were found most frequently and were associated with posttraumatic migraine in about half the cases.<sup>1</sup> Other visual field defects include optic nerve-related scotomata, quadrantanopia, homonymous hemianopia, bitemporal hemianopia, and cerebral blindness.

Patients who have injury to the nondominant parietal, temporal, and occipital areas may exhibit visual attention problems as well as difficulty with spatial orientation and visual recognition. Visual cognition may be disrupted after head trauma, which results in difficulty judging the spatial properties of objects and impaired mental manipulation of three-dimensional images. When spatial organization and constructive abilities are impaired, the frontal lobe is provided with inadequate feedback for the execution of motor movements. Nondominant hemisphere injury often causes impaired comprehension of visual images, which may be expressed by the patient as inability to read, despite excellent visual acuity. Words may appear to run together on the printed page. Trauma to the optic chiasm simulates a pituitary region tumor, with bitemporal hemianopia and see-saw nystagmus. Damage to the brainstem structures leads to pupillary asymmetry or irregularity, ocular motor nerve paresis, unilateral and bilateral internuclear ophthalmoplegia, skew deviation, dorsal midbrain syndrome, and nystagmus.<sup>1</sup> Saccadic deficits may occur, including failure to initiate contralateral saccades, prolonged saccadic latency, decreased saccadic accuracy toward a hemianopic field, and a tendency for the patient to be distracted by peripheral stimuli.<sup>4</sup>

### Diagnosis and Ancillary Testing

Visual complaints after head injury vary widely. The ophthalmological examination often reveals a treatable problem. However, patients may be difficult to examine because of cognitive and communication disorders.

#### BOX 9.25.1 Visual Symptoms and Signs Associated With Head Trauma

Symptoms	Signs
Blurred or decreased vision	Convergence insufficiency
Diplopia	Abnormal saccades
Difficulty reading	Oculomotor dysfunction
Photophobia	Accommodative disorders
Visual hallucinations	Fixation instability
Oscillopsia	Nystagmus
Phosphenes	Lagophthalmos
Visual field defects	
Visual perceptual-motor dysfunction	
• impaired spatial relationships	
• right-left discrimination problems	
Visual cognition deficits	
Visual inattention	

Multiple examinations may be needed to fully assess a patient with brain injury. A complete assessment may include evaluation of the eye, refraction, and examination of ocular motility, accommodation, vergence, stereopsis, visual perception, and visual fields.<sup>5</sup> The diagnosis of convergence insufficiency is made on the basis of measurement of the convergence fusional reserves. The near point of convergence alone is an unreliable measure. Skull radiographs have limited usefulness, as they show only bony pathology. Computed tomography is most useful to demonstrate skull base fractures and acute bleeding, whereas magnetic resonance imaging (MRI) shows the soft tissues and brainstem with greater clarity.<sup>6</sup>

## Differential Diagnosis

When there is a temporal association between the patient's symptoms and the head injury, a causal association is presumed. However, minor head trauma may draw attention to visual deficits from other causes that had been unrecognized previously. Patients who have homonymous or bitemporal visual field defects after trauma require neuroimaging studies to exclude a hemorrhage, tumor, stroke, or vascular malformation. Patients who seek compensation or other secondary gain may have functional visual loss. It is often difficult to separate real disability from nonorganic visual abnormalities in patients who are malingering.

Hallucinations and other visual disturbances observed in patients with head trauma also may be caused by medications, migraine, encephalitis, hepatitis, or other systemic disorders. Other causes of convergence insufficiency are wide interpupillary distance, refractive errors, delayed development, malnutrition, encephalitis, hepatitis, and drug intoxication.

## Systemic Associations

TBI is sudden and devastating. The patient may be in deep coma or have multiple injuries that affect motor function, speech, and cognition. With a mild TBI, visual symptoms can be part of the postconcussion syndrome. Sometimes, the head injury may seem quite minor, with no loss of consciousness. Early symptoms of TBI include headache, dizziness, vertigo, tinnitus, hearing loss, blurred vision, diplopia, convergence insufficiency, sensitivity to light and noise, diminished sense of taste and smell, irritability, fatigue, sleep disturbances, decreased libido, decreased appetite, short- and intermediate-term memory dysfunction, impaired concentration and attention, and slowing of reaction time.<sup>7</sup> Anxiety, depression, and personality changes may occur later and are confounded by social and economic comorbidity.<sup>8</sup>

## Pathology

A structural injury, such as a skull fracture, hematoma, contusion, stroke, or foreign body, accounts for many of the neurological sequelae of severe head trauma. The rigid skull encasement means that secondary pressure effects from intracranial injuries are common. The cranial nerves are susceptible to injury because of their long course at the base of the skull. Orbital fractures can lead to muscle entrapment and diplopia. Optic canal fractures, often associated with basilar skull fractures, can produce an optic neuropathy.

The pathophysiology of mild TBI is not understood completely. Subtle changes may be missed on neuroimaging studies. The most apparent neuropathological change in mild traumatic brain injury is diffuse axonal damage.<sup>9</sup> Acutely, the axons are damaged and swollen. This may be attributed to stretching of axons during the injury, with subsequent edema and detachment. The secondary changes of edema and disconnection may take 4–24 hours to develop. The synaptic terminals derived from the degenerating axons are disrupted, which results in diffuse deafferentation. Animal models of TBI suggest that an active neuroplastic response occurs, with repopulation of injured axon terminals by the remaining intact fiber populations. Changes in neurotransmitters are likely to occur in TBI. Excitatory neurotoxins are released acutely. Acetylcholine is increased in the cerebrospinal fluid and in several areas of the brain after injury. Altered binding to cholinergic and glutaminergic receptors occurs in the cerebral cortex.

## Treatment

Early diagnosis of visual problems after TBI is essential to maximize the overall rehabilitation potential.<sup>1</sup> The sooner the visual problems are addressed after head trauma, the better the chances for a faster and more

complete recovery. Treatments advocated for posttraumatic visual symptoms include eye exercises, prism spectacles, and surgery. Treatment should emphasize the design of lenses, filters, or prisms to address the specific defect in the visual system. Accommodative insufficiency is typically corrected by using a plus power that is often excessive for the patient's age. Patients who have hemianopic field defects require visual retraining to move the eyes and head consciously into the blind hemifield. In addition, computer-based training programs have been developed to improve visual function in patients with visual field defects.<sup>10</sup> Occasionally, prisms are useful in these patients to shift part of the missing hemifield into view. Other techniques for reading include using guides for lines and margins and moving or tilting the page into the intact visual field. Therapists and caregivers must be aware of the patient's visual limitations that militate against adaptation to activities of daily life. Single vision reading spectacles may help patients who have inferior visual field defects.

Patients who have diplopia are helped by prisms, patching, or surgery. Prisms are most useful for relatively comitant ocular deviations. Because most patients improve, a temporary Fresnel prism allows easy prism replacement as the strabismus lessens over time. Patching one eye may reduce discomfort initially, but in the long term, this produces a monocular condition that stresses the visual and motor systems, causing difficulty with midline concepts and affecting balance and posture. Strabismus surgery should not be considered for at least 9 months after the injury because a high rate of spontaneous improvement occurs. Visual rehabilitation may include activities designed to enhance the patient's awareness of visual deficits and increase function to maximize residual vision.

## Course and Outcome

The visual system impacts all aspects of life. Rehabilitation is much more difficult if the visual system is not efficient. Patients who have severe brain injuries often have permanent visual field and motility defects. The Glasgow Coma Scale, a measure of the depth of coma, is useful for predicting overall functional outcome when applied on the second or third day after injury. Posttraumatic amnesia that persists for more than 2 months is a poor prognostic sign with regard to independent living, memory, and work capacity.

Most patients who have mild TBI experience improvement. The majority recovers completely within the first year after sustaining the injury. These patients should be reassured that their symptoms are valid and their prognosis is good. Headaches, dizziness, and memory problems are the primary symptoms associated with mild head injury; most patients have resolution of these symptoms by 6 months. It is not uncommon for patients to complain of diplopia many months after suffering the injury, although most cases of diplopia tend to resolve spontaneously in 6–12 months. Those with a late onset of symptoms may have an underlying psychogenic cause. Patients who have convergence insufficiency secondary to trauma and those who have idiopathic convergence insufficiency do not seem to respond to treatment.

## DRUGS, TOXINS, AND THE BRAIN

### Introduction

Visual phenomena are observed with an endless list of drugs, including prescription medications. Many neurotoxic agents have a major effect on the visual pathways.

### Epidemiology and Pathogenesis

Hallucinations and other visual symptoms are induced by hallucinogens and stimulants, but they are also reported frequently as side effects of a variety of medications commonly used in clinical practice. Visual disturbances from digitalis were observed more than 200 years ago and are experienced by up to 95% of patients, particularly those who have digitalis intoxication.<sup>11</sup> As early as 1843, cases of cerebral blindness secondary to carbon monoxide poisoning were reported.<sup>12</sup> Toxic levels of many chemical substances, such as toluene and other solvents, can produce devastating visual deficits. The deliberate inhalation of volatile substances to achieve intoxication has been associated with pleasant as well as unpleasant visual changes. Abuse of volatile substances is seen in most parts of the world, mainly among adolescents, individuals living in remote communities, and those whose occupations afford ready access to such substances.<sup>13</sup>

## Ocular Manifestations

Hallucination is a potential side effect of many medications. The most common medications with hallucinogenic potential are histamine 2 (H<sub>2</sub>) blockers, dopaminergic agents, antihypertensives, anticholinergics, sedative hypnotics, benzodiazepines, antidepressants, anti-inflammatory agents, and corticosteroids.<sup>14</sup> Many of the mydriatic and parasympatholytic drugs (e.g., scopolamine [hyoscine], atropine, cyclopentolate) used in ophthalmology have considerable hallucinogenic potential. Amantadine, atropine, and other anticholinergics may produce “Lilliputian” hallucinations, in which people appear greatly reduced in size.<sup>15</sup> Visual symptoms from digitalis include dimness; scotomata; flickering or flashing lights of yellow, green, or red; haloes; cycloplegia; amblyopia; diplopia; and blindness. Hydroxychloroquine has similar side effects, as well as photophobia and oculogyric crisis. Perception of a bluish haze and increased light sensitivity may occur with sildenafil use.<sup>16</sup> Hallucinogenic phenomena, particularly visual hallucinations, are observed with lysergic acid diethylamide, amphetamines, cocaine, marijuana, phencyclidine, and inhalants. Lysergic acid and several prescribed medications, such as trazodone, mirtazapine and topiramate have been linked to akinetopsia (abnormal movement perception) and palinopsia (perseveration of a visual image in time). The visual experiences of lead encephalopathy may resemble delirium tremens, with illusions or misperceptions of objects and shadows.

Many types of visual complaints follow carbon monoxide toxicity. Visual field defects range from concentric constriction to homonymous hemianopia. Patients often have fluctuating visual acuity with normal pupils, typical of an occipital lobe process. Visual object agnosia, polyopia, metamorphopsia, kakopsia (abnormally bright appearance of colors), and asthenopia (cerebral blurred vision) may occur. A distinct clinical syndrome grouped under the term *mitochondrial optic neuropathy* (MON) can be caused by several drugs, including ethambutol, chloramphenicol, linezolid, erythromycin, streptomycin, and antiretroviral agents.<sup>17</sup> MON is characterized by slowly progressive bilateral loss of central vision, dyschromatopsia, central or cecentral scotomas, and loss of high spatial frequency contrast sensitivity.

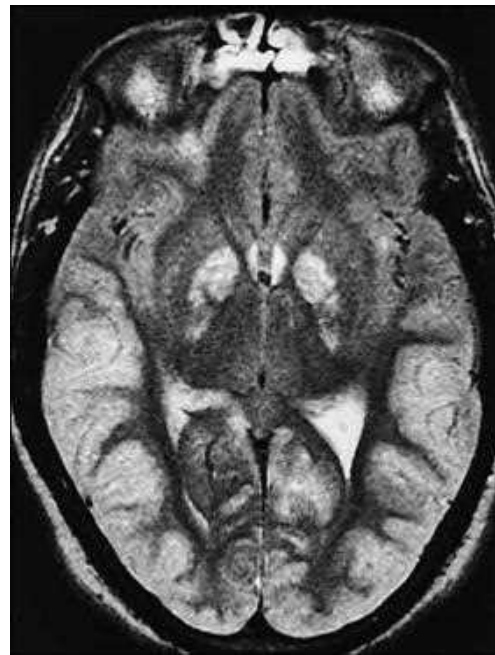
## Diagnosis and Ancillary Testing

For the evaluation of a patient who has unexplained visual loss or visual disturbances, a detailed history is required; this includes determining the usage of prescription and nonprescription drugs, the ingestion of herbal and other natural remedies, and possible environmental exposure to toxins or chemicals. In suspected cases of toxic exposure, toxicological analysis of blood, urine, and tissue is indicated. Optical coherence tomography is a useful ancillary test in drug-related retinopathy or optic neuropathy. MRI may reveal abnormalities in the basal ganglia or the occipital lobes with carbon monoxide poisoning (Figs. 9.25.1 and 9.25.2).

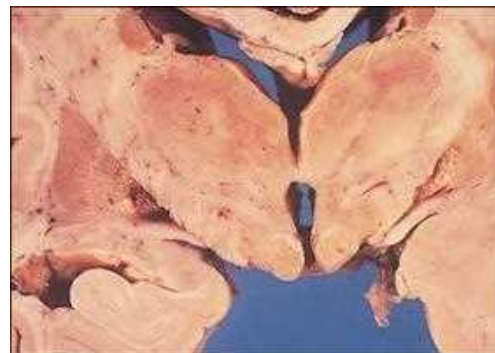
## Differential Diagnosis

Intracranial lesions, visual loss, vitreous or retinal detachment, seizures, migraine, and metabolic abnormalities must be considered in the evaluation of hallucinations. Both formed and unformed hallucinations occasionally occur with intracranial tumors, infarcts, and vascular malformations. Lesions in the temporal lobe typically produce formed images, whereas unformed, geometrical patterns arise from the occipital lobe. Vivid hallucinations may accompany a thalamic or midbrain infarction.<sup>18</sup> Patients who have a homonymous hemianopia may see images in their blind hemifield.<sup>19</sup> Partial seizures sometimes are accompanied by visual disturbances, which may herald the impending seizure. Positive and negative visual phenomena are common features of migraine with or without headache.

Metabolic derangements usually produce hallucinations with an encephalopathy. Flashes and floaters of ocular origin typically are monocular. Charles Bonnet's syndrome consists of formed hallucinations in patients who have bilateral visual loss. Typically, these are nonthreatening, and the patient knows that the apparitions are not real.<sup>20</sup> Formed and unformed hallucinations are also common in patients with retinal disease and often are not reported.<sup>21</sup> Patients who have bilateral blindness may see formed or unformed hallucinations as a release phenomenon. The visual hallucinations of psychiatric disease most often can be menacing and are accompanied by auditory hallucinations.



**Fig. 9.25.1** Magnetic resonance imaging of the brain shows areas of infarction following carbon monoxide poisoning. This T2-weighted image shows abnormally high signal intensity in the basal ganglia, right frontal lobe, and cerebral cortex.



**Fig. 9.25.2** Bilateral cavitory lesions in the globus pallidus following carbon monoxide poisoning.

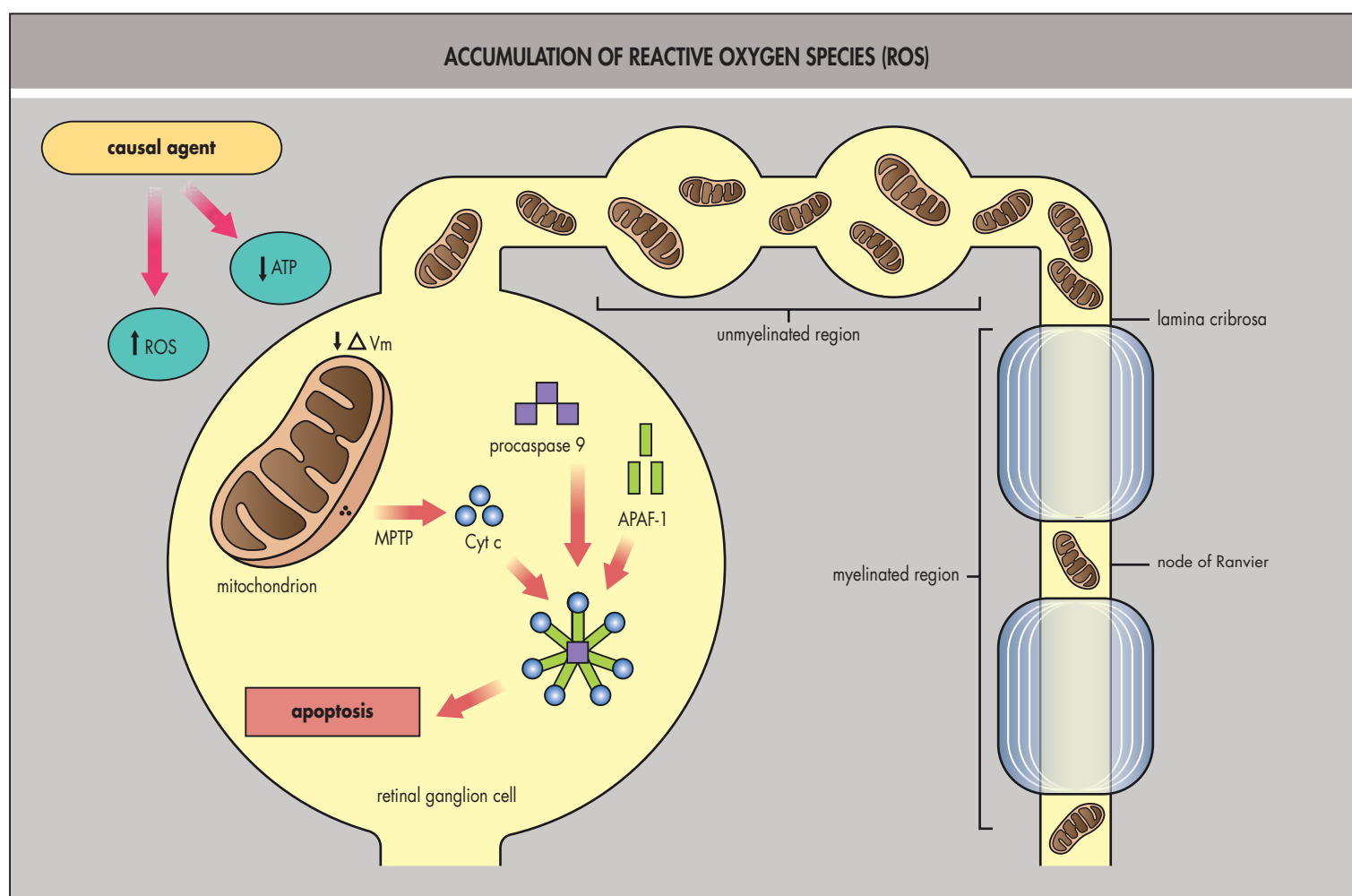
## Systemic Associations

Headache, fatigue, malaise, and drowsiness are side effects of many drugs. Hallucinogens are absorbed efficiently from the gastrointestinal tract, and this results in multiple systemic effects, such as disordered thought processes, mood changes, anorexia, tachypnea, tremors, hyperreflexia, hypertension, and tachycardia. Hallucinogens, medication reactions, and toxins can produce hallucinations that resemble psychiatric states.<sup>14</sup>

## Pathology

Some drugs affect the visual system by their effects on the ocular media, retina, and optic nerve. The anticonvulsant vigabatrin produces irreversible visual field loss by its effect on inner electroretinal function at the level of the Müller cell. Vigabatrin also produces outer retinal dysfunction that may be reversible.<sup>22,23</sup> Macular edema is a dose-dependent adverse effect of fingolimod, the first approved oral agent for the treatment of relapsing forms of multiple sclerosis, with an incidence of 0.4% at the recommended dose of 0.5 mg/day.<sup>24</sup> Drugs that cause MON are thought to block mitochondrial oxidative phosphorylation processes affecting the more vulnerable fibers of the papillomacular bundle (Fig. 9.25.3).<sup>17</sup> Treatment with tumor necrosis factor- $\alpha$  blockers may predispose patients to develop central nervous system demyelinating disease, including optic neuritis.<sup>25</sup> Nonarteritic anterior ischemic optic neuropathy has been reported in temporal association with the use of phosphodiesterase type 5 inhibitors used for treating erectile dysfunction.<sup>26</sup> In other cases, drugs have direct action on the brain cells. The dopaminergic and cholinergic neurons in mesolimbic pathways may be important in the development of hallucinations. Digitalis and other toxic agents produce visual changes as a result of profound excitatory effects on nerve cells. Severe reduction in visual acuity in patients who have carbon monoxide poisoning is thought to result from cerebral blindness secondary to brain anoxia.





**Fig. 9.25.3** Accumulation of reactive oxygen species (ROS) leads to a decrease in the electrical potential across the mitochondrial membrane, which allows for an opening of the mitochondrial permeability transition pore (MPTP), allowing for leakage of cytochrome c (Cyt c) into the cytosol. Cyt c then binds to apoptosis activating factor-1 (APAF-1), which activates procaspase-9, triggering the caspase cascade and apoptosis. (Source: Drug-related mitochondrial optic neuropathies. *J Neuroophthalmol* 2013 Jun;33(2):172–8.)

## Treatment, Course, and Outcome

The most important aspect of treatment is removal of the source of exposure. Hallucinations induced by hallucinogenic drugs can also be treated effectively with antipsychotic medications. Treatment of carbon monoxide poisoning consists of inhalation of supplemental oxygen and aggressive supportive care, including hyperbaric oxygen therapy for selected cases.<sup>27</sup>

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# Vascular Disorders

Peter A. Quiros, Michelle Y. Wang

# 9.26

**Definition:** Vascular lesions are congenital or acquired abnormalities of blood vessels and may affect any part of the sensory and motor visual pathways.

## Key Feature

- Aneurysms, carotid-cavernous fistulas and shunts, and arteriovenous malformations can produce damage to the eye and brain and have discrete, often disparate, clinical features and management.

## Associated Features

- Transient visual loss, both monocular and binocular, may or may not be associated with demonstrable vascular lesions.
- Transient ischemic attacks and stroke manifest characteristic symptoms and signs. Their diagnosis, investigation, and management depend on the locale of the insult to the central nervous system.

## INTRODUCTION

The visual pathways and oculomotor system can be affected by virtually all types of vascular diseases. Aneurysms most commonly cause third nerve palsy, although visual loss also may occur. Carotid-cavernous (C-C) fistulas, especially shunts, can be mistaken for other more benign causes of an inflamed eye. Arteriovenous malformations (AVMs), especially cryptic AVMs, can cause highly variable cerebral neurological deficits. Transient visual loss (TVL) and cerebral ischemic attacks cause concern about impending stroke.

## ANEURYSMS

### Epidemiology and Pathogenesis

The incidence of saccular aneurysms is estimated at 1%–2%.<sup>1</sup> Most saccular aneurysms occur as isolated, nonhereditary lesions. However, because intracranial aneurysms of 2 mm or smaller are found in 70% of routine autopsies, this incidence is significantly underestimated. Women are more susceptible, especially to internal carotid-posterior communicating (PCOM) artery aneurysms. The peak incidence of aneurysms occurs during the fifth and sixth decades. About 85% of aneurysms originate from branches of the internal carotid artery (ICA), usually at the PCOM or ophthalmic artery or within the cavernous sinus. The rupture rate depends on the size and location of the aneurysms, with the ones in the posterior circulation and PCOM artery being the highest risk locations. The International Study of Unruptured Intracranial Aneurysms conducted a retrospective study on 727 patients without a history of subarachnoid hemorrhage from a different aneurysm and 722 patients with a history of ruptured aneurysm. The rupture rate was 0.5% per year for aneurysms less than 10 mm in patients with a history of prior rupture and the risk increased to 0.7% per year for aneurysms 10 mm or larger. Those without a history of prior rupture had a lower risk.<sup>2</sup> Aneurysms may be multiple in about 25% of adults.<sup>2</sup>

### Ocular Manifestations

Aneurysms that affect the following portions of the circle of Willis have ophthalmological manifestations:

- The PCOM-ICA junction—causing third nerve palsy.
- The carotid-ophthalmic artery junction—causing compression of the optic nerve, optic chiasm, or both.
- The intracavernous carotid artery—causing dysfunction of isolated or multiple cranial nerves, including the oculomotor, trochlear, abducens, trigeminal nerves, and (rarely) optic nerves.

PCOM artery aneurysms most commonly affect young women; they can manifest as a sudden apoplectic event as a result of subarachnoid hemorrhage or produce third nerve palsy by slow enlargement without rupture.<sup>3</sup> This type of aneurysm is responsible for 13%–30% of acquired oculomotor palsy<sup>4,5</sup>; 90% of otherwise asymptomatic, unruptured PCOM artery aneurysms cause signs of third nerve palsy.

Carotid-ophthalmic aneurysms (rarer than PCOM artery aneurysms) affect the sensory visual pathways by compression of the optic nerve and chiasm, occur most commonly in women during the fourth to seventh decades of life, and often are associated with other intracranial aneurysms. Carotid-ophthalmic aneurysms may rupture and cause subarachnoid hemorrhage, but most often they produce symptoms by compression of the adjacent optic nerves and chiasm,<sup>6</sup> and this results in unilateral visual loss with an inferior visual field defect. These aneurysms arise from the ophthalmic artery beneath the optic nerve and compress the nerve superiorly against the superior dural shelf of the optic canal.<sup>7</sup> Insidious, slowly progressive visual loss occurs in most cases. Rarely, an acute painful course with central scotoma and ipsilateral afferent pupillary deficit can mimic retrobulbar optic neuritis.<sup>8</sup> When ophthalmic aneurysms expand posteriorly and superiorly, chiasmal or optic tract syndromes can be seen. Medial expansion may even compress the contralateral optic nerve.<sup>9</sup>

The main difference between PCOM artery aneurysms and internal carotid-ophthalmic aneurysms is that the former produce motor (third cranial nerve) signs and symptoms and the latter produce sensory (optic nerve and chiasm) symptoms and signs.

Aneurysms that arise from the internal carotid artery within the cavernous sinus behave differently. They can grow to quite a large size before rupturing; when they do rupture into the cavernous sinus, they may produce a C-C sinus fistula.

Intracavernous carotid aneurysms enlarge gradually within the cavernous sinus. Anterior expansion may erode the optic foramen and the superior orbital fissure, resulting in compressive optic neuropathy, ocular motor nerve paresis, and proptosis.<sup>3</sup> Erosion medially into the sella may produce hypopituitarism.

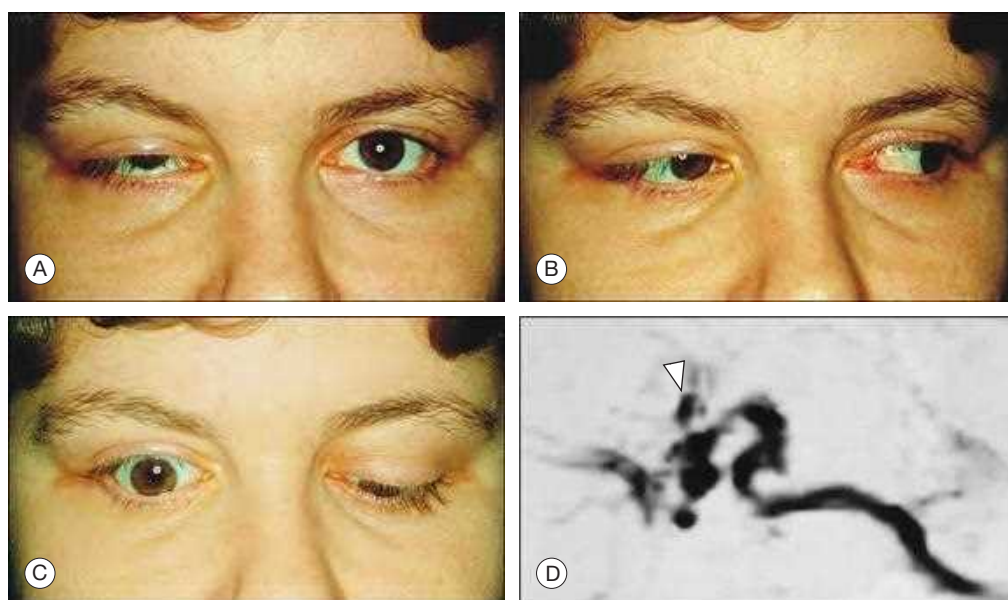
Patients with unruptured intracavernous aneurysms have cranial nerve palsies, with the sixth cranial nerve involved most commonly. The trigeminal nerve may be involved late in the disease, which results in facial pain.<sup>10</sup> Apparent pupillary sparing of the third cranial nerve may occur because of involvement of both oculosympathetic and parasympathetic pupillary pathways.<sup>11</sup>

Most patients who develop an acute oculomotor nerve paresis are left with a permanent disorder—often with secondary oculomotor nerve synkinesis or develop aberrant regeneration (including lid retraction on downgaze; Fig. 9.26.1) despite no previous acute third nerve dysfunction. Primary oculomotor nerve synkinesis more commonly occurs with meningiomas.<sup>12</sup>

Trigeminal nerve dysfunction commonly accompanies intracavernous aneurysms.<sup>13</sup> The first division of the fifth cranial nerve is affected most often. Pain usually is constant, lancinating, and severe, but it can be episodic. Trigeminal sensory loss is rare, and only occurs late in the disease.

Visual loss is not as characteristic of intracavernous aneurysm as it is with ophthalmic aneurysms, unless the aneurysm arises from the most distal portion of the intracavernous artery.





**Fig. 9.26.1** A 36-Year-Old Patient With Aberrant Regeneration—Third Cranial Nerve Synkinesis. (A) Ptosis. (B) Medial rectus paresis with lid retraction on adduction. (C) Typical lid retraction on downgaze. (D) Magnetic resonance angiogram showing internal carotid-posterior communicating artery aneurysm (arrow).

## Diagnosis

Three clinical signs usually are apparent:

- Ipsilateral facial, orbital, or eye pain.
- Extraocular muscle and levator involvement.
- Pupillary paresis.

### Head Pain

Head pain can be caused by both ruptured and unruptured aneurysms. Ruptured aneurysm pain is severe, sudden in onset, throbbing, and radiates posteriorly. Neck pain and stiffness are signs of subarachnoid hemorrhage. Third nerve palsy most commonly occurs concomitantly but may not develop for hours or days. Headache and eye pain from unruptured aneurysms may occur intermittently for weeks or months before third nerve palsy or aneurysm rupture occurs.

### Ophthalmoplegia

Ophthalmoplegia is variable but develops in virtually all patients eventually. Ptosis and extraocular motor paresis occur at the same time almost invariably, especially with ruptured aneurysms. An apoplectic onset with subarachnoid hemorrhage may overshadow the signs of diplopia or ptosis. Any muscle supplied by the third cranial nerve can be affected; however, the superior rectus and levator muscles are damaged most commonly because the aneurysm presses on the nerve from above in the subarachnoid space (Fig. 9.26.2).

### Pupillary Involvement

Pupillary involvement can be the initial sign of an unruptured or “about to rupture” aneurysm but is rarely, if ever, an isolated sign in a ruptured aneurysm. Pupillary dilatation may occur shortly before, at the same time, or shortly after oculomotor paresis occurs. Pupil involvement mandates immediate efforts to rule out an aneurysm by magnetic resonance imaging (MRI) or magnetic resonance angiography (MRA). Computed tomography angiography (CTA) is also very useful in detecting these aneurysms,<sup>14</sup> but digital subtraction angiography is still the gold standard. In an emergency, computed tomography (CT) can be performed immediately to rule out subarachnoid hemorrhage. Complete pupil sparing, which may accompany extraocular muscle paresis with a PCOM artery aneurysm, has been reported rarely.<sup>15,16</sup> Although pupil involvement can be seen in as many as 20% of patients with ischemic oculomotor palsies, anisocoria of more than 1.5 mm is very rare.<sup>17</sup>

## Differential Diagnosis

The appropriate ophthalmic management of possible aneurysms is to make the right diagnosis expeditiously. Any patient with a possible third nerve palsy should be observed carefully for pupillary dysfunction. Complete third cranial nerve paresis and a normal pupil are extremely unlikely in a patient with an aneurysm.<sup>18</sup>

However, Miller<sup>3</sup> states that any patient with an incomplete oculomotor palsy and a normal pupil should undergo neuroimaging. When aneurysms are greater than 4 mm in diameter, they can be demonstrated by dynamic CT and MRI,<sup>19</sup> as well as MRA. The author feels, however, that an older patient with hypertension or diabetes, without head pain, need be only observed because most likely there is a microvascular etiology for the third nerve palsy. Symptoms and signs may occur directly after injury or several days to weeks later. Although relatively rare, direct fistulas may develop spontaneously. Such patients may suffer from diffuse arterial disease manifested by aortic, femoral, and popliteal aneurysms,<sup>20</sup> as well as other signs of large vessel disease, such as systemic hypertension, arteriosclerosis,<sup>21</sup> or an underlying connective tissue disorder.

## Treatment, Course, and Outcome

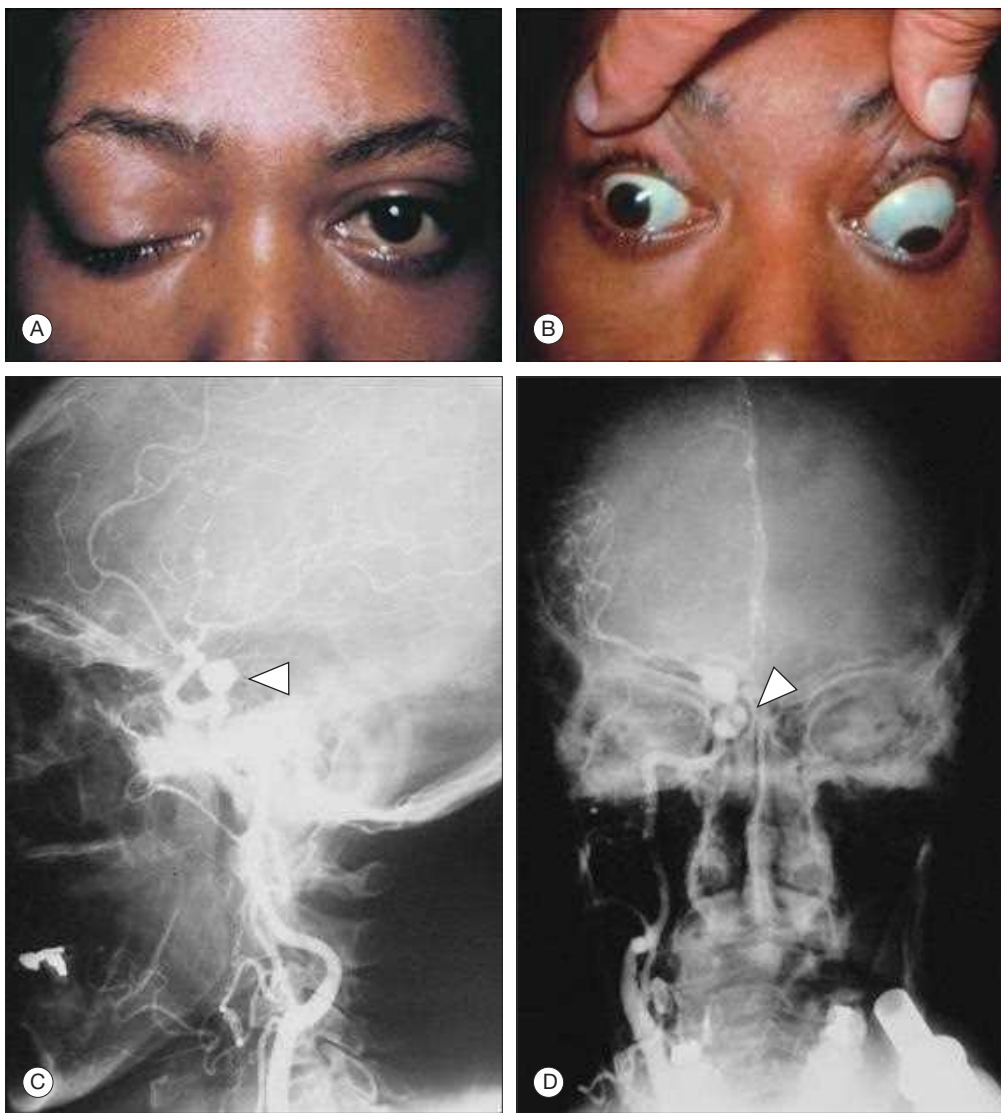
Recovery of extraocular muscle function occurs in most patients with PCOM artery aneurysms, either spontaneously or after surgical treatment, whether or not the aneurysm has ruptured. Recovery is most likely in incomplete paresis, when no rupture has occurred and when successful clipping is performed within 1–2 weeks of onset.<sup>22</sup> Incomplete recovery after several months leaves secondary oculomotor nerve synkinesis or aberrant regeneration of the oculomotor nerve (see Fig. 9.26.1).

## CAROTID-CAVERNOUS SINUS FISTULAS AND DURAL SHUNTS

### Epidemiology and Pathogenesis

Abnormal communications between the cavernous sinus and dural veins and the carotid arterial system can be classified according to cause (traumatic versus spontaneous), velocity of blood flow (high versus low flow), and anatomy (direct [sinus] versus indirect [dural]; internal carotid versus external carotid, versus both). C-C fistulas, characterized by direct flow into the cavernous sinus from the intracavernous carotid artery, are of the high-flow type; these usually are traumatic and most often diagnosed in young men. Nontraumatic, low-flow dural fistulas may develop spontaneously or with atherosclerosis, hypertension, collagen vascular disease, and during or after childbirth; these fistulas more often are seen in middle-aged women. Spontaneous shunts occur between the cavernous sinus and one or more meningeal branches of the internal carotid artery (usually the meningohypophyseal trunk), the external carotid artery, or both. These shunts have a low amount of arterial flow and almost always produce signs and symptoms spontaneously.

Dural shunts between the arterial and venous systems have lower flow, yet they may produce symptoms in younger patients spontaneously or in older patients as a result of hypertension, diabetes, atherosclerosis, or other vascular disorders. Anatomically, these shunts arise between the meningeal arterial branches and the dural veins. The meningohypophyseal



**Fig. 9.26.2** A 40-Year-Old Patient With Right Internal Carotid-Posterior Communicating Artery Aneurysm. (A) Primary position ptosis. (B) Paralysis of vertical gaze and dilated pupil. (C-D) Arteriograms showing internal carotid-posterior communicating artery aneurysm directed down, out, and inferiorly on the third cranial nerve (arrows).

trunk and the artery of the inferior cavernous sinus provide the arterial supply to most dural shunts.<sup>23</sup>

Such shunts may be caused by an expansion of congenital arteriovenous malformation<sup>24</sup> or spontaneous rupture of one of the thin-walled dural arteries that traverse the sinus.<sup>25</sup>

## Ocular Manifestations

Ocular signs of C-C fistulas are related to venous congestion and reduced arterial blood flow to the orbit. Diminished arterial flow to cranial nerves within the cavernous sinus may cause diplopia. Stasis of venous and arterial circulation within the eye and orbit may cause ocular ischemia, and increased episcleral venous pressure may cause glaucoma. These abnormalities usually are unilateral, but they can be bilateral or even contralateral to the fistula.<sup>26,27</sup>

Exophthalmos is a common sign that occurs in almost all patients who have C-C fistulas; rapid-flow fistulas may cause exophthalmos within hours or several days. The orbit can become “frozen,” with no ocular motor function. Usually, this is accompanied by conjunctival chemosis and hemorrhage. Vision may be reduced markedly because of optic nerve ischemia.<sup>28</sup>

“Pulsating exophthalmos” is uncommon in C-C fistula. Usually, the orbit is too rigid from hemorrhage and edema for “pulsation.”

Chemosis of the conjunctiva and arterialization of the episcleral vessels occurs in most patients. Arterialization of episcleral veins is the hallmark of all C-C fistulas or dural shunts (Fig. 9.26.3).

Bruits associated with fistulas and dural shunts can be appreciated both subjectively and objectively. A bruit can be heard best when the examiner uses a bell stethoscope over the closed eye, over the superior orbital vein, or over the temple. A bruit is not pathognomonic of C-C fistula. It also can be heard in normal infants, in young children, and in patients with severe anemia.

In cases of C-C fistula, the abducens nerve is affected most often because it lies in the cavernous sinus itself. Because the third and fourth

cranial nerves are encased in the superior internal dural wall of the sinus, they may be protected from changes caused by the fistula.<sup>29</sup> Mechanical restriction from venous congestion and orbital edema also may contribute to limitation of eye movements.

Immediate or delayed visual loss occurs frequently in direct C-C fistulas<sup>29</sup> because of optic nerve ischemia from apical orbital compression. Long-standing fistulas can lead to loss of vision from distension of the cavernous sinus or retrobulbar ischemia.<sup>28</sup>

Ophthalmoscopic findings caused by venous stasis and impaired retinal blood flow include retinal venous engorgement and dot-and-blot retinal hemorrhages. Central retinal vein occlusion may be observed in high-velocity C-C fistulas with arterialized venous channels. In the unusual cases of central vein occlusion, neovascular glaucoma can occur.

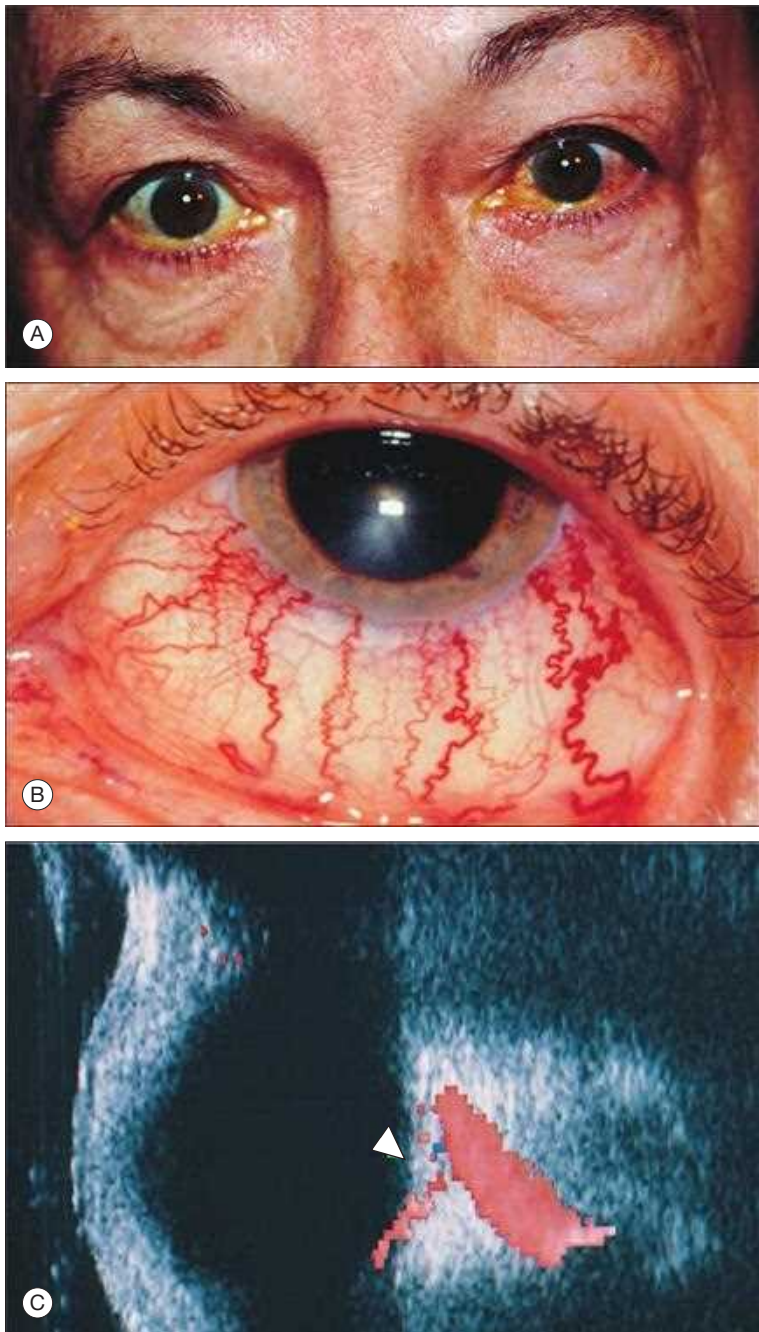
Misdiagnosis is more common with dural shunts than with C-C fistulas. Dural shunts may be mistaken for chronic conjunctivitis, orbital cellulitis, orbital pseudo-tumor, or thyroid disease.<sup>30</sup> However, in dural shunts the palpebral conjunctiva is not involved, and the bulbar vessels are not affected as diffusely as in inflammatory processes. Signs of dural shunt usually are unilateral, but they can be bilateral or even contralateral to the shunt.<sup>27</sup> Enlargement of the superior ophthalmic vein on contrast-enhanced CT or MRI is a telltale sign of most fistulas.

Exophthalmos generally occurs to a varying degree (see Fig. 9.26.3A and B), and ocular motor (usually abducens) palsies may be seen. A subjective bruit (heard by the patient) almost always can be obtained from the history; however, an objective bruit heard over the orbit or temple by auscultation is relatively uncommon.<sup>3</sup> Wide pulsation of Schiötz or applanation intraocular pressure amplitude is an important clue to the diagnosis.

## Differential Diagnosis

A direct C-C fistula should be suspected in any patient who suddenly develops a red eye with chemosis and exophthalmos, especially after head trauma. Orbital ultrasonography, CT, and MRI often show a “hockey stick”





**Fig. 9.26.3 Exophthalmos.** (A) A 60-year-old female patient, who has left chronic “red eye.” (B) Corkscrew (arterialized) vessels caused by low-flow (carotid–cavernous sinus) fistula. (C) Color Doppler image that shows impedance and reversal of flow in superior orbital vein (arrow). (B, Courtesy Dr. Christopher Kelley, Wills Eye Hospital.)

sign of an engorged superior ophthalmic vein, which also may be demonstrated by Doppler imaging. The ultimate test, however, is selective arteriography of both internal and external carotid arteries.

Treatment, Course, and Outcome

As with a C-C fistula, the diagnosis of a dural shunt can be made using CT, MRI, and Doppler imaging because each reveals superior ophthalmic vein enlargement (see Fig. 9.26.3C). Carotid color Doppler imaging may show reversal of flow in the ophthalmic artery, which may help to establish the diagnosis (see Fig. 9.26.3C).<sup>31</sup> CTA and MRA can also be helpful in the diagnosis of C-C fistula. However, selective intra-arterial angiography is usually necessary to define the dural shunt, and angiography remains the gold standard test.

Many patients with dural shunts improve spontaneously. Thus, proper diagnosis, reassurance, and conservative follow-up usually suffice.<sup>30,32</sup> However, embolization is necessary in patients with leptomeningeal venous drainage, variceal or aneurysmal venous dilation,<sup>33</sup> as well as those with visual loss (e.g., central vein occlusion), diplopia, severe exophthalmos, uncontrolled intraocular pressure, or intolerable bruit.<sup>34</sup> Although significant risks of neurological or visual sequelae from treatment must

TABLE 9.26.1 Terminology of Transient Visual Loss		
Type	Duration	Characteristics
Transient Monocular Visual Loss		
Visual obscuration	Seconds to minutes	Optic disc swelling and anomalies
Amaurosis fugax	Seconds to minutes	Often altitudinal; carotid, cardiac source (embolic) or vasospastic
Prolonged transient	15–60 minutes	Hypertension; hematopoietic visual loss and other systemic (vascular) problems; “retinal” migraine
Transient Binocular Visual Loss		
Aura without Headache	10–30 minutes	No other symptoms

be considered, treatment of the dural fistula should precede surgery in cases of high intraocular pressure. Endovascular treatment of the fistula via a transarterial or transvenous route often leads to resolution of visual deficits.<sup>32</sup>

The prognosis of direct C-C fistula varies, but severe visual loss is often immediate and permanent, especially when a “frozen orbit” is encountered. Some patients may not be aware of the visual loss because of an overriding concern for the chemosis, proptosis, and lid swelling.

Compared with the dural shunt syndrome, C-C fistula is a much more serious prognosis because direct fistulas do not resolve spontaneously and are less amenable to occlusive techniques. Expedient consultation with neurosurgery or neurointerventional radiology for fistula closure is indicated. The optimal treatment of C-C fistula is closure of the fistula along with preservation of carotid artery patency. Older procedures that required occlusion of the carotid artery to trap the fistula resulted in orbital hypoxia, which often made matters worse.

Endovascular closure has become the choice of treatment for C-C fistula.<sup>35</sup> Complications, such as worsening of orbital congestion and ocular motor nerve paresis, may occur. Fortunately, these complications are usually transient.<sup>3</sup> Successful occlusion usually results in gradual resolution of orbital signs within days, weeks, or sometimes months. Visual loss is often permanent.<sup>26</sup>

Arteriovenous Malformations

AVMs are the most common form of intracranial vascular hamartoma. The occasional relationship between cerebral (mesencephalic) and retinal AVMs was recognized first by Wyburn-Mason in 1943.<sup>36</sup> Most intracranial AVMs involve only pial vessels, but some involve both pial and dural vessels. Most AVMs are of congenital origin, but those that involve the meningeal arteries or vertebral arteries that drain into the dural sinuses may be acquired.<sup>23</sup>

AVMs that are only a few millimeters in size cannot be identified by neuroimaging and are referred to as *cryptic* or *occult*. Conversely, AVMs may be so large as to occupy an entire cerebral hemisphere. Although AVMs usually are congenital, they may become symptomatic at any age. However, 70% of AVMs produce symptoms during the second and third decades of life.

Most cerebral AVMs produce signs of intracerebral or subarachnoid hemorrhage, which include seizures or isolated neurological symptoms and signs. Headache is a frequent symptom and may mimic migraine, although the headaches always are on the same side, in contrast to typical migraines.

Improvements in microguidewire and microcatheter technology have made it possible to treat previously unreachable and untreatable AVMs. Treatment options include microsurgery, radiosurgery, and endovascular approaches. The specific techniques vary according to the anatomy of the lesion.<sup>37</sup>

TRANSIENT VISUAL LOSS

Epidemiology and Pathogenesis

TVL is a common symptom that may be benign or a harbinger of serious disease. Because clinical findings often are absent in patients with TVL, taking a medical history is imperative.

Ocular Manifestations

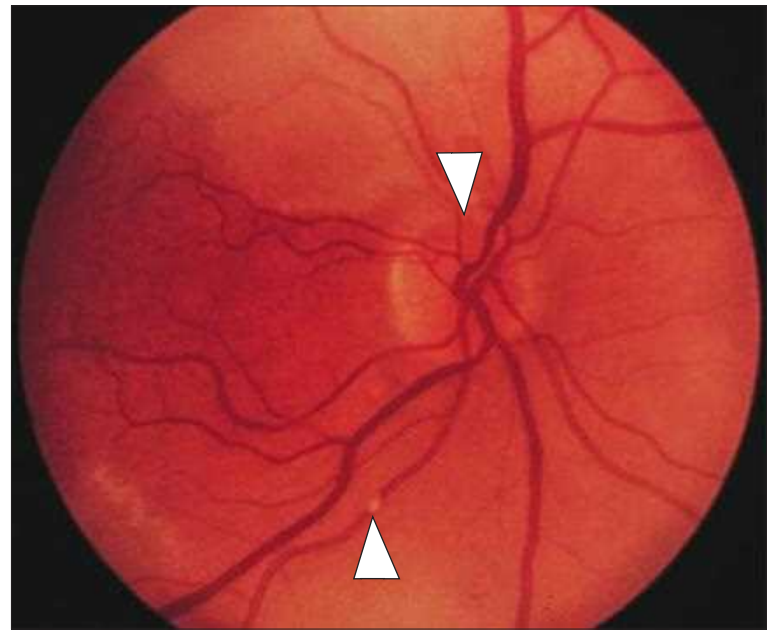
The terminology of TVL (Table 9.26.1) is important because it designates not only the anatomical location of the problem but also its pathogenesis.



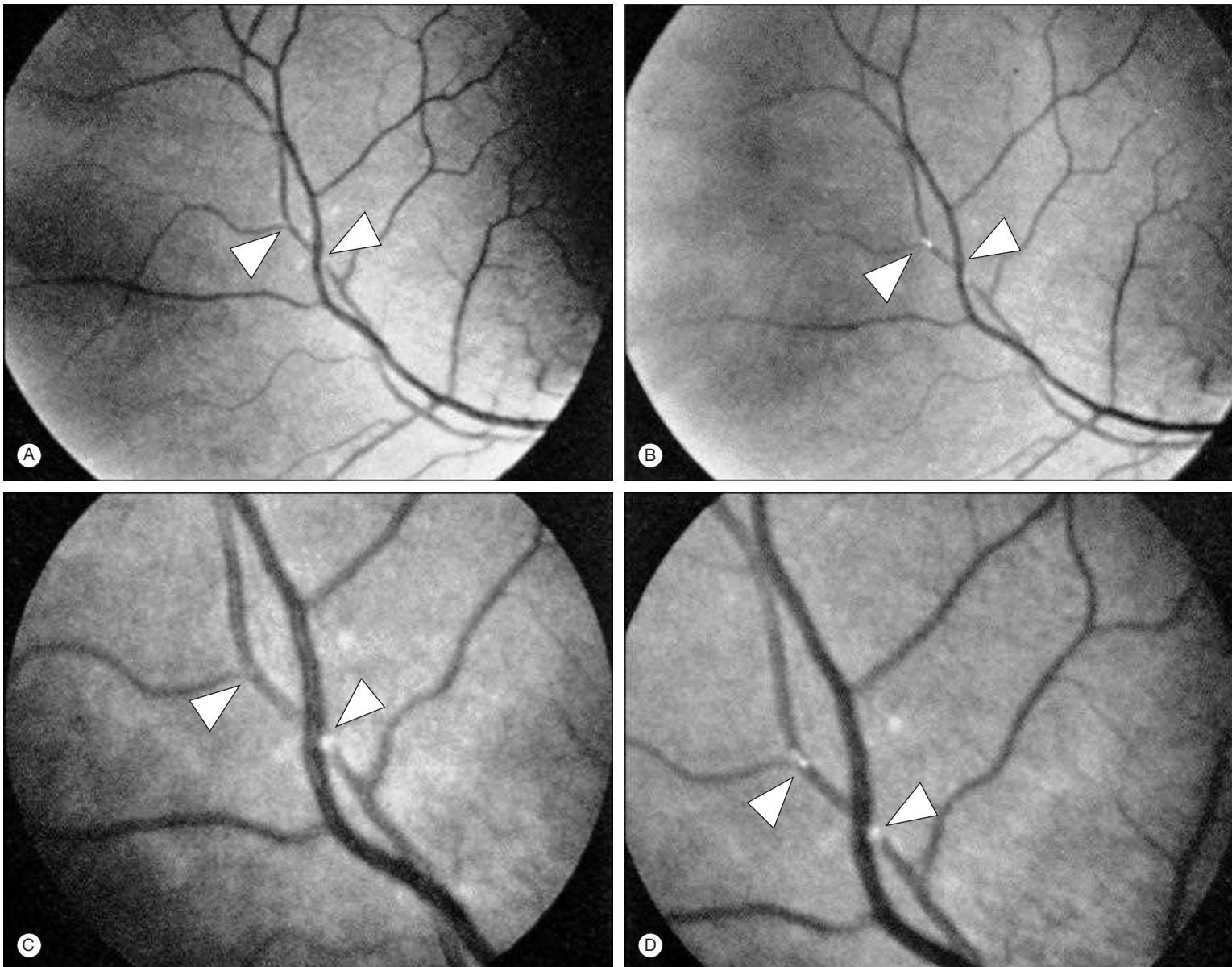
Specific types of transient, monocular visual loss include transient visual obscurations, which are very brief (1–5 seconds) episodes of visual loss typically seen in patients with papilledema due to increased intracranial pressure), amaurosis fugax (1–5 minutes), caused by embolic or hemodynamic retinal arterial insufficiency, and prolonged monocular TVL, (>10 minutes), which occurs in patients with hypertension, blood dyscrasias, and “retinal migraine.” Binocular TVL may be seen with migraine, in the absence of headache (aura without headache), and in other rare binocular or homonymous disturbances caused by occipital ischemia or seizures.

Physical clues that help in the diagnosis of patients with TVL include abnormalities of vision, pupillary abnormalities, color vision loss, Amsler Chart defects, and abnormalities of the optic nerve or retina. The most important ocular finding in monocular TVL is an impacted embolus in the arteries within the optic nerve or in the retina. The appearance of different types of emboli can provide clues to the source. Localized, hard, white material suggests calcium, which may come from a damaged aortic or mitral valve. Platelet-fibrin emboli usually conform to a segment of a retinal branch arteriole and may have a white or gray appearance. Hollenhorst or cholesterol plaques are yellow or golden and tend to gleam (Fig. 9.26.4). Both platelet-fibrin emboli and cholesterol emboli can be missed easily, especially if they are small. Gentle pressure on the eye often makes the embolic material “light up,” which allows better visualization of an embolus (Fig. 9.26.5).<sup>38</sup>

Retinal emboli are the major cause of amaurosis fugax; the carotid artery is the likely source, although such emboli also can come from the



**Fig. 9.26.4** Cholesterol emboli impacted in superior and inferior retinal arterioles with branch occlusion (arrows).



**Fig. 9.26.5** Combined thromboplatelet retinal emboli digital pressure maneuver (arrows). (A) Before pressure. (B–D) During digital pressure on the eye to elicit previously only suspected embolus.

aorta or heart. Auscultation of a bruit in the neck at the angle of the jaw further indicates the need for carotid magnetic resonance arteriography or, at least, carotid Doppler imaging.

An often-neglected anterior sign in any of the ocular ischemic syndromes is sludging of the conjunctival microcirculation. Slit-lamp magnification with red-free light shows micropools and a varying degree of sludging in the conjunctival blood vessels when a vascular impedance or hyperviscosity is present. In patients with ocular ischemia from severe carotid artery stenosis or occlusion, TVL may occur when the eye on the affected side is exposed to bright light.

## Diagnosis

The age of the patient with TVL is very important—older patients with vasculopathy have different causes compared with younger individuals. The character of the episode must be ascertained in detail.

### Nature of the Episodes

The following need to be established:

- Where, when, and how did the episode occur?
- Did it appear and disappear suddenly or gradually?
- Did field loss occur, and, if it did, what type was it?

The typical curtain effect of altitudinal, monocular visual field loss is most significant because this implies carotid occlusive disease or a cardiac source.

### Type of Visual Loss

Monocularity is not always easy to determine. Although most patients with monocular TVL often are clear about monocularity, patients with binocular TVL or migraine aura commonly state that the right or left eye is involved when, in reality, loss of vision may have occurred only in the larger temporal homonymous visual field.

### Length of Episodes

The duration of transient monocular loss of vision caused by carotid artery disease typically lasts 1–5 minutes. The patient often does not initially calculate the duration accurately, but with recurrent attacks, both monocularity and duration are better appreciated.

### Frequency of Episodes

An isolated monocular attack may be sufficient to warrant investigation, at least with carotid Doppler studies. Recurrent attacks over a short interval are a strong indication for a full workup.

### Associated Symptoms

Accompanying symptoms usually are absent in TVL. It is the isolation that makes TVL episodes unique. It is rare for a patient with an isolated aura without headache to proffer any other neurological symptoms. Contralateral numbness or weakness that occurs with transient monocular loss of vision implies severe carotid stenosis. Cerebral TIAs imply either emboli to the brain or a hemodynamic cause, such as hypertension. Transient binocular blindness caused by posterior circulation ischemia from atherosclerosis often occurs with other symptoms of vertebrobasilar insufficiency, such as dizziness, lightheadedness, or syncope.

### Underlying Risk Factors

Contributory causes can be determined from a thorough history and appropriate investigation. Hypertension, diabetes, or hematopoietic disorders in all age groups are important. In young people, contraceptive pill use and congenital acquired heart disease must be excluded. In older patients, any history of myocardial, femoral, or aortic disease is an important indication of a diffuse arteriopathic state.

Young patients with TVL should be screened carefully for hyperviscosity or hypercoagulable disorders. Elevated antiphospholipid–cardiolipin antibody levels in a young woman with a strong history of migraine may be important. Cardiac workup may identify mitral and aortic valvular disease, mural thrombi, arrhythmia, especially intermittent atrial fibrillation, and patent foramen ovale.

## Treatment, Course, and Outcome

The goal in the management of patients with TVL is to prevent further episodes that could lead to permanent visual loss or cerebral stroke. However,

a single attack of monocular TVL does not necessitate invasive studies. Noninvasive carotid and orbital color Doppler imaging, when properly performed, may be sensitive enough to provide the required information; many patients who have TVL therefore may not require more invasive studies. Older patients with risk factors for large-vessel disease probably should be assessed by using MRA. Any patient with a history of cardiac signs or symptoms should be assessed by using echocardiography.

In summary, symptomatic patients with or without retinal emboli or a bruit should be assessed by using carotid and orbital color Doppler imaging or MRA. Invasive angiography may not be necessary.

## TRANSIENT ISOLATED BILATERAL LOSS OF VISION

### Aura Without Headache

Transient binocular loss of vision is one of the most common complaints encountered in ophthalmic practice. It has been called *acephalgic migraine*, *migraine accompaniment*, *visual migraine*, and *ophthalmic migraine*. The term *isolated aura without headache*, however, clearly identifies an isolated transient binocular attack, similar to that described as the aura or prodrome of migraine.

Symptoms may last from 15 seconds to 1 hour; however, the classic description of kaleidoscopic, heat-wave, or scintillating bright lights that last for 10–20 minutes confirms the diagnosis, which usually is a great relief to the patient.

Visual field testing sometimes should be performed. It is still the best way to be sure that stroke, AVM, or tumor is not the problem.

Monocular loss almost always needs investigation. Management of binocular episodes usually is conservative. The typical 10- to 20-minute attack of transient bilateral homonymous loss of vision with a kaleidoscopic or heat-wave visual disturbance is so characteristic of isolated aura without headache that a diagnosis can be made with confidence, the patient reassured, and no further investigation made. These patients primarily need reassurance and do not need further investigation unless extenuating circumstances are present.

## STROKES

### Epidemiology and Pathogenesis

#### Transient Ischemic Attacks and Stroke

The most reliable indicator of impending stroke is a transient ischemic attack (TIA). Vascular sites of disease that produce TIAs and stroke are as follows:

- Carotid–ophthalmic artery.
- Middle cerebral artery (MCA).
- Posterior cerebral (terminal basilar) artery.
- Basilar artery.

#### Carotid–Ophthalmic Ischemic Attacks and Stroke

Carotid–ophthalmic artery TIAs most commonly manifest as amaurosis fugax caused by hypoperfusion of the retina. The patient is at risk of permanent visual loss, usually from occlusion of the central retinal artery. This constitutes an ocular “stroke” and requires investigation of carotid, cardiac, and hemodynamic diseases (see Chapter 6.19).

Severe chronic common or bilateral internal carotid artery diseases may lead to hypoperfusion of the optic nerve and retina and cause the ocular ischemic syndrome (see Chapter 6.23). The hallmark of this syndrome is venous stasis retinopathy (Fig. 9.26.6).<sup>39,40</sup> Impacted cholesterol or platelet–fibrin emboli in the retina are an indication of carotid artery atheroma as the source; they are seen in 60%–70% of patients with branch retinal artery occlusion.<sup>41</sup> Nonarteritic ischemic optic neuropathy, both anterior and posterior, rarely may be the initial manifestation of internal carotid artery occlusion.

### Ocular Manifestations

Monocular blindness with contralateral hemispheric symptoms and signs (e.g., hemiparesis) is a well-recognized, although rare, entity in patients with carotid artery disease.<sup>42</sup> Blindness occurs as a result of retinal





**Fig. 9.26.6 Venous Stasis Retinopathy.** Typical diffuse dot-and-blot hemorrhages and venous dilatation without tortuosity in inferior fundus.

ischemia. However, these patients may have the simultaneous occurrence of cerebral infarction and ipsilateral ischemic optic neuropathy.<sup>43</sup>

Ocular ischemic syndrome causes insidious, slowly progressive loss of vision, in contrast to the acute loss resulting from retinal or optic nerve infarction. The affected eye is often injected, and vision is poorer than expected by the initial clinical examination. Neovascular glaucoma and vitreous hemorrhage often follow. Atherosclerotic occlusion or severe stenosis of the common, external, and internal carotid arteries is found in most patients who have a risk of stroke caused by poor cerebral perfusion<sup>44,45</sup> (see Chapter 6.23).

The second major ocular sign of carotid occlusive disease is partial or complete contralateral homonymous hemianopia,<sup>3</sup> often the result of hypoperfusion in the MCA, although posterior cerebral occlusion is, by far, the most common cause of homonymous hemianopia. Cerebral TIAs tend to be longer in duration compared with ocular TIAs. Ischemic reversible neurological deficit occurs when symptoms, such as numbness or weakness, disappear. When the defect persists, the term *stroke* should be used.

Ischemia of the cortical and deep cerebral branches of the left MCA produces isolated motor aphasia and, often, contralateral hemiparesis and sensory loss. When TIAs of the MCA are on the right (nondominant) side, transient motor or sensory loss is produced on the left, without aphasia.

The frequency of TIAs of the MCA is much less than that of internal carotid arteries (64% versus 20%); additionally, the internal carotid artery has more TIAs per patient (103 versus 3). Binocular TVL is not usually considered a manifestation of TIAs of the MCA, even though homonymous hemianopia is common in a completed MCA stroke. Caplan et al.<sup>46</sup> found TIAs of the MCA to be more common in people who are young, African American, and/or women.

The MCA stroke often fluctuates and progresses gradually. Anterior MCA branch occlusion produces hemiparesis in the leg and loss of sensation without hemianopia. Posterior MCA branch occlusion produces incomplete incongruous homonymous hemianopia, without macular sparing. Optokinetic responses may be reduced when stripes or checks are moved in the direction of the affected parietal lobe. Left MCA stroke produces aphasia, in contrast to right-sided lesions that produce contralateral hemispatial neglect and supranuclear horizontal gaze paresis toward the side of the lesion.

Homonymous hemianopia is the major neuro-ophthalmic sign of MCA stroke; it may be the only sign.<sup>3</sup> It is the result of damage to the optic radiations. The prognosis in MCA stroke is poor, but early treatment with intravenous tissue plasminogen activator may lead to greater recanalization rate and early neurological improvement.<sup>47</sup>

Transient visual symptoms caused by posterior cerebral artery (PCA) hypoperfusion are encountered less commonly and are less dramatic to the patient than amaurosis fugax of carotid origin. Isolated visual migraine must be differentiated from that of an impending stroke. Fisher<sup>41</sup> states that aura that occurs as a spectral march (buildup) or progression of the visual phenomenon often differentiates aura with or without headache from occipital TIA and stroke. Clinically, aura without headache is very common, in contrast to occipital TIA, although each can mimic the migraine with aura. True vascular TIAs that involve the occipital lobes

usually are sudden in onset, with a complete or incomplete homonymous hemianopia. They may be accompanied by vertebral-basilar symptoms, such as unsteadiness, dysarthria, facial numbness, or weakness.

Isolated homonymous hemianopias usually are caused by vascular occlusion of the PCA and thus are the hallmarks of occipital stroke. Infarction of the PCA is the result of embolism; rarely is it caused by atherosclerosis. Usually, PCA strokes occur without warning.<sup>48</sup>

Calcarine cortex infarction results in complete or incomplete hemianopia and usually spares the macular field. Invariably, hemianopia is congruous. A complete homonymous hemianopia spares the macula as a rule, and usually visual acuity is normal, although patients often complain of blurred vision. Many patients are unaware of the defect until it is pointed out.

Hemianopia with splitting of the macula often causes difficulty with reading. The Amsler chart or the Humphrey visual field is a valuable test by which to prove macular involvement; it also is a great asset when explaining the problem to the patient.

Clinically, homonymous hemianopia due to stroke in the temporo-parietal and occipital areas can be differentiated by diminished optokinetic nystagmus. When stripes or other stimuli are moved in the direction of a lesion that involves the deep parietal lobe, the responses are dampened, whereas in isolated occipital (calcarine) lesions the responses are equal. Improvement of the field defect is rare.

Hemianopia always should lead to inquiry as to other neurological deficits. Ophthalmologists should recognize alexia without agraphia, wherein the patient usually can name individual letters or numbers but cannot recognize simple words, although able to write words.<sup>49</sup> Right PCA occlusion can result in *prosopagnosia*, the inability to recognize familiar faces. Cerebral dyschromatopsia (color blindness) also can occur in occipital stroke. Rehabilitation is very difficult in permanent homonymous hemianopia.

Reduction in vertebral-basilar blood flow produces neurological and visual disturbances, from damage to the midbrain, pons, medulla, cerebellum, and occipital lobes. These disturbances may be transient, persistent, inconsequential, or catastrophic. Both extraocular movement and visual symptoms play a role in diagnosis.

In the vertebrobasilar territory, TIAs are much more varied than they are in the carotid system. Vertigo is the most common neurological symptom, along with dysarthria, transient weakness, drop attacks, and occipital headaches.<sup>3</sup> The most common visual symptom is a characteristic brief, binocular “white-out” of vision, which lasts a few seconds (rarely, up to 5 minutes). Transient diplopia is a rare symptom from ischemia of the ocular motor nerves or nuclei, or supranuclear and internuclear pathways. Typically, this symptom lasts 5–10 minutes. Episodic oscillopsia or “jumping vision” may occur during attacks of vertigo or dizziness.

The cause of vertebrobasilar TIA is speculative. Congenital vascular anomalies, hypertension, and hematological disorders are possible causes; however, atheromatous disease is the major problem in most patients.<sup>50</sup>

Stroke usually occurs without previous TIAs in vertebrobasilar disease. Hypertension and atherosclerosis are the most common causes, in addition to emboli from the heart or distal large arteries. Combined brainstem symptoms and signs include vestibular nystagmus, miotic pupils, and sixth cranial nerve, as well as conjugate gaze, internuclear, and facial palsies. Terminal PCA ischemia may occur alone or with a homonymous hemianopia. Lesions here can produce bilateral deficits, whereas carotid lesions produce unilateral deficits.

Brainstem signs most often arise from the lesions in the dorsal midbrain, primarily characterized by abnormal vertical gaze, upgaze, or downgaze paresis with lid retraction, or as isolated upgaze paresis. Pupillary signs, internuclear ophthalmoplegia, and skew deviation also may be present.

See-saw and convergence retraction nystagmus accompany periaqueductal midbrain infarction. The more ventral medial midbrain syndrome of oculomotor nerve dysfunction and contralateral hemiplegia (Weber’s syndrome) and Benedikt’s syndrome with contralateral cerebellar signs also may result from infarction of midbrain. Strokes that involve these structures can be identified by using MRI.

Pontine stroke produces primarily horizontal disorders of eye movement. Such strokes usually are associated with dizziness, facial nerve palsy, contralateral hemiparesis, hemisensory symptoms, and cerebellar signs. Isolated sixth nerve palsy without neurological signs also has been shown, by using MRI, to be caused by a fascicular lesion.<sup>51</sup> Unilateral internuclear ophthalmoplegia may be caused by infarction of the medial-longitudinal fasciculus in the pons.



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# Electrophysiology

Rustum Karanjia, Stuart G. Coupland

# 9.27

**Definition:** Electrophysiology is an ancillary test that provides functional data on the inner and outer retina. In neuro-ophthalmology, it can be used to measure the electrical activity of the ganglion cells (pattern electroretinography and photopic negative response) and the occipital lobe (visual evoked potentials).

## Key Features

- Minimally invasive, reproducible, and quantitative.
- Defines and differentiates specific forms of optic neuropathy.
- Provides a direct functional measure of the ganglion cells.
- Helps correlate functional changes to anatomical changes in the retinal nerve fiber layer and macular ganglion cell layer.
- Useful adjuvant measures for following up patients with optic neuropathies.

## INTRODUCTION

Recording the electrical activity in the eye provides a useful objective measure of the function of the retina and the optic nerve. The utility of electrophysiology from a retina perspective is covered elsewhere (see Chapter 6.9). In neuro-ophthalmology, electrophysiology is used to assess patients suspected to have inorganic vision loss and those with possible optic nerve disease.

## NONORGANIC VISION LOSS

Nonorganic vision loss presents a diagnostic dilemma for most clinicians. Electrophysiology testing can be a useful adjunct to demonstrate that the visual system is functioning normally. This typically involves two types of assessments: (1) electroretinography (ERG) to assess retinal function and (2) visual evoked potentials (VEPs) to assess cortical function. Each of

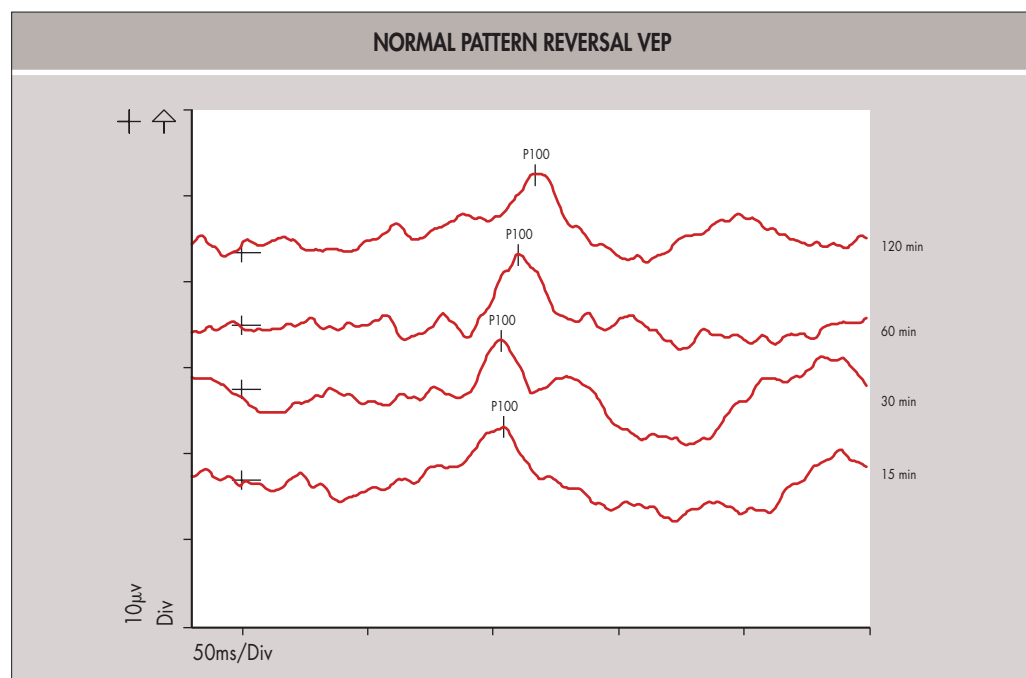
these responses can be recorded in a variety of different ways. Full-field Ganzfeld stimulation can be used to record a full-field electroretinography (ff-ERG) or a flash or flicker VEP (f-VEP).<sup>1,2</sup> Pattern stimulation can be used to assess focal areas of the visual system by either pattern electroretinography (p-ERG)<sup>3</sup> or pattern VEP (p-VEP).<sup>2</sup> Furthermore, by altering the stimulus check size, an estimate of visual acuity can be obtained with a p-VEP (Fig. 9.27.1).<sup>4</sup> Assessment of retinal function is important when performing p-VEP because any deficiency in the retina will be reflected in an abnormal p-VEP. As the p-VEP correlates with central vision, a multifocal ERG (mf-ERG) is a recommended adjunct to ensure that there is no corresponding abnormality in the retina.

Choosing the appropriate test is dependent on the type of vision loss reported. Clinically, the objective in the assessment of nonorganic vision loss is to demonstrate that the patient's vision is better than the amount reported by the patient. The better the vision reported, the more clinically challenging it is. In patients who report no light perception, f-VEP can be useful to demonstrate that the system is functioning (Fig. 9.27.2). For patients with a reported vision of 20/80 or worse, a p-VEP can be useful to demonstrate better visual acuity.

Testing patients with nonorganic vision loss can also be technically challenging because patient cooperation can affect the quality of the data collected. Standards for clinical electrophysiology testing have been published by the International Society for Clinical Electrophysiology of Vision, and it rests with the treating physician to ensure that the testing is in compliance with these standards or to understand and explain any deviation from the standards.<sup>1-3</sup>

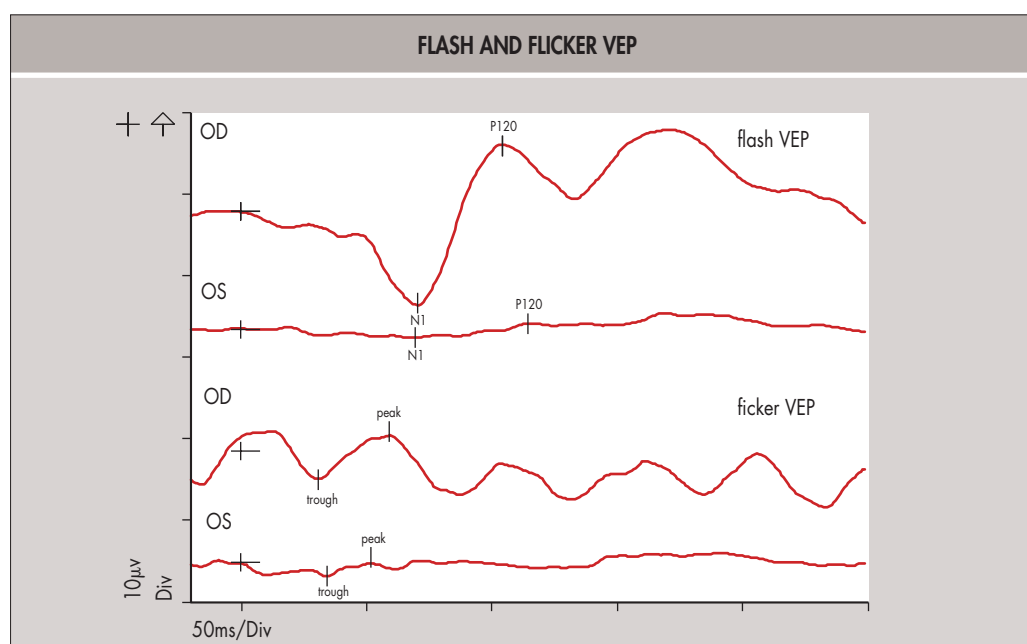
One essential element in testing patients with nonorganic vision loss is to ensure the patient is correctly fixating as all non-Ganzfeld stimuli require consistent accurate fixation. This can be monitored either directly by the test administrator or indirectly by using a pupil tracker. Lack of fixation can create some characteristic changes in the electrophysiological recordings, for example, a shift of the foveal peak on the mf-ERG (Fig. 9.27.3).

It is important to remember that the diagnosis of nonorganic vision loss is a diagnosis of exclusion. Thus, all appropriate tests must be performed

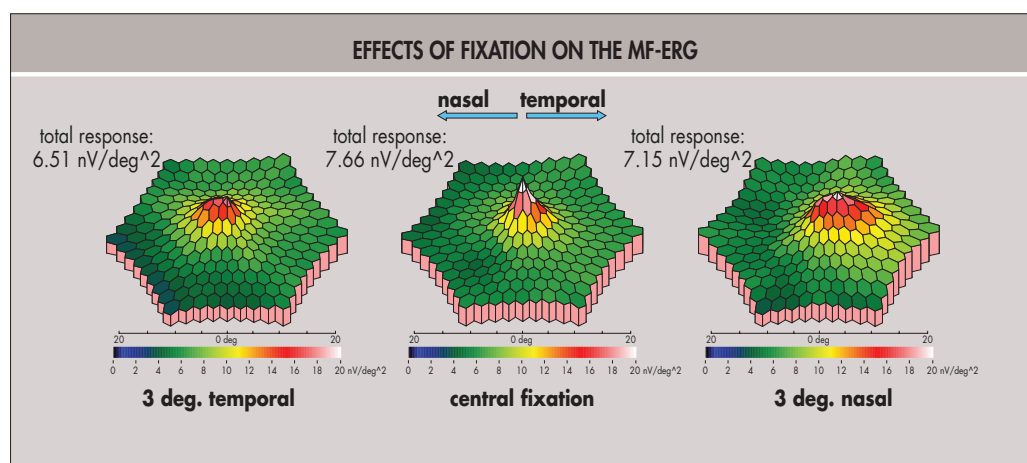


**Fig. 9.27.1 Normal Pattern Reversal Visual Evoked Potential (VEP) to Checkerboard Stimulation.** Check size is indicated in minutes of arc. A normal pattern VEP to 15-minute check size is consistent with visual acuity of 20/30 or better.<sup>4</sup> (From Gundogan FC, Sobaci G, Bayer A. Pattern visual evoked potentials in the assessment of visual acuity in malingering. *Ophthalmology* 2007;114(12):2332-7.)





**Fig. 9.27.2 Effect of True Light Perception Vision on the Flash and Flicker Visual Evoked Potential (VEP).** Set of flash and flicker VEPs from a patient with normal vision in the right eye and light perception vision in the left eye, demonstrating the effect of true light perception vision on the full-field VEP.



**Fig. 9.27.3 Effects of Fixation on Multifocal Electroretinography (mf-ERG).** The mf-ERG waveform morphology changes with eccentric fixation because of changes in stimulus hexagon scaling. The peak takes on an asymmetrical shape, with a sharp decline on one side and a shallower decline on the opposite side. This is characteristic with fixation deviation.

prior to arriving at this diagnosis, and electrophysiology is most useful to confirm the clinical diagnosis.

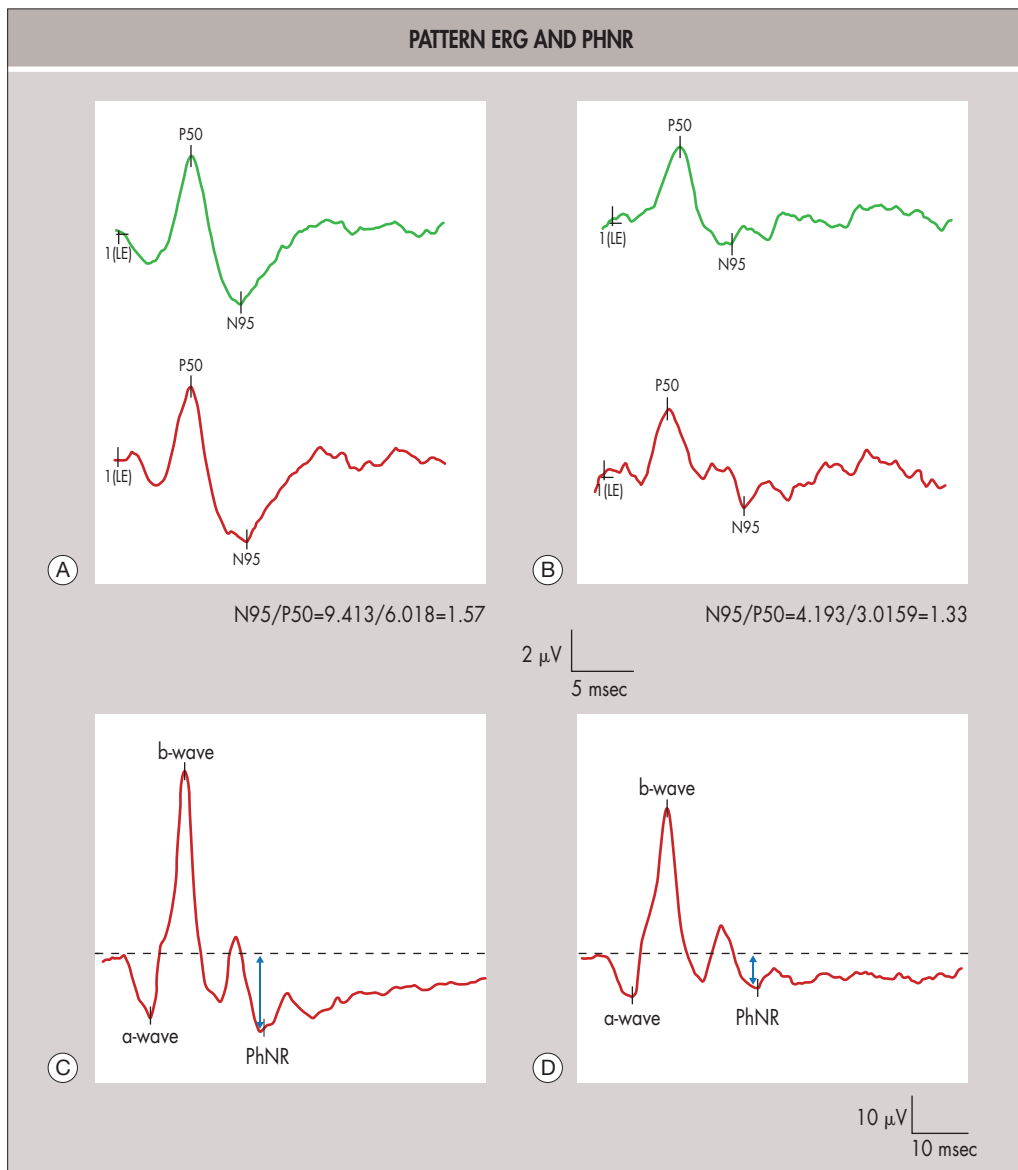
## OPTIC NERVE DISEASE

Direct assessment of ganglion cell function has become an area of great interest in neuro-ophthalmology.<sup>5</sup> It offers the ability to detect pre-perimetric glaucomatous optic nerve damage and to follow up patients to better understand and track the progression of optic nerve diseases, such as Leber's hereditary optic neuropathy (LHON) and idiopathic intracranial hypertension (IIH). There are two main methods of assessing the function of the retinal ganglion cells: (1) the N95 amplitude of p-ERG and (2) the amplitude of the photopic negative response (PhNR) of the ff-ERG (Fig. 9.27.4). The N95 component of p-ERG has been shown to be useful in patients with glaucoma, LHON and other optic neuropathies.<sup>6-8</sup> The PhNR

component of ff-ERG has also been shown to correspond with retinal ganglion cell function, and the amplitude has been found to correspond to the degree of optic nerve swelling in IIH.<sup>9</sup> By using a Ganzfeld stimulator, the PhNR is able to overcome the challenge of refractive correction and consistent fixation, which are required for p-ERG and can be challenging for patients who have central scotoma common in optic neuropathies.<sup>10</sup> But the main value of PhNR is that the retinal ganglion cell function is tested independent of the complexities posterior to the lamina cribrosa. Hence, oligodendrite dysfunction or lesions posterior to the optic chiasm will not affect the waveforms.

As more treatments are being developed for patients with optic neuropathies, the ability to detect pre-perimetric changes and to objectively follow up patients with profound vision loss is becoming more important. Electrophysiology, specifically PhNR and p-ERG, has an important role in objectively assessing the retinal ganglion cells and should prove useful in future clinical studies.

## PATTERN ERG AND PHNR



**Fig. 9.27.4 Pattern Electretinography (p-ERG) and Photopic Negative Response (PhNR) Recordings in Patients With Optic Neuropathies.** A normal p-ERG from the left eye (A) and abnormal p-ERG from the right eye (B) from a patient with a monocular optic neuropathy showing decreased N95 amplitude and N95/P50 ratios. A normal PhNR (C) and an abnormal PhNR (D) from a carrier and affected patient with Leber's hereditary optic neuropathy (LHON) demonstrating decreased PhNR amplitude in the affected patient.

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# Epidemiology of Glaucoma

Osamah J. Saeedi, Sachin P. Kalarn, Pradeep Y. Ramulu, David S. Friedman

# 10.1

**Definition:** The distribution and types of glaucoma and the characteristic demographics of the disease.

### Key Features

- Glaucoma types:
  - Open angle:
    - Primary open angle glaucoma.
    - Secondary open angle glaucoma.
  - Angle closure:
    - Primary angle closure.
    - Primary angle closure suspects.
    - Primary angle closure glaucoma.
- Glaucoma suspect.
- Glaucoma prevalence and incidence.
- Glaucoma blindness.
- Risk factors for glaucoma:
  - Ocular.
  - Systemic.

### INTRODUCTION

Two major forms of glaucoma exist: open-angle glaucoma, in which aqueous humor has free access to the trabecular meshwork, and angle-closure glaucoma, in which access of the aqueous humor to the trabecular meshwork is obstructed. Both forms of glaucoma are characterized by a progressive optic neuropathy with visual field loss and characteristic structural changes, including thinning of the retinal nerve fiber layer and excavation of the optic nerve head.<sup>1</sup> Intraocular pressure (IOP) does not define glaucoma, and many with glaucoma have IOP measurements that overlap with individuals without glaucoma.

The nomenclature of angle-closure glaucoma has evolved over the past decade. The most commonly used system is that of Foster and colleagues, in which affected eyes are defined based on examination findings.<sup>2</sup> Primary angle-closure suspects (PACS) exhibit iridotrabecular contact (originally defined by  $\geq 270^\circ$ , but now more commonly defined as  $\geq 180^\circ$ ) without elevated IOP or peripheral anterior synechiae (PAS). Persons with primary angle closure (PAC) meet the criteria for PACS and have elevated IOP, PAS, or both. These individuals are believed to have suffered adverse sequelae of the iridotrabecular contact but do not have glaucoma. Finally, persons with primary angle-closure glaucoma (PACG) meet the criteria for PACS and have characteristic optic nerve damage. In addition, there is a group of patients who suffer an acute, symptomatic elevation of IOP in association with angle closure, referred to as acute angle closure (AAC).

Both open-angle and angle-closure glaucoma can occur secondary to other ocular conditions, though this chapter will mostly focus on primary open-angle glaucoma (POAG) and PACG. Although the optic neuropathies resulting from POAG and PACG may differ in some ways,<sup>3-6</sup> even more distinct is the epidemiology of these two conditions, which will be discussed separately later.

### PREVALENCE AND RATES OF ASSOCIATED BLINDNESS

Population-based studies are the gold standard for measuring the prevalence of eye diseases, and many have been conducted specifically for glaucoma, particularly in recent years. Table 10.1.1 outlines some major studies based on ethnicity.<sup>7-13</sup> Study techniques and definitions of glaucoma are not uniform across studies, prompting the publication of a suggested standardized definition of glaucoma to be used in prevalence surveys.<sup>2,14</sup>

A troublesome yet consistent finding across population-based studies is that a large portion of glaucoma remains undiagnosed. Population-based studies in United States, Ireland, and Australia reveal that 50% of those with glaucoma do not know they have it,<sup>8,15,16</sup> a percentage that rises to between 62% and 75% in Hispanic populations within the United States.<sup>10,17</sup> The rate of undiagnosed glaucoma is greater than 70% in Singapore<sup>18</sup> and greater than 90% in Japanese, Korean, Indian, and African populations.<sup>7,11,19,20</sup> That so many with a potentially blinding but treatable condition are unaware that they have the disease underscores the need for better screening strategies to identify those with glaucoma.

Glaucoma is a leading cause of blindness worldwide.<sup>21</sup> The frequency of bilateral blindness among persons with glaucoma varies across populations,<sup>7-9,11,17,22-26</sup> with substantial bilateral blindness from glaucoma observed in developing countries with poor access to eye care<sup>7,11</sup> and in populations where angle-closure glaucoma predominates (Table 10.1.2).<sup>9,22,23,24</sup> The rate of blindness may be reduced with improved glaucoma therapy. Notably, in Olmsted County, Minnesota, the rate of unilateral blindness in glaucoma has been cut in half, likely due to advances in glaucoma diagnostics and therapeutics.<sup>27</sup> When demographic projections with prevalence models for open-angle and angle-closure glaucoma are combined, it has been estimated that 112 million people worldwide will have glaucoma by 2040, with a heavier burden on Asian and African populations (Table 10.1.3).<sup>28</sup> Growth and aging of the world's population are expected to result in significant increases in these numbers. Although PACG remains less common than POAG, the numbers of individuals expected to be blind from both types of glaucoma is nearly equal given the higher morbidity of PACG.<sup>28</sup>

Cross-sectional associations seen in population-based studies help to define who is at risk for a disease, but they do not necessarily explain causality. That said, there are clear associations seen in the literature regarding POAG and PACG risk.

TABLE 10.1.1 The Prevalence of Open-Angle and Angle-Closure Glaucoma in Population-Based Studies

Ethnicity	European	African	Hispanic	South Asian	Chinese
Study (Country)	Roscommon, West Ireland <sup>8</sup>	Kongwa, Tanzania <sup>7</sup>	Proyecto VER, United States <sup>10</sup>	Aravind, India <sup>11</sup>	Handan, China <sup>12</sup>
Age range (years)	50+	40+	40+	40+	40+
Prevalence, all glaucoma (%)	2.4	4.2	2.1	2.6	1.5%
Prevalence, primary open-angle glaucoma (%)	1.9	3.1	2.0	1.7	1.0%
Prevalence, primary angle-closure glaucoma (%)	0.1	0.6	0.1	0.5	0.5%
Prevalence, ocular hypertension (%) (IOP cutoff)	4.2 (22)	2.7 (24)	2.3 (22)	1.1 (22)	N/A
IOP, Intraocular pressure.					

TABLE 10.1.2 Frequency of Bilateral Blindness in Populations With Mostly Open-Angle and Mostly Closed-Angle Glaucoma

Study	Country	% Glaucoma Patients Bilaterally Blind
Open-Angle Glaucoma		
Los Angeles Latino Eye Study <sup>7</sup>	United States	1.0
Beaver Dam Eye Study <sup>25</sup>	United States	2.5
Baltimore Eye Study <sup>23</sup>	United States	4.4
Roscommon Eye Study <sup>8</sup>	Ireland	7.3
Aravind Comprehensive Eye Study <sup>11</sup>	India	9.4
Kongwa Eye Study <sup>7</sup>	Tanzania	9.6
Angle-Closure Glaucoma		
Northwest Alaska Eskimo <sup>24</sup>	United States	20.0
Hövsigöl <sup>22</sup>	Mongolia	21.4
Andhra Pradesh Eye Study <sup>21</sup>	India	25.0
Tanjong Pagar <sup>9</sup>	Singapore	31.6

TABLE 10.1.3 Projections of Total Numbers of Persons (Millions) With Primary Open-Angle Glaucoma (POAG) and Primary Angle-Closure Glaucoma (PACG) and of Resultant Associated Blindness

Year	POAG	PACG	Total
2020	52.68	23.36	76.02
2040	79.76	32.04	111.82

PACG, Primary angle-closure glaucoma; POAG, primary open-angle glaucoma. Adapted from Tham Y-C, Li X, Wong TY, et al. Global prevalence of glaucoma and projections of glaucoma burden through 2040: a systematic review and meta-analysis. *Ophthalmology* 2014;121:2081–90.

BOX 10.1.1 Primary Open-Angle Glaucoma Risk Factors

Demographic

- Race (African, Caribbean)
- Age
- Family history in parent or sibling

Ocular

- Intraocular pressure
- Nerve fiber layer thickness
- Myopia – central corneal thickness

Systemic

- Perfusion pressure

PRIMARY OPEN-ANGLE GLAUCOMA

The risk factors for POAG are summarized in Box 10.1.1.

Demographic Risk Factors for Primary Open-Angle Glaucoma

Race

Population-based studies demonstrate that POAG is most common in black Africans and African-descended persons living in the Caribbean and the United States (Fig. 10.1.1).<sup>7,24,29</sup> Seven percent of Afro-Caribbeans over the age of 40 living in Barbados had POAG, several times the prevalence of white and mixed-race individuals living in the same area.<sup>29</sup> A true racial difference in prevalence is also supported by a mixed-race study in Baltimore in which African Americans had nearly four times the prevalence of POAG than people of European descent living in the same neighborhoods.<sup>24</sup> POAG is also more prevalent in Hispanic populations compared with white populations, particularly in persons over the age of 60.<sup>10,17</sup> POAG appears to be more common in Chinese and Asian Indian populations than previously recorded, with comparable or slightly lower prevalence than seen in white populations.<sup>9,11,12,28,30–32</sup>

Age

The prevalence of POAG increases significantly with age, particularly for Hispanic people, who have the highest prevalence of POAG among

AGE-SPECIFIC PREVALENCE OF PRIMARY OPEN ANGLE GLAUCOMA (POAG) BY ETHNICITY

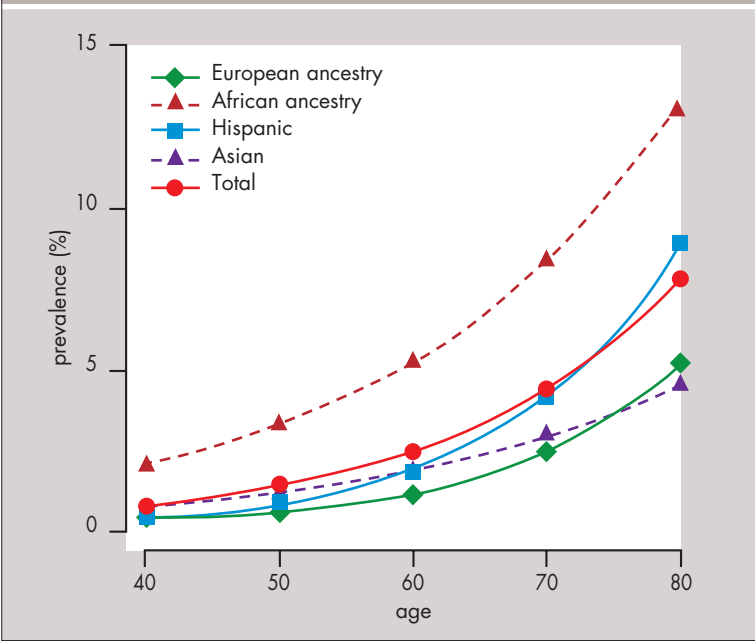


Fig. 10.1.1 Age-Specific Prevalence of Open-Angle Glaucoma by Ethnicity. (Adapted from Tham Y-C, Li X, Wong TY, et al. Global prevalence of glaucoma and projections of glaucoma burden through 2040: a systematic review and meta-analysis. *Ophthalmology* 2014;121:2081–90.)

all races for persons over 80 years of age (see Fig. 10.1.1).<sup>33</sup> A multiethnic population-based study in Baltimore showed tenfold increases in POAG prevalence for both white Americans and African Americans between the fifth and ninth decades of life.<sup>24</sup>

Gender

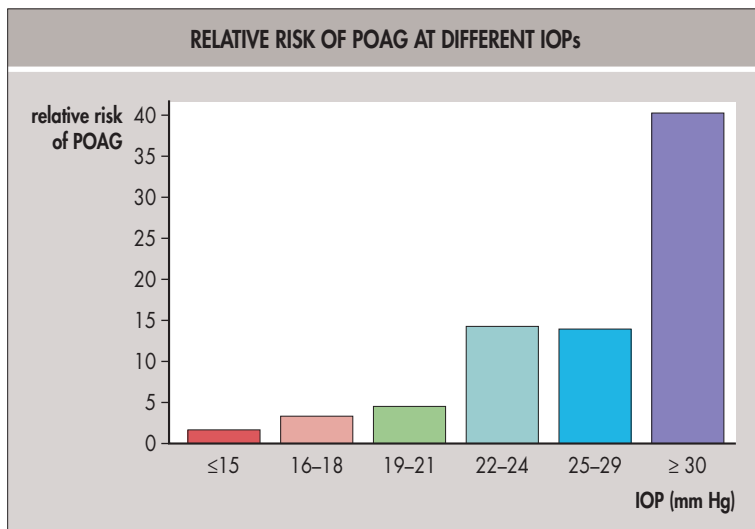
Although meta-analyses show a higher prevalence of POAG in men than in women,<sup>28,34,35</sup> this association is not consistent across all population-based studies. A few notable studies found no differences between men and women,<sup>8,12,24</sup> and still others show a higher prevalence in women.<sup>15,30</sup>

Family History

Persons in Baltimore who reported having a family member with glaucoma had a two- to fourfold increased risk of having glaucoma themselves. Knowledge of a sibling or parent with glaucoma conferred the greatest risk, whereas reporting a child with glaucoma showed no increased risk for glaucoma.<sup>36</sup> Those who were aware of their glaucoma were significantly more likely to report a family history than those who were unaware of their disease, suggesting that patients often learn about glaucoma in their family only after realizing that they themselves have it.<sup>36</sup>

A population-based case-control study from Holland more accurately assessed the importance of having a family member with POAG by directly examining first-degree relatives of patients with and without POAG. They found that siblings of patients with glaucoma were nine times more likely to have glaucoma than siblings of controls, suggesting that family history plays a greater role than what is shown by studies assessing family history using patient interviews.<sup>37</sup> In a high-risk Afro-Caribbean population, almost 30% of first-degree relatives of persons with POAG either had POAG, were POAG suspects, or had ocular hypertension, despite a relatively young median age of 47.<sup>38</sup> Given the substantial risk of POAG in siblings and children of glaucoma patients—and reports documenting that family members often are not informed by relatives<sup>36,39</sup>—it is important that patients with POAG be counseled to tell their siblings and children about their increased risk of having glaucoma.

The genetic basis of this familial transmission of glaucoma is largely unknown. Multiple genes responsible for POAG have been identified to date, although presumed disease-causing mutations are found in only a small percentage of POAG patients. These include myocilin,<sup>40</sup> optineurin,<sup>41</sup> WDR36, CYP11B1, and ASB10.<sup>41,42</sup> Notably, in an Australian disease registry study, 16% of advanced glaucoma patients with IOP above 21 at diagnosis, at least two affected relatives, and onset prior to age 50 had myocilin mutations.<sup>43</sup> Relatives of patients with myocilin mutations were then examined



**Fig. 10.1.2 Relative Risk of Primary Open-Angle Glaucoma (POAG) at Different Intraocular Pressures (IOPs).** (Adapted from Sommer A. Doyne Lecture. Glaucoma: facts and fancies. Eye 1996;10[Pt 3]:295–301.)

and 17% were diagnosed as glaucoma suspects,<sup>44</sup> indicating the potential utility of cascade genetic screening for glaucoma. The genetics of most glaucoma is likely complex, with disease resulting from the interactions of several genes that have yet to be identified.<sup>45</sup> No environmental factors (other than corticosteroid use<sup>46</sup>) have been associated with the development of POAG.

## Ocular Risk Factors for Primary Open-Angle Glaucoma

### Intraocular Pressure

IOP clearly plays an important role in the development of glaucoma and is one of the strongest known risk factors for the condition. Numerous studies across multiple ethnicities show an increased prevalence<sup>7,11,16</sup> and incidence<sup>47,48</sup> of glaucoma as IOP increases. Although the risk of glaucoma is substantial for persons with IOPs in the high 20s, data from virtually all population-based studies demonstrate that the risk for glaucoma increases steadily with increasing IOP, starting even with IOPs as low as 12 mm Hg (Fig. 10.1.2).<sup>7,11,16</sup>

The importance of IOP in causing glaucomatous damage is supported by the finding that in patients with asymmetric IOP, visual field loss is usually more severe in the eye with the higher IOP.<sup>49,50</sup> Furthermore, multiple studies show that lowering IOP in participants predisposed to glaucoma or with glaucoma decreases the rate of visual field loss.<sup>47,48,51</sup>

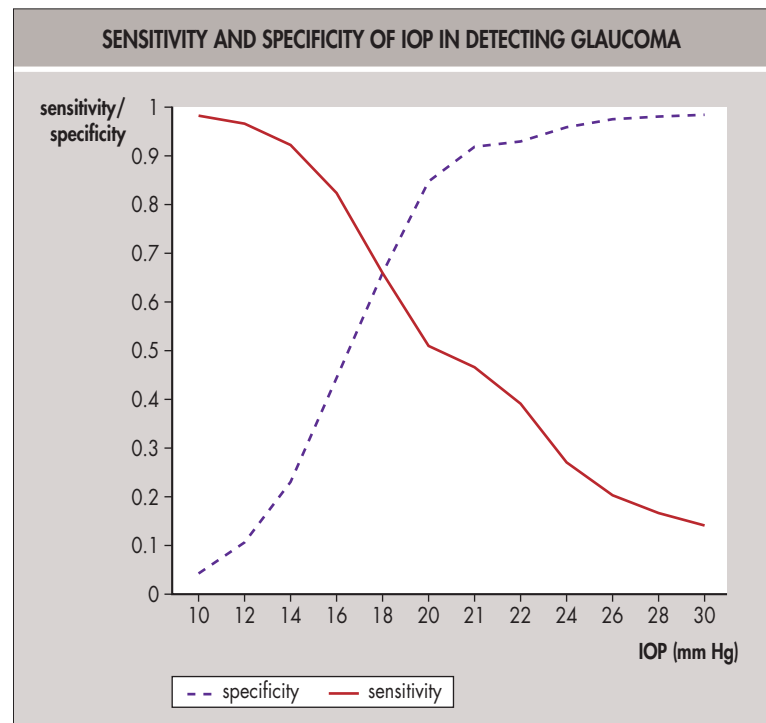
Despite the strong association between IOP and glaucoma, the large degree of overlap between intraocular pressures in people with and without glaucoma makes IOP a poor screening tool for glaucoma. Indeed, no IOP cutoff yields a good combination of sensitivity and specificity (Fig. 10.1.3).<sup>52</sup> In one study of Hispanic Americans in the United States, using an IOP of 22 mm Hg or higher to screen for glaucoma would miss 80% of POAG cases.<sup>10</sup>

### Optic Nerve Parameters

As optic nerve assessment is used to define glaucoma, it is not a true risk factor. Numerous quantifiable features of the optic nerve, including cup-to-disc ratio, rim area, and narrowest rim width, do a poor job of identifying glaucoma patients.<sup>52</sup> Optic nerve parameters sometimes fail to detect glaucoma because they fail to take into account disc size, with cup-to-disc ratios increasing as the size of the optic nerve head increases.<sup>53</sup> Confocal scanning laser microscopy with the Heidelberg Retinal Tomograph (HRT, Heidelberg Engineering, Dossenheim, Germany) as well as optical coherence tomography (OCT) have been used to determine optic nerve parameters. A Cochrane review of optic nerve head imaging found sensitivity and specificity of the vertical cup-to-disc ratio as determined by HRT to be 0.67 and 0.94, respectively. For OCT the sensitivity and specificity were similar, at 0.72 and 0.94.<sup>54</sup>

### Nerve Fiber Layer Imaging

A characteristic feature of POAG is thinning of the nerve fiber layer (NFL) as a result of ganglion cell death. This sometimes produces visible defects



**Fig. 10.1.3 Sensitivity and Specificity of Intraocular Pressure (IOP) in Detecting Glaucoma.** (Adapted from Tielsch JM, Katz J, Singh K, et al. A population-based evaluation of glaucoma screening: the Baltimore Eye Survey. Am J Epidemiol 1991;134:1102–10.)

in the NFL that can be observed at the slit lamp or photographically.<sup>55,56</sup> While clinical assessment of NFL may identify persons at higher risk of developing glaucoma,<sup>57,58</sup> they do not reliably distinguish patients with and without glaucoma.<sup>55,56</sup>

Thickness of the peripapillary nerve fiber layer has been measured by scanning laser polarimetry using the GDx VCC (Carl Zeiss Meditec, Inc.) and by OCT. The sensitivity and specificity of GDx for differentiating patients with glaucoma from those without glaucoma is 0.76 and 0.92, which is similar to that of OCT RNFL mean thickness, which has a sensitivity of 0.72 and specificity of 0.92.<sup>54,59–69</sup> Similarly, segmentation of the macular ganglion cell complex (GCC) or ganglion cell-inner plexiform layer (GC-IPL) via spectral-domain OCT can detect glaucoma with a similar sensitivity of 0.63 and specificity 0.93.<sup>54</sup>

### Myopia

Numerous clinic-based studies show an association between myopia and POAG, and population-based studies in different ethnic groups find rates of open-angle glaucoma two to four times higher for myopes.<sup>11,70,71</sup> The risk of glaucoma appears greatest in persons with higher degrees of myopia.<sup>11,70,72–75</sup> Myopia of greater than 6.00 diopters (D) confers a five times greater risk of glaucoma in East Asian populations.<sup>74</sup> Longer axial lengths and flatter corneas are also associated with a higher prevalence of POAG in Hispanic populations.<sup>76</sup>

### Peripapillary Atrophy

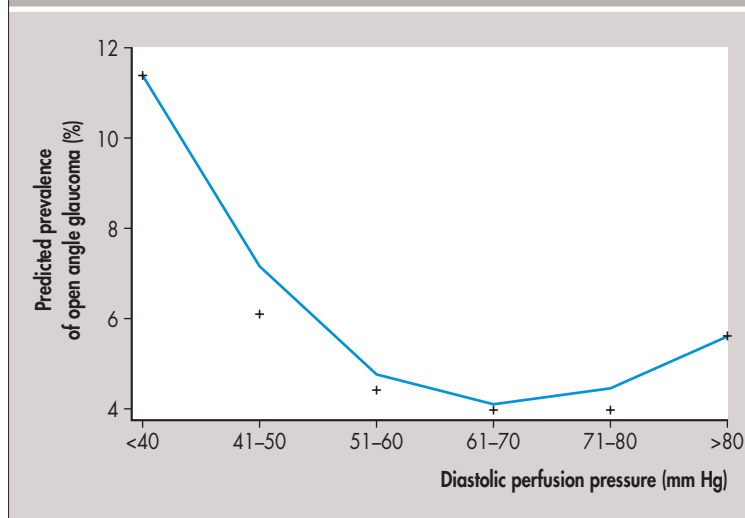
Population-based data from Hispanic people in Los Angeles showed that peripapillary atrophy was found in 83% of glaucomatous eyes, almost twice as often as ocular hypertensives in the same population.<sup>17</sup> However, no strict criteria were set forth to define peripapillary atrophy, and this finding was common among those without glaucoma. Prospective clinic-based studies have also demonstrated that a large zone of peripapillary atrophy is predictive of glaucomatous progression in eyes with pressures above 21 mm Hg.<sup>77,78</sup>

### Corneal Thickness and Hysteresis

Central corneal thickness was found to be an independent risk factor for progression to glaucoma in the Ocular Hypertension Treatment Study (OHTS),<sup>47</sup> although this association has not been found in East Asian populations.<sup>79,80</sup> There is conflicting evidence as to whether thin central corneal thickness is a risk factor for the presence or progression of glaucoma.<sup>81</sup> A number of studies assessed the association between glaucoma and corneal hysteresis, with some showing that patients with different forms of glaucoma have lower corneal hysteresis as compared to nonglaucomatous eyes



## GLAUCOMA PREVALENCE IS HIGHEST WITH LOW DIASTOLIS PERFUSION PRESSURE



**Fig. 10.1.4 Relationship Between Diastolic Perfusion Pressure (DPP) and the Predicted Prevalence of Open-Angle Glaucoma (OAG) in Participants of the Los Angeles Latino Eye Study.** (From Memarzadeh F, Ying-Lai M, Chung J, et al. Los Angeles Latino Eye Study Group. Blood pressure, perfusion pressure, and open-angle glaucoma: the Los Angeles Latino Eye Study. *Invest Ophthalmol Vis Sci* 2010;51:2872–7.)

and others showing no difference or even a higher corneal hysteresis value in glaucomatous eyes.<sup>82</sup>

## Systemic Risk Factors for Primary Open-Angle Glaucoma

### Diabetes

Two large meta-analyses suggested an increased risk of developing glaucoma in patients with diabetes.<sup>83,84</sup> Furthermore, duration of diabetes portends an increased risk of glaucoma, with a 5% yearly increased risk of glaucoma from diabetes diagnosis.<sup>84</sup>

### Hypertension

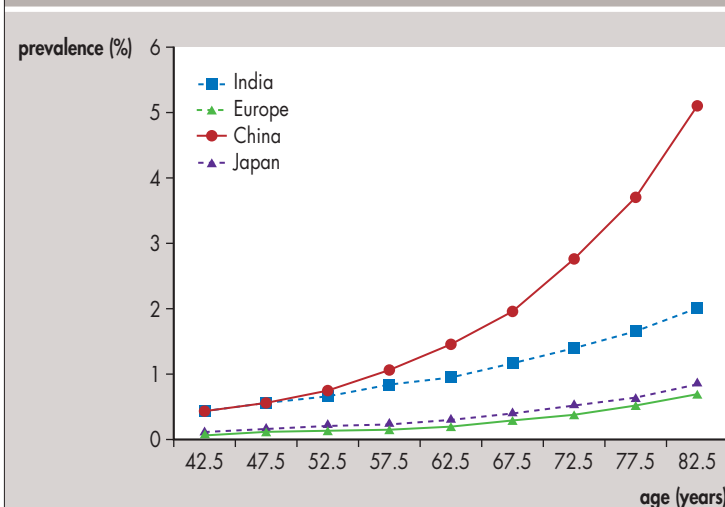
Higher systolic and diastolic blood pressures are associated with increased IOP.<sup>85,86</sup> In the Baltimore Eye Study, IOP was 1.5 mm Hg higher for patients with a systolic blood pressure over 160 mm Hg when compared to systolic blood pressures lower than 110 mm Hg.<sup>86</sup> The same study, however, did not find a statistically significant association between hypertension and glaucoma. Likewise, no association was seen between POAG and hypertension in South Indian participants<sup>11</sup> or Hispanic participants in the southwestern United States.<sup>10</sup>

The idea that insufficient perfusion of the optic nerve may contribute to glaucoma led the Baltimore Eye Study investigators to examine the relationship between POAG and diastolic perfusion pressure (defined as the difference between diastolic blood pressure and IOP). They found a significant increase in the rates of POAG for diastolic perfusion pressures under 50, with a greater than sixfold odds of having POAG noted when the diastolic perfusion pressure dipped below 30.<sup>7</sup> Similar findings were also reported for Caribbean and Hispanic populations (Fig. 10.1.4).<sup>10,87,88</sup> It is difficult to fully separate the influence of IOP from perfusion pressure epidemiologically.<sup>89</sup> There is no evidence to suggest that raising blood pressure delays the progression of glaucoma.<sup>90</sup>

### Cigarette Smoking, Alcohol Use, and Caffeine Consumption

Some clinic-based studies suggest an association between alcohol consumption and glaucoma. However, no differences in the prevalence of glaucoma were noted with mild, moderate, or heavy alcohol consumption in the Beaver Dam Eye Study,<sup>91</sup> nor in the nurses or health professionals study.<sup>92</sup> No definitive association was found with caffeine consumption either.<sup>93</sup> While a small increase in IOP was noted in smokers in the Australia Blue Mountains Eye Study even after adjusting for numerous other variables,<sup>94</sup> the prevalence of POAG has not been observed to vary between smokers and nonsmokers in other studies.<sup>10,91,95</sup>

## AGE-SPECIFIC PREVALENCE OF ACG BY ETHNICITY



**Fig. 10.1.5 Age-Specific Prevalence of Angle-Closure Glaucoma by Ethnicity.** (Adapted from Quigley HA, Broman AT. The number of people with glaucoma worldwide in 2010 and 2020. *Br J Ophthalmol* 2006;90:262–7.)

## BOX 10.1.2 Primary Angle-Closure Glaucoma Risk Factors

### Demographic

- Race (Chinese, Eskimo, Indian)
- Age
- Female gender
- Family history

### Ocular

- Anterior chamber depth
- Limbal anterior chamber depth
- Hyperopia
- Lens thickness
- Small radius of corneal curvature
- Lens vault

### Systemic

- None

## PRIMARY ANGLE-CLOSURE GLAUCOMA

The risk factors for PACG are summarized in Box 10.1.2.

## Demographic Risk Factors for Primary Angle-Closure Glaucoma

### Race

The highest reported prevalence of PACG is among Eskimo populations.<sup>50,96</sup> However, younger Eskimo participants in one recent study were significantly more myopic than previously reported, and this myopic shift may lead to lower rates of PACG in the future.<sup>97,98</sup> Additionally, numerous studies found a much higher prevalence of angle-closure glaucoma in East Asian populations when compared to black and white populations<sup>33</sup>—a difference almost certainly due to race. The prevalence of angle-closure glaucoma also increases substantially with age, particularly in Chinese individuals (Fig. 10.1.5).<sup>12,33</sup> Acute angle closure is presumed to be more common in Asian populations given the higher rate of PACG in cross-sectional samples from Asian countries and the demonstrated high proportion of angle closure in East Asian and Indian populations.<sup>23,99–101</sup> Researchers from Singapore assessed the rates of hospital admissions for AAC within different ethnic groups and found more than twice the rate for Chinese residents than for Indian and Malaysian residents.<sup>100</sup>

## Gender

Multiple studies performed in different ethnic backgrounds confirm that women are significantly more likely to get attacks of AAC and to develop PACG, with odds ratios ranging from 1.5 to 3.9.<sup>9,25,99,102</sup>

## Family History

An increased risk of PACG exists in family members of patients with PACG.<sup>103</sup> Work in Eskimo populations found strong familial determination of anterior chamber depth.<sup>96</sup> Siblings of Eskimo participants with PACG were also 3.5 times as likely to have PACG, suggesting that a familial predilection toward angle-closure glaucoma may result from heritable anatomic features.<sup>96</sup> Furthermore, in a South Indian population, siblings of individuals with angle closure have a greater than 1 in 3 risk of having some form of angle closure.<sup>104</sup>

The genes responsible for these familial associations had not been known until recently. While genes associated with nanophthalmos had been described previously,<sup>105</sup> more recent work using genome-wide association studies have identified multiple genetic loci associated with all forms of angle closure.<sup>106</sup>

## Ocular Risk Factors for Primary Angle-Closure Glaucoma

### Anterior Chamber Depth

Numerous studies demonstrate that the mean anterior chamber depth (ACD) in eyes with occludable angles or PACG is 0.3–1.0 mm shallower than in eyes without angle closure.<sup>5,99,100,107–109</sup> Eyes with AAC may have an even shallower mean ACD than PACG eyes.<sup>5,109</sup> In Chinese residents of Singapore, peripheral anterior synechiae became increasingly likely as ACD decreased, and the rate of glaucomatous optic neuropathy increased significantly when the ACD was less than 2 mm.<sup>102</sup> However, in South Indian and Taiwanese populations, no difference in ACD was noted between eyes with PACG and eyes of PACS, suggesting that greater shallowing of the anterior chamber does not necessarily imply worse disease.<sup>99,108</sup>

Shallower anterior chambers may partially account for the gender, age, and racial distribution of AAC and PACG. Women in multiple ethnic groups have been noted to have anterior chamber depths 0.1–0.2 mm shallower than men.<sup>99,103,110,111</sup> Population-based studies have also demonstrated that ACD decreases steadily with age, at least until the ninth decade.<sup>110,111</sup> Eskimo populations have the shallowest documented ACD.<sup>112</sup> The limited overlap of anterior chamber depths found in eyes with open angles and eyes with occludable angles<sup>96,99,108,113</sup> has led to the use of ultrasound and optical pachymetry to screen for occludable angles. Using these techniques, several groups have been able to identify persons with occludable angles (defined by gonioscopy) with sensitivities and specificities exceeding 80%.<sup>100,113</sup>

### Anterior Segment Optical Coherence Tomography

Use of anterior segment OCT (AS-OCT) has identified several risk factors for development of angle closure. Lens vault into the anterior chamber is correlated with ACD and independently associated with angle closure.<sup>114–116</sup> Anterior chamber width, area, and volume are other risk factors for angle closure identified by anterior segment OCT.<sup>117</sup>

A classification algorithm using these variables, in addition to iris thickness and iris area as determined from a single horizontal anterior segment OCT scan, identified gonioscopic angle closure more than 95% of the time in a Chinese population.<sup>118</sup> A separate prospective study of 342 mainly Chinese participants with gonioscopically open angles at baseline found that angle closure in at least one quadrant on baseline AS-OCT predicted development of gonioscopic angle closure at 4 years.<sup>119</sup>

### Limbal Anterior Chamber Depth

Although gonioscopy remains the gold standard for evaluating the anterior chamber angle, it can also be evaluated at the slit lamp through the van Herick method (or limbal anterior chamber depth, LACD), or modifications thereof.<sup>111</sup> Also, imaging techniques such as ultrasound biomicroscopy (UBM) and Scheimpflug photography suggest that compared to control eyes, eyes with AAC or PACG—and fellow eyes of patients with unilateral angle closure—have narrower anterior chamber angles and smaller angle opening distances (measured between the iris and posterior corneal surface at a defined distance from the scleral spur).<sup>109,120</sup>

Van Herick described how LACD can be estimated at the slit lamp by directing a slit beam at the temporal limbus with the light source offset 60° from the axis of the microscope and comparing the depth of anterior

chamber to the thickness of the cornea.<sup>121</sup> Work in Mongolia and Singapore showed that a LACD equal to 15% corneal thickness has a slightly better predictive value than using a cutoff of 25% (as initially proposed by van Herick).<sup>100,101</sup> In Chinese residents of Singapore, LACD measured at the slit lamp performed better as a screening test for detecting occludable angles or primary angle closure than did central anterior chamber depth, with both techniques significantly outperforming autorefractometry.<sup>100</sup> With gonioscopy as the gold standard, LACD has a sensitivity of 94% and specificity of 87% for detecting angle closure in a Chinese population.<sup>122</sup>

### Axial Length/Refractive Error

Work from multiple groups shows that axial length in eyes with PACG is 0.5–1.0 mm shorter than population-based controls,<sup>5,99,107–110,112</sup> with even shorter axial lengths found in AAC eyes.<sup>5,109</sup> These shorter axial lengths translate into more hyperopic refractions, with PACG eyes having a mean refractive error approximately 1.00 diopters (D) more hyperopic than eyes without PACG.<sup>5,99,107–110,112</sup> Hyperopia is a risk factor for PACG, and South Indians with hyperopia greater than 2.00 D developed PACG 3.7 times as often as those whose refractive error was on the myopic side of +2.00 D.<sup>22</sup>

White, black, Chinese, and South Indian women all have axial lengths about 0.5 mm shorter than their male counterparts.<sup>99,107</sup> Additionally, an Eskimo population with a high rate of ACG was noted to have a mean refraction 0.50 D more hyperopic than the average refraction for other races.<sup>112</sup> On the other hand, black, white, and Chinese populations have similar mean refractions despite highly dissimilar rates of PACG.<sup>107</sup> Hyperopia greater than 2.00 was actually found to be more common among individuals of European descent than among Chinese individuals in one study, although PACG rates were much higher among the Chinese group.<sup>107</sup>

In a South Indian population, axial length and refractive error were not risk factors for PACG when a multiple regression analysis was used, suggesting that these factors may predispose to PACG because of their association with other ocular biometric features, such as anterior chamber depth.<sup>99</sup> Indeed, strong correlations have been demonstrated between ACD and refractive errors.<sup>123</sup>

### Lens Thickness

Several studies confirm that eyes with PACG or AAC—and fellow eyes in patients with unilateral AAC—have lenses 0.2–0.6 mm thicker than controls,<sup>5,108–110</sup> although work from South India showed very similar lens thickness in PACG eyes, eyes with occludable angles, and controls.<sup>99</sup> Groups that are more susceptible to angle closure tend to have thicker lenses. Mean lens thickness in Eskimo populations is 0.3–0.4 mm greater than that of white and black populations, whereas mean lens thickness in Chinese populations is 0.1–0.2 mm thicker than in white and black populations.<sup>112</sup> Lens thickness increases with age and may be an important explanation for the progressive shallowing of the anterior chamber and increased prevalence of PACG observed in older age groups.<sup>112</sup>

### Radius of Corneal Curvature

A smaller radius of corneal curvature results in a more crowded anterior chamber, which is associated with a higher risk of angle closure. Most studies have found that eyes with PACG and fellow eyes of patients with unilateral AAC have a slightly smaller average corneal radius of curvature than controls,<sup>5,108,120</sup> although one study noted a similar mean corneal radius of curvature in control eyes and eyes with PACG.<sup>107</sup> Little racial variation in corneal curvature exists, although women of all races have a smaller mean corneal radius of curvature compared to men.<sup>107</sup>

TABLE 10.1.4 Prevalence of Pseudo-Exfoliation in Different Population-Based Studies

Study	Country	Age Group Studied	Prevalence of Pseudo-Exfoliation Noted Per 100 Persons
Middle-Norway <sup>126</sup>	Norway	65+	16.9
Thessaloniki <sup>125</sup>	Greece	60+	11.9
Blue Mountains <sup>15</sup>	Australia	50+	2.2
Roscommon <sup>8</sup>	Ireland	50+	1.3
Aravind <sup>11</sup>	India	40+	0.4
Kongwa <sup>7</sup>	Tanzania	40+	<0.1
Proyecto VER <sup>10</sup>	United States	40+	<0.1
Chinese <sup>9</sup>	Singapore	40–79	<0.1

TABLE 10.1.5 Prevalence of Glaucoma Suspects in Population Studies

Study (Ethnic Group)	Type of Glaucoma	Criteria to Identify Glaucoma Suspects	Prevalence Per 100 Persons	Age (Range)
Roscommon <sup>8</sup> (European white population)	Open-angle	IOP of 22 or greater <i>and</i> CD of 0.5 or greater <i>and</i> no visual field changes	1.1	50+
Andhra Pradesh <sup>29</sup> (South Indian population)	Open-angle	Disc criteria for glaucoma <i>and</i> absence of visual field changes	1.1	40+
Barbados <sup>28</sup> (African Caribbean population)	Open-angle	Disc criteria without field changes <i>or</i> visual field changes not meeting disc criteria	3.6	40–86
Framingham <sup>34</sup> (US white population)	Open-angle	IOP 22 or greater <i>or</i> CD 0.5 or greater <i>or</i> CD asymmetry (≥0.2 difference between eyes) <i>or</i> IOP asymmetry (≥3 mm Hg difference with IOP of ≥16)	7.9	52–85
Chennai <sup>97</sup> (South Indian population)	Angle closure	Posterior trabecular meshwork not visible 180° <i>and</i> IOP 22 or greater	6.3	40+
Hövsjö <sup>122</sup> (Mongolian population)	Angle-closure	Pigmented trabecular meshwork not visible 270° without indentation	6.4	40+
Tanjong Pagar <sup>98</sup> (Singapore Chinese population)	Angle-closure	Posterior trabecular meshwork not visible 180°	6.5	40–79

CD, Cup-to-disc ratio; IOP, intraocular pressure.

Systemic Risk Factors for Primary Angle-Closure Glaucoma

No systemic factors are known to contribute to the development of PACG, and a population-based study in South India found no associations of PACG with diabetes or hypertension.<sup>99</sup>

SECONDARY GLAUCOMAS

Population-based studies with low rates of pseudo-exfoliation report rates of secondary glaucoma (resulting from pseudo-exfoliation, vein occlusions, diabetes, uveitis, trauma, and other causes) between 0.15% and 0.7%, with secondary glaucoma comprising 4%–18% of all glaucoma cases.<sup>7,8,15,124,125</sup> Whether pseudo-exfoliation glaucoma is a primary or secondary form of glaucoma depends on definition, and researchers vary in how they present their data. Secondary glaucomas other than pseudo-exfoliation occur infrequently. In populations where pseudo-exfoliation is found, its prevalence varies substantially, with the highest rates found in Greek and Scandinavian populations (Table 10.1.4).<sup>7–11,15,126–128</sup> People with pseudo-exfoliation have substantially higher mean IOPs, a significantly higher risk of developing glaucoma, and a higher rate of glaucoma progression.<sup>8,11,15,126</sup>

OCULAR HYPERTENSION

Ocular hypertension is a condition in which the IOP is higher than would be expected based on population statistics for normal IOP. In populations of European descent the traditional cutoff has been 22 mm Hg because this number is outside two standard deviations from the mean.<sup>129</sup> However, some Asian populations have a lower mean IOP, and a pressure above 19 mm Hg would be considered elevated in these individuals. Many now think of an IOP of 24 mm Hg or higher as consistent with ocular hypertension, as was required for enrollment in the OHTS.<sup>47</sup>

The percentage of people with an IOP elevated to 22 mm Hg or greater in the absence of glaucoma ranges from 1%–4% in most population-based studies (see Table 10.1.1). In the OHTS trial, the rate of developing either disc or field loss without eye-pressure-lowering treatment was about 10% at 5 years,<sup>47</sup> similar to the 5-year incidence of glaucoma noted in mostly untreated ocular hypertensives from a population-based study in Barbados.<sup>130</sup> Persons with certain risk factors (large baseline cup-to-disc ratio, thin corneas, older age, higher IOP, and subtle decrements in the baseline visual field) have much higher rates of glaucoma development, whereas those lacking these risk factors are very unlikely to develop glaucoma even if untreated.<sup>47</sup>

GLAUCOMA SUSPECTS

Some individuals present with concerning optic nerve appearances and either borderline visual field loss or normal visual fields. Physicians typically monitor these persons without treatment, although certain individuals with this presentation will be treated. Studies use a wide variety of definitions to identify angle closure suspects and open-angle glaucoma suspects, reporting a prevalence of 1%–8% for open-angle glaucoma suspects<sup>8,22,29,35</sup> and 6%–7% for angle-closure suspects (Table 10.1.5).<sup>23,99,100</sup>

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# Screening for Glaucoma

Brian C. Stagg, Paul P. Lee, Joshua D. Stein

## 10.2

**Definition:** Ideal disease screening identifies all individuals with a given disease (100% sensitivity) and excludes all those without it (100% specificity).

### Key Features

- Cost-effective screening for any disease requires that the disease is progressive, can be reliably detected prior to clinically significant effects on patients, and that interventions can retard, stop, or reverse damage.
- Screening of general populations for the current case definition of glaucoma is not currently deemed cost effective, but current office-based detection is cost effective from a societal perspective. Using a stepped approach targeting higher prevalence populations may also be cost effective.
- Additional information about the natural history and impact of glaucoma on patient functioning prior to the onset of detectable visual field loss is critically needed to assess the desirability of screening for glaucoma without visual field loss (currently defined as “early” or “pre-perimetric” glaucoma).

## INTRODUCTION

The glaucomas are a diverse group of eye conditions sharing the common feature of pathological optic neuropathy without (the open-angle variants)<sup>1</sup> or with (the closed-angle variants)<sup>2</sup> visible occlusion of the trabecular meshwork (the drainage angle in the anterior chamber). Because these represent two distinct groups of entities with fundamentally different mechanisms of initial dysfunction at two distinct ocular anatomic areas, comprehensive screening for all glaucomas requires at minimum two distinct approaches. This chapter uses a general approach to the understanding of screening programs that is applicable to both approaches. However, specific comments and an analysis of screening studies are limited to the more common, open-angle forms (for such aspects of closed-angle screening, see Friedman et al.<sup>3</sup>).

## HISTORICAL REVIEW

### Screening Programs

Screening should ideally identify every person with a given condition (100% sensitivity) while clearing everyone without it (100% specificity). In reality, however, no such ideal test exists. Thus, a reasonable balance between sensitivity and specificity is sought. The definition of reasonable balance may be arbitrary, achieved through consensus over time, or based on empirical analyses of test performance (for example, by using a C-statistic or assessing the area under receiver-operating characteristic [ROC] curves) and associated costs of screening and cost per true case identified.<sup>4</sup> To be a practical reality, screening tests must detect an important health problem and be simple and inexpensive to perform, requiring, ideally, the assistance of lay persons or midlevel or technician-level providers, and must allow for rapid testing in the community setting.<sup>5–8</sup> It should be performed only when adequate resources exist to care for any disease detected and do so in a cost-effective manner.<sup>7,9</sup> Such techniques are desirable because enhancing current office-based case detection, while cost effective,<sup>10</sup> may overtax the available supply of optometrists and ophthalmologists in the future (assuming that current care patterns continue).<sup>11</sup>

### Prior Glaucoma Screening Efforts

Glaucoma screening traditionally relied on intraocular pressure (IOP) measurements based on a now outdated case definition of glaucoma requiring an elevated IOP (except for so-called normal-tension glaucoma), together with the presence of visual field defects and optic nerve or nerve fiber layer (NFL) abnormalities. Performance of IOP measurements alone has proven unacceptably poor for glaucoma screening.<sup>5,9,12,13</sup>

A large 5-year study conducted in Sweden showed that patients with glaucoma were identified earlier through community-based screening compared to routine clinical practice.<sup>14</sup> However, to date, no randomized, controlled trial has assessed population screening for glaucoma, particularly for the detection of structural optic nerve abnormalities alone.<sup>15,16</sup> Several studies have evaluated the use of various screening parameters, such as numerous automated visual field screening and suprathreshold strategies, optic nerve head cup-to-disc ratios, optic nerve neuroretinal rim indicators, and risk factor analyses (involving variables such as age, sex, race, or ocular and other medical history).<sup>13,17</sup> All such indicators have proven inadequate as single screening tools. Significant interest remains in finding an approach to screen for glaucoma, given the relatively high incidence of glaucoma in certain populations<sup>18</sup> and considering that at least half of all persons (and up to 90% in less developed economies) with glaucoma are unaware that they have it.<sup>1,18,19</sup>

### Current Definition of Open-Angle Glaucoma

The results of studies prior to 2000 need to be read cautiously, however, in light of the current definition of primary open-angle glaucoma (POAG), first promulgated by the American Academy of Ophthalmology (AAO) in 1996<sup>1</sup>: “a chronic, progressive optic neuropathy in which there is a characteristic acquired atrophy of the optic nerve and loss of retinal ganglion cells and their axons.” Early or mild—also referred to as “pre-perimetric”—glaucoma is characterized by optic nerve abnormalities with normal visual fields.<sup>1</sup> This definition is an explicit recognition of the limitations of current visual function testing, since over 30% of the optic nerve fibers are lost before current functional testing can differentiate patients with and without glaucoma.<sup>19–22</sup> Thus, visual field defects are no longer part of the case definition of glaucoma; those with visual field loss are referred to as “perimetric” glaucoma and are staged as “moderate” or “severe.” Moderate glaucoma is defined as visual field abnormalities in one hemifield, not within 5° of fixation, whereas severe glaucoma involves visual field abnormalities in both hemifields or loss within 5° of fixation.<sup>1</sup>

The current definition has inherent limitations due to the need for the optic nerve structures to demonstrate “acquired” changes, making case diagnoses, especially of pre-perimetric glaucoma, problematic with assessments at a single point in time. Such uncertainty in case definition will decrease the test performance of approaches to screen for pre-perimetric glaucoma using this conceptual framework due to misclassification in both directions. As such, suggestions have been made to define glaucoma purely as “perimetric” glaucoma on the basis of the population distribution of optic nerve characteristics (2.5% on a one-sided basis) and a reproducible visual field defect<sup>19,21</sup>—or potentially even on the basis of the optic nerve characteristic alone to encompass the most likely pre-perimetric cases. This “instrument”-based approach has also been proposed to leverage new insights on anatomic structures revealed by spectral-domain ocular coherence tomography (SD-OCT). Analyses of structures using SD-OCT demonstrate that existing techniques of assessment do not accurately differentiate neural from other tissues in many patients; initial studies demonstrate significantly better performance than current indices as expressed in likelihood ratios.<sup>23</sup> Thus, future definitions of OAG based on “instrument criteria” may be one potential approach of defining glaucoma.



Just like current systemic hypertension is diagnosed via a blood pressure measurement, glaucoma may be diagnosed on structural or functional characteristics—understanding that as with systemic hypertension, not everyone with the diagnosis will go on to lose vision.

## PURPOSE OF THE TEST

The purpose of a glaucoma-screening test is to detect those with disease so that they can then be treated before significant reduction in visual function occurs. The current definition raises two sets of fundamental questions. The first is a threshold inquiry of whether screening should seek to identify pre-perimetric glaucoma prior to the onset of visual field loss or if it should seek to identify those who have moderate glaucoma, with the onset of reproducible visual field loss on automated perimetry.<sup>19</sup> This has become a critical question due to the repeated findings of the US Preventive Services Task Force (USPTF)<sup>24</sup> and other expert bodies that screening for pre-perimetric or even mild perimetric glaucoma is not supported by the available scientific evidence.<sup>9,16,19,24–26</sup> Among the key factors cited by USPTF for ratings of “uncertain” are the lack of evidence in three key areas:

- Those without reproducible visual field defects using standard automated perimetry have significant functional or patient-centered limitations.
- Delay in diagnosis until later in the disease would have a measurable impact on patient outcomes prior to death.
- The benefits of early detection outweigh the harms resulting from screening activities.<sup>24</sup>

In contrast to earlier assessments, there is strong evidence supporting screening for at least moderate perimetric POAG that meets the WHO criteria<sup>7,9</sup> for screening for diseases. Indeed, the Global Association of International Glaucoma Societies Committee on Screening for Open Angle Glaucoma noted that the case for POAG screening has been strengthened considerably in recent years and stated that the “evidence weakly supports justification for community glaucoma screening on a limited scale and for specific purposes.”<sup>27</sup> First, therapy for glaucoma is sufficient to slow or prevent progressive loss of vision as measured by visual fields, based on the results of several randomized controlled trials.<sup>19,27,28</sup> Second, visual field loss and the amount of loss is associated with meaningful decreases in patient functioning, as measured by patient self-report of function, observed or measured performance by patients at home or in office or laboratory settings, and rates of significant mishaps such as falls or motor vehicle accidents or self-restrictions.<sup>29–39</sup> Third, results from randomized controlled trials such as the Collaborative Initial Glaucoma Treatment Study (CIGTS) provide meaningful data about the performance characteristics of standard automated perimetry, so that protocols can be established to optimize the performance of perimetry.<sup>40</sup> Fourth, community-based exams will detect glaucoma with visual field loss on standard automated perimetry among those without prior knowledge of glaucoma earlier than routine patient-driven, office-based detection.<sup>14</sup> Fifth, knowledge of the effect of suboptimal vision on patients’ function has increased considerably in recent years.

For patients with “trouble seeing,” the quality of life (QOL) impact is commensurate with that of several major systemic illnesses.<sup>41–43</sup> Yet glaucoma patients traditionally have been thought not to have noticeable vision problems until relatively late in the disease course. A prospective case-control study reported that patients with glaucoma had significantly lower general functional status than those without glaucoma,<sup>29</sup> although results of other studies contradict this finding.<sup>30,31</sup> However, Hyman et al. found that under  $-4.15$  mean deviation (MD), there was no significant effect of glaucoma on QOL as measured by the Visual Function Questionnaire (VFQ).<sup>35</sup> Patients with MD scores of  $-4.16$  to  $-19.08$  had clinically and statistically meaningful VFQ deficits. Economic modeling has shown that detection and treatment of moderate stages of glaucoma of around  $-4.0$  dB of mean deviation loss in the better eye is significantly cost effective, ranging from \$28,000 to \$48,000 per quality-adjusted life year (QALY).<sup>10</sup>

What is lacking is consistent evidence that detection of visual field loss prior to the threshold of  $-4$  dB loss in the better eye is beneficial to patients. While some studies indicate that unilateral visual field loss is associated with a significant increase in falls among the elderly (including those without glaucoma),<sup>44</sup> most papers indicate that bilateral visual field loss or loss in the better eye (especially in those with glaucoma alone as a cause) is needed before significant decrements are detected, even using innovative techniques such as global positioning system (GPS) devices and accelerometer tracking of physical activity.<sup>45</sup>

This lack of data raises a second set of two important questions:

- What are the likelihood and rate of progressive loss of function in persons with early and minimal moderate glaucoma (i.e., those with only optic nerve or retinal NFL loss or visual field loss less than 4 dB of mean deviation in the better eye or on binocular testing)?
- Is treatment success over a person’s life in terms of preservation of visual function compromised if the therapy is initiated later in the disease course?

Answering these inquiries is key to understanding the value and usefulness of screening even high-risk patient populations.

Results of trials provide important information. Estimates of the likelihood of progression from early optic nerve loss to subsequent additional loss depend on the stage of disease.<sup>46–48</sup> Among untreated persons with elevated IOP in the Ocular Hypertension Treatment Study (OHTS), 9% had progression of optic nerve changes or visual field loss over 6 years.<sup>49</sup> Risk factors for incremental progression included an increased cup-to-disc ratio, indicating the possibility of subtle prior glaucomatous damage (early glaucoma, by definition). For those with manifest glaucoma (including early visual field loss), the Early Manifest Glaucoma Trial showed that 62% of untreated patients had worsening of their visual field over 5 years.<sup>49,50</sup> On the basis of a meta-analysis of these and other data, Maier and colleagues concluded that reducing IOP “in patients with ocular hypertension or manifest glaucoma is beneficial in reducing the risk of visual field loss in the long term.”<sup>51</sup> On a population basis, Czudowska et al. estimated that the 10-year incidence of developing glaucomatous visual field loss was 1.9% among those age 55–59, rising to 6.4% among those age 80 or older in the Rotterdam Eye Study.<sup>52</sup>

The second question is whether early treatment is related to a better outcome over the course of the disease. A study from Olmstead County, Minnesota, looked at the rates of glaucoma progression to blindness in patients undergoing filtration surgery.<sup>53</sup> One of the key findings from this study was that patients who had more severe visual field loss at presentation had an increased risk of blindness following surgery. This suggests that intervening earlier in the course of the disease, prior to the development of significant field loss, is beneficial. Considering that most patients will demonstrate disease worsening during their lifetimes despite therapy, if patients are identified earlier through screening, they may not progress to blindness or significant visual impairment. Thus, the importance, value, and timing of screening for glaucoma has become more positive, but it remains an open question pending additional information on the functional impact of early visual loss and on whether later treatment can effectively halt progression of vision loss. Modeling of a lifetime of therapy starting at different levels of severity of disease on the rates of levels of visual loss to endpoints less severe than WHO standards of visual impairment or blindness would provide important information in this regard. Understanding the impact at rates of visual loss less than impairment or blindness is important because population-based studies indicate that visual functioning is linearly related to visual measures such as acuity, contrast sensitivity and visual field.<sup>54,55</sup>

## UTILITY OF THE TEST AND INTERPRETATION OF RESULTS

The Prevent Blindness America Glaucoma Advisory Committee has promulgated criteria for minimum performance characteristics for adjunctive devices used in glaucoma screening, including 95% specificity (98% preferable) and at least 85% sensitivity for moderate-to-severe visual field defects.<sup>8</sup> The desirability of these or any other criteria for specificity or sensitivity must be evaluated in light of the effect of such performance on the probability of correctly identifying a person with glaucoma by applying Bayes’ theorem. As Table 10.2.1 shows, such a screening test performance,

**TABLE 10.2.1 Application of Bayes’ Theorem to Screening Test Performance**

	General Population Age 40+		Family Members/Nerve Head Only	
	Glaucoma	No Glaucoma	Glaucoma	No Glaucoma
Prior probability	0.02	0.98	0.09	0.91
Test performance	0.85	(1.00–0.95)	0.85	(1.00–0.95)
Posterior probability	0.017	0.049	0.0765	0.0455
Positive test (%)	26	74	63	37

TABLE 10.2.2 Application of Bayes’ Theorem to Enhanced Screening Test Performance

		General Population Age 40+		Family Members/Nerve Head Only	
		Glaucoma	No Glaucoma	Glaucoma	No Glaucoma
Increased sensitivity	Prior probability	0.02	0.98	0.09	0.91
	Test performance	1.00	(1.00–0.95)	1.00	(1.00–0.95)
	Posterior probability	0.02	0.049	0.09	0.0455
	Positive test (%)	29	71	66	34
Increased specificity	Prior probability	0.02	0.98	0.09	0.91
	Test performance	0.85	(1.00–0.98)	0.85	(1.00–0.98)
	Posterior probability	0.017	0.030	0.0765	0.0182
	Positive test (%)	46	54	81	19

given the low prior probability of glaucoma in the general population older than 40 years of age (using the old case definition), still results in three false positives for every true positive. However, if the prior probability could be raised to, for example, 8%–10% (as with testing family members only or using the current definition of glaucoma with only optic nerve head findings required), test performance at these criteria would be enhanced significantly and yield two true cases for every false positive identified.

As Table 10.2.2 shows, using a screening test with 100% sensitivity barely affects the posterior probability that a positive test correctly identifies a patient as having glaucoma. Thus, changing the sensitivity of the test beyond 85% has much less effect than the application of methods to alter the prior probability of having glaucoma in the populations being screened. However, an increase in the specificity of the test to 98%, as suggested by PBA, improves test performance the most. An example of the limitations of programs to identify patients in populations with relatively low prevalence is seen in the low yield even among African Americans age 50–59, where 58 persons would need to be screened to detect one case of glaucoma and 875 to prevent one case of blindness, with a technique (frequency-doubling technology [FDT] screening) with a modeled 92% sensitivity and 94% specificity.<sup>56</sup> Therefore, approaches that increase the prior probability of having glaucoma and methods using tests with better specificity may be efficient means of screening for glaucoma, provided adequate sensitivity exists.<sup>57</sup>

Because the comparison of tests with different sensitivities and specificities at different cutoff or threshold levels is difficult to evaluate fully, the use of ROC curves or the c-statistic is essential in comparing the test performances of different glaucoma screening tools.<sup>58,59</sup> Superior tests or methods can be readily distinguished from others through comparison of the areas under the curves and the graphic displays of such curves. Similarly, c-statistics can demonstrate the ability of tests to discriminate those with and without disease. Thus future comparisons of screening methods should use ROC curves, provide c-statistics, or perform similar analyses.

PROCEDURE

The goal (detection of early versus moderate glaucoma) and target population (general population or higher prevalence subpopulation) of the screening program will strongly influence the choice of methods and the procedures used. For the detection of those with moderate glaucoma with visual field loss of more than 4 dB of mean deviation loss in the better eye, either standard automated perimetry or a proxy for such perimetry will provide a definitional test. As noted in the CIGTS study, however, many patients with initially qualifying visual field losses did not have such losses confirmed on repeat testing.<sup>39</sup> Screening even with automated perimetry for moderate glaucoma will require confirmatory testing or evaluations, especially for those with relatively minimal visual field loss. Further, patients seen in a general population will have other potential causes for visual field loss. Therefore, as Francis et al. reported about the Los Angeles Latino Eye Study, “no single screening parameter is useful for glaucoma screening. However, a combination of vertical cup to disc ratio, Humphrey Visual Field, and IOP provides the best balance of sensitivity/specificity [0.92/0.92]...”<sup>60</sup>

In the case of detecting glaucoma before the onset of visual field loss, screening for glaucoma can potentially be simplified to an evaluation of the results of optic nerve assessments based on the current case definition of glaucoma as an optic neuropathy and the demonstration that optic nerve fiber loss may be identified before visual field loss occurs.<sup>46,61</sup> With the definition of what optic nerve or NFL findings constitute “characteristic” loss, the current AAO preferred practice pattern contains one possible

set of indicators for screening: thinning or notching of the rim, progressive change (cupping), or NFL defects.<sup>1</sup> Screening programs that determine that one or more of these findings exist have, by definition, screened appropriately for glaucoma.

Optic nerve and retinal NFL imaging is used to determine structural loss. The rapid advances in imaging techniques over the past decade—including confocal scanning laser tomography (CSLT), scanning laser polarimetry (SLP), optical coherence tomography (OCT), and retinal thickness analysis—have shown significant promise for glaucoma screening. More recently, the higher definition obtained by SD-OCT has enabled investigators to better anatomically define the structures of the optic nerve and optic nerve head, resulting in a measure with a reported 79% sensitivity and 95% specificity.<sup>62</sup> Many authors have published reviews of these and other techniques in the last few years.<sup>63–66</sup>

For example, a comparative study concluded that when used alone, CSLT, SLP, and OCT summary reports “did not provide sensitivities and specificities that justify implementing them as primary population screening tools for early to moderate glaucoma.”<sup>67</sup> However, other investigators have noted that use of the summary parameters from multiple imaging devices together can improve the specificity considerably.<sup>68</sup> A major disadvantage of these technologies is the need for a skilled operator. (For a review of the advantages and disadvantages of these technologies, see Michelson and Groh.<sup>69</sup>) Conventional photographic imaging of the optic disc by an experienced examiner remains the most sensitive early detection method<sup>70</sup>; however, these new imaging technologies hold potential for glaucoma screening, particularly in combination with functional testing such as FDT. Assessing these new imaging technologies is difficult because the accuracy of a test can be determined only by comparing it with a “gold standard” reference test, yet no single test available today can definitively diagnose glaucoma. In evaluating the optic nerve, uncertainty and inaccuracy related to screening arise from the inherent variability between observers in the assessment of the same clinical situation (interobserver variability), with the same observer at different points in time (intraobserver variability), and with the accuracy of the method used to measure the optic nerve head or NFL. Although in some studies experts have had relatively high levels of interobserver agreement and intraobserver consistency for certain indicators, other investigations have observed significant variation or noted that levels of agreement decreased with less experienced observers and the method used.<sup>71–73</sup> In OHTS, which used a rigorous quality assurance protocol, trained technicians’ repeated gradings of the baseline horizontal cup-to-disc ratio from optic disc stereophotographs were highly reproducible.<sup>74</sup> However, the OHTS investigators noted that these findings are nongeneralizable to routine clinical practice. If agreement rates for the presence or absence of glaucoma are substituted as equivalents for sensitivity and specificity, likely posterior probabilities can be generated for an accurate screening result for glaucoma status by using these technological techniques. In contrast, even highly experienced and skilled glaucoma specialists can accurately identify only 60% of worsening optic discs in a masked fashion relative to the temporal time relationship of the photos taken.<sup>75</sup>

COMPLICATIONS

The risks associated with screening for glaucoma fall into two categories. The first is the risk of false identification of the true ocular status. Persons falsely assured that they are disease-free risk experiencing subsequent undetected visual loss. In contrast, persons falsely identified as having glaucoma may experience concomitant anxiety and incur expenses before their true status can be clarified, or, worse, they may subsequently undergo

uncalled-for treatment, thus needlessly being put at risk for therapy-related complications, such as cataract formation.<sup>24,76</sup>

The second area of risk is related to the nature of the examination itself. For screening efforts involving proper assessment of the optic nerve or retinal NFL, the necessary use of dilating agents may precipitate an angle-closure attack in as many as 1 in 333 persons.<sup>77</sup>

## ALTERNATIVE TESTS

### Analysis of Tests

Before the current definition of glaucoma was established, investigators had reported several promising methods for identifying individuals with visual field loss on standard suprathreshold static perimetry or kinetic perimetry (Goldmann), including scotopic sensitivity testing,<sup>78</sup> Henson visual field analysis and Damato campimetry (and oculokinetic perimetry),<sup>79,80</sup> peripheral color contrast,<sup>81</sup> and simultaneous interocular brightness sense testing.<sup>82</sup> All these techniques are designed to screen for moderate glaucoma. Such techniques, however, have not been demonstrated to be beneficial in screening for pre-perimetric glaucoma.

In the past two decades significant interest and investigation has been devoted to determining the utility of several new techniques in detecting glaucoma prior to standard automated perimetry (SAP) and thus expand detection to what would have otherwise been pre-perimetric glaucoma. These techniques include FDT perimetry, short wavelength automated perimetry (SWAP), Swedish Interactive Threshold Algorithm (SITA) perimetry,<sup>83,84</sup> multifocal electroretinography (mERG), and multifocal visual evoked potential (mVEP).<sup>64–66</sup>

Of these techniques, FDT has shown the greatest promise as a practical means of glaucoma screening to detect perimetric glaucoma and potentially pre-perimetric glaucoma. In a prospective study by Cello and colleagues,<sup>85</sup> FDT demonstrated 85% sensitivity and 90% specificity for detecting early glaucomatous visual field loss and 96% sensitivity and 96% specificity for detecting moderate glaucomatous visual field loss. These data suggest that FDT would meet PBA's minimum performance characteristics. Moreover, other studies have found FDT to be effective in screening for moderate glaucomatous damage.<sup>86,87</sup> FDT is performed significantly more rapidly than SAP or SWAP, making it well suited for screening. With FDT, the reported average testing time per eye is less than 2 minutes (instrument time) with glaucoma patients and less than 30 seconds with healthy controls.<sup>87,88</sup> In addition, FDT perimetry is relatively inexpensive and portable, requires no special training for the examiner or patient, and can be used in adults with reading disabilities.<sup>89,90</sup> Furthermore, FDT may have less intertest and intratest variability than conventional perimetry does.<sup>91</sup> However, FDT has yielded a substantial proportion of false-positive results in patients with diabetes mellitus and a significantly increased rate of false positives in patients' left eye compared with the right.<sup>92,93</sup> While promising, the American Academy of Ophthalmology's Ophthalmic Technology Assessment (OTA) indicated that "the screening FDT protocol can detect most eyes with visual field defects on SAP with an acceptable level of specificity. The data are also consistent with the concept that some of these apparent false-positive results actually may represent the detection of glaucoma damage by FDT earlier than by SAP."<sup>64</sup>

Other perimetric techniques also show promise but have disadvantages that make them impractical for screening in their current forms. For example, SWAP, or blue–yellow perimetry, may detect field defects earlier than can white-on-white standard threshold automated perimetry,<sup>94</sup> but SWAP—even with the SITA version—requires expensive standardized automated perimetry equipment and trained personnel, with the same or greater issues of intertest reliability.<sup>64,95</sup>

Electrophysiology, which is the use of minimally invasive electrical equipment to measure the function of the retina and optic nerve, has the potential to provide objective detection of early glaucoma.<sup>96,97</sup> Pattern electroretinography (pERG) is perhaps the best studied form of electroretinography in glaucoma.<sup>97</sup> PERG detects glaucomatous vision loss up to 4 years earlier than standard visual fields, with a sensitivity of 75% and a specificity of 76%.<sup>98</sup> In a study from Australia, measurement of mVEPs compared favorably with traditional visual fields for detection of glaucoma.<sup>99</sup> mVEP measures the localized electrical responses from the occipital cortex for the central visual field. The sensitivity and specificity of mVEP were 80.6% and 89.2%, whereas sensitivity and specificity for visual fields were 81.9% and 79.5%.<sup>99</sup> However, no electrophysiological test for glaucoma is in widespread use at this point, in large part because of the lack of strong evidence that it is superior to traditional methods and the need for specialized equipment and technical skills.<sup>96,97</sup>

If screening for the earliest stage of glaucoma—that of optic nerve fiber loss alone—is desired, these methods will require extensive and lengthy follow-up to determine if individuals detected with abnormalities eventually do worsen. However, if screening is found efficient or cost effective only for those with visual field loss, methods predicated on field loss should receive further attention and evaluation as potential screening techniques.

## Telemedicine and Glaucoma Screening

Advances in structural and functional technology to detect patients with glaucoma—along with improved computer and information transfer capabilities—have made glaucoma screening in remote communities possible through the use of telemedicine.<sup>100,101</sup> A recent systematic review by Thomas et al. thoroughly summarizes 45 studies that evaluated the use of telemedicine for glaucoma screening. The pooled estimates of sensitivity and specificity for telemedicine detection of glaucoma were 83.2% and 79.0%. Telemedicine was more sensitive but less specific than in-person examination, by their analysis. However, further randomized research is necessary as all 45 studies evaluated were observational. They also found that the mean cost for every case of glaucoma detected by telemedicine was US\$1098.67.<sup>100</sup>

### Marker Testing for Glaucoma

In the past 15 years genetic analysis of families with POAG has identified numerous genetic loci that may be involved in the pathogenesis of the disease.<sup>102–108</sup> Although tests for genes such as *TIGR*/myocilin have been developed, these tests have limited usefulness<sup>109</sup> because they only detect less than 5% of people who will later develop POAG in adulthood.<sup>110–112</sup> However, genetic testing for glaucoma may become a reality.<sup>113</sup> Moreover, Challa and colleagues showed that patients expressed relatively positive attitudes toward hypothetical genetic testing for glaucoma.<sup>114</sup> Thus, genetic linkage analysis, genome-wide analysis, and other techniques offer the promise that patients might be screened for glaucoma on a genetic basis through analysis of peripheral blood or other specimens in the future, although current technology is not sufficient.

Evidence has also grown on the potential role that the immune system and inflammation may play in glaucoma pathogenesis.<sup>115</sup> To the extent that autoimmune or other inflammatory mechanisms are implicated in glaucoma, testing for specific or general biomarkers of inflammation or autoimmunity may also play a role in screening or diagnosing glaucoma.

Again, however, the performance of these techniques may vary depending on the case definition of glaucoma used. Similarly, the utility of such screening also presupposes that effective treatments exist and that the cost–benefit ratio of such screening, based in large part on the test's performance characteristics, justifies screening a given population.

## FUTURE DIRECTION OF GLAUCOMA SCREENING

A critically important study from Australia found that optometrists and ophthalmologists frequently failed to diagnose early to moderate (98% moderate) glaucoma among patients with pertinent risk factors, visual field changes, and optic nerve damage. These findings underscore the need for diagnostically precise approaches and potentially technological devices in the accurate identification of persons with glaucoma.<sup>116</sup> The first step in improving the health of our population is therefore to more accurately detect glaucoma among those who already access the care system and see an optometrist or ophthalmologist.

Automated image processing techniques such as deep learning, artificial neural networks, and fuzzy logic may eventually decrease our reliance on human evaluation for glaucoma screening.<sup>117,118</sup> Deep learning has successfully been employed in screening for diabetic retinopathy.<sup>119,120</sup> These methods could potentially make glaucoma screening less expensive and more efficient. However, none of these are of sufficient accuracy at this point for clinical use.<sup>118</sup>

Additional interventions may lie in developing approaches or devices that can identify persons with early or moderate glaucoma who will develop further visual loss, particularly at a rapid pace.<sup>21,121</sup> Identifying patients earlier in the course of the disease who never go on to develop visual loss to the extent that it affects health-related QOL is not prudent. Such a strategy will result in our subjecting many individuals to costly medications that have side effects with little benefit, at least as we understand the impact of glaucoma today. Alternatively, waiting until an individual already has significant functional damage from glaucoma before detecting and treating such patients is also potentially of serious concern



even if treatment is initiated, since such patients may continue to suffer additional loss of visual function, as noted in the Olmstead County data.<sup>53</sup>

New approaches to screening are likely to arise as more is learned about the pathophysiology of glaucoma and the impact lower amounts of nerve tissue loss has on patients. In the future, we may adopt an instrument-based definition of glaucoma, use a combination of tools either collectively or in sequence, or combine a range of factors to target those who would be most likely to lose vision without early detection and treatment. For example, applying Bayes' theorem would suggest that the population to be screened should have a higher prevalence or prior probability than the general population level of 2% of those over the age of 40. Using factors from the ocular or medical history, blood testing, diagnostic testing, or examination features could easily increase prevalence to 10% or higher. This enriched population would then have a single (or combination) test applied to more accurately detect affected individuals.

Finally, for any screening program to be effective, integrated healthcare delivery systems must be in place to ensure that those individuals who are identified to be at risk for vision loss from glaucoma receive appropriate treatment.<sup>122</sup> Otherwise, spending resources to simply identify individuals at risk through screening efforts will not improve outcomes, as the patients will not receive the treatment necessary to delay or prevent damage and loss of vision.

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# Mechanisms of Glaucoma

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## 10.3

**Definition:** Glaucoma occurs through a number of mechanisms, usually related to intraocular pressure that is too high for the optic nerve to withstand. High intraocular pressure is almost always due to poor aqueous outflow (low outflow facility). Mechanical damage, impaired optic nerve blood flow, withdrawal of neurotrophic factors, and production of neurotoxic molecules in the optic nerve have each been proposed as possible mechanisms of optic nerve damage in glaucoma.

### Key Features

- Aqueous humor physiology in health and disease.
- Aqueous humor pathophysiology in glaucoma.
- Mechanisms of glaucomatous optic neuropathy.

### INTRODUCTION

Glaucomatous optic neuropathy is the second leading cause of irreversible blindness in the United States<sup>1</sup> and is characterized by the demise of retinal ganglion cells (RGCs) and their axons that can lead to impaired visual function and blindness. Clinically glaucoma is characterized by its progressive optic atrophy with a typical excavation of the nerve head that lacks prominent pallor of the neuroretinal rim and a progressive loss of peripheral visual sensitivity in the early stages of the disease, which may ultimately progress and impair central visual acuity.<sup>2</sup> Although glaucomatous optic neuropathy is typically observed in open- or closed-angle glaucoma and associated with elevated intraocular pressure (IOP), a high percentage of patients (20%–30% in Western countries, >50% in Japan) have findings that are anatomically identical but without IOP elevation above population norms.<sup>3,4</sup>

Glaucoma is unique among the ophthalmic diseases because its clinical management and the underlying pathophysiology requires knowledge of ocular structures that span both the anterior and posterior segment. This chapter will describe the basic mechanisms that underlie aqueous production and outflow, optic nerve axon damage and degeneration, and RGC death in glaucomatous optic neuropathy.

Although IOP was removed as an integral part of the definition of glaucoma, for most forms of the disease, IOP is a major risk factor for both the development<sup>5</sup> and the progression<sup>6,7</sup> of glaucoma. Even in normal-tension glaucoma in which IOP does not exceed 21 mm Hg, IOP remains a risk factor for progressive optic nerve damage.<sup>8</sup> Elevated IOP associated with most forms of glaucoma is associated with increased resistance to aqueous humor outflow, while the rate of aqueous humor formation is not different from that in nonglaucomatous individuals.

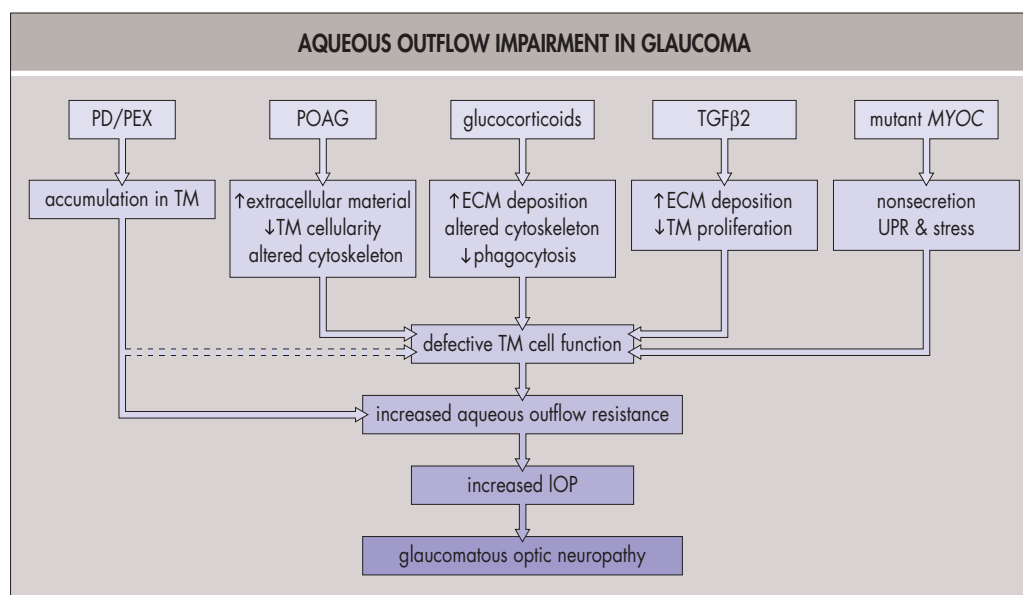
The causes of impaired aqueous humor outflow are different for the different subtypes of glaucoma (Fig. 10.3.1). In angle-closure glaucoma, the outflow pathway is blocked by physical occlusion of the outflow pathway by the iris. In the particulate forms of open-angle glaucoma, including pigmentary glaucoma, pseudoexfoliation glaucoma, and uveitic glaucoma, particulate matter “clogs” the trabecular meshwork (TM) and impairs aqueous outflow. Defects in development of the outflow pathway are responsible for most forms of congenital glaucoma. In primary open-angle glaucoma (POAG) and corticosteroid-induced glaucoma, there are no clinically observable findings that can explain the increased outflow resistance responsible for elevated IOP.

### PHYSIOLOGY OF AQUEOUS PRODUCTION

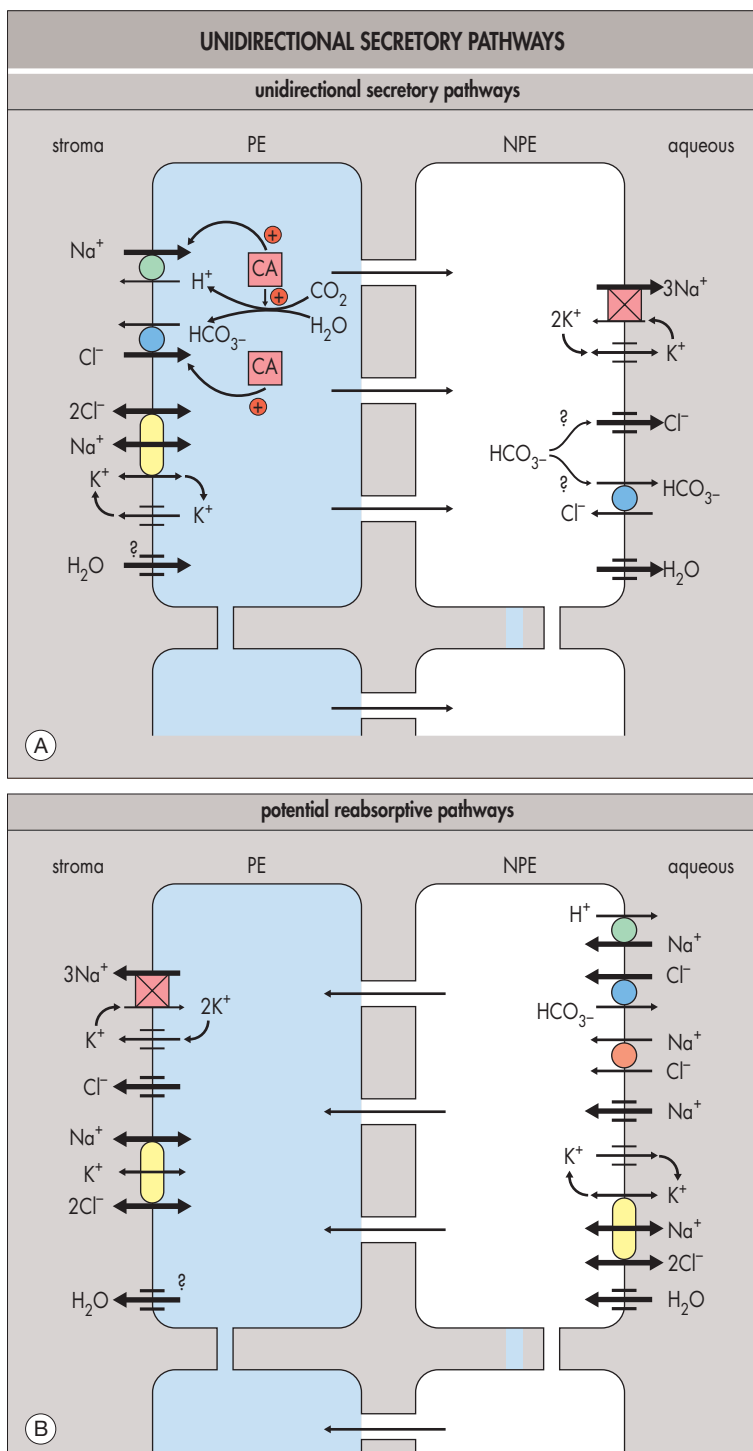
Secretion of aqueous humor sustains metabolism of the avascular anterior segment, ensures inflation of the globe, and may play other roles.<sup>9</sup> The composition of the aqueous humor is largely similar to that of protein-free plasma with several exceptions, including a much higher concentration of ascorbic acid in the aqueous humor. Understanding the physiology of aqueous production relates to reducing its rate, a major strategy for lowering IOP in glaucoma.

### Structural and Functional Overview of Aqueous Humor Formation

Aqueous humor is secreted by the ciliary epithelium. The structure is unique in juxtaposing the apical surfaces of its two component layers (Fig. 10.3.2). The basolateral surfaces of the pigmented ciliary epithelial (PE)



**Fig. 10.3.1 Mechanisms of Aqueous Outflow Impairment in Glaucoma.** A variety of glaucomatous insults to the trabecular meshwork can lead to elevated IOP and the development of glaucomatous optic neuropathy. ECM, Extracellular matrix; IOP, intraocular pressure; MYOC, myocilin gene; PD, pigmentary dispersion; PEX, pseudoexfoliation; POAG, primary open-angle glaucoma; TGF-β2, transforming growth factor-beta-2; TM, trabecular meshwork; UPR, unfolded protein response.



**Fig. 10.3.2** Mechanisms of unidirectional secretory pathways (A) and potential reabsorptive pathways (B) across the ciliary epithelium.

and nonpigmented ciliary epithelial (NPE) cells face the stroma of the ciliary processes and aqueous humor, respectively. Gap junctions link cells within and between the two cell layers,<sup>10</sup> such that the epithelium is conventionally considered a functional syncytium. Ablation of ciliary epithelial cells through laser diode or endocyclophotocoagulation has risen in utility as an approach to decrease IOP.

Aqueous humor secretion essentially depends on transfer of solute, primarily NaCl, from the stroma to the posterior chamber of the eye. This transfer establishes a small osmotic gradient driving water passively into the aqueous humor. Secretion proceeds in three steps: uptake of solute and water from the stroma by PE cells, fluid transfer through gap junctions linking PE to the NPE cells, and release of solute and water by NPE cells into the aqueous humor. These steps involve an expanding number of transport proteins, and the energy required for the secretion is derived from adenosine triphosphate (ATP) utilized by  $\text{Na}^+$ ,  $\text{K}^+$ -activated ATPase located predominantly at the aqueous humor surface of the NPE cells.

## Three Steps in Aqueous Secretion

### *Ion and Fluid Uptake From the Stroma*

The PE cells can take up NaCl from the stroma by two major electroneutral processes (Fig. 10.3.2A). One entry mode for  $\text{Na}^+$  from the stroma into the PE cells is through an  $\text{Na}^+/\text{H}^+$  counter-exchanger (the NHE-1 antiporter), in exchange for  $\text{H}^+$  leaving the cells. In parallel,  $\text{Cl}^-$  can be taken up by the PE cells in exchange for  $\text{HCO}_3^-$  release through an anion counter-exchanger (the AE2 antiporter). Cytosolic carbonic anhydrase II stimulates this NaCl uptake in two ways, increasing the rate of delivery of  $\text{H}^+$  and  $\text{HCO}_3^-$  to the two antiports and directly activating them both (see Fig. 10.3.2A). The clinical reduction in secretion and IOP produced by carbonic anhydrase inhibitors is likely mediated by reducing turnover of NHE-1 and AE2 antiports.

The second mode of NaCl uptake from the stroma by the PE cells is through a  $\text{Na}^+ - \text{K}^+ - 2\text{Cl}^-$  cotransporter (symport). The rate of uptake depends on the concentration gradient for the three ions transported and is particularly dependent on the concentration ratio of external to intracellular  $\text{Cl}^-$ .<sup>11</sup> The diuretic bumetanide blocks the symport and inhibits  $\text{Cl}^-$  secretion and aqueous humor formation in vitro but not (by itself) in vivo, presumably because of compensatory uptake through the paired antiports.

The pathways for water uptake are not as well studied. Water likely crosses the stromal surface of the PE cells through channels but not through known aquaporin water channels. Alternatively, water might simply diffuse across the PE cell membranes, for example, but membranes with low contents of sphingomyelin and cholesterol display relatively high water permeability.<sup>12</sup>

### Fluid Transfer Through Gap Junctions

The gap junctions linking PE to NPE cells are more numerous than those linking cells within the PE and NPE layers.<sup>10</sup> These PE–NPE gap junctions are formed of connexin proteins (Cx43 and Cx40), with Cx43 likely playing a dominant role.<sup>13,14</sup> The connexins comprising the links between adjacent NPE cells are different (Cx26 and Cx31), and evidence for these connexins within the PE-cell layer is still lacking.<sup>15</sup> The PE–NPE gap junctions are not only more numerous but possibly more robust to experimental perturbation<sup>16</sup> than the PE–PE and NPE–NPE gap junctions. This suggests that aqueous humor is fundamentally formed by parallel couplets of PE–NPE cells.<sup>16</sup> Interruption of the PE–NPE gap junctions with heptanol or octanol markedly reduces ionic current and net  $\text{Cl}^-$  movement across the ciliary epithelium.<sup>17</sup> However, these inhibitors are too nonselective to be clinically relevant.

### Fluid Transfer Into the Aqueous Humor

The final step in secretion is the transport of solute and water across the basolateral membranes of the NPE cells into the aqueous humor (Fig. 10.3.2A).  $\text{Na}^+$  is pumped by  $\text{Na}^+$ ,  $\text{K}^+$ -ATPase against an electrical gradient.  $\text{Cl}^-$  is released down its electrochemical gradient through  $\text{Cl}^-$  channels into the aqueous humor.<sup>17</sup> Water is released passively through aquaporin AQP1 and AQP4 channels in response to the osmotic gradient established by net solute transport.  $\text{HCO}_3^-$  likely exits both through  $\text{Cl}^-/\text{HCO}_3^-$  exchangers<sup>18,19</sup> and  $\text{Cl}^-$  channels.<sup>19,20</sup>  $\text{Cl}^-$ -channel activity at the aqueous surface likely limits the rate of secretion.<sup>17</sup>

Other transporters involved in net secretion have been identified, and many pharmacological agents, hormones, and signaling pathways clearly modulate secretion,<sup>17</sup> but their physiological significance is unclear.

### Regulation of Net Aqueous Humor Formation

Much of our understanding of the transport mechanisms underlying inflow is derived from in vitro measurements. Some of these insights have been validated in living animals. The mouse is advantageous for study because of the greater similarity of its conventional outflow pathway to the human than those of other commonly studied nonprimate models. The availability of transgenic animals and advances in imaging modalities also enhance the strength of the mouse model in addressing clinically relevant issues.<sup>21,22</sup>

The diurnal rate of aqueous humor inflow varies substantially and is 2.5 times higher during waking than during nocturnal hours. Any putative transporter limiting the rate of inflow would also be expected to undergo substantial changes in activity. Among the factors reported to stimulate NPE-cell  $\text{Cl}^-$  channel activity<sup>17</sup> are cell swelling, stimulation of  $\text{A}_3$ -subtype adenosine receptors, inhibition of protein kinase C (PKC) activity, and production of cyclic-3', 5'-adenosine monophosphate (cAMP). Modulation of inflow by  $\text{A}_3$ -subtype adenosine receptors is of physiological,

pathophysiological, and pharmacological interest. These receptors are overexpressed in the NPE cells from patients with the pseudoexfoliation syndrome.<sup>23</sup> In vitro electrophysiological and volumetric measurements have suggested that stimulation of A<sub>3</sub> adenosine receptors increases Cl<sup>-</sup> and fluid release by NPE cells and that A<sub>3</sub> antagonists block those effects. Adenosine is physiologically delivered to the receptors by autocrine/paracrine release of ATP through large-diameter pannexin-1 and connexin hemichannels and vesicular release.<sup>24</sup> The ATP is subsequently converted to adenosine by ecto-ATPases. Modulation of adenosine receptor activity pharmacologically may decrease IOP.

The precise regulatory roles of second-messenger pathways and the multiplicity of the transporters targeted complicate formulation of a comprehensive model of inflow regulation. For example, beta-blockers are clinically used to lower inflow, presumably by reducing cAMP. However cAMP exerts multiple actions producing opposing effects on secretion.<sup>17</sup> Increasing evidence now suggests that compartmentation of second messengers such as cAMP and Ca<sup>2+</sup> is essential to their signaling function.<sup>25,26</sup>

## Conclusions and Future Directions

In summary, aqueous humor is formed by transferring solute from stroma to the posterior chamber, establishing an osmotic gradient, with water moving in response to that gradient. Many of the proteins underlying fluid transport have been identified, but their integrated actions and regulation are less well understood. Pharmacological or surgical (e.g., by laser ablation) inhibition of inflow is a common powerful strategy for lowering IOP in glaucoma. Clarification of the roles of second-messenger compartmentation and functional topography may facilitate development of novel strategies for slowing aqueous production and thereby lowering IOP in glaucomatous patients.

## THE AQUEOUS HUMOR OUTFLOW PATHWAY

Aqueous humor exits the eye via two pathways. The trabecular pathway is considered the primary, pressure-dependent pathway, whereas the uveoscleral pathway is considered the secondary, pressure-independent pathway, although the pressure dependence/independence of these pathways is not absolute.<sup>27</sup> Anatomically, the trabecular pathway consists of the uveal and corneoscleral TM, the juxtacanalicular tissue (JCT), and Schlemm's canal (SC). The major site of aqueous outflow resistance in a normal eye is thought to reside mainly in the JCT and inner wall of SC.<sup>28</sup> In the uveoscleral outflow pathway, aqueous humor exits the eye through the iris root through the interstitial spaces between the ciliary muscle bundles into the superchoroidal space, where it is absorbed into the venous system.

What are the regulators of normal aqueous outflow? This is an important question, and recent progress in our understanding of TM cell biology suggests that TM cells themselves have a "rheostat" for IOP control. The recently discovered cilium on TM cells harbors compartmented, subcellular signaling properties that directly sense IOP through mechanotransduction and feedback to regulate IOP.<sup>29</sup> This has generated important targets for considering new approaches to IOP control, including cell therapy (discussed later).

## Pathology of the Glaucomatous Outflow Pathway

There are age-related changes to both the trabecular and the uveoscleral outflow pathways. On the relatively less well-studied uveoscleral pathway, glaucomatous eyes show ultrastructural evidence of increased extracellular material deposition.<sup>18</sup> Prostaglandin analogues, now the primary first-line pharmacological class of antihypertensive medications, lower IOP and enhance uveoscleral outflow in association with stimulation of ciliary muscle matrix metalloproteinases (MMPs) and degradation of ciliary muscle and scleral extracellular matrix (ECM) components.<sup>30</sup>

The TM has received much more study. There is decreased TM cellularity with age<sup>31-33</sup> and increased extracellular deposition in the TM<sup>34</sup> associated with age-dependent decreased aqueous outflow.<sup>35,36</sup> TM tissues from POAG donor eyes are significantly "stiffer" (i.e., less elastic) compared to TM tissues from age-matched control eyes.<sup>37</sup> Decreased TM tissue cellularity and alterations in extracellular material are observed in POAG eyes compared to age-matched controls.<sup>38</sup> Ultrastructural assessment of numerous eyes from patients with glaucoma showed a thickening of trabecular beams and elastic tendons, increased plaque material, and lattice collagen in the TM.<sup>39,40</sup> The ECM does play an important role in regulating aqueous humor outflow in the TM. Perfusion of cultured human anterior segments with MMPs or agents that activate TM MMPs,

which degrade ECM proteins in the TM, enhances aqueous outflow,<sup>41,42</sup> while perfusion with MMP inhibitors increases outflow resistance.<sup>41</sup> There also appears to be enhanced deposition of the extracellular matrix adhesive glycoprotein fibronectin in the TM of glaucomatous eyes.<sup>43,44</sup> The composition of TM glycosaminoglycans (GAGs) is altered in the glaucomatous TM, with decreased hyaluronan and increased chondroitin sulfate and GAGase-resistant proteoglycans.<sup>45</sup> Several groups reported increased expression of transforming growth factor-beta-2 (TGF-β2) in the aqueous humor of POAG patients,<sup>46,47</sup> and this cytokine has been shown to elevate IOP in perfusion cultured human eyes<sup>48,49</sup> and in transduced mouse eyes,<sup>50</sup> promote ECM deposition in cultured TM cells,<sup>49,51</sup> and enhance covalent cross-linking of ECM proteins via tissue transglutaminase<sup>51</sup> and lysyl oxidase (LOX).<sup>52</sup>

The TM cytoskeleton also regulates aqueous humor outflow. Agents that disrupt TM cell actin microfilaments, including cytochalasin, latrunculin, and various kinase inhibitors including Rho kinase (ROCK) inhibitors now under active clinical investigation, also increase aqueous humor outflow.<sup>53</sup> In contrast, glucocorticoids elevate IOP by decreasing aqueous humor outflow and reorganize the TM microfilaments into cross-linked actin networks<sup>54,55</sup> associated with decreased TM cell functions such as proliferation, migration, and phagocytosis.<sup>54</sup>

Corticosteroid-induced glaucoma mimics POAG in many ways, including the clinical manifestations of elevated pressure and glaucomatous damage to the optic nerve head.<sup>56</sup> Elevated IOP in both diseases is due to increased aqueous humor outflow resistance and is associated with similar biochemical and morphological changes to the TM. Similar changes in the TM extracellular matrix, including increased deposition of fibronectin,<sup>57,58</sup> GAG profiles,<sup>59,60</sup> and reorganization of the actin cytoskeleton<sup>54,55</sup> occur in the glucocorticoid-treated TM.<sup>61</sup> However, a unique ultrastructural feature of corticosteroid-induced glaucoma is the presence of "fingerprint-like" extracellular deposits in the TM.<sup>62</sup> Not all individuals treated with glucocorticoids develop elevated IOP. However, those who do (i.e., corticosteroid responders) have a significantly greater risk of developing POAG in their lifetime,<sup>63</sup> and the majority of POAG patients are corticosteroid responders.<sup>64,65</sup> Differences in glucocorticoid sensitivity between normal and glaucomatous individuals may be explained by an alternative splice variant of the glucocorticoid receptor GR-beta, which acts as a dominant negative regulator of glucocorticoid activity. Glaucomatous TM cells have lower levels of GR-beta compared to nonglaucomatous cells, making these glaucomatous TM cells more responsive to glucocorticoids.<sup>66</sup> This mechanism may also be responsible for differences in corticosteroid responsiveness among normal individuals.

The reduction in TM cellularity may also play a role in the pathophysiology of glaucomatous IOP elevation. There are both age- and glaucoma-dependent loss of TM cells.<sup>31,33,38</sup> Cultured TM cells have been used effectively to provide experimental support for the hypothesis that their biology determines aqueous outflow and thus IOP.<sup>67</sup> A subset of TM cells behave like TM progenitor or stem cells, can be expanded in three-dimensional cultures, and express markers and gene expression profiles consistent with TM stem cells.<sup>68</sup> Exploring TM cell transplant as an approach to enhance outflow and lower IOP is in preclinical testing.

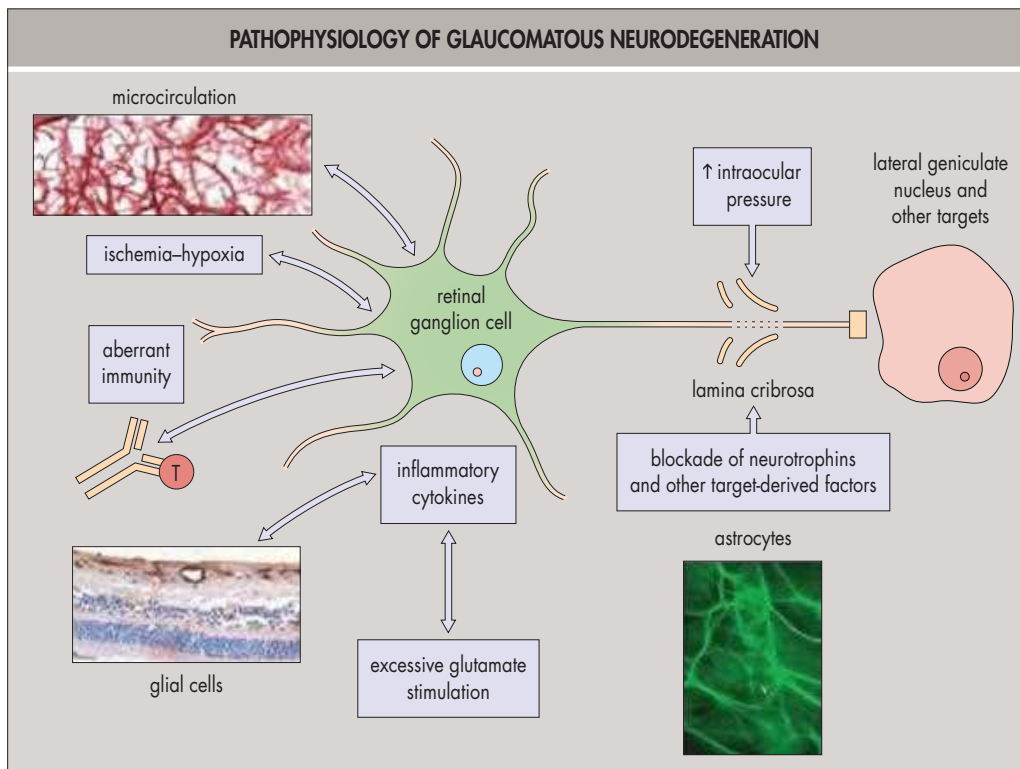
## Conclusions and Future Directions

Molecular genetic, genomic, and proteomic techniques increasingly are being used to better understand glaucomatous damage to the aqueous outflow pathways, which leads to increased outflow resistance and elevated IOP. Advances in genetics and in the cell and molecular biology of aqueous outflow regulation will undoubtedly identify new therapeutic targets and the development of new therapeutic agents that will intervene in the disease process(es) and provide better future therapy targeting IOP for patients with glaucoma.

## PATHOPHYSIOLOGY OF GLAUCOMATOUS OPTIC NEUROPATHY

Although the clinical course and features of glaucomatous optic neuropathy are well characterized, the cellular and molecular mechanisms that underlie the pathogenesis of the degeneration of optic nerve axons and death of RGCs are incompletely understood. Decades of observation have revealed that there are variations in the appearance of the optic nerve and in the progression of visual field damage that occur within the spectrum of glaucoma patients. For example, patients with normal pressure glaucoma are commonly found to have visual field defects that are steeper (in





**Fig. 10.3.3 Mechanisms Contributing to Pathophysiology of Glaucomatous Neurodegeneration.** Intraocular pressure can cause blockade at the lamina cribrosa of axonal protein transport, causing neuronal retinal ganglion cell death by trophic insufficiency. Other implicated factors include local ischemia-hypoxia, excessive stimulation of the glutamatergic system, alterations in glial cells or astrocytes, and aberrant immunity. Reprinted with permission from Elsevier (Weinreb RN, Khaw PT. Primary open-angle glaucoma. *Lancet* 2004;363:1711–20.)

the gradient of light sensitivity loss across retinal area), deeper (increased severity of scotoma), and closer to fixation than their elevated IOP patient counterparts.<sup>69,70</sup> In addition, their optic nerve cupping occurs focally and segmentally, at least in the early stage of neuropathy. It is unlikely that a single pathophysiological mechanism accounts for either the initiation or progression of glaucomatous damage in all afflicted patients. The putative mechanisms that underlie glaucomatous optic neuropathy are most likely multiple (Fig. 10.3.3); each mechanism may have variable impact on the phenotype seen clinically. These mechanisms may also interact, and they likely involve multiple cellular elements in the retina, although their commonly observed clinical effect is RGC preservation or demise.<sup>71</sup>

## Glaucomatous Neuropathy Occurs in Response to Increased Cell Stress Conditions

Causes of glaucomatous optic neuropathy may be disease specific, a pathological response to excessive physiological stress in neurons or glial cells of the retina or optic nerve, or an accelerated process of normal aging that individually or together lead to axon damage and RGC death. These stress conditions may be generalized as IOP-dependent or -independent, although evidence suggests that most eyes with glaucoma are likely affected by pathogenic mechanisms involving both components.

Hypotheses for glaucomatous pathophysiology have been longstanding, but other than for the contribution of IOP to disease progression, remain without conclusive proof. Two of the oldest theories still active today were proposed in the same year, 1858, by individuals who are recognized for their substantial contributions even today.<sup>72,73</sup> Heinrich Müller, a German anatomist who was soon to prove conclusively that phototransduction occurred in rods and cones and whose namesake describes the principal retinal glial cell, was the first to suggest that mechanical compression due to elevated IOP was the cause of glaucomatous damage. Eduard von Jaeger, the ophthalmologist who was the father of clinical perimetry and who first described the use of iridectomy for the treatment of angle-closure glaucoma, proposed that eyes with poor vascular supply to the optic nerve head were predisposed to glaucoma. He further suggested that optic nerve head ischemia could occur in patients with either elevated or normal IOP.

## Disrupted Axon Transport

The mechanical theory of elevated IOP as the cause of glaucoma has been greatly enhanced in recent times. In the late 1960s and early 1970s, blockade of axoplasmic flow was demonstrated in experimental glaucoma in animals.<sup>74–76</sup> This provided a long-sought physiological aspect to the mechanical theory in which optic nerve cupping and excavation were

thought to be the primary observable sequelae of elevated IOP. In the 1990s, it was found that trophic factors, including brain-derived neurotrophic factor (BDNF), are retrogradely transported from the RGC axonal terminals to the cell bodies of the neurons and that trophic factors are essential to RGC survival. Thus, IOP-dependent RGC axon compression was shown to reduce axonal transport trophic factors causing RGC death by trophic insufficiency, as was first demonstrated in experimental glaucoma in rats<sup>77,78</sup> and later in primates.<sup>79</sup>

Recently, animal models of glaucoma have further linked the progressive visual decline in glaucoma to axonal degeneration. Degeneration is detected early where RGC axons terminate in the superior colliculus (RGCs' primary target in the rodent brain), and transport deficits progress in a retrograde fashion toward the retina.<sup>80</sup> Susceptibility to damage is dependent on increasing age, as smaller IOP elevations lead to RGC damage in older animals.<sup>81</sup>

## Vascular Hypothesis

Similarly, considerable support remains for a vascular theory in which chronic or intermittent hypoxia or ischemia is thought to contribute to glaucomatous optic neuropathy.<sup>82–85</sup> Immunohistochemistry studies in postmortem human glaucomatous eyes found that the oxygen-regulated transcription activator hypoxia-inducible factor-1 alpha (HIF-1 $\alpha$ ) was upregulated in retinal locations that were highly concordant with the location of the visual field defects recorded in these eyes.<sup>86</sup> In addition, endothelin-induced chronic ischemia in monkey eyes elicits optic nerve damage that is non-IOP dependent and results in axon loss that is similar to the damage observed in human glaucoma.<sup>87</sup>

## Excitotoxicity Due to Excessive Glutamate

The discovery that excessive and perhaps extrasynaptic concentrations of the neurotransmitter glutamate act as a potent neurotoxin led to the term excitotoxicity. The vitreous humor of glaucomatous monkeys and humans contain elevated glutamate,<sup>88</sup> which initially led to the hypothesis that excitotoxicity could be a significant pathogenic mechanism in glaucoma.<sup>89</sup> However, initial studies were not reliably reproduced,<sup>90,91</sup> and the result from the negative outcome of the phase III clinical trial of memantine, a selective glutamate antagonist,<sup>92</sup> have together decreased enthusiasm for this hypothesis.

## Oxidative Stress and Free Radical Damage

The role of oxidative stress, free radical damage, and mitochondrial function has been studied in various models of glaucoma and in human

disease. There is a compelling body of evidence to suggest that mitochondrial dysfunction can trigger apoptosis signaling via activation of the mitochondrial permeability transition pore complex, which is a key regulator of oxidative stress-induced apoptotic cell death.<sup>92</sup> Evidence for the central role of mitochondrial dysfunction in animal and human glaucoma<sup>93</sup> includes the proteomic identification of oxidatively modified retinal proteins in ocular hypertensive animals.<sup>94</sup> Studies in human glaucoma patients found mitochondrial DNA alterations suggestive of oxidative stress<sup>95</sup> as well as impaired mitochondrial respiratory activity. In addition, lower levels of circulating reduced glutathione were found in the sera of glaucoma patients<sup>96</sup> along with decreased antioxidant enzymes in the aqueous humor of glaucoma patients.<sup>97</sup> Genetic evidence also supports a role for mitochondrial dysfunction, in that some patients with normal pressure glaucoma have been found to express genetic polymorphism of their mitochondrial DNA that bears similarities to those found in patients with Leber's hereditary optic neuropathy and dominant optic atrophy.<sup>98</sup>

## Inflammatory Cytokines

A pathogenic role for inflammatory cytokines such as tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) and nitric oxide have been postulated based on tissue examination of postmortem human glaucomatous eyes.<sup>99–102</sup> Functional studies of cultured RGCs and experimental glaucoma also demonstrated that RGC death could be reduced favorably by treatment with agents that neutralize or halt production of TNF- $\alpha$ <sup>103–105</sup> or nitric oxide synthase,<sup>106</sup> although the role of nitric oxide synthase remains controversial,<sup>107</sup> and nitric oxide donors are currently moving through clinical trials as IOP-lowering agents. The suggestion that TNF is causally implicated in glaucoma was initially supported by the finding that there were mutations in the gene for optineurin, a protein involved in the TNF signaling cascade, in a cohort of glaucoma patients.<sup>108</sup> However, it is not clear if this mutation or if TNF- $\alpha$  polymorphisms are significant factors for all the patient populations in which they have been studied.<sup>109–111</sup> A role for other signaling molecules considered cytokines or members of inflammatory cascades such as complement proteins like C1q<sup>112–114</sup> and interleukins such as IL-6 and IL-1 $\alpha$ <sup>115,116</sup> have also been implicated as causative agents in promoting RGC death or as key to regenerative failure.

## Aberrant Immunity

Both the humoral and cellular immune system have been implicated in glaucomatous neurodegeneration. For the humoral system of immunoglobulins, an increased prevalence of monoclonal gammopathy,<sup>117</sup> retinal immunoglobulin deposition,<sup>118</sup> elevated serum autoantibody titers to optic nerve head glycosaminoglycans<sup>119</sup> or to retinal antigens, including rhodopsin,<sup>120</sup> heat shock proteins,<sup>121,122</sup> gamma-enolase,<sup>123</sup> alpha-fodrin,<sup>124</sup> neurofilament protein, phosphatidylserine,<sup>125</sup> and glutathione S-transferase,<sup>126</sup> have been reported in patients with glaucoma. The majority of these studies demonstrate that most of these elevated antibody titers occur in patients with normal pressure glaucoma, although many patients with elevated IOP appear to have elevated or, in some cases, decreased antibody titers as well.<sup>127</sup> An autoimmune mechanism that elicits glaucomatous neurodegeneration is hypothesized to occur either directly by autoantibodies<sup>128</sup> or indirectly by a “mimicked” autoimmune response to a sensitizing antigen, which in turn results in neuronal injury.<sup>121,129</sup> It is still unclear whether any of the autoantibodies found in glaucoma patients are of pathogenic importance or whether the autoantibody findings are merely epiphenomena that accompany the disease process.

Evidence supporting the involvement of the cellular immune system in glaucoma includes the presence of HLA-DR-positive microglia in the glaucomatous optic nerve head,<sup>130</sup> the induction of HLA-DR expression and antigen-presenting capacity of optic nerve head astrocytes in glaucoma,<sup>131</sup> and alterations in the cellular immune system, such as an increased percentage of CD8<sup>+</sup> T lymphocytes and altered serum levels of soluble IL-2 cytokine receptors in some patients with glaucoma. On the other hand, a protective immunity may be evoked in injured optic nerve to reduce the secondary degeneration of neurons, which can be induced by active or passive immunization with self-antigens.<sup>132–135</sup> Better understanding the regulation of balance between this protective autoimmune response and induction of an autoimmune disease will be critical to

take advantage of the immune system for neuroprotective strategies in glaucoma.

## Cellular Mechanisms of Apoptosis in Glaucoma

Although the physiological conditions that may mediate glaucomatous optic neuropathy are known, the mechanisms that govern cell survival decisions of the RGC confronted by excessive stress have not been completely elucidated. Unlike the cell necrosis that is accompanied by cell swelling, organelle disintegration, and plasma membrane fracture after, for example, acute severe ischemic insult, the glaucomatous process in RGCs is thought to occur by apoptosis—a degenerative process that features cell shrinkage, plasma membrane blebbing, nuclear DNA cleavage by caspase endonucleases, and cytoskeletal degeneration. The initial evidence for apoptosis in glaucoma relied on markers of nuclear DNA cleavage<sup>136,137</sup> but has since been far more extensively studied.<sup>92,93</sup> Mitochondrial-dependent apoptosis involves the induction of proapoptotic proteins such as BAX (and related family members BAK, BI, and BAD) that increase mitochondrial membrane permeability. This subsequently promotes activation of the cell executioner caspase enzymes, which in turn activate DNA breakdown. Normally, BAX activation is balanced intracellularly by activation of a family of BCL-2 (or BCL-XL) proteins that decrease mitochondrial membrane permeability and reduce or prevent apoptosis. The central role of the cellular proteins BAX and BCL-2 lie in stoichiometric balance with one another (Fig. 10.3.4) that ultimately determines whether apoptosis will occur.<sup>92,138,139</sup>

## Neurotrophic Factors for Survival and Growth

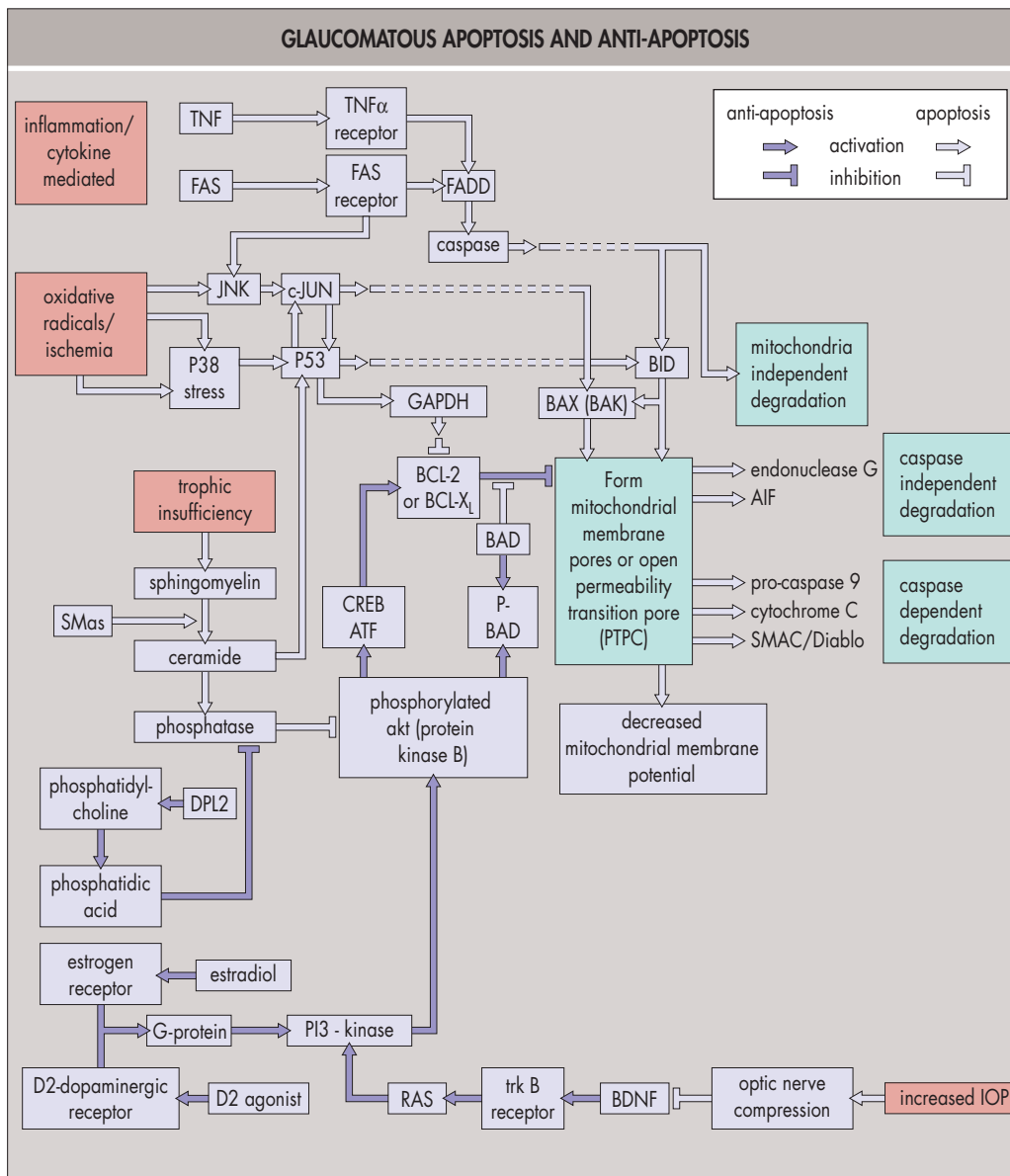
The extracellular signaling from neurotrophic factors and their cellular receptors appear also to have major effects (both helpful and harmful) on RGC cell fate.<sup>92</sup> These proteins are found in the developing and adult visual system and normally support RGC survival and axon growth. As noted above, RGC axon damage at the optic nerve head results in a blockade of the transport of factors such as BDNF and its receptors in acute glaucoma.<sup>79,140,141</sup> In preclinical models, RGC neuroprotection can be elicited by BDNF<sup>142</sup> or other neurotrophic factors, including ciliary neurotrophic factor (CNTF),<sup>143</sup> glial-derived neurotrophic factor (GDNF),<sup>144</sup> and nerve growth factor (NGF).<sup>145,146,147,148</sup> Neurotrophic factors have entered human testing, including trials in glaucoma for CNTF and NGF.

## Central Visual Pathway Degeneration in Glaucoma

Although glaucoma is characterized best as an axonopathy that initiates or propagates at the optic nerve head, it is also characterized by changes in RGCs' axon target fields in their central visual pathways in the brain, such as at the lateral geniculate nucleus (LGN) and even downstream at the visual cortex. Chronic IOP elevation in primates leads to microglial cell and astrocyte activation in the LGN, observed by positron emission tomography imaging and by histology.<sup>149</sup> Neuroimaging of human glaucoma patients suggests differences in LGN volume measurable by magnetic resonance imaging (MRI), and RGC loss in glaucoma patients is associated with transsynaptic death of the neurons in the LGN.<sup>49,50,150,151</sup> Thus glaucomatous neuronal death is not limited to the retina, because neurons in the lateral geniculate and the visual cortex also appear to be lost.<sup>152,153</sup>

## CONCLUSIONS AND FUTURE DIRECTIONS

Glaucoma is no longer viewed simply as elevated IOP that damages the optic nerve. In addition to high IOP, functional evidence is rapidly accumulating that suggests damage to the optic nerve may be initiated or sustained by many factors, including ischemia, excitotoxicity, neurotrophin insufficiency, inflammatory cytokine damage, the immune environment (including aberrant immunity), neuronal–glial interactions, complement regulation of synaptic transmission, and other factors not yet defined. Our understanding of glaucoma more broadly as a neurodegenerative disease broadens the candidate approaches to treatment beyond just lowering IOP to include neuroprotective and regenerative therapies. Such novel therapies may complement current glaucoma therapy and move us toward targeted treatment of neural injury and regeneration throughout the visual system.



**Fig. 10.3.4 Cellular Signaling Mechanisms for Glaucomatous Apoptosis and Anti-Apoptosis.** The schematic is drawn to illustrate the role of BAX and BCL family of proteins in the induction of increased mitochondrial membrane permeability that allows the release of the different factors (endonuclease G, AIF, pro-caspase 9, cytochrome C, and SMAC/Diablo) leading to caspase-dependent or independent apoptotic degradation in retinal ganglion cells in glaucoma in response to several physiological stress conditions thought to be pertinent to the etiology of glaucomatous degeneration. (Adapted from Tatton W, Chen D, Chalmers-Redman R, et al. Hypothesis for a common basis for neuroprotection in glaucoma and Alzheimer's disease: anti-apoptosis by alpha-2-adrenergic receptor activation [Review]. *Surv Ophthalmol* 2003;48:S25–37.)

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# Clinical Examination of Glaucoma

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# 10.4

**Definition:** Glaucoma is a group of acute and chronic, progressive, multifactorial optic neuropathies and is diagnosed via history, clinical examination, and ancillary testing in which intraocular pressure and other contributing factors are responsible for a characteristic acquired loss of retinal ganglion cell axons leading to atrophy of the optic nerve with demonstrable visual field defects.

## Key Features

- Obtaining relevant information.
- Assessing the patient's functional status.
- Obtaining the patient's history.
- Examination techniques.
- Visual acuity testing.
- Pupillary response testing.
- Tonometry.
- Pachymetry.
- External examination.
- Slit-lamp examination.
- Gonioscopy.
- Optic nerve examination.
- Testing for glaucoma.

## INTRODUCTION

The clinical evaluation of glaucoma requires thorough review of a patient's medical and ocular history as well as a comprehensive ocular examination that should include visual acuity testing, pupillary response testing, slit-lamp biomicroscopy, tonometry, gonioscopy, and optic nerve examination. In addition to the information obtained during the clinical examination, ancillary diagnostic tests can also help the clinician assess the structural and functional integrity of the optic nerve.

The goal of the clinical evaluation is to diagnose the type of glaucoma affecting the patient, assess its severity, and determine the presence of progression over time. Based on the findings, appropriate individualized therapeutic options may be offered to the patient.

## OBTAINING CLINICALLY RELEVANT INFORMATION

### Assessing the Patient's Functional Status

The first step in the clinical evaluation of glaucoma is determining the functional status of the patient. An indirect way of measuring the functional status consists of estimating the general health and life expectancy of the patient. This assessment can also provide the clinician with important insight regarding the patient's conceptions and attitudes toward their disease. Since glaucoma is a chronic disease, the clinician must gauge the patient's degree of understanding, motivation, and willingness to participate in his or her care.

Assessment of a patient's functional status enables the clinician to individualize and appropriately adjust the intensity and aggressiveness of treatment. Matching the physician's expectations with the patient's understanding of his or her disease is likely to result in better communication, which may lead to better adherence to therapy by the patient.

## Obtaining the Patient's History

### Medical History

It is important to establish a chronology of events leading up to the patient's current condition by documenting the onset, duration, location, severity, and perceived progression of his or her symptoms, if any. Additionally, the clinician must identify drug allergies, the patient's ability to tolerate topical and systemic medications, and the presence of systemic health disorders that could be associated with the patient's type of glaucoma.

Clinicians should pay special attention to a patient's use of corticosteroids, regardless of the duration of use, since these have been associated with elevated intraocular pressures (IOP).<sup>1</sup> Patients with a history of glaucoma or a family history of glaucoma are more prone to IOP increases with corticosteroid use than both glaucoma suspects and normal patients. While an increase in IOP is more likely to occur with topical corticosteroid administration, it may also occur with various systemic routes of administration. Other important systemic drugs to note include sulfonamide drugs such as topiramate and acetazolamide, bupropion, oseltamivir, and antidepressant medications, which have been reported to cause acute myopia with uveal effusions and acute, bilateral, angle-closure glaucoma.<sup>2,3</sup> In addition, drugs like antihistamines and antispasmodics may lead to mydriasis and compromising narrow angles.<sup>1</sup>

### Ocular History

A thorough review of the patient's ocular history should include an assessment of the following factors:

- Refractive status – Hyperopic eyes may be predisposed to developing angle-closure glaucoma. Myopic eyes may be predisposed to developing pigmentary glaucoma<sup>4</sup> or primary open-angle glaucoma<sup>5</sup> (POAG) and may have suspicious discs, which should be differentiated from congenitally tilted discs that remain stationary throughout life.
- Previous intraocular surgery – Refractive surgery such as laser-assisted in situ keratomileusis (LASIK) or photorefractive keratectomy (PRK) may lead to corneal biomechanical changes and thinning, which can affect accurate measurement of IOP (see later). Complications of previous intraocular surgeries may predispose to inflammatory glaucoma.
- History of blunt ocular trauma – Blunt trauma can lead to hyphema, traumatic dysfunction of the trabecular meshwork, angle recession, and glaucoma.
- Ability of the patient to tolerate topical glaucoma medications.

### Family History

A positive family history is a known risk factor of glaucoma.<sup>6</sup> The prevalence of glaucoma, enlarged cup-to-disc ratio (CDR), and increased IOP have been found to be higher in children and siblings of glaucoma patients compared to the relatives of controls.<sup>7</sup> In addition, several genes and different modes of inheritance have been implicated in the development of various forms of glaucoma and will be discussed in greater detail in Chapter 10.34. Therefore, patients should be asked about any relatives who have been diagnosed with glaucoma. Special attention should be paid to the age of diagnosis, presentation, systemic associations, progression, and visual status of the affected relative.

### Ethnicity

The prevalence of glaucoma varies among different ethnic groups. Angle-closure glaucoma is more common among East Asian,<sup>8</sup> Indian,<sup>9</sup> and Inuit<sup>10</sup> populations than among white populations.

POAG is more prevalent, appears earlier, and progresses more rapidly in individuals of African descent compared with individuals of European descent.<sup>11,12</sup> The Los Angeles Latino Eye Study also found that POAG was



more prevalent in Hispanic patients than in non-Hispanic white patients in the United States.<sup>13</sup>

EXAMINATION TECHNIQUES

Visual Acuity Testing

Visual acuity testing is an essential part of the evaluation of the glaucoma patient since it provides information to the clinician about the patient’s functional status.

However, in the early stages of glaucoma, central visual acuity is preserved and may remain intact even until the last stages of the disease. Therefore, visual acuity alone does not always provide sufficient information to evaluate the severity of glaucoma. Nevertheless, in very advanced glaucoma cases, visual acuity can play an important role in the selection of one treatment option over another. Subjective decreases in visual acuity in very advanced cases may also be an indicator of progression when visual field testing is no longer reliable.

Pupillary Response Testing

Testing for a relative afferent pupillary defect (RAPD) is an often overlooked component of the glaucoma evaluation. A positive RAPD is found only in the presence of a definite abnormality of the afferent limb of the pupillary light reflex pathway and may signify the presence of asymmetrical optic nerve damage. It has been suspected that a positive RAPD may present before visual field and optic disc changes become apparent.<sup>14</sup> Two studies<sup>15,16</sup> evaluating the relationship between RAPD and retinal nerve fiber layer (RNFL) thickness suggest that an RAPD will be detectable when there is a greater than 17%–27% reduction in RNFL thickness in the eye with the RAPD relative to the fellow eye.

While pupillometry<sup>14,17,18</sup> has been used for RAPD detection, RAPD testing is still traditionally performed using the swinging flashlight method (SFM).<sup>19</sup> The sensitivity of RAPD detection using the SFM may be increased by using the magnifier-assisted swinging flashlight method in which a +20.00 diopter (D) lens is held in front of the tested eye.<sup>14,20</sup> After an RAPD is detected, it can be quantified with the aid of tools such as neutral density filters,<sup>21</sup> cross-polarized filters,<sup>22</sup> or a Sbisa bar.<sup>23</sup>

Tonometry

The Role of Intraocular Pressure in Glaucoma

The measurement of IOP plays a central role in the examination of the glaucoma patient. While the mean IOP in population studies has been measured to be roughly 15–17 mm Hg,<sup>24</sup> it is important to note that the IOP distribution among the general population does not follow a normal bell-shaped (Gaussian) curve. Instead, the distribution is skewed toward higher pressures. As a result of this skewed distribution, it is incorrect to determine 95% limits using the equation mean  $\pm$ 2.5 standard deviations (SD). In other words, 21 mm Hg (i.e., 2.5 SD above the mean) cannot truly be considered a standard cutoff value to differentiate normal from abnormal IOP. Instead, consideration of a patient’s IOP should be individualized.

IOP is dynamic; IOP monitoring studies have shown that individual IOP exhibits significant long-term, diurnal, positional, and nocturnal fluctuations.<sup>25–32</sup> These studies (1) illustrate the importance of multiple pressure readings in patients being evaluated for glaucoma, and (2) highlight the limitations of office-based tonometry in which only a snapshot of the patient’s pressures is recorded and peak IOP levels are missed in up to 62% of patients.<sup>33,34</sup> Some, though not all, long-term IOP fluctuation studies have also reported an association between IOP fluctuation and disease progression.<sup>26–32</sup> Therefore, it is important for clinicians to consider the possibility that patients may benefit from the assessment and modulation of IOP fluctuations. In select glaucoma patients, IOP fluctuations may also justify the use of diurnal pressure curves and possibly, in the future, continuous/home IOP monitoring.<sup>35</sup>

Factors reported to be associated with IOP elevation and reduction are listed in Table 10.4.1.<sup>1,36–44</sup>

IOP is the only known modifiable factor that has been shown to delay progression of disease in both ocular hypertensive<sup>45</sup> and glaucoma patients.<sup>46–48</sup> Therefore, most recognized therapeutic interventions for glaucoma (medications, laser, and surgery) are directed at lowering IOP.

Clinical measurement of IOP has undergone several technical advances since the era of digital tension measurements and indentation tonometry. While the future of IOP testing now rests with novel techniques of achieving continuous IOP monitoring, the current reference standard and most

TABLE 10.4.1 Factors Associated With Elevation and Reduction of Intraocular Pressure (IOP)

Factors Associated With IOP Elevation	Factors Associated With IOP Reduction
Supine position	Prolonged exercise
Valsalva maneuver	Pregnancy
Elevated episcleral venous pressure	Metabolic acidosis
Sympathomimetics and anticholinergic agents in narrow angles	Intake of alcohol Marijuana
Corticosteroids Ketamine and succinylcholine	General anesthetics (except for ketamine and succinylcholine)

widely used method for the measurement of IOP remains the Goldmann applanation tonometer (GAT). The principles and technique of Goldmann tonometry are described in detail later. Listed in Table 10.4.2 are the mechanisms, advantages, and disadvantages of other tonometry methods<sup>49,50</sup> including Schiøtz indentation tonometry, Tono-Pen, noncontact tonometry, pneumotonometry, rebound tonometry, dynamic contour tonometry, and transpalpebral tonometry.

Applanation Tonometry

GAT is based on the Imbert–Fick principle, which states that the force necessary to applanate a perfectly elastic, infinitely thin, dry sphere divided by the area flattened ( $P = F/A$ ) equals the pressure inside the sphere. In an attempt to account for corneal thickness, scleral rigidity, and the tear film’s surface tension, the area of applanation was set at 7.35 mm<sup>2</sup> (diameter 3.06 mm).

The tonometer’s head is made of plastic; the tip has a built-in transparent biprism, which divides the image seen through the tonometer head into two equal semicircles or mires. The cornea is anesthetized and fluorescein is applied to improve visualization of the two semicircles using a cobalt blue light. The tonometer’s head is gently applied to the surface of the cornea, and a variable force is applied using a sensitive spring system regulated by a dial. The dial is turned in either direction until the inner edges of the mires just meet. This corresponds to the applanating force necessary to flatten an area 3.06 mm in diameter. The force magnitude on the dial is expressed in dynes, and this value is multiplied by 10 to determine the IOP (mm Hg).

IOP measurements with GAT are limited by the presence of corneal astigmatism greater than 3.00 D.<sup>51</sup> This potential error can be avoided by using the average of two measurements taken 90° apart (vertical and horizontal axes at right angles) or by aligning the tonometer biprisms so that the red line on the prism holder is aligned to the corneal axis of negative cylinder or least corneal curvature.<sup>52</sup>

Careful attention must be paid by the examiner to avoid complications associated with GAT, including corneal abrasions and corneal decompensation secondary to topical anesthetic use. The tip of the tonometer should always be wiped with either hydrogen peroxide solution or with a 70% isopropyl alcohol pad to prevent infection<sup>53</sup> and thoroughly dried before use to avoid a chemical burn to the cornea. Special steps should be taken after applanation of patients with hepatitis C virus (HCV) to ensure adequate sterilization. Options include wiping the tonometer tip with povidone iodine 10% for 15 seconds, or soaking the tip in 3% hydrogen peroxide or 70% isopropyl alcohol for 5 minutes.<sup>54</sup> Calibration of this instrument should be performed at least twice a year. A modified version of the Goldmann tonometer, the Perkins and Draeger tonometer, is portable and may be used while the patient is supine.

Pachymetry

Assessment of central corneal thickness (CCT) has become an important element of the clinical evaluation of the glaucoma patient. Ultrasound pachymetry is easy, portable, and the most widely used method of measuring CCT, though several other methods have been employed, including optical pachymetry, optical coherence tomography (OCT), specular microscopy, and Scheimpflug imaging.

A large meta-analysis of 230 data sets found the normal CCT to be 536  $\mu$ m (SD 31  $\mu$ m).<sup>55</sup> Twin studies<sup>56,57</sup> have shown that CCT is a highly heritable trait, and several population studies indicate that CCT varies among different ethnic groups.<sup>58</sup> For example, individuals of African descent have thinner mean CCT values than Hispanic people and non-Hispanic white people in the United States. CCT may also vary between different diagnoses; eyes with normal-tension glaucoma and ocular hypertension may have thinner and thicker CCT values relative to controls, respectively.<sup>59</sup>

TABLE 10.4.2 The Mechanisms, Advantages, and Disadvantages of Different Tonometry Methods

Tonometry Method	Mechanism	Advantages	Disadvantages
Goldmann applanation	See text	Widespread use Considered the reference standard	Overestimation with too much fluorescein, very thick or steep corneas, eyelid squeezing, direct or indirect pressure on the globe, Valsalva maneuvers Underestimation with too little fluorescein, corneal edema, thin corneas Affected by scleral rigidity Cannot be used reliably in corneas with significant irregularities or scarring Affected by operator bias
Schiøtz indentation	The cornea is indented by a metallic footplate attached to a plunger of known (and variable) weight. Movement of a lever along an attached scale indicates pressure. A large displacement of the lever represents low pressure, and small displacement represents high pressure. Conversion table used to obtain IOP in mm Hg.	Portable May be sterilized for OR use	Cannot be used upright (unless head tilted far back) Affected by corneal thickness, irregular/scarred cornea, and scleral rigidity Risk of corneal abrasion if eye moves
Tono-Pen	Mixed indentation and applanation mechanism. A small strain gauge surrounded by an annular applanation surface detects pressure at point of applanation. Applanation point detected by a small decrease in the pressure transmitted through strain gauge (when the applanation surface shares a portion of the force). Pressure is calculated from multiple readings (4 or 10) taken electronically.	Highly portable, easy to use Position-independent Digital readout Can use over bandage contact lens Disposable covers (no need to sanitize) Can be used on corneas with significant scarring or irregularity	Cost of disposable covers and battery In some cases, readings can vary significantly from Goldmann
Non-contact (Airpuff)	Similar to Goldmann, except applanation (diameter 3.06 mm) achieved by a column of air that increases in intensity. A sensor detects applanation  A newer version, the ocular response analyzer, has ability to measure corneal hysteresis by detecting the difference between two applanation pressures, one on initial applanation and the other on applanation following indentation beyond the initial applanation point.	No anesthesia or sterilization required	Most are not portable Frequent maintenance needed Corneal thickness may influence measurement more than Goldmann (except ocular response analyzer)
Pneumotonometry	A slightly convex tip resting on a cushion of air is used to applanate the cornea. A strain gauge detects the pressure. The tip is held for at least 5 seconds and IOP pulsation can be traced.	Portable Position-independent	Expensive parts Frequent maintenance needed Sanitation is difficult
Rebound	A small magnetized, ball-shaped probe is projected forward to bounce off the cornea at the push of a button. The speed of deceleration is used to calculate pressure. More rapid deceleration indicates higher pressure.	Portable Easy to use No anesthesia required Patient comfort Disposable probes	Cost of disposable probes Corneal thickness may influence measurement more than Goldmann
Dynamic contour tonometry (Pascal)	A concave-shaped plastic tip (contour-matched to the cornea) with a central pressure sensor is applied to the cornea at a constant force of 1 g. No applanation or indentation. Pressure is read from outside the cornea, 100 times/sec for several seconds, until an audible signal is heard. Reports IOP (based on average diastolic pressure), ocular pulse amplitude (systolic minus diastolic IOP), and quality of reading.	Digital readout Disposable covers (no need to sanitize) More independent of corneal thickness than Goldmann Accurate in thin eyes and post-LASIK eyes Reports ocular pulse amplitude	Expensive Cost of disposable covers Learning curve
Transpalpebral	Pressure measured mechanically or electronically (depending on device) through the upper eyelid or by digital palpation	Only useful when conventional tonometry not possible—corneal prostheses, extremely irregular or scarred corneas, uncooperative patient Lack of need for anesthesia or sterilization	Readings vary significantly from Goldmann Reading significantly affected by corneal thickness

IOP, Intraocular pressure; LASIK, laser-assisted in situ keratomileusis.

Measurement of CCT is important for two reasons. CCT influences the measurement of IOP in many types of tonometry, including GAT, and CCT may have a prognostic value for patients with ocular hypertension. Although CCT is set as a constant variable in the Goldmann tonometry formula, pachymetry studies have demonstrated that CCT varies significantly between individuals and influences IOP measurement. “True” IOP is underestimated in thin corneas and overestimated in thicker corneas. Therefore, clinicians should consider interpreting borderline or unusual IOPs in light of a patient’s CCT and, in cases of doubt, consider re-evaluating IOP using a tonometry method that is less dependent on CCT. In several studies,<sup>60–62</sup> including the Ocular Hypertension Treatment Study (OHTS)<sup>63</sup> and the European Glaucoma Prevention Study (EGPS),<sup>64</sup> CCT was found to be a powerful and independent predictor of the development of POAG. In OHTS, ocular hypertensive eyes with thin corneas (<555 μm) were found to have a threefold increased risk of developing POAG compared to eyes with thick corneas (>588 μm). It is important to note, however, that OHTS did not adjust IOP values to account for CCT. Measured IOP values in eyes with lower CCT could have been a significant underestimation of their true values compared to measurements from eyes with thicker corneas. Because possible CCT-induced GAT measurement error were not adjusted for, these studies did not truly separate CCT from IOP.

To address this issue, another study<sup>65</sup> re-evaluated the OHTS data and applied five different correction formulas to adjust the IOP values for CCT. In this analysis, CCT remained a statistically significant predictor of glaucoma development in ocular hypertensives, though the hazard ratio decreased from 1.84 to 1.38–1.69 with the different correction formulas. Although this result is not conclusive<sup>66</sup> due to the inherent limitations of correction formulas and requires more investigation, it does suggest the possibility that CCT may be important not only for adjusting IOP assessments but also as an indicator of glaucoma risk. The cause of this potentially increased risk conferred by thinner central corneas remains unknown, though it is possible that CCT is biomechanically related to other anatomical structures implicated in glaucoma pathogenesis, such as the optic disc, lamina cribrosa, and sclera.

### External Examination

The importance of the external examination of the ocular adnexae is emphasized in this section because a variety of systemic conditions have been associated with characteristic external findings and the development of secondary glaucomas (Table 10.4.3).

In addition, external examination of the lids and the ocular surface can provide the clinician with important clues regarding the presence of

TABLE 10.4.3 Ocular Adnexae Abnormalities and Systemic Findings Associated With Secondary Glaucomas

Condition	Periocular Findings	Intraocular Findings	Systemic
<b>Tuberous Sclerosis</b>	Ash-leaf sign (hypopigmented macules) Angiofibromas (yellow–red papules in malar regions of face)	Retinal/optic nerve hamartomas Punched-out chorioretinal depigmentation Iris abnormalities	Benign tumors in various organs Renal abnormalities Seizures Shagreen patches
<b>Neurofibromatosis Type 1</b>	Plexiform neurofibroma (S-shaped upper lid tumor) Pulsating proptosis	Angle abnormalities Lisch nodules Choroid hamartomas Retinal tumors Optic nerve glioma	Café-au-lait spots Axillary/inguinal freckling Distinct bone abnormalities
<b>Juvenile Xanthogranuloma</b>	Reddish or yellow–brown papules, plaques, or nodules on eyelid	Iris heterochromia Iris masses Spontaneous hyphema	Reddish or yellow–brown papules, plaques, or nodules on head/neck/trunk Subcutaneous or deep soft tissue nodule/mass Systemic lesions in various organs
<b>Ocular or Oculodermal Melanocytosis (Nevus of Ota)</b>	Gray–brown to blue–black lesion in distribution of first and second cranial nerves involving episclera or periocular skin	Pigmentary-like glaucoma	Increased incidence of melanoma involving uvea, central nervous system, orbit, skin
<b>Axenfeld–Rieger Syndrome</b>	Hypertelorism (increased distance between the two orbits)	Posterior embryotoxon Abnormal angle tissue Iris abnormalities (corectopia, polycoria)	Maxillary and dental hypoplasia Microdontia, hypodontia, anodontia Pituitary abnormalities Hypospadias (males) Umbilical abnormalities
<b>Orbital Varices</b>	Variable or intermittent unilateral proptosis, engorgement, and pain	Elevated episcleral venous pressure	
<b>Thyroid Ophthalmopathy</b>	Exophthalmos Lid retraction	Motility restriction Conjunctival chemosis Elevated episcleral venous pressure	Hyperthyroid Hypothyroid Euthyroid
<b>Sturge–Weber Syndrome</b>	Facial capillary malformation (port wine stain)	Vascular malformations of conjunctiva, episclera, choroid, retina Iris heterochromia Elevated episcleral venous pressure	Intracranial capillary–venous malformations
<b>Superior Vena Cava Syndrome</b>	Proptosis Facial edema Eyelid edema	Conjunctival chemosis Elevated episcleral venous pressure	Lung cancer or non-Hodgkin's lymphoma Dyspnea Venous distension in neck and chest Extremity swelling

medication-related toxicity. Ocular and systemic side effects associated with the use of glaucoma medications are listed in Table 10.4.4. Systemic side effects from topical glaucoma therapy can be minimized by performing punctal occlusion, blotting of excess drops, and possibly closing the eyelids after instillation.<sup>67</sup>

Allergic contact dermatitis is manifested with thickening of the skin overlying the lids. Alpha-2 agonists (brimonidine) have been implicated with this condition along with other older medications such as epinephrine, apraclonidine, and pilocarpine. This allergic contact dermatitis can progress and lead to scarring and obstruction of the lacrimal punctae.<sup>68</sup>

Topical administration of prostaglandin analogs has been associated with hypertrichosis, hyperpigmentation of the eyelashes and periocular area, irreversible iris darkening,<sup>69</sup> and deepening of the upper eyelid sulcus, possibly caused by periorbital fat atrophy.<sup>70</sup>

Topical glaucoma medications can be toxic to the ocular surface and can worsen the signs and symptoms of dry eye. This can make susceptible patients intolerant to some preparations and may limit their choices of topical glaucoma therapy. A methodical investigation of the ocular surface and the identification of dry eye and blepharitis can help the clinician address the underlying cause before the institution or adjustment of glaucoma treatment.

## Slit-lamp Examination

### Conjunctiva, Sclera, and Episclera

The conjunctiva plays an important role in the evaluation of glaucoma patients because the success of glaucoma surgery depends on the health and integrity of this tissue. Improving the health of the ocular surface can result in better surgical outcomes in glaucoma.

The clinician must evaluate the presence of conjunctival hyperemia and determine the etiology of this finding to treat the underlying cause. There are three major causes of conjunctival hyperemia that need to be recognized: (1) medication or preservative-induced hyperemia; (2) dilated episcleral vessels; and (3) infectious causes when a filtering bleb is present.

The presence of conjunctival hyperemia, conjunctival follicles, and superficial punctate keratitis should be assessed when patients are using IOP-lowering eyedrops. A significant number of patients using topical

glaucoma medications suffer from ocular surface disease (OSD).<sup>71</sup> Furthermore, OSD incidence and symptom severity is positively correlated with the number of eyedrops administered.<sup>71</sup> Much of the OSD caused by glaucoma medications is likely attributable to added preservatives. Although preservatives function to prevent bacterial contamination and improve ocular penetration, patients using preserved eyedrops have a significantly increased incidence of OSD signs and symptoms such as discomfort upon instillation, burning or stinging, foreign body sensation, and dry eye sensation.<sup>72</sup> The most common preservative employed in glaucoma medications is benzalkonium chloride (BAK). Recently, milder proprietary preservatives such as SofZia (Travatan Z; Alcon Laboratories, Inc.) and Purite (Alphagan P; Allergan, Inc.) have been introduced. Several glaucoma drops are also available in preservative-free formulations, such as timolol, tafluprost, and fixed-combination timolol-dorzolamide.

The presence of dilated episcleral vessels should prompt the physician to investigate the presence of elevated episcleral venous pressure, which can reduce aqueous outflow and lead to an elevation of IOP.<sup>73</sup> Patients with elevated episcleral venous pressure often have blood in Schlemm's canal that is visible on gonioscopy.<sup>73,74</sup> Etiologies of elevated episcleral venous pressure include: (1) carotid cavernous sinus fistula<sup>74</sup>; (2) Sturge–Weber syndrome,<sup>73</sup> which is associated with a facial port wine stain; (3) the systemic form of Klippel–Trenaumay–Weber syndrome,<sup>75</sup> which is associated with ipsilateral limb hypertrophy and cutaneous hemangiomas; (4) thyroid ophthalmopathy; and (5) superior vena cava syndrome. A single dilated episcleral vessel should prompt an investigation for an occult ciliary body melanoma,<sup>76</sup> which should include a dilated exam and diagnostic ultrasound biomicroscopy.

The presence of a filtering bleb should be noted in the patient's chart, with careful documentation of the bleb's height, extent, vascularity, and integrity (Seidel test).<sup>77</sup>

### Cornea

Examination of the cornea should be performed carefully to establish the presence of infiltrates, edema, staining, or abnormalities associated with the development of secondary glaucomas. Eyes with a history of penetrating keratoplasty have a high incidence of developing secondary glaucoma, with initial elevations in IOP occurring an average of 6 months after surgery.<sup>78</sup>



TABLE 10.4.4 Local and Systemic Side Effects of Commonly Used Glaucoma Medications

Medication Class	Preservative	Ocular Side Effects	Systemic Side Effects
<b>Prostaglandin Analogs</b> <ul style="list-style-type: none"><li>• Bimatoprost</li><li>• Latanoprost</li><li>• Tafluprost</li><li>• Travoprost</li></ul>	<ul style="list-style-type: none"><li>• BAK</li><li>• SofZia (Travoprost)</li><li>• Preservative-free (Tafluprost)</li></ul>	<ul style="list-style-type: none"><li>• Increased iris, eyelash, and periocular pigmentation</li><li>• Hypertrichosis</li><li>• Keratitis</li><li>• Cataract</li><li>• Macular edema</li><li>• Uveitis</li></ul>	<ul style="list-style-type: none"><li>• Angina, chest pain</li><li>• Arthralgia, myalgia</li><li>• Flu-like symptoms</li><li>• Headache</li></ul>
<b>Docosanoids</b> <ul style="list-style-type: none"><li>• Unoprostone</li></ul>			
<b>Beta-Adrenergic Antagonists</b>			
<b>Nonselective</b> <ul style="list-style-type: none"><li>• Carteolol</li><li>• Levobunolol</li><li>• Metipranolol</li><li>• Timolol</li></ul>	<ul style="list-style-type: none"><li>• BAK</li><li>• Preservative-free (Ocudose Timolol)</li></ul>	<b>Nonselective</b> <ul style="list-style-type: none"><li>• Corneal anesthesia</li><li>• Punctate keratitis</li></ul>	<b>Nonselective</b> <ul style="list-style-type: none"><li>• Bradycardia</li><li>• Heart block</li><li>• Hypotension</li><li>• Bronchospasms</li><li>• Decreased libido</li><li>• CNS depression</li><li>• Headache</li><li>• Masking of hypoglycemia and hyperthyroidism</li><li>• Aggravation of peripheral vascular disease, Raynaud's disease, or myasthenia gravis</li></ul>
<b>Selective</b> <ul style="list-style-type: none"><li>• Betaxolol</li></ul>		<b>Selective (Betaxolol)</b> <ul style="list-style-type: none"><li>• Same as nonselective</li></ul>	<b>Selective (Betaxolol)</b> <ul style="list-style-type: none"><li>• Fewer pulmonary side effects</li></ul>
<b>Carbonic Anhydrase Inhibitors</b>			
<b>Topical</b> <ul style="list-style-type: none"><li>• Brinzolamide</li><li>• Dorzolamide</li></ul>	<ul style="list-style-type: none"><li>• BAK</li></ul>	<b>Topical</b> <ul style="list-style-type: none"><li>• Myopic shift</li><li>• Keratitis</li><li>• Dermatitis</li></ul>	<b>Topical</b> <ul style="list-style-type: none"><li>• Bitter taste</li></ul>
<b>Oral</b> <ul style="list-style-type: none"><li>• Acetazolamide</li><li>• Methazolamide</li></ul>		<b>Oral</b> <ul style="list-style-type: none"><li>• None</li></ul>	<b>Oral</b> <ul style="list-style-type: none"><li>• Acidosis, hypokalemia</li><li>• Depression</li><li>• Lethargy</li><li>• Hirsutism</li><li>• Tinnitus</li><li>• Paresthesias</li><li>• Diarrhea</li><li>• Weight loss</li><li>• Altered taste</li><li>• Renal stones</li><li>• Bone marrow suppression</li><li>• Abnormal liver function tests</li></ul>
<b>Alpha-2 Adrenergic Agonists</b>			
<b>Selective</b> <ul style="list-style-type: none"><li>• Apraclonidine</li></ul>	<ul style="list-style-type: none"><li>• BAK</li><li>• Purite (Alphagan P 0.1% and 0.15%)</li></ul>	<b>Selective</b> <ul style="list-style-type: none"><li>• Eyelid retraction</li><li>• Conjunctival blanching</li><li>• Conjunctival folliculosis</li><li>• Dermatitis</li><li>• Cataract</li></ul>	<b>Selective</b> <ul style="list-style-type: none"><li>• Dry mouth and nose</li><li>• Fatigue, somnolence</li><li>• Hyper/hypotension</li></ul>
<b>Highly selective</b> <ul style="list-style-type: none"><li>• Brimonidine</li></ul>		<b>Highly selective</b> <ul style="list-style-type: none"><li>• Less likely to cause above findings</li></ul>	<b>Highly selective</b> <ul style="list-style-type: none"><li>• Same as above but less likely</li></ul>
<b>Cholinergic Agonists</b>			
<ul style="list-style-type: none"><li>• Carbachol</li><li>• Pilocarpine</li></ul>	<ul style="list-style-type: none"><li>• BAK</li></ul>	<ul style="list-style-type: none"><li>• Brow ache</li><li>• Ciliary spasm</li><li>• Myopia</li><li>• Retinal detachment</li><li>• Miosis</li><li>• Cataract</li><li>• Angle closure</li></ul>	<ul style="list-style-type: none"><li>• Increased salivation</li><li>• Diaphoresis</li><li>• Diarrhea, nausea</li></ul>
<b>Hyperosmotic Agents</b>			
<ul style="list-style-type: none"><li>• Mannitol</li><li>• Glycerin</li></ul>	<ul style="list-style-type: none"><li>• N/A</li></ul>	<ul style="list-style-type: none"><li>• Increased aqueous flare</li></ul>	<ul style="list-style-type: none"><li>• Congestive heart failure</li><li>• Electrolyte disturbances</li><li>• Renal failure</li><li>• Nausea, vomiting</li><li>• Headache</li></ul>
<b>Combination Drugs</b>			
<ul style="list-style-type: none"><li>• Timolol/dorzolamide</li><li>• Timolol/brimonidine</li><li>• Brinzolamide/brimonidine</li><li>• Timolol/prostaglandin (not available in U.S.)</li></ul>	<ul style="list-style-type: none"><li>• BAK</li><li>• Preservative-free (Cosopt PF, certain preparations of timolol/prostaglandins)</li></ul>	<ul style="list-style-type: none"><li>• See individual drugs above</li></ul>	<ul style="list-style-type: none"><li>• See individual drugs above</li></ul>
^Many of these medications may cause conjunctival hyperemia, conjunctivitis, blurred vision, eye discomfort, foreign body sensation, dry eye, or allergic reactions; therefore these side effects are not included in the table. BAK, Benzalkonium chloride; CNS, central nervous system.			

Relevant epithelial abnormalities in glaucoma patients include inferior staining associated with medicamentosa reactions, microcystic edema associated with acutely elevated IOP, and the presence of map-dot-finger-print dystrophy, which can be associated with recurrent corneal erosions. The presence of dendrites on the cornea associated with endotheliitis,

elevated IOP, anterior chamber cell and flare, and keratic precipitates should prompt the clinician to think about a possible trabeculitis caused by a herpes simplex virus infection.<sup>79</sup> The presence of circumferential breaks in Descemet's membrane, also called Haab's striae, indicates the presence of glaucoma of infancy. A

distinction should be made between the horizontally oriented Haab's striae and vertically oriented breaks in Descemet's membrane that occur with forceps-related injuries at birth.<sup>80</sup> Haab's striae should also be differentiated from the endothelial bands seen with posterior polymorphous dystrophy representing epithelialization of endothelial cells, which can invade the anterior chamber angle.<sup>81</sup>

Examination of the corneal endothelium can provide important clues regarding secondary forms of glaucoma. The presence of pigment deposition in a spindle configuration over the inferior portion of the endothelium (also called Krukenberg spindle), iris transillumination defects, and deposition of pigment in the lens capsule have been associated with the pigment dispersion syndrome, which in some cases can lead to IOP elevation and development of pigmentary glaucoma.<sup>4</sup> The presence of corneal guttae and endothelial cells should also be noted, especially when one is considering a combined cataract and glaucoma operation in patients with Fuchs' dystrophy.

A beaten bronze appearance to the corneal endothelium with associated corneal guttae and edema, associated iris abnormalities, and elevated IOP should prompt the diagnosis of the Chandler variant of iridocorneal endothelial (ICE) syndrome, which predominantly presents in young female patients with unilateral glaucomas.<sup>82</sup>

The presence of a prominent and anteriorly displaced Schwalbe's line (also called posterior embryotoxon) along with the presence of high peripheral iris–cornea touch, elevated IOP, and associated systemic findings suggests the diagnosis of Axenfeld–Rieger syndrome.<sup>83</sup> It is important to note that posterior embryotoxon can be found in up to 15% of normal eyes.<sup>84</sup>

Anterior Chamber

Examination of the anterior chamber should include an assessment of the anterior chamber depth using the van Herick method<sup>85</sup> (Table 10.4.5), which will be described in more detail later.

The presence of cell and flare should be determined to establish whether IOP elevation is caused by mechanical obstruction of the trabecular meshwork by inflammatory cells, red blood cells, or macrophages (filled with inflammatory debris, pigment, lens material, or protein), because the management of these conditions may differ significantly.<sup>86</sup>

Iris

The pupil shape should be inspected carefully to identify the presence of corectopia, posterior synechiae, ectropion uvea, or irregularities from previous trauma or acute angle-closure attacks. Unilateral corectopia with patchy, irregular iris atrophy associated with elevated IOP should warrant evaluation for essential iris atrophy variant of ICE syndrome.<sup>87</sup> Bilateral cases would suggest congenital Axenfeld–Rieger syndrome.

Assessment of the curvature of the iris and its anatomical relationship to the cornea may help to identify iris bombé. The surface of the iris must also be inspected for the presence of nodules, masses, and inflammatory membranes. Examining the iris using the red reflex as a background source of illumination can also help the clinician determine the presence of iris transillumination defects, such as those seen with the pigment dispersion syndrome,<sup>4</sup> aniridia, sector atrophy with herpes zoster, and the presence of peripheral iridotomies.

Changes in iris color (heterochromia) should prompt the clinician to look for additional signs associated with Fuchs' heterochromic iridocyclitis, which include diffuse white stellate keratic precipitates, iris atrophy, cells in the anterior chamber, and lens opacities.<sup>88</sup> The presence of associated iris surface matting, nodules, stromal atrophy, and corneal edema is suggestive of Cogan–Reese syndrome.<sup>87</sup> Prostaglandin-induced iris heterochromia can also be present and is irreversible, occurs more frequently in two-tone irides (especially hazel), and is thought to be caused by increased melanogenesis.<sup>89</sup>

Patients with pseudoexfoliation syndrome can present with pupillary ruff defects, iris sphincter transillumination, a characteristic whorl-like

pattern of particulate pigment deposition on the iris sphincter, particulate pigment deposition on the peripheral iris and trabecular meshwork, and exfoliation material on the zonules and ciliary body.<sup>90</sup>

Iris neovascularization in its earlier stages usually presents as vascular tufts at the pupillary margin, which can be easily overlooked if high magnification is not used. Its presence strongly warrants examination of the angle for neovascularization. Although neovascularization of the iris typically precedes the angle, up to 10% of patients with central retinal vein occlusions can develop angle neovascularization without the presence of iris vessels.<sup>91</sup>

Lens

Lens examination is performed through a dilated pupil in order to determine the size, clarity, and stability of the lens (phacodonesis). The anterior surface of the lens should be inspected for the presence of glaukomflecken, which are white subcapsular lens opacities seen after an acute angle-closure glaucoma attack. The presence of pseudoexfoliation material<sup>90</sup> should also be apparent to the examiner once the pupil is dilated. In such cases, the integrity of the zonular apparatus and the amount of pupillary dilation should be noted when considering cataract extraction.

In patients with a history of trauma, examination may reveal instability of the lens (phacodonesis, subluxation, dislocation) or the presence of an annular pigment ring (Vossius ring) on the anterior lens capsule.<sup>92</sup>

The presence of a Scheie line, which consists of pigment deposition on the posterior lens capsule behind the lens equator, is usually associated with the pigment dispersion syndrome.

Pseudophakic glaucoma patients should be carefully examined to determine the type of lens implant present, position of the lens, and integrity of the capsular bag and posterior capsule to rule out the presence of iris chafing syndrome.<sup>93</sup>

Gonioscopy

Estimation of the Peripheral Anterior Chamber Angle

The depth of the peripheral anterior chamber can be assessed at the slit lamp using the van Herick method.<sup>85</sup> A narrow slit beam of light is shone at an angle of 60° in a plane perpendicular to the peripheral cornea. The depth of the space between the corneal endothelium and the peripheral iris is estimated in terms of the thickness of the cornea. This method only provides information about the depth of the anterior chamber angle and in no way replaces the information derived from the direct or indirect visualization of the angle using a goniolens. Grading of the anterior chamber angle according to the van Herick method is described in Table 10.4.5.

Principles of Gonioscopy

Gonioscopy is the technique used to examine the anterior chamber angle or iridocorneal angle. The anterior chamber angle is defined as the angle formed between the anterior surface of the iris and the posterior surface of the cornea and comprises the following anatomical landmarks: Schwalbe's line, anterior and posterior trabecular meshwork, scleral spur, and ciliary body band (Fig. 10.4.1). This angle cannot be visualized directly; the light

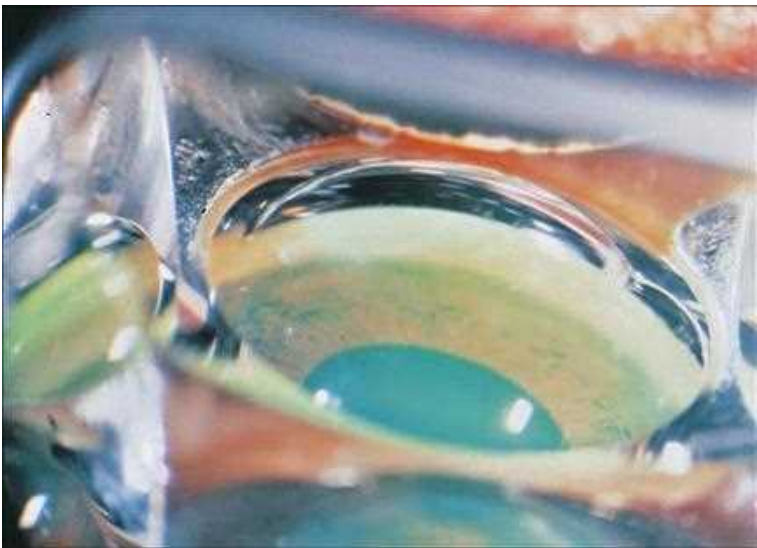


Fig. 10.4.1 The Normal Anterior Chamber Angle. This is viewed through the Zeiss lens. Notice the ciliary body band, scleral spur, and trabecular meshwork.

TABLE 10.4.5 Van Herick Grading System

Grade	Depth of Peripheral Anterior Chamber in Terms of Peripheral Corneal Thickness (PCT)
4	≥1 PCT
3	= ¼ to ½ PCT
2	= ¼ PCT
1	≤¼ PCT
0	Narrowed to a slit or no angle

emanating from the anterior chamber angle has an angle of incidence that exceeds the critical angle of the tear–air interface and thus undergoes total internal reflection back into the eye. In gonioscopy, a direct or indirect goniolens is used to overcome total internal reflection and visualize the iridocorneal angle.

Direct Gonioscopy

Direct gonioscopy is performed with a Koepple lens, a dome-shaped, 50.00 D lens that requires an optical coupling solution. The lens is placed over the cornea while the patient is in the supine position, and a direct (i.e., nonreflected) view of the angle is obtained. Although direct gonioscopy may be performed in the office setting using a Barkan microscope in one hand and a light source in the other, its use is now generally reserved for the operating room, using an operating microscope to examine children and perform certain surgical procedures.

Indirect Gonioscopy

Indirect gonioscopy involves the use of goniolenses with built-in mirrors to facilitate visualization of the iridocorneal angle. These mirrors reflect light originating from the opposite section of the anterior chamber angle. Indirect goniolenses include the Zeiss lens (see Fig. 10.4.1) and the Goldmann lens (Fig. 10.4.2).

The Goldmann lens typically has three built-in mirrors, each providing different levels of magnification. The lens requires a viscous coupling solution and is placed against the anesthetized cornea. Lens placement is facilitated by asking the patient to look upward and gently inserting the inferior rim of the lens into the lower fornix. After the lens is in place, the patient is instructed to look forward. With the room lights dimmed and the slit-lamp beam narrowed and shortened (to avoid light entering the pupil), the mirror of the goniolens is illuminated. Visualization of the angle may be optimized by asking the patient to look in the direction of the mirror being examined or gently tilting the lens. The lens is rotated to examine the remaining clock hours of the angle.

The Zeiss lens is a four-mirror lens and is distinguished from the Goldmann lens in three important ways: (1) it does not require a coupling solution; (2) its four mirrors allow visualization of four angle quadrants without rotation of the lens; and (3) it can be used to perform indentation gonioscopy. The initial steps are similar to Goldmann gonioscopy. The lens is placed gently on the center of the cornea, and each angle quadrant is visualized by illuminating the opposite mirror. In the same fashion as the Goldmann lens, asking the patient to look in the direction of the mirror or tilting the lens can enhance the examiner’s view of the angle. The Zeiss lens has a contact surface that is smaller than the diameter of the cornea. This allows for dynamic compression of the cornea, a technique known as indentation gonioscopy. Applying pressure to the cornea will result in displacement of aqueous humor within the anterior chamber and posterior displacement of the peripheral iris, widening of the anterior chamber angle. Indentation gonioscopy allows the clinician to differentiate between appositional closure and synechial closure of the anterior chamber angle; in the latter, indentation will not lead to widening of the angle.<sup>94</sup>

The Zeiss lens may be mounted on a holding fork. Modified Zeiss lenses include the handheld Sussman lens, which is held between the fingers, and the Posner lens, which uses a handle.



Fig. 10.4.2 The Goldmann Lens.

Gonioscopic Grading Systems  
Gonioscopic Anatomy of the Angle

The anatomical landmarks of the anterior chamber angle help orient the examiner and provide important clues for proper grading and description of the angle. When performing gonioscopy, the examiner should identify these landmarks, estimate the angle between the peripheral iris and the cornea, evaluate the insertion and contour of the iris, and note the degree of posterior trabecular meshwork pigmentation.

Several gonioscopic grading systems have been described, among which the two most common are the Shaffer and Spaeth systems.

Shaffer System

The Shaffer system describes the gonioscopic findings in terms of the angular width of the anterior chamber and has a grading system ranging from closed (grade 0) to wide open (grade 4). The angle width is defined by two lines, one extending anteriorly from the point of iris insertion to Schwalbe’s line and the other extending across the surface of the iris from the point of iris insertion.<sup>95</sup> Table 10.4.6 summarizes this system.

Spaeth System

The Spaeth system<sup>96</sup> provides a more complete description of the anterior chamber angle, which includes: (1) the level of iris insertion; (2) the geometric angle formed by the intersection of a line tangential to the trabecular meshwork with a line tangential to the surface of the iris (measured at the point of Schwalbe’s line); (3) the peripheral iris contour; and (4) the degree of pigmentation of the posterior trabecular meshwork (Table 10.4.7). Typically, separate grading of each quadrant is performed.

In addition, the Spaeth classification also uses the dynamic information obtained from indentation gonioscopy, allowing the examiner to differentiate between appositional and synechial closure of the angle (Fig. 10.4.3). The examiner describes the apparent iris insertion as it is first seen and then uses indentation gonioscopy to determine the actual insertion of the iris.

Occludable Angles

Defining an occludable angle is difficult and no standard interpretation exists. Any evidence of peripheral anterior synechiae formation in the setting of gonioscopic narrow angles is suggestive of the development of angle-closure glaucoma and warrants a laser peripheral iridectomy. Based on the Spaeth classification, an eye with an iris insertion of either A or B

TABLE 10.4.6 The Shaffer Angle Grading System

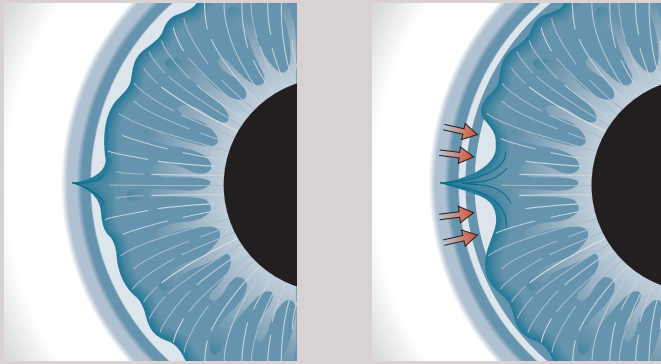
Grade	Angle Width	Description	Risk of Closure
4	35°–45°	Wide open	Impossible
3	20°–35°	Wide open	Impossible
2	10°–20°	Narrow	Possible
1	≤10°	Extremely narrow	Probable
0	0°	Closed	Closed

TABLE 10.4.7 The Spaeth Angle Grading System

Insertion of the Iris
A: Anterior to Schwalbe’s line
B: Between Schwalbe’s line and posterior edge of trabecular meshwork
C: Scleral spur visible
D: Deep, ciliary body visible
E: Extremely deep, >1 mm of ciliary body visible
The <i>apparent</i> insertion ( <b>prior</b> to indentation) is written as (A), (B), or (C)
The <i>true</i> insertion is written without parentheses, e.g., A, B, C, D, E
Iris Angularity (in Degrees)
Possible grades: 0, 5, 10, 15, 20, 25, 30, 35, 40, 45, 50
Iris Curvature
f: flat
b: bowed anteriorly
p: plateau configuration
c: concave posterior bowing
Pigmentation of the Posterior Pigmented Trabecular Meshwork
Pigmentation is graded as 0 (no pigmentation), 1+ (just visible), 2+ (mild), 3+ (marked), or 4+ (intense)
An example of an angle classified by the Spaeth system is (B)C40f 2+. This means that without indentation, the iris insertion is seen anterior to the scleral spur, but after indentation, the scleral spur is visible. The angular width is 40°; the iris has a flat shape; and there is mild pigmentation of the trabecular meshwork.



PORTION OF ANGLE WITH A SYNECHIA AND AREA OF APPOSITIONAL CLOSURE



**Fig. 10.4.3** Portion of Angle With a Synechia and Area of Appositional Closure. Angle view with and without indentation gonioscopy.



**Fig. 10.4.4** Broad Peripheral Anterior Synechiae With Angle Closure.

or an angle of  $10^{\circ}$ – $20^{\circ}$  with a very bowed contour may benefit from a laser iridectomy.<sup>97</sup> Other definitions of an occludable angle include angles with a width of  $20^{\circ}$  or less (Shaffer  $\leq 2$ ) or angles where the posterior trabecular meshwork is visible in less than  $90^{\circ}$  of the angle circumference.<sup>98</sup>

### Specific Findings of the Anterior Chamber Angle

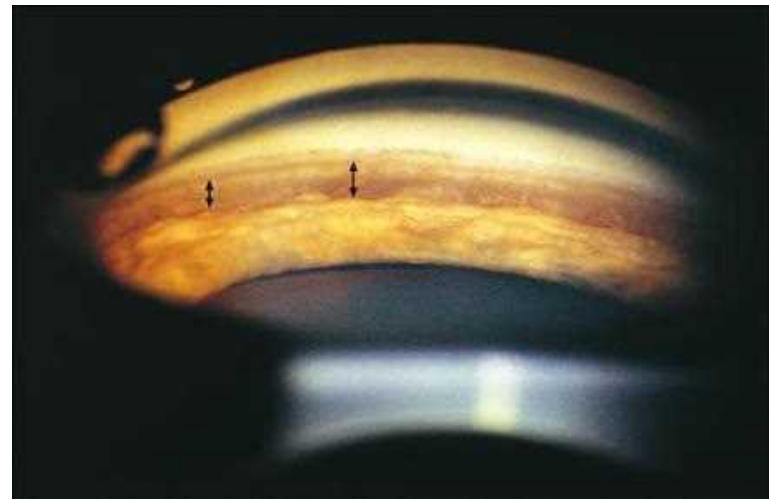
Common gonioscopic findings such as nonuniform iris insertion, peripheral anterior synechiae (Fig. 10.4.4), angle recession (Fig. 10.4.5), cyclodialysis cleft, increased pigmentation of the angle (Fig. 10.4.6), Sampaoles's line, blood vessels in the angle (Fig. 10.4.7), and blood in Schlemm's canal are listed with possible associations in Table 10.4.8.

## Optic Nerve Examination

The examination of the optic nerve probably represents the most important element of the clinical evaluation of the glaucoma patient because structural changes in the optic disc can precede detectable visual field loss in glaucoma.<sup>99</sup> The optic nerve is usually described using the cup-to-disc ratio (CDR) introduced by Armaly in 1967.<sup>100</sup> The CDR is based on the results of three population studies that concluded that the CDR is genetically inherited, symmetric between the two eyes, and not influenced by age.<sup>100</sup> Measurements of the CDR have been shown to have large interobserver variations, likely attributable to differences in definitions and examination methods.<sup>101</sup>

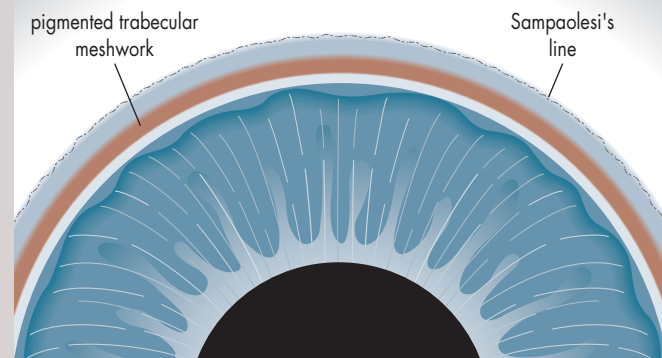
Using CDR alone is not sufficient and has the following limitations:

- It focuses only on the cup size.
- Disc size is not taken into consideration.

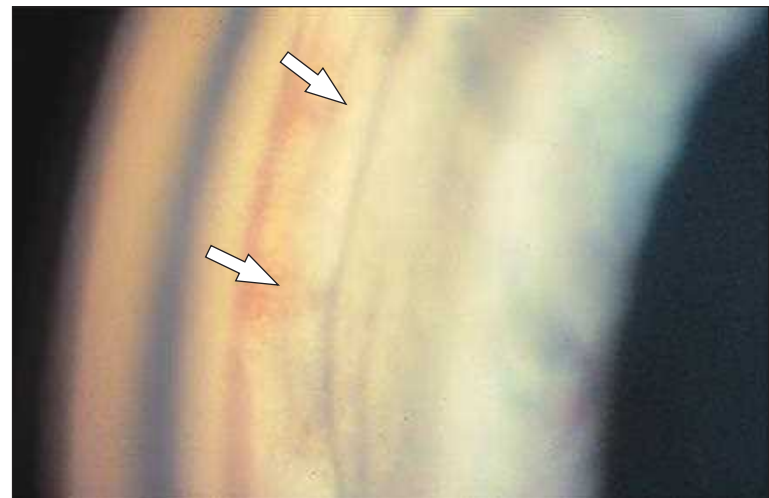


**Fig. 10.4.5** Angle Recession (arrows).

DARKLY PIGMENTED TRABECULAR MESHWORK



**Fig. 10.4.6** Darkly Pigmented Trabecular Meshwork.



**Fig. 10.4.7** Neovascularization of an Angle (arrows).

- Focal changes occurring in the neuroretinal rim are not described.
- A disc with a “normal” CDR may have focal thinning or notching.

The size of the optic disc must always be considered when evaluating a patient for glaucoma. Large discs are known to have larger cups and narrower neuroretinal rims without being considered pathological; in contrast, small discs with large cups are usually pathological.

Assessment of the neuroretinal rim has a high diagnostic value in differentiating between normal and glaucomatous discs.<sup>102</sup> An optic nerve head with a normal CDR may have an eccentric cup with a localized neuroretinal rim notch. There is a close relationship between the morphology of the neuroretinal rim and corresponding visual field defects.<sup>103</sup> The neuroretinal rim is defined as the tissue between the disc margin and outer

TABLE 10.4.8 Common Gonioscopic Findings

Common Gonioscopic Findings	Possible Associations
Nonuniform iris insertion	PAS, iris cyst, ciliary body cyst, abnormalities in lens position
PAS (adhesions between the peripheral iris and angle wall)	Distinguish from nonpathological iris processes that are fine, not broad, and do not extend into trabecular meshwork Angle-closure glaucoma, uveitis, neovascularization of the angle, ICE, Axenfeld–Rieger syndrome
Angle recession (posterior displacement of the iris root due to separation of the circular and longitudinal fibers of the ciliary muscle)	Blunt trauma May result in increased intraocular pressure and secondary glaucoma
Cyclodialysis cleft (disinsertion of ciliary body from scleral spur)	Blunt trauma, surgical complication May lead to hypotony
Increased pigmentation of the angle	Pigment dispersion syndrome, pseudoexfoliation syndrome, iris melanoma, trauma, pseudophakic iris chafing syndrome
Sampaolesi’s line (pigment deposition just anterior to Schwalbe’s line)	Pseudoexfoliation syndrome
Blood vessels in the angle	Normal blood vessels are radially oriented, do not arborize, and do not cross the scleral spur Pathological blood vessels are fine, arborizing, and invade the iris surface and extend over the trabecular meshwork to Schwalbe’s line in a nonspecific pattern (see Fig. 10.4.7) Ischemia, e.g. ocular ischemic syndrome, retinal vein occlusion Fuchs’ heterochromatic iridocyclitis
Blood in Schlemm’s canal	Episcleral venous pressure (normal 8–10 mm Hg) that exceeds intraocular pressure Carotid-cavernous fistula, Sturge–Weber syndrome, thyroid ophthalmopathy, superior vena cava syndrome, orbital varices, ocular hypotony











ICE, Iridocorneal endothelial syndrome; PAS, peripheral anterior synechiae.

limits of the optic cup. The “ISNT rule” (which states that, in a normal eye, the neuroretinal rim width follows a characteristic pattern of Inferior ≥ Superior ≥ Nasal ≥ Temporal) may be helpful as a general principle to differentiate normal from glaucomatous nerves, but clinicians should remember that there are many exceptions that do not follow this pattern. Further, closely observing the curvature of blood vessels can aid in identifying the inner edge of the neuroretinal rim.

Based on the limitations of the CDR, several other disc-grading systems have been developed. Among them, the disc damage likelihood scale (DDLS)<sup>104</sup> developed by Spaeth arguably offers the most complete assessment of the optic nerve. The DDLS stages glaucomatous optic nerve damage based on the narrowest width of the neuroretinal rim or, if no rim is present, the circumferential extent of rim absence. This grading system also takes into account the size of the optic disc. The DDLS uses a scoring system ranging from 1 to 10, where 1 is a disc with a low likelihood of glaucomatous damage and 10 represents a severely damaged disc (Table 10.4.9).

The DDLS has several advantages.<sup>104</sup> It has been shown to (1) have a higher intra- and interobserver reproducibility than the CDR system; (2) strongly correlate with visual field changes in patients with glaucoma; and (3) have the best predictive ability to identify glaucomatous damage in comparison with the CDR system and structural imaging with Heidelberg retina tomography (HRT).<sup>105</sup> In addition, the DDLS score can be plotted against the patient’s age and can be used as a means of following the

TABLE 10.4.9 The Disc Damage Likelihood Scale (DDLS)

	DDLS Stage	Narrowest Rim Width (rim/disc ratio) (Average Disc Size: 1.50–2.00 mm)	Example
At risk	1	0.4 or more	
	2	0.3 to 0.39	
	3	0.2 to 0.29	
	4	0.1 to 0.19	
Glaucoma damage	5	less than 0.1	
	6	0 (extension: less than 45°)	
	7	0 (extension: 46°–90°)	
Glaucoma disability	8	0 (extension: 91°–180°)	
	9	0 (extension: 181°–270°)	
	10	0 (extension: more than 270°)	

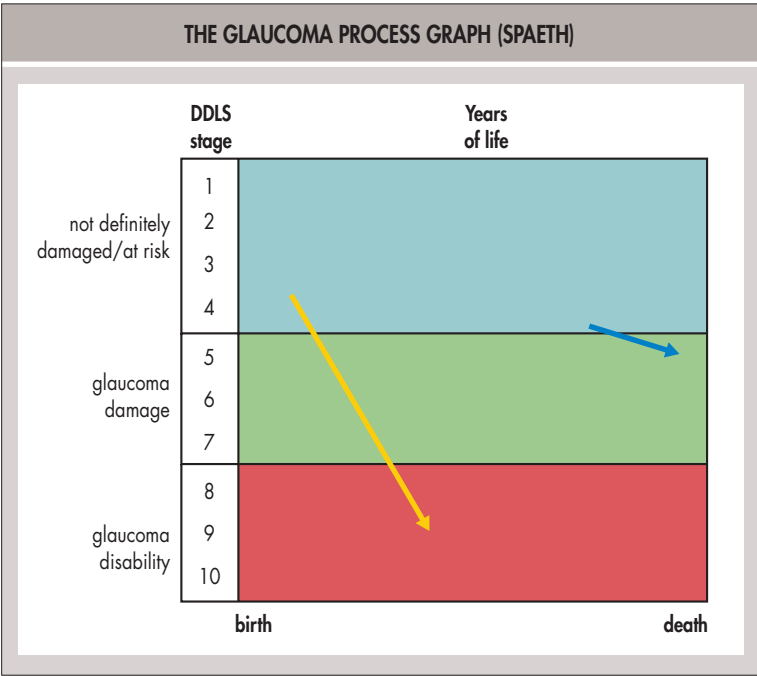
For small discs (diameter <1.5 mm) the DDLS stage should be increased by 1, for large discs (diameter >2.0 mm) the DDLS stage should be decreased by 1, and for very large discs (diameter >3.0 mm), the DDLS stage should be decreased by 2.

rate of change of the optic nerve and progression of glaucoma over time (Fig. 10.4.8).

Lastly, the clinician should also assess for the presence of other key qualitative optic nerve findings including wedge-shaped RNFL defects, splinter or flame-shaped disc hemorrhages, acquired pit of the optic nerve, visibility of the pores of the lamina cribrosa, nasal shift of the central retinal vessels, peripapillary atrophy, and optic disc pallor.

TESTING FOR GLAUCOMA

Several ancillary diagnostic methods can assist the physician by complementing the clinical evaluation of the glaucoma patient. These technologies include ultrasound biomicroscopy, automated perimetry, scanning laser ophthalmoscopy, and optical coherence tomography, among others. These technologies are presented at length in other chapters of this book and will not be discussed here.



**Fig. 10.4.8 The Spaeth Colored Glaucoma Graph.** By plotting the patient’s disc damage likelihood scale (DDLS) stage on this graph, the clinician can monitor progression of disc damage. When combined with estimates of life expectancy, extrapolations of the progression curve can assist the clinician in formulating individualized treatment strategies. The yellow line represents the expected disease trajectory of an individual with early onset, rapidly progressing glaucoma, and the blue line represents the expected disease trajectory of an individual with late onset, slowly progressing glaucoma. The clinician should constantly reassess a patient’s expected disease trajectory at every visit and plan treatment accordingly. In the above figure, the yellow line shows a much steeper and earlier descent into disability compared to the blue line, and therefore warrants a markedly different treatment regimen.

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# Visual Field Testing in Glaucoma

Donald L. Budenz, John T. Lind

# 10.5

**Definition:** A diagnostic test critical to the diagnosis and management of glaucoma that measures visual function by assessing sensitivity to light at various points in the field of vision.

## Key Features

- A stimulus of specific size and intensity projected onto a background of standard luminance.
- The threshold light intensity eliciting response to the stimulus is measured at points throughout the field of vision via patient response.

## Associated Features

- Standard automated perimetry uses white light on a white or gray background.
- Short wavelength automated perimetry uses blue light on a yellow background.
- Frequency-doubling technology.
- Testing algorithms—SITA, TOP.
- Software to compare patient to the healthy population (normative database) and measure magnitude and location of any deviation from normal.
- Software to compare multiple tests to assess progression over time.

## INTRODUCTION

Testing of the visual field is the primary method of assessing visual function in glaucoma patients and glaucoma suspects. Because central visual function is most commonly lost late in glaucoma, central visual acuity is a poor test of visual function in glaucoma. Visual field testing is used in three distinct ways in glaucoma evaluation and management: diagnosis, assessment of severity, and determination of progression.

Automated static perimetry using a white stimulus projected onto a white background—also called standard automated perimetry (SAP)—has become the most commonly performed visual field test in glaucoma for a variety of reasons. First, it is more sensitive to early defects than manual kinetic perimetry. Second, since it is computerized, there is less variation in the way the test is performed from operator to operator. Third, statistical programs can be used to do important tasks such as comparing the patients' responses to a normal group of subject responses, subtract out the effect of diffuse depression on the field as occurs in cataract, and provide information on progression. While manual kinetic perimetry is still performed in rare cases, most offices no longer have the equipment or personnel trained in this technique. Instances where manual kinetic perimetry can be useful includes patient with a history of unreliable SAP testing, patients that need to be coached through the test (children of young ages or the elderly), or patients who have difficulty with the standard testing apparatus. And although newer automated techniques such as short wavelength automated perimetry (SWAP) and frequency-doubling technology (FDT) may provide supplemental information in very early cases (both) or in community screening programs, SAP remains the gold standard for assessing visual function in the clinical practice of glaucoma.

## STANDARD AUTOMATED PERIMETRY

### Testing Algorithms in Standard Automated Perimetry

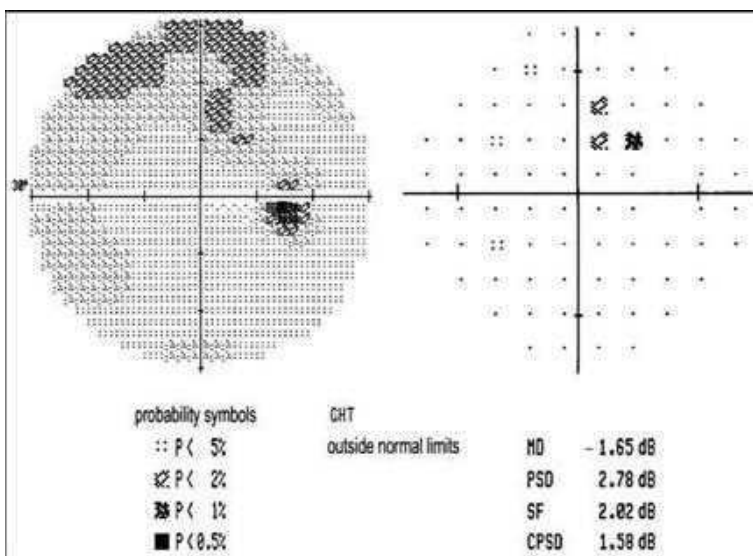
There are a number of different ways to test the visual system's sensitivity to light. Suprathreshold tests present a stimulus brighter than usually seen at a particular location by a normal subject of a particular age and determine whether the subject being tested can see it or not. The actual sensitivity to light is not determined. Suprathreshold testing may be appropriate in a community screening setting or when assessing neuro-ophthalmic, retinal disease, or visual disability (the binocular Esterman field) but is not recommended for glaucoma diagnosis or follow-up. Full-threshold testing is a trial-and-error system whereby stimuli are shown and then increased or decreased in intensity until an estimate is made of the amount of light that can be seen approximately 50% of the time. Full-threshold testing requires greater testing time, and this can result in fatigue effect and false-positive testing. To shorten the test and improve efficiency, the Swedish Interactive Threshold Algorithm (SITA) was developed for the Humphrey Field Analyzer (Carl Zeiss Meditec, Dublin, CA, USA) and the tendency-oriented perimetry (TOP) strategy for the Octopus perimeter (Haag Streit, Berne, Switzerland). There are two SITA programs to choose from: SITA Standard and SITA Fast. With respect to the diagnosis and follow-up of glaucoma, the SITA Standard algorithm is preferred because it appears to give the right balance between sensitivity and specificity while reducing test-taking time by approximately 50% in normal and glaucoma subjects.<sup>1</sup> There is some evidence, however, that the SITA Fast algorithm is more reproducible, which may make it better for following established glaucoma.<sup>2</sup> From a practical standpoint, it is important to stay with the same perimeter and program to follow established glaucoma patients because comparisons between visual field tests performed with different perimeters or algorithm is difficult in judging progression.

### Visual Field Testing and Glaucoma Diagnosis

Visual field testing is critical in the diagnosis of glaucoma. Because of the wide variation in the appearance of the optic disc, it is often difficult to be certain that a patient has glaucoma based on a single observation of the disc in time. Even patients with a cup-to-disc ratio of 0.9 may not have glaucoma. Changes in the optic disc appearance in the form of focal or diffuse loss of neuroretinal rim resulting in an increase in the cup, while diagnostic for glaucoma, generally take years to develop. It is difficult to document this change without serial stereoscopic photographs of the optic disc. Even with optical coherence tomography (OCT), there can be intra- and intersession variability, which makes diagnosis and evaluation for progression challenging. For these reasons, testing visual function with the visual field is a helpful diagnostic tool, although perhaps less sensitive than observed changes to the optic disc or retinal nerve fiber layer, at least with standard white-on-white perimetry. However, in severely cupped nerves, structural identifiers of progression may be nearly impossible to discern, thus placing a much large burden for determining progression on perimetry.

Box 10.5.1 provides a guideline for minimal abnormality on a visual field required to make the diagnosis of glaucoma by SAP. The first two criteria, abnormal glaucoma hemifield test and pattern standard deviation, were used in the Ocular Hypertension Treatment Study (OHTS) as visual field endpoints for the development of primary open-angle glaucoma.<sup>3</sup> The latter criterion, pointwise analysis, may be more sensitive to very early defects. If any of the three criteria listed are present in the absence of other causes—such as nonglaucomatous optic neuropathies or posterior segment pathology (particularly retinal vascular occlusions)—then the





**Fig. 10.5.1 Early Paracentral Scotoma From Glaucoma.** A cluster of three or more points in the expected area of the visual field, all with  $P$  values  $<5\%$ . MD, Mean deviation; PSD, pattern standard deviation.

#### BOX 10.5.1 Minimal Abnormality for Glaucomatous Visual Field Defect<sup>9</sup>

- Abnormal glaucoma hemifield test
- Pattern standard deviation abnormal at  $P < 5\%$  level
- Cluster of 3 or more points on pattern deviation plot abnormal at  $P < 5\%$  level, at least 1 at the  $P < 1\%$  level in an expected area of the visual field

If any one of the above criteria is met, glaucoma should be suspected provided that the visual field defect is repeatable on a second visual field test in a similar location and is not attributable to other pathological findings such as nonglaucomatous optic neuropathy or chorioretinal disease.

From Hodapp E, Parrish RK, Anderson DR. Clinical decisions in glaucoma. St Louis: Mosby; 1993.

#### BOX 10.5.2 Characteristics of Glaucomatous Visual Field Defects

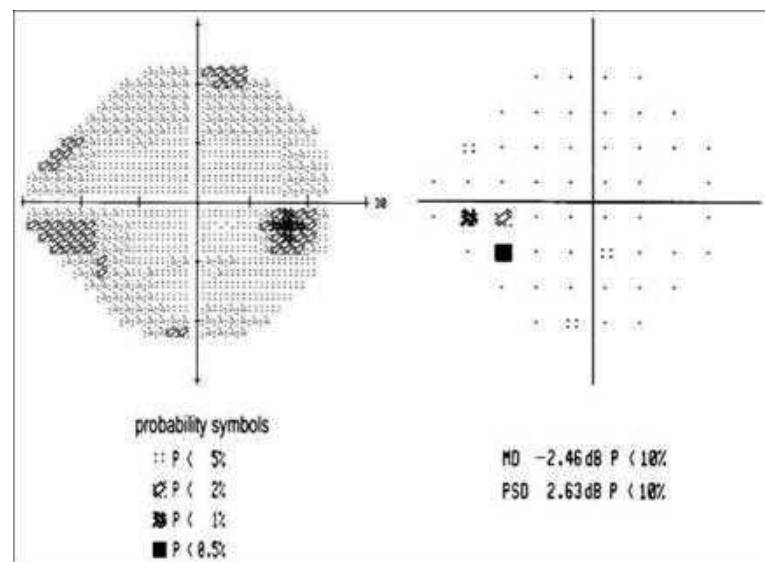
- Almost always localized
- Respect horizontal meridian
- Begin nasal to the blind spot
- Almost always detectable within the central  $30^\circ$

diagnosis of glaucoma should be considered. Typically, but not always, there will be corresponding thinning of the nerve fiber layer or cupping of the optic nerve that correlates well with the defect found on the visual field. False-positive testing in glaucoma suspects and ocular hypertensives has been found to be fairly common, so repeat testing of a suspected early visual field defect is important before concluding that glaucoma is present. In the OHTS, for instance, 86% of suspected new visual field defects disappeared on repeat testing.<sup>4</sup>

Although diffuse depression of the visual field may rarely occur as an early change in glaucoma,<sup>5</sup> most defects are localized, taking the form of a paracentral scotoma (Fig. 10.5.1) or nasal step (Fig. 10.5.2). The best place to look for early glaucomatous visual field defects is the pattern deviation plot rather than the graytone printout or total deviation plot. As glaucoma progresses, these defects typically enlarge and coalesce into arcuate defects corresponding to thinning of the retinal nerve fiber layer. Characteristics typical of glaucomatous visual field defects are listed in Box 10.5.2. Types of glaucomatous visual fields are listed in Box 10.5.3.

### Visual Field and Assessing the Severity of Glaucoma

The severity of visual field defects can be used to assess functional damage to the visual system from glaucoma. This is important to determine the



**Fig. 10.5.2 Early Nasal Step From Glaucoma.** The cluster criterion is met.

#### BOX 10.5.3 Types of Visual Field Defects Commonly Seen in Glaucoma Patients

- Nasal step
- Arcuate defect
- Altitudinal defect
- Paracentral defect
- Temporal wedge
- Generalized depression

aggressiveness of initial therapy (the worse the visual field, the greater the need for intraocular pressure lowering) and to assess the success of ongoing treatment. (Patients who go from moderate to severe visual field defect under treatment, for example, might require more aggressive therapy.)

There are several visual field severity grading scales, including those used in the Advanced Glaucoma Intervention Study,<sup>6</sup> the Collaborative Initial Glaucoma Treatment Study,<sup>7</sup> the Glaucoma Staging System developed by Brusini and colleagues,<sup>8</sup> and the Hodapp–Anderson–Parrish system.<sup>9</sup> We prefer to use an expanded version of visual severity scale proposed by Hodapp, Anderson, and Parrish shown in Table 10.5.1 for the Humphrey Field Analyzer and Table 10.5.2 for the Octopus perimeter.<sup>10</sup> This scale is easy to use in clinical practice, captures the full range of stages in glaucoma progression, and is based on three distinct features of the visual field that should be assessed when deciding on the severity of the functional loss, which include the size of the defect, the depth of the defect, and the proximity of the defect to fixation. It is important to note that all of these severity scales are arbitrary and are not validated by correlation with the severity of axonal loss in the retinal nerve fiber layer—but they serve as important tools in assessing the severity of functional loss in glaucoma.

Figs. 10.5.1 and 10.5.2 are both examples of early visual field defects. Figs. 10.5.3 and 10.5.4 are examples of moderate visual field defects. Figs. 10.5.5 and 10.5.6 are examples of advanced and severe visual field defects, respectively. The pattern of visual field progression in glaucoma from early to severe is predictable in light of the pattern of thinning of the retinal nerve fiber layer, which usually begins with the superior and inferior arcuate fibers, then the papillomacular bundle, and finally the nasal fibers. When the arcuate fibers are lost, the visual field shows only the central and temporal islands remaining, which correspond to the remaining papillomacular and nasal fibers. The next fibers to be lost are typically the papillomacular fibers, which results in central visual acuity loss and eccentric fixation.

In very severe glaucoma, when the majority of the points are depressed to 15 dB or less, special testing is helpful. Fig. 10.5.6 is an example of a visual field defect that is so severe that it is impossible to tell whether points are worsening because most of the values are 0 dB. Increasing to a size V stimulus, retesting the visual field with a size III stimulus using the 10–2 program (thus testing many locations within the central  $10^\circ$ ), or using the macula test (which double determines 16 points in the central  $5^\circ$  using a size III stimulus) are three ways of improving the chance of determining

whether the visual field is worsening in such a patient. Increasing the stimulus size from size III to a size V increases the patient’s ability to see the stimuli and therefore increases the dynamic range of possibilities for responses, thus making progression more easily detected. One can even perform a 10° field with a size V stimulus. Fig. 10.5.7 shows visual field testing performed using these methods in the same patient with severe glaucoma. As a last resort, Goldmann kinetic perimetry may be employed in patients with severe visual field defects, although few offices still have the equipment or technical expertise to perform these tests.

While 10–2 testing strategies have been used traditionally in severe glaucoma, the testing strategy can be used at any stage of the disease. In a review of 35 patients with mild glaucomatous damage, Ancil and Anderson

describe decreased foveal sensitivity in 15 of these patients.<sup>11</sup> Testing the central 10° of vision inpatients with pre-existing paracentral glaucoma has been shown to detect progression at a higher rate than continuing with standard 24–2 testing strategies. Focused testing on the central 10° can aid in glaucoma diagnosis and longitudinal surveillance for progression.<sup>12</sup>

Visual Field and Assessing Progression in Glaucoma

Glaucoma progression is due to the death of retinal ganglion cells and their axons, which usually results in peripheral—followed by central—vision

TABLE 10.5.1 Visual Field Severity Grading System for the Humphrey Visual Field Analyzer (Stages 0–5) <sup>a</sup>	
Stage 0: No or Minimal Defect/Ocular Hypertension	
Does not meet any criteria for stage 1	
Stage 1: Early Defect	
MD ≤−6.00 dB and at least one of the following:	
A	On pattern deviation plot, there exists a cluster of 3 or more points in an expected location of the visual field depressed below the 5% level, at least 1 of which is depressed below the 1% level
B	Corrected pattern standard deviation/pattern standard deviation significant at $P < 0.05$
C	Glaucoma hemifield test “outside normal limits”
Stage 2: Moderate Defect	
MD of −6.01 to −12.00 dB and <i>at least one of the following</i> :	
A	On pattern deviation plot, greater than or equal to 25% but fewer than 50% of points depressed below the 5% level, and greater than or equal to 15% but fewer than 25% of points depressed below 1% level
B	At least 1 point within central 5° with sensitivity of <15 dB but no point within central 5° with sensitivity of <0 dB
C	Only 1 hemifield containing a point with sensitivity <15 dB within 5° of fixation
Stage 3: Advanced Defect	
MD of −12.01 dB to −20.00 dB and <i>at least one of the following</i> :	
A	On pattern deviation plot, greater than or equal to 50% but fewer than 75% of points depressed below the 5% level and greater than or equal to 25% but fewer than 50% of points depressed below 1% level
B	Any point within central 5° with sensitivity of <0 dB
C	Both hemifields containing a point(s) with sensitivity <15 dB within 5° of fixation
Stage 4: Severe Defect	
MD of −20.00 dB and at least one of the following:	
A	On pattern deviation plot, greater than or equal to 75% of points depressed below the 5% level and greater than or equal to 50% of points depressed below 1% level
B	At least 50% of points within central 5° with sensitivity of <0 dB
C	Both hemifields containing greater than 50% of points with sensitivity <15 dB within 5° of fixation
Stage 5: End-stage Disease	
Unable to perform Humphrey visual fields in “worst eye” due to central scotoma or “worst eye” visual acuity of 20/200 or worse due to primary open-angle glaucoma. “Best eye” may be any stage.	
MD, Mean deviation. From Mills RP, Budenz DL, Lee PP, et al. Categorizing the stage of glaucoma from pre-diagnosis to end-stage disease. Am J Ophthalmol 2006;141:24–30.	

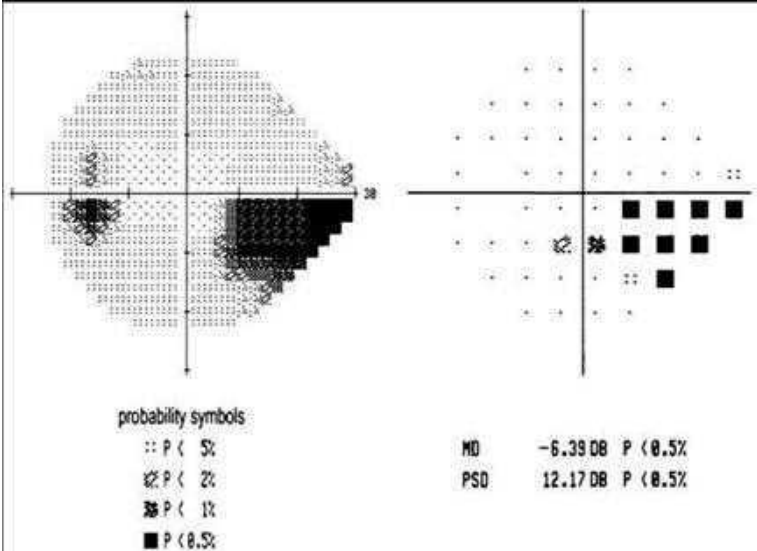


Fig. 10.5.3 Moderate Inferior Arcuate Visual Field Defect From Glaucoma.

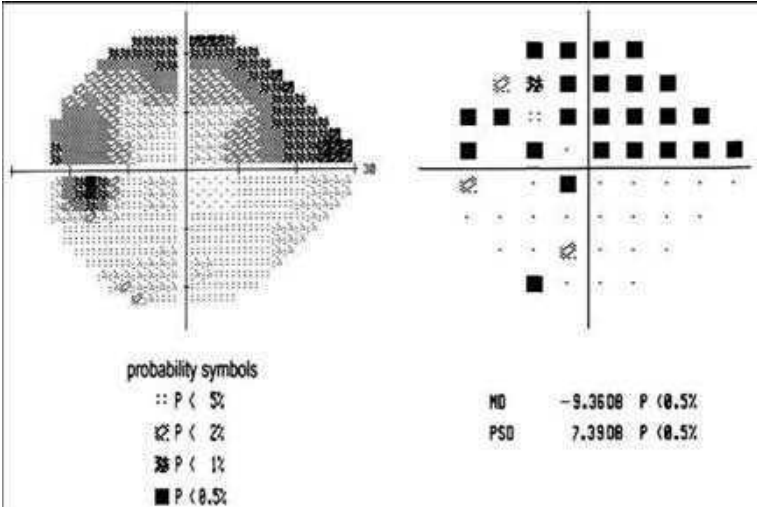
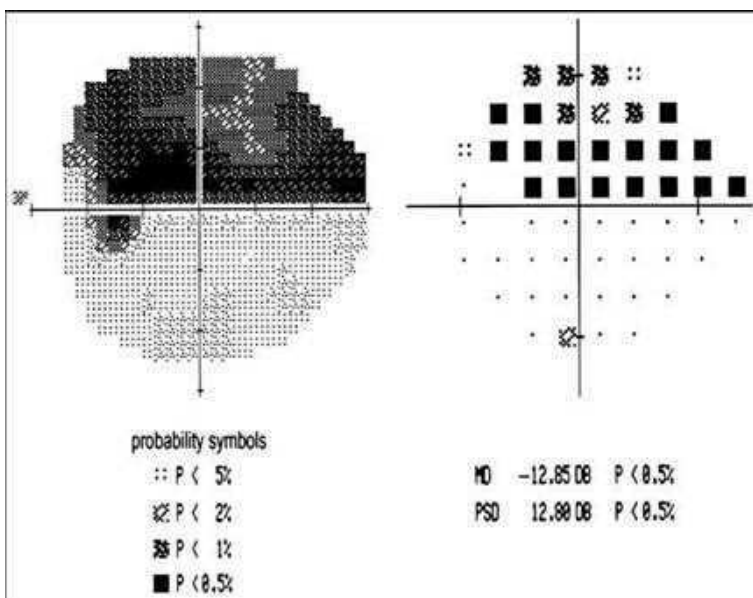
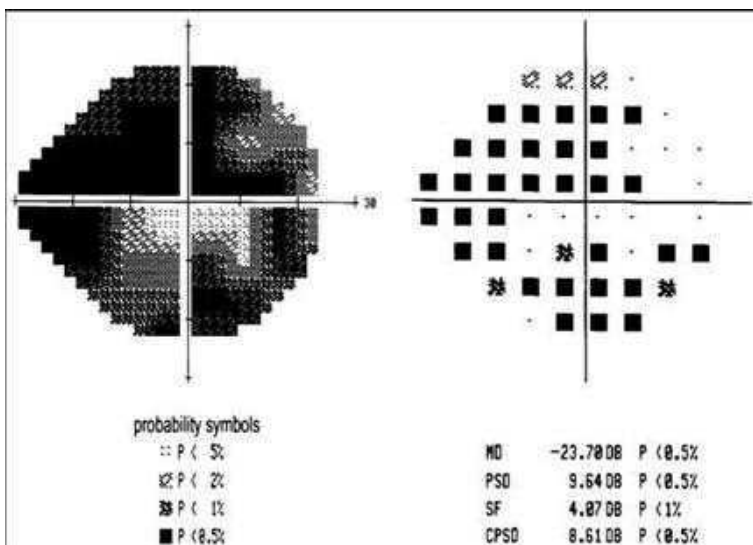


Fig. 10.5.4 Moderate Superior Arcuate Defect From Glaucoma Splitting Fixation.

TABLE 10.5.2 Visual Field Severity Grading System for the Octopus Perimeter (Stages 0–5)		
Stage	Octopus MD Score	Probability plot/pattern deviation The N-Value in the Bebie Curve up to 50 (up to 100) Where the Lower Confidence Limit Line Intersects with the Patient Line
Stage 0: Ocular hypertension/earliest glaucoma	≤−.08	51 and above (101 and above)
Stage 1: Early glaucoma	−0.7 to +4.4	41–50 (81–100)
Stage 2: Moderate glaucoma	+4.5 to +9.5	31–40 (51–80)
Stage 3: Advanced glaucoma	+9.5 to +15.3	21–30 (41–50)
Stage 4: Severe glaucoma	+15.4 to +23.1	11–20 (21–40)
Stage 5: End-stage glaucoma/blind	≥+23.2	≤10 (≤20) or Octopus VF not possible attributable to scotoma in “worst” eye or “worst” eye with acuity of 20/200 or worse due to glaucoma
MD, Mean deviation; VF, visual field. If probability plot is in a less severe stage than preliminary MD stage, then qualify VF as a less severe stage If probability plot is in a more severe stage than preliminary MD stage, then qualify VF as a more severe stage If no intersection of patient line and lower confidence limit, must qualify VF as one stage more than preliminary MD score From Mills RP, Budenz DL, Lee PP, et al. Categorizing the stage of glaucoma from pre-diagnosis to end-stage disease. Am J Ophthalmol 2006;141:24–30.		



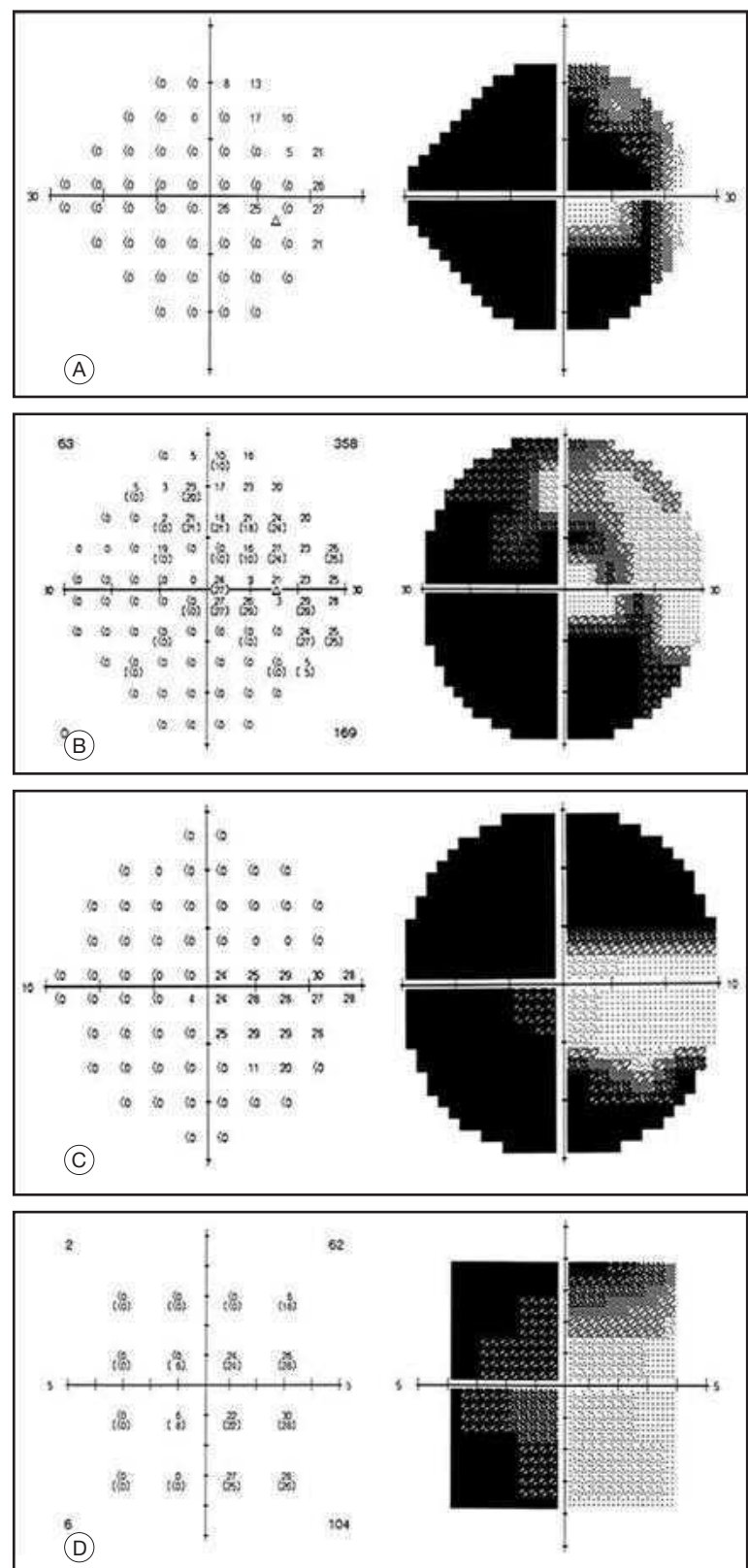
**Fig. 10.5.5** Severe Superior Arcuate Defect Splitting Fixation. Note temporal sparing.



**Fig. 10.5.6** Visual Field of the Left Eye of a Glaucoma Patient. Severe double arcuate scotomas have left the patient with central and temporal islands of vision only. Temporal sparing is common in end-stage glaucoma, which may help distinguish this type of field defect from those associated with nonglaucomatous optic neuropathies.

loss. Assessment of changes in the visual field, optic disc, and retinal nerve fiber layer are the primary ways one diagnoses progression in glaucoma. It is generally believed that structural changes in the optic nerve and retinal nerve fiber layer can be detected before functional changes with SAP, although the Early Manifest Glaucoma Trial found all of their progressive cases except one with SAP rather than optic disc photographs evaluated with flicker chronoscopy.<sup>13</sup> It is possible that with more sensitive functional testing, such as short wavelength automate perimetry, frequency-doubling technology, and pattern electroretinography, functional changes may be found concurrently with structural changes. More research is needed in this area. In clinical practice, following SAP for signs of change is critical in the management of glaucoma and is typically performed every 6–12 months, or more frequently if glaucoma is poorly controlled or rapidly progressive.<sup>14</sup>

There are several ways in which a visual field defect can progress in glaucoma. In the rare case that diffuse depression of the visual field is the only type of field defect, the diffuse depression can get worse or show signs of a new localized defect within the diffuse depression. Localized defects can enlarge or deepen, and finally a new distinct localized defect can appear. In the latter case, the cluster criteria described in [Box 10.5.1](#) are used. When looking for enlarging or deepening of existing defects, one can apply numerical pointwise criteria such as are used in the Collaborative



**Fig. 10.5.7** Advanced Visual Field Testing in a Patient With Severe Glaucoma. The initial visual field, performed using the 24-2 program with a size III stimulus, is so severely depressed that there are too few points to follow for future progression (A). Increasing the stimulus to size V provides more points for comparison and quadrant totals (B), although there are no specific recommendations on what constitutes significant change on visual fields performed with size V stimuli. (C) 10-2 program performed on the same patient as in parts A and B, which tests a size III stimulus within the central 10°. Focusing on the central 10° has increased the number of useful points to follow compared to the central 24° in part A. (D) Performed with the macula test, which double determines 16 points in the central 5° and provides quadrant totals.

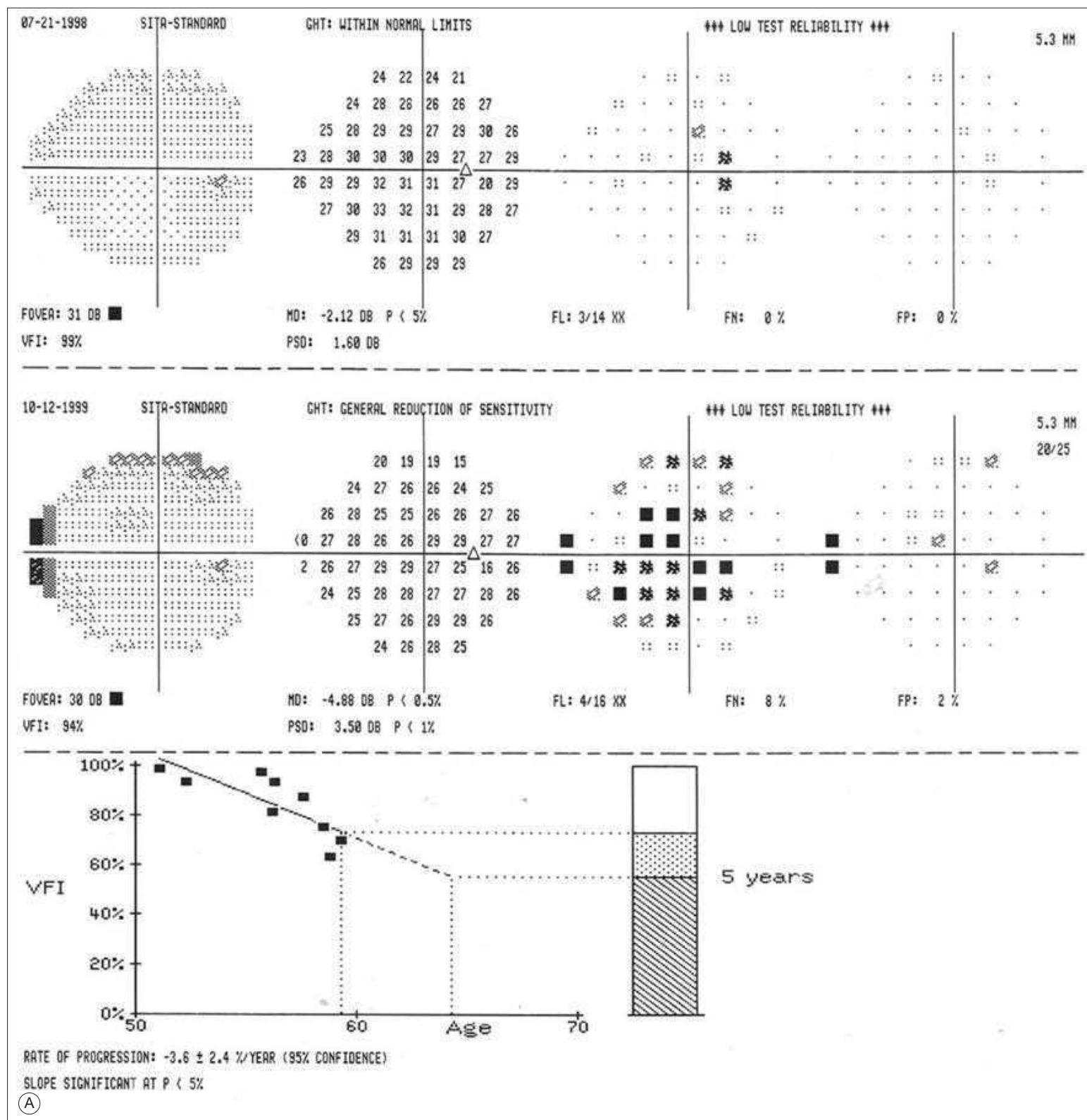


Normal-Tension Glaucoma Study<sup>15</sup> (Table 10.5.3) or one of several statistical programs that analyze individual points, such as the Guided Progression Analysis program for the Humphrey Visual Field Analyzer (Fig. 10.5.8; Zeiss Meditec, Dublin, CA) or the Progressor Programme.<sup>16</sup> Using the global indices, such as worsening of the mean deviation (MD) and pattern standard deviation (PSD), can be difficult for several reasons. The MD is a single measure of the depression of the patient's visual field compared to age-matched controls. It may be getting worse from localized or diffuse changes, the latter most commonly a manifestation of cataract worsening. If the MD and PSD are both worsening, this is better evidence of worsening of a localized defect such as commonly occurs in glaucoma.

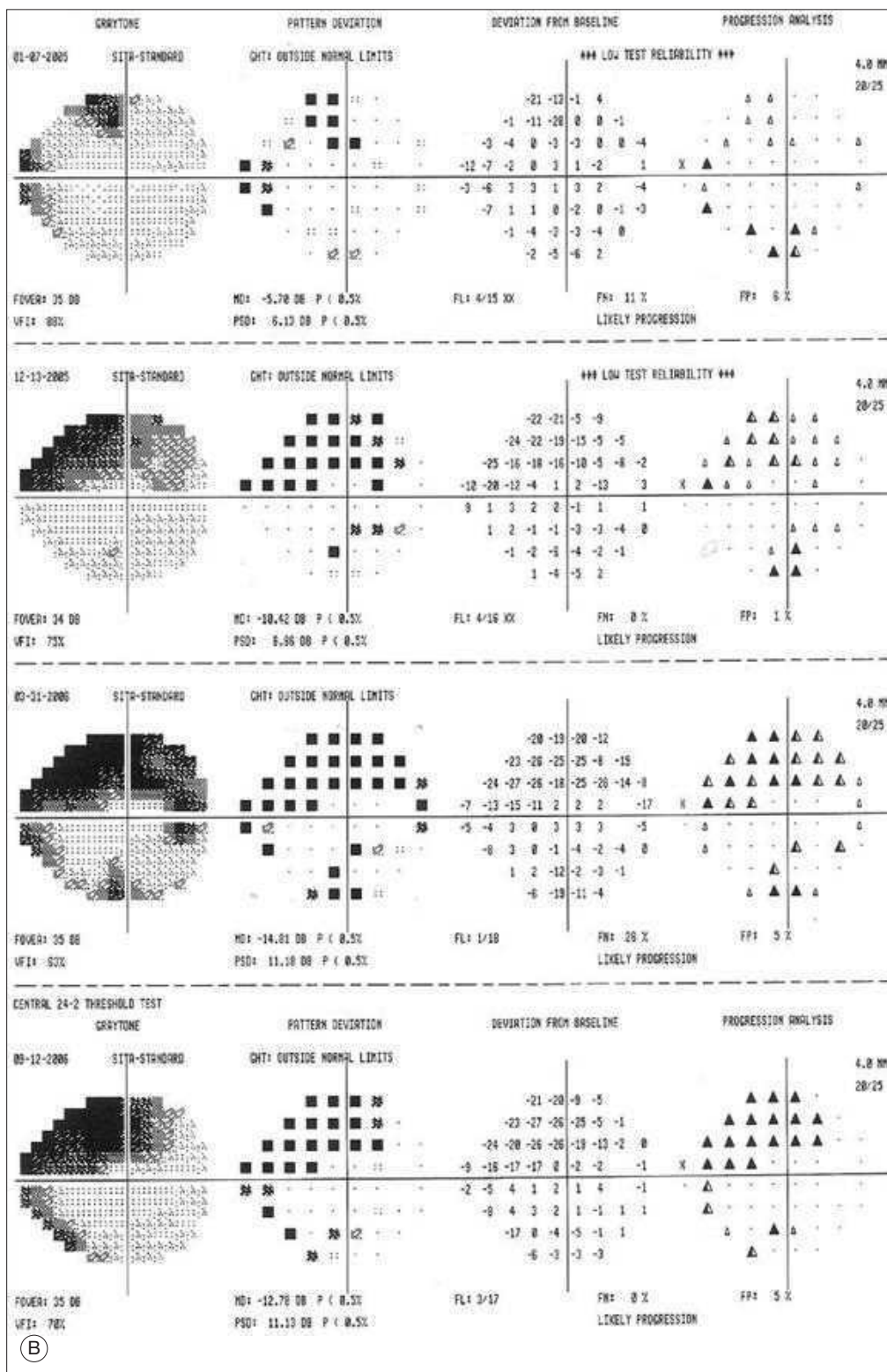
TABLE 10.5.3 Criteria for Judging Glaucoma Progression

Point-wise comparison <sup>15</sup> (Normal-Tension Glaucoma Study)	Defect has deepened or enlarged if 2 or more points within or adjacent to an existing scotoma have worsened by at least 10 dB or 3 times the average of the short-term fluctuations, whichever is larger
Glaucoma progression analysis <sup>17</sup>	Deterioration of 3 or more points at the same location at the $P < 5\%$ level on 3 consecutive visual fields
Regression analysis of mean deviation	Deterioration of slope of mean deviation at the $P < 5\%$ level per year

All criteria assume confirmation on at least 1, and better yet 2, subsequent field and clinical correlation with no other explanation for deterioration.



**Fig. 10.5.8 Glaucoma Progression Analysis.** Visual fields of the right eye of a glaucoma patient analyzed with the Glaucoma Progression Analysis program. (A) shows the two baseline visual fields that are merged for future comparison as well as the Visual Field Index (VFI). The plot of VFI (X-axis) by age (Y-axis) indicates deterioration of visual field function from nearly 100% at age 51 and 75% at age 59. The trend line continues another 5 years and predicts a decline to 60% VFI by age 64 if the progression is not slowed by more aggressive therapy.



**Fig. 10.5.8, cont'd** (B) shows follow-up visual fields with numerous half- and fully darkened triangles indicating significant change at these points on repeat testing. The follow-up fields all give "Likely Progression" messages because three or more points have worsened in the exact same location on at least three follow-up fields (intervening fields not shown).

The pattern deviation value is not the best measure of a worsening visual field in glaucoma, however, because it gets higher initially in glaucoma but then lower as more and more of the visual field becomes affected.

Guided Progression Analysis (GPA) is based on test-retest data and was used in the Early Manifest Glaucoma Trial.<sup>17</sup> The GPA software analyzes the change in a patient's visual field results from two baseline fields to the current visual field. If the change at an individual point has less than a 5% probability of falling within the range considered to be noise, that change is counted as "possible progression." Of course, at this level of statistical significance, we would expect one in 20 patients to produce a false positive at any particular point. But the program requires that three or more of the same points show change on three consecutive fields before the message "Likely Progression" is displayed. A new global index available for the Humphrey Visual Field Analyzer, the Visual Field Index (VFI), provides a measure of the percentage of visual field remaining, from 0%

(perimetrically blind) to 100% (full visual field function).<sup>18</sup> VFI differs from MD, the traditional global index for following perimetric function over time, in that it uses the pattern deviation probability values rather than the total deviation probability values in an attempt to reduce the effect of cataract on the index. Additionally, it weights defects closer to fixation higher than those away from fixation. VFI provides trend analysis, as opposed to the event analysis provided by GPA, by plotting VFI graphically. The advantage of VFI is that one can determine the rate of visual field progression to date and then predict how much additional visual field function would be lost over the subsequent 5 years if there were no change in the rate of loss. Fig. 10.5.8 is an example of the GPA and VFI analyses in a patient with progressive glaucoma. It is important to differentiate real glaucomatous visual field change from artifactual change. Long-term fluctuation is the most common reason for a false-positive follow-up field in glaucoma but can be minimized by repeat testing. It cannot be stressed enough that

any suspected change on the visual field must be confirmed on two subsequent visual fields before concluding that the field is truly worse.<sup>15</sup>

As mentioned previously, even under ideal testing circumstances, fluctuations in visual fields are common. It is of paramount importance to always evaluate the reliability of the visual fields (false positives, false negatives, and fixations losses) and to communicate with the tester to determine if there was cooperation of the patient with the test. Artifacts in visual field testing, such as lens rim artifact, use of an incorrect corrective lens, testing the incorrect eye, entering an incorrect date of birth, miotic pupil, eyelid position, or incorrect fixation, must be ruled out as well. Conditions other than glaucoma can mimic glaucomatous progression, so a complete and careful examination looking for, particularly, retinal or nonglaucomatous optic neuropathies and central nervous system-type defects should be undertaken before glaucoma is blamed for progression on the visual field.

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# Advanced Psychophysical Tests for Glaucoma

## 10.6

Chris A. Johnson

**Definition:** Threshold estimation strategies, test procedures, and analysis methods provide improvements in the accuracy, sensitivity, and reproducibility of perimetry and visual field testing.

### Key Features

- Swedish Interactive Threshold Algorithm.
- Zippy Estimation by Sequential Thresholds.
- Tendency-oriented perimetry.
- Dynamic strategy.
- Frequency-doubling technology.
- Matrix perimetry.
- Pulsar perimetry.
- Rarebit perimetry.
- Heidelberg edge perimetry.
- Tablet-based perimetry.
- Visual field index.
- Guided Progression Analysis 2.

## INTRODUCTION

Evaluation of glaucomatous functional deficits is important for practitioners and investigators. Although color vision, contrast sensitivity, and other psychophysical tests have been used,<sup>1</sup> perimetry remains the primary basis for evaluating glaucomatous visual function. Recent innovations for perimetry have enhanced its utility. This chapter provides a brief review of new test strategies, assessment procedures, and analysis techniques.

## TEST STRATEGIES

Visual field testing initially consisted of detecting a moving target (kinetic) or luminance increment (static) on a uniform background. Automated perimetry introduced the staircase procedure, which was variable and time consuming, so better strategies were developed.

The Swedish Interactive Threshold Algorithm (SITA) incorporates a Bayesian (forecasting) strategy that improves accuracy, efficiency, and reliability.<sup>2-5</sup> SITA uses prior information from normal and glaucoma populations of various ages to determine probability density functions (pdfs) for each location. During testing the pdf is modified until the 95% confidence limits are within acceptable limits (dynamic termination). SITA has better test-retest reliability and reduces testing time by 25%–50% compared to staircase tests. Two strategies are available: SITA Standard and SITA Fast. The SITA Fast procedure allows a larger window of acceptable error, making it a faster test with more variability.

The Zippy Estimation by Sequential Thresholds (ZEST) procedure is a Bayesian strategy similar to SITA, with two differences. First, the pdf is uniform over the range of stimulus intensities, making it less vulnerable to response biases. Second, it uses a fixed number of presentations to estimate threshold, but “suspicious” values are retested.<sup>6-9</sup> Testing time is consistent regardless of the patient’s visual field status or reliability.<sup>7-9</sup>

Tendency-oriented perimetry (TOP) is a strategy based on a spatial averaging staircase.<sup>10,11</sup> TOP provides an efficient evaluation of visual field properties,<sup>10</sup> although it can miss small visual field defects and underestimate the slope of borders of visual field loss.<sup>11</sup>

The dynamic strategy is similar to a staircase, but the size of the change between stimulus presentations is proportional to the current threshold level, whereas the staircase uses fixed changes.<sup>12,13</sup> The dynamic strategy is similar to the modified binary search (MOBS).<sup>12-14</sup> The dynamic strategy reduces test time and response variability by approximately 50%.

These strategies are currently implemented in commercial automated perimeters, and results are often similar.<sup>14</sup>

## TEST PROCEDURES

Frequency-doubling technology (FDT) perimetry presents a low spatial frequency (under 1 cycle per degree) sinusoidal grating undergoing high temporal frequency (over 15 Hz) counterphase flicker.<sup>15-17</sup> The observer detects the FDT stimulus on a uniform background, and the minimum contrast for detection is measured at each location. The original FDT device tested 19 locations within the central 30° radius, with a threshold test procedure in approximately 4 minutes per eye and a rapid screening test in 30–60 seconds per eye. A second generation FDT device, the Humphrey Matrix, has additional features and incorporates several different stimulus patterns for evaluating the central 30° (24–2 and 30–2 tests) and the macula (10–2 and macula tests). These tests provide useful assessments for characterization of glaucomatous visual field loss.<sup>15-17</sup> Fig. 10.6.1 presents an example of the Humphrey Matrix 24–2 test performed on the left eye of a patient with inferior paracentral visual field loss.

Pulsar perimetry is similar to FDT perimetry in that it presents a low spatial frequency sinusoidal grating that undergoes high temporal frequency counterphase flicker.<sup>18-20</sup> However, the sinusoidal grating is two dimensional, with contrast tapered toward the edge of the stimulus. The stimulus appears as a bullseye target radiating outward from the center. Because several spatial and temporal frequency combinations are employed for each stimulus location, the final measure is presented in spatial resolution contrast units (src units). A tendency-oriented perimetry (TOP) test strategy is used.<sup>18-20</sup> Fig. 10.6.2 presents an example of pulsar perimetry obtained for the right eye of an observer with a superior nasal step.

Rarebit perimetry is a suprathreshold test procedure in which small dots (pixels) are presented on a computer monitor.<sup>21-23</sup> For each stimulus presentation, 0, 1, or 2 dots are presented within a small localized visual field region, and the observer indicates whether they observed 0, 1, or 2 dots. It is intended to provide fine detail mapping of the central visual field to identify areas of heterogeneous or “patchy” visual field loss and gaps in overlapping ganglion cell–receptive field areas from glaucomatous damage. For each visual field region, the procedure determines the “hit rate” (percent correct) and “miss rate” (percent incorrect).<sup>21-23</sup> An example of a glaucomatous arcuate visual field defect for the right eye is presented in Fig. 10.6.3.

Heidelberg edge perimetry (HEP) utilizes flicker-defined form. The background and stimulus consist of an array of random dots that are presented on a computer monitor. The dots are flickering at a rapid rate, and a stimulus is generated by rapid counterphase flicker.<sup>24,25</sup> Fig. 10.6.4 presents an example of a superior arcuate glaucomatous visual field defect for a right eye that was evaluated with Heidelberg edge perimetry.

The advent of smartphones and tablets has prompted the development of new visual function test procedures that can be utilized for

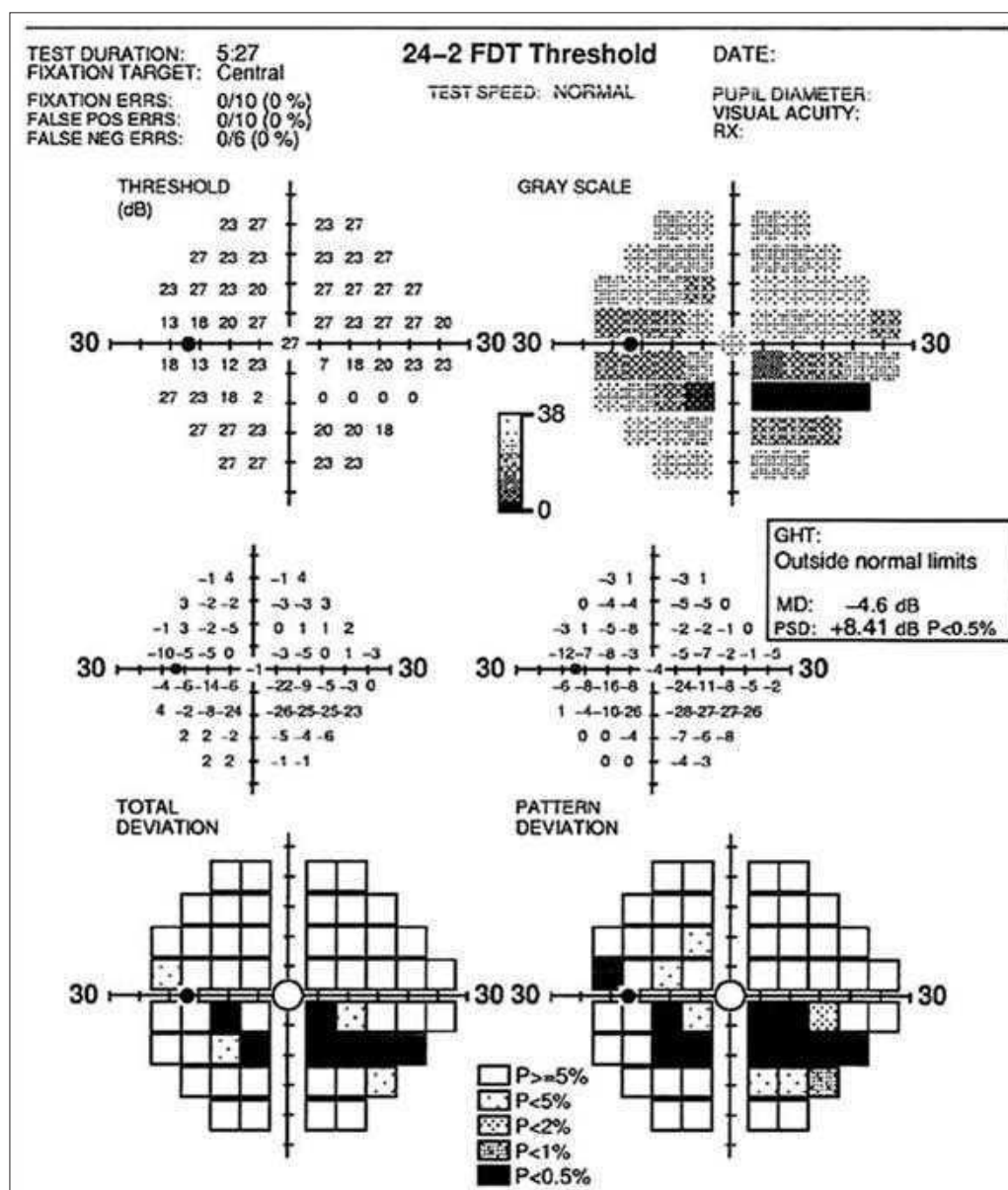


Fig. 10.6.1 Humphrey Matrix Frequency-Doubling Technology (FDT). Results for the left eye of a glaucoma patient with an inferior arcuate visual field defect.

population-based screening, home testing, and evaluation in the waiting room of an eye care specialist's office. Several investigators have developed procedures for visual field screening and quantitative threshold assessment of the central 30° visual field.<sup>26-28</sup> The results compare favorably with the Humphrey Field Analyzer and provide a portable, battery-operated means of performing visual field testing in remote areas, for populations at high risk of developing visual problems, and for those with limited access to traditional health care and eye examinations. It is likely that refinements of this procedure may incorporate virtual reality goggles that could permit testing to be performed while patients are seated in the waiting area before being seen by an eye care specialist.

## ANALYSIS METHODS

Overviews of methods to evaluate visual fields longitudinally and stage glaucomatous visual function loss have been published by many investigators.<sup>29-34</sup>

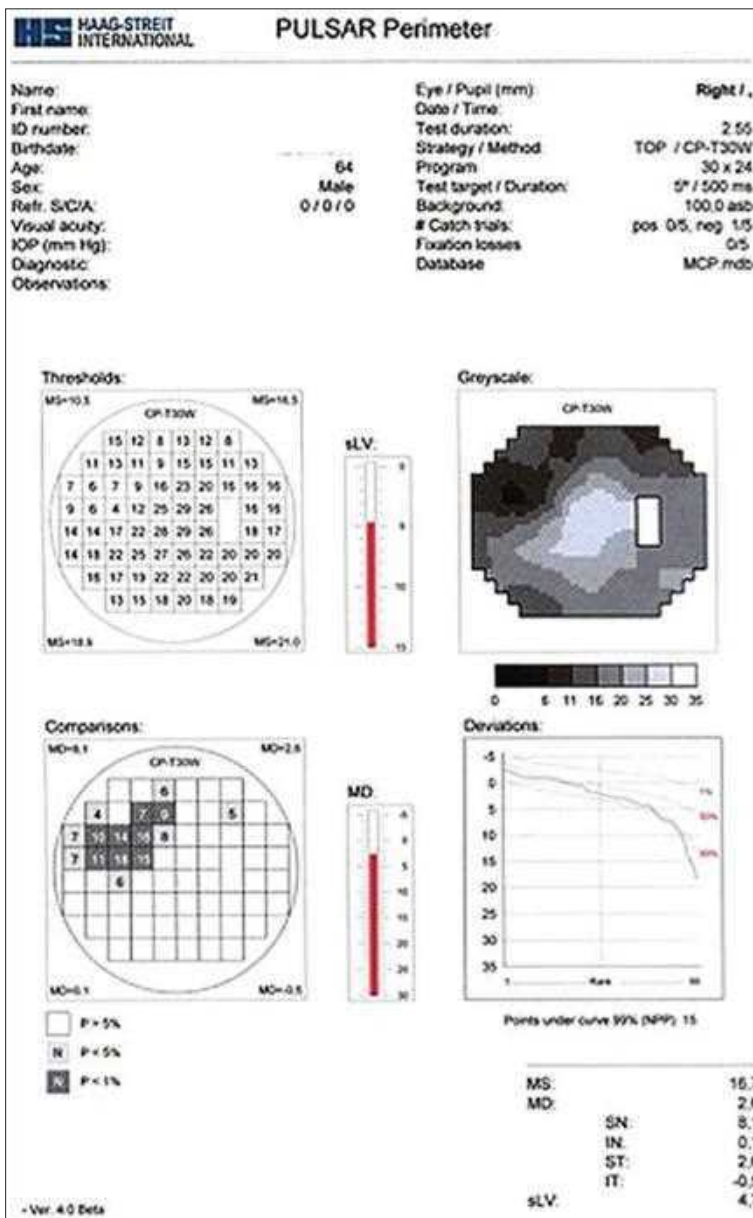
The visual field index (VFI) estimates the rate of change in glaucomatous visual fields over time.<sup>33</sup> It is based on an analysis of mean deviation (MD) but expresses visual field loss as a percentage between 100% (normal) to 0% (blind). To minimize the influence of cataract, the VFI uses

probability values from pattern deviations rather than total deviations and applies greater weight to more centrally located points. The VFI provides a continuous, quantitative assessment of visual field damage. However, it is relatively insensitive to early glaucomatous visual field loss (MD no worse than -6 dB), is more optimistic in its assessment than expert visual field evaluators, and lacks evidence basis to indicate that it is superior or inferior to MD as a measure of visual field damage.<sup>33</sup>

A method that utilizes the VFI is the Guided Progression Analysis 2 (GPA 2).<sup>34</sup> The GPA 2 provides a linear regression of the VFI over time to estimate rate of progression and demonstrates defect depth and probability levels for individual test locations. The GPA 2 provides information concerning glaucomatous visual field progression, it can localize and identify visual field locations with the most change, and printouts can be evaluated and interpreted efficiently and accurately.<sup>35</sup>

Permutation analysis is used for magnetic resonance imaging (MRI) and positron emission tomography (PET) to determine whether variations are systematic, sequential, or due to random variation. It was adapted to ocular imaging<sup>35</sup> and is now applied to visual field analysis. Permutation analysis performs a random shuffle of visual field tests to generate a set of distributions to determine whether the proper chronological sequence of tests provides more effective information.



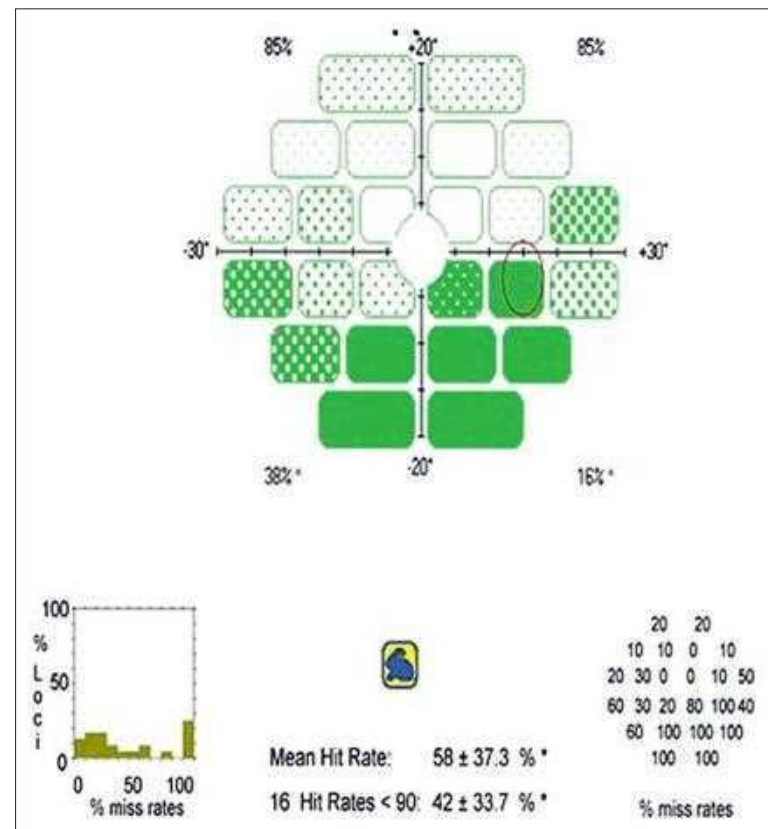


**Fig. 10.6.2 Pulsar Perimetry.** Results for the right eye of a glaucoma patient with a superior nasal step and partial arcuate visual field defect. The values are in spatial resolution contrast (src) units.

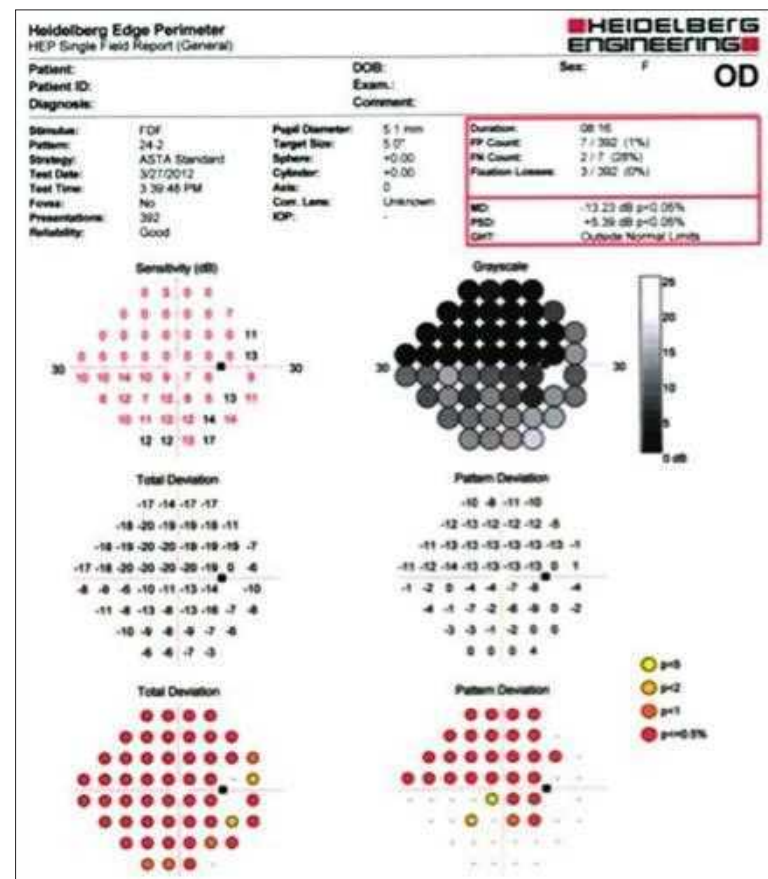
Although there are many different statistical and mathematical models currently being developed and validated for evaluating glaucomatous visual field progression, many of the more sophisticated ones require a large amount of background familiarity, require considerable computational power, and have complex outcomes, which limits their use in a busy clinic. Recently, Gardiner and Demirel<sup>36</sup> compared three common visual field indices: mean deviation (MD), pattern standard deviation (PSD), and visual field index (VFI). They found that MD was able to detect more cases than PSD or VFI and was also able to detect visual field deterioration earlier than the other two indices.

## CONCLUSION

The clinical value of perimetry has significantly improved through the innovative procedures for functional evaluation of glaucoma. Efforts to improve the accuracy and efficiency of testing strategies, develop test procedures that target key mechanisms, and create analysis procedures that combine functional, structural, and clinical information should make detection of glaucomatous damage and progression easier.



**Fig. 10.6.3 Rarebit Perimetry.** Results for the right eye of a glaucoma patient with an inferior arcuate defect and some superior partial arcuate sensitivity loss. The percentage miss rate (100% minus the hit rate) is shown for each visual field region tested.



**Fig. 10.6.4 Heidelberg Edge Perimetry (HEP).** Results for the right eye of a glaucoma patient with a superior arcuate visual field defect. The HEP performs testing using a flicker-defined-form stimulus.

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# Optic Nerve Analysis

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# 10.7



**Definition:** Ancillary testing to document the characteristic glaucomatous changes in optic disc morphology, which are critical to the diagnosis and longitudinal management of all forms of glaucoma.

## Key Features

- Focal and/or generalized thinning of the neuroretinal rim.
- Progression of glaucomatous optic neuropathy over time.

## Associated Features

- Blood vessel baring.
- Lamina cribrosa “show”.
- Disc hemorrhage.
- Peripapillary atrophy.
- Retinal nerve fiber layer loss.

## Diagnostic Technologies

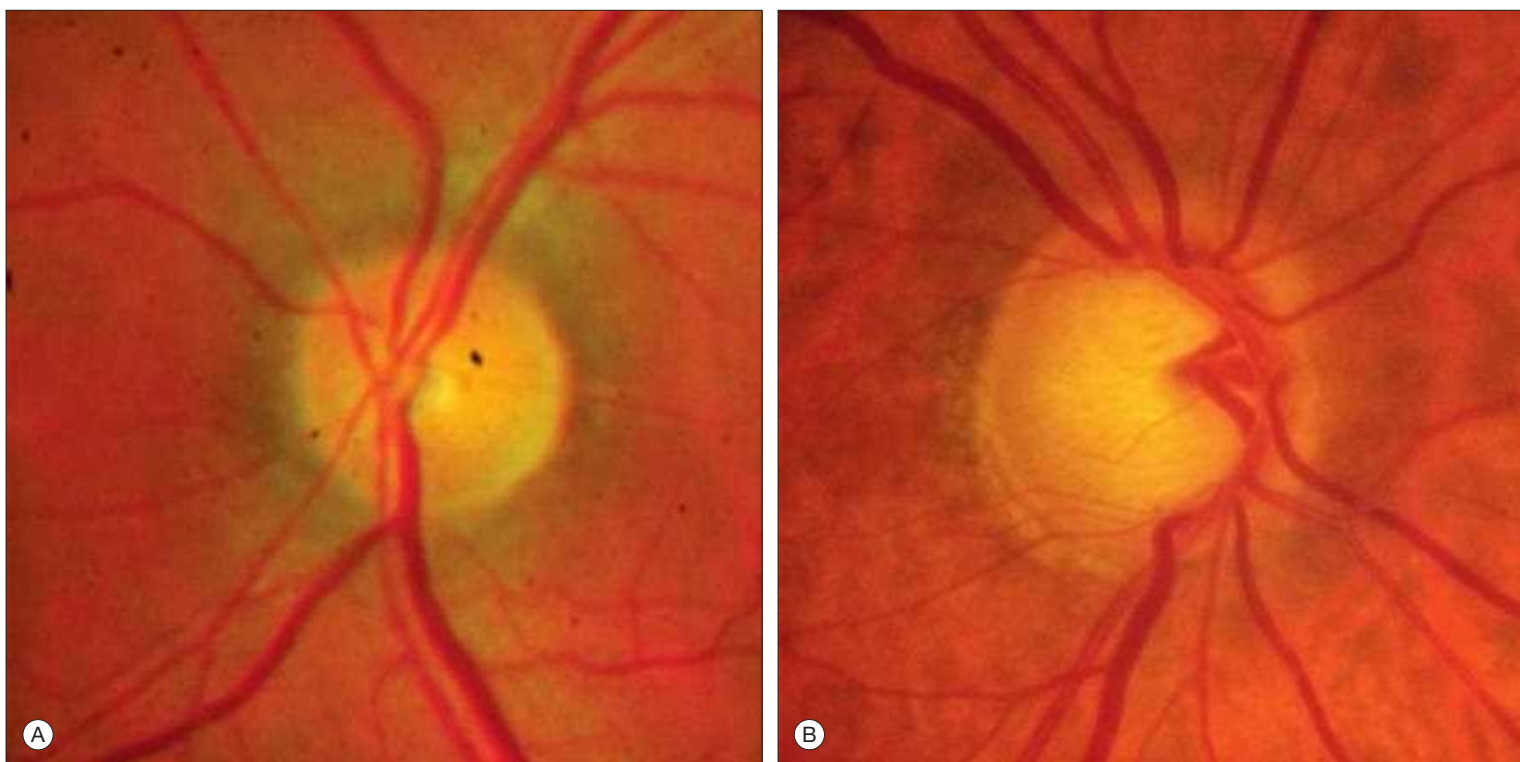
- Stereobiomicroscopy.
- Stereo disc photographs (and red-free filter).
- Confocal scanning laser ophthalmoscopy.
- Optical coherence tomography.

## INTRODUCTION

Optic nerve head (ONH) assessment is a crucial part of the glaucoma clinical examination. Owing to the large variability in the ONH features among healthy subjects, the identification of glaucomatous abnormality is challenging, particularly in the early stages of the disease. Nevertheless, it has been suggested that structural glaucomatous abnormalities precede the appearance of functional abnormalities, further emphasizing the importance of disc assessment clinically and with ancillary tools.<sup>1</sup>

## NORMAL ANATOMY

The ONH is composed of neural fibers, blood vessels, glial cells, and other support tissues. The axons, which constitute the major component of the ONH, originate in the retinal ganglion cell somas, traveling in the retinal nerve fiber layer (RNFL) and gathering together from throughout the retina in the ONH (Fig. 10.7.1). This pathway transfers the neural signal from the retina to the visual cortex in the brain. Approximately 1.2 million nerve fibers pass through the ONH, organized into bundles passing through the lamina cribrosa, which provides the structural support to the neural tissue. The total number of nerve fibers passing through the ONH is related to the disc size, with larger discs composed of more fibers compared with smaller discs. The typical healthy disc is oval in shape with the



**Fig. 10.7.1** Optic disc photographs of a healthy left eye optic nerve head with small central cupping (A), and a glaucomatous eye with enlarged cupping, focal neuroretinal rim thinning not respecting the ISNT rule, blood vessel nasalization, lamina cribrosa show, and peripapillary atrophy (B).

long axis vertically oriented. The average diameter of the disc is 1.5 mm and average disc area is 1.8 mm<sup>2</sup>. The optic disc is usually divided into two main structural components: the neuroretinal rim and the disc cup. The rim is the location of all axons, whereas the cup is the space devoid of any axons. The ONH cup is oval shaped and centrally located in healthy eyes, with the long axis horizontally oriented. The perpendicular orientations of the disc and the cup combine to lead to the typical configuration of the rim, where the thickest area is in the inferior quadrant, followed by the superior, nasal, and temporal quadrants (the ISNT rule).<sup>2</sup> In eyes with a larger ONH, the cup can be larger than in eyes with a smaller disc as the remaining area of the rim still allows all axons to pass through. The spatial distribution of the fibers is organized such that the main arcuate bundles of the RNFL enter through the poles and those originating from the posterior pole form the papillomacular bundle entering the temporal aspect of the ONH. Fibers originating in the retinal periphery tend to be located toward the disc margin, whereas fibers originating from the posterior pole tend to be located in the center of the disc. The central retinal artery enters and the vein exits the eye at the center of the ONH and divide into their branches while still within the optic disc area. Circumlinear vessels that leave the central blood vessels' trunk toward the macula can often be observed. These vessels lie superficially and are supported by the rim tissue at the edge of the cup. In up to a third of eyes, a cilioretinal artery can be observed at the temporal periphery of the disc. The typical shape of the ONH described so far can vary markedly between subjects. Common examples of natural variability are an optic nerve that enters the eyeball at a steep angle, so that the disc appears tilted, and myopic eyes with a shallow cup that may be difficult to delineate.

## CLINICAL EXAMINATION: GLAUCOMATOUS FEATURES

### Disc Cup

Several structural features have been associated with glaucomatous damage. The neural tissue loss, which is the hallmark of glaucoma, is seen in the ONH as an enlargement of the cup and thinning of the rim. These changes can occur throughout the disc as global thinning of the rim or as a localized thinning, which is often described as a *rim notch*. The neural loss also leads to deepening of the cup with exposure of the lamina cribrosa at the bottom of the cup. The cup size is often described as the vertical ratio between the cup and disc diameters (cup-to-disc ratio). However, this method is prone to inaccurate estimations, especially in the presence of atypical cups. The disc size should also be taken into account because larger discs can have a larger cup, whereas in smaller discs, even a small cup can represent a substantial level of tissue damage. Disc area can vary among healthy individuals by as much as six times and thus directly affect the outcome of the examination.<sup>2</sup> The disc size can be estimated clinically by adjusting the slit height to the disc margins and reading the measurement scale of the slit lamp after applying the correction factor for the magnifying lens used. The cup-to-disc ratio varies markedly in the population but a ratio greater than 0.65 was found in less than 5% of healthy subjects.<sup>3</sup> The cup tends to be symmetrical between eyes with a difference 0.2 or less in the cup-to-disc ratio observed in greater than 96% of healthy subjects.<sup>2</sup> Therefore, when asymmetry between eyes is noted, the possibility of glaucomatous damage should be considered.

### Blood Vessels

Because the blood vessels are mainly supported by the neural tissue, bends along the blood vessels, especially in the circumlinear vessels, are useful indicators as to the location of the cup margin. As the disease progresses with concomitant neural tissue loss, the trunk of the main blood vessels tends to shift toward the nasal aspect of the disc. In some cases, the vessels remain in an unchanged position, but with loss of tissue support—the so-called “baring of the circumlinear vessels.” Segmental changes in the caliber of the blood vessels, as well as splinter disc hemorrhages, can be noted in some eyes. These hemorrhages are transient and are usually followed by localized rim thinning at the same location, with corresponding visual field abnormality. Although the hemorrhages are not common in glaucomatous eyes, their prevalence in the healthy population is low, and thus the presence of this finding should raise suspicion of ongoing glaucomatous damage.<sup>4</sup> Furthermore, disc hemorrhages are associated with higher likelihood of glaucoma progression.<sup>5</sup>

## Peripapillary Atrophy

A common sign in glaucoma is the appearance of atrophic changes adjacent to the disc margin. Hyperpigmented or hypopigmented atrophy (also known as the *alpha zone*) and, in many cases, both types of atrophy are present side by side. The atrophy is not specific for glaucoma and appears in other ocular conditions. However, the appearance of a central area of atrophy of the retinal pigment epithelium and the choriocapillaris close to the disc (*beta zone*) has been shown to occur with high prevalence in glaucomatous eyes.<sup>6</sup>

## IMAGING

The introduction of imaging devices for ONH evaluation allows for an objective documentation and quantification of this region of the eye. Given the considerable variation in ONH appearance among healthy subjects, the various patterns of glaucomatous cupping, and the wide variation in the assessment of ONH appearance among examiners from visit to visit, it can be very difficult to make consistent decisions. Moreover, because the glaucomatous changes progress slowly, these quantitative modalities allow detection of minute changes that are difficult to observe during clinical examination. This, in turn, improves glaucoma detection and might also improve the ability to identify glaucoma progression over time, influencing management and decision making for subjects with glaucoma.

## OPTIC DISC PHOTOGRAPHY

Stereoscopic ONH photography is currently a commonly used technology to document disc appearance. It is performed by using either consecutive photographs after a manual shift of the camera or simultaneously acquired photographs with a fixed base distance. The photography provides the structural information in the most intuitive way for the clinician, acquisition is rapid and images are highly detailed (see Fig. 10.71). This method also allows for recording of various features, such as hemorrhages, that can only be appreciated by a human examiner. Although the photograph itself is an objective record, this method requires subjective interpretation, which is highly dependent on the examiner's skills and has high variability among examiners. Numerous studies have demonstrated similar ability for discrimination between healthy and glaucomatous eyes by expert assessment of ONH photographs and imaging devices.<sup>7,8</sup> However, when detection of glaucoma progression was compared between assessment of consecutive ONH photographs and visual field tests, a poor agreement was noted between the two methods.<sup>9</sup> This discrepancy might reflect the temporal differences between structural progression and functional progression. As glaucoma assessment typically requires both aspects, the appearance of a lag between progression of structure and of function complicates the ability to detect glaucoma progression.

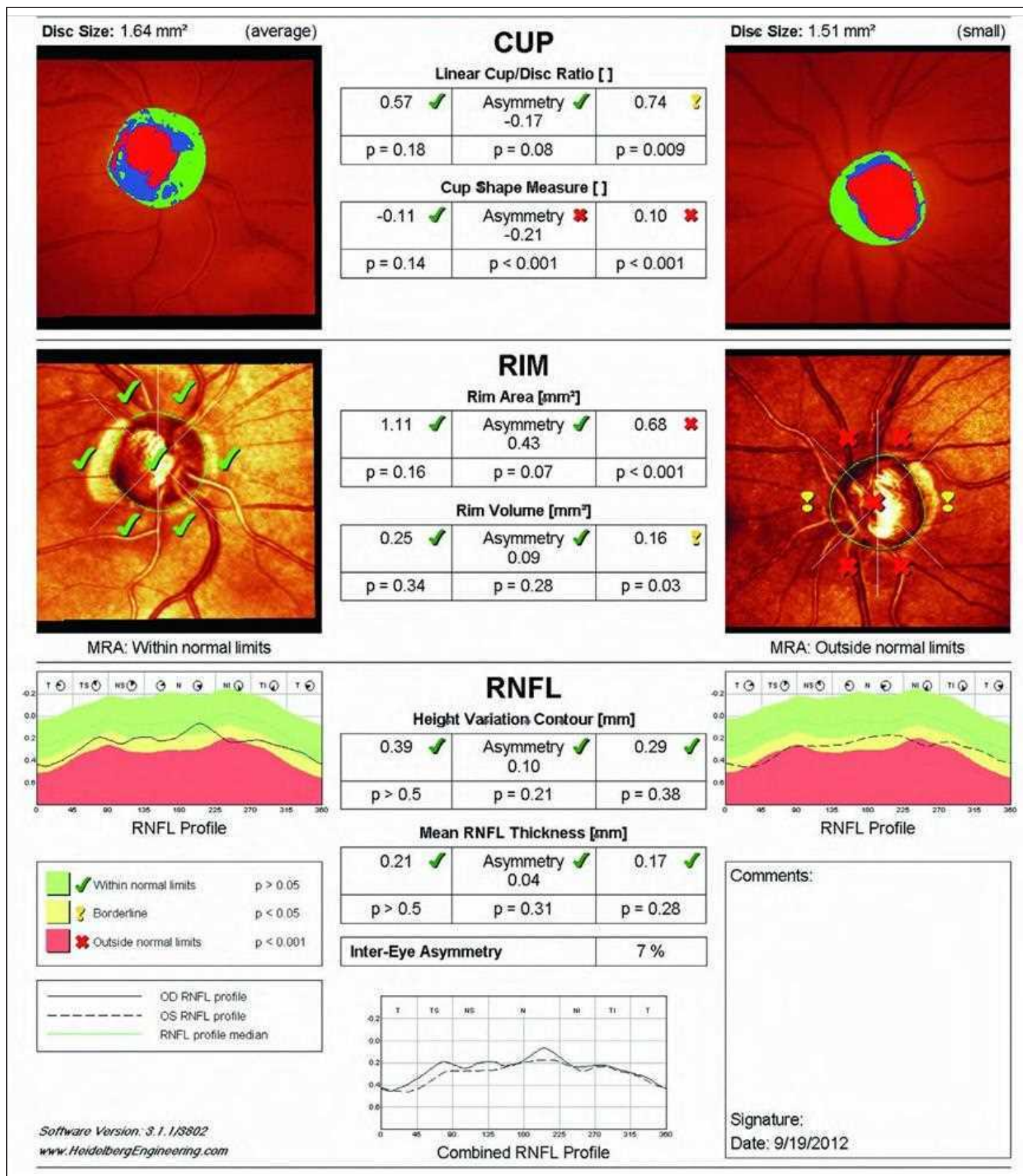
## CONFOCAL SCANNING LASER OPHTHALMOSCOPY

Confocal scanning laser ophthalmoscopy (CSLO) technology is based on the principle that light projected toward the plane of interest through a conjugated set of pinholes allows light to reach the detector only from the desired plane, whereas light coming from all other locations is blocked. The device acquires multiple scans at parallel planes and thus enables the three-dimensional reconstruction of the scanned region. The Heidelberg Retina Tomograph (HRT; Heidelberg Engineering, Heidelberg, Germany) is a CSLO device that was designed to scan the ONH region. It uses a diode laser as the light source (wavelength: 670 nm) to acquire a stack of parallel ONH scans that start anterior to the ONH and end posterior to the bottom of the optic cup. The machine identifies the location of the highest level of reflected light throughout the stack of scans for each pixel, which corresponds to the location of the vitreoretinal interface. The transverse resolution of the HRT is 10 μm with axial resolution of 300 μm.

Numerous studies have reported that HRT measurements are highly reproducible<sup>10</sup> and have provided the ability to discriminate between healthy and glaucomatous eyes.<sup>11,12</sup> The best discriminative parameters are cup shape measure, rim area, and cup volume, although considerable overlap exists between healthy and glaucomatous eyes (Fig. 10.72). Improved discrimination is achieved when several HRT parameters are combined.

The Moorfields regression analysis, which is part of the HRT software, adjust the rim area for the subject's global disc size and in predefined





**Fig. 10.7.2** Heidelberg Retina Tomograph report of healthy (right eye) and glaucomatous (left eye) eyes. The upper panel is a topographic image overlaid with the neuroretinal rim (green and blue) and cup (red) marking. The reflectance map (middle image) provides an image similar to the appearance observed when examining the eye. The optic nerve head margin is marked with the green line. Moorfields regression analysis results are overlaid on the image with check marks denoting all sectors and global measurements are within normal limits in the healthy eye (left column), and most sectors are borderline and outside normal limits (yellow and red markings, respectively) in the glaucomatous eye (right column). The retinal nerve fiber layer thickness profile surrounding the optic nerve head appears at the bottom with comparison to the population derived normal range. Stereometric parameters and the symmetry of measurements between the eyes (center column) show abnormal cup and rim measurements in the glaucomatous eye.



sectors, thus enabling the detection of focal as well as global abnormalities. This method has been reported to provide good discrimination between healthy and glaucomatous eyes.<sup>13,14</sup> The device also includes the Glaucoma Probability Score (GPS), which automatically obtains structural measurements without the need for subjective intervention.<sup>15</sup> This method analyzes the shape of the ONH and the peripapillary RNFL and calculates a probability of structure abnormality based on similarity to healthy or glaucomatous shapes. The GPS has been shown to perform as well as other HRT parameters that require human intervention.<sup>12</sup> The HRT software also includes a glaucoma progression analysis tool—the Topographic Change Analysis. This method calculates the probability at each point that the change from baseline exceeds the measurement variability between baseline scans.<sup>16</sup>

Several HRT parameters have been shown to precede functional abnormality. This was demonstrated in a small group of healthy subjects who developed glaucomatous visual field abnormality during the period of follow-up.<sup>17</sup> The ancillary study of the Ocular Hypertension Treatment Study showed that 55% of subjects who had ocular hypertension and later developed glaucomatous visual field abnormality had abnormal HRT results at the baseline visit, whereas the results of the visual field and expert examinations of the ONH were normal.<sup>18</sup>

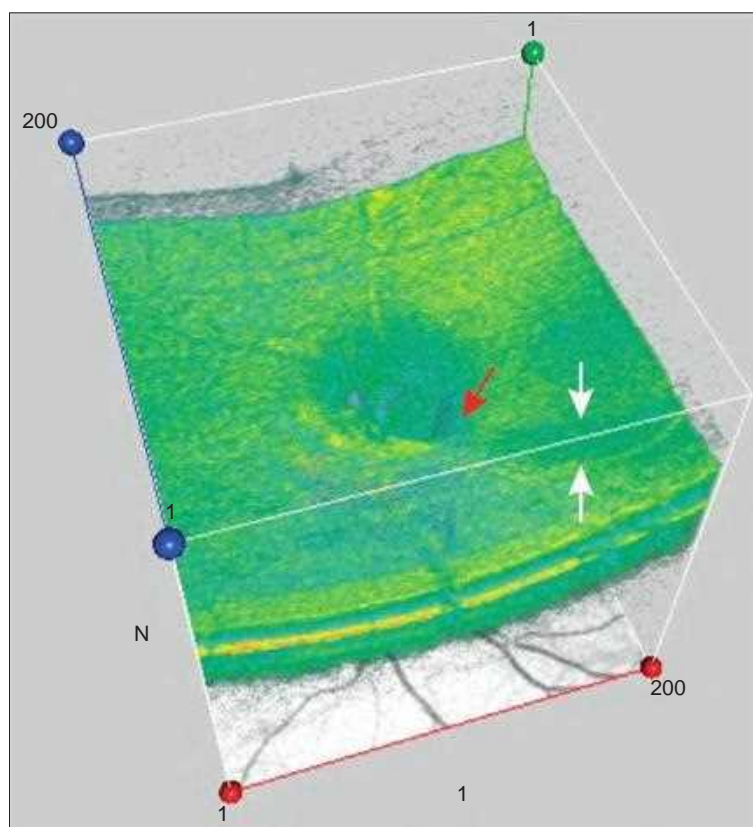
## OPTICAL COHERENCE TOMOGRAPHY

Optical coherence tomography (OCT) is a noninvasive, real-time, high-resolution technology that provides optical cross-sections of the scanned region. The current commercially available iteration of the technology, spectral-domain OCT (SD-OCT), samples broad spectral information in each particular location in the tissue. By taking the Fourier transform of this information, it is able to recover tissue reflectivity information. SD-OCT uses a spectrometer and a charge-coupled-device camera to separate and detect the spectrally resolved signal. Several commercial devices of this technology are available, all using a near infrared super-luminescent diode (SLD) light source (center wavelength: 840 nm). Scanning speed ranges between the devices from 25 000 to 70 000 axial-scans per second, axial resolution of 5–6  $\mu\text{m}$ , transverse resolution of approximately 20  $\mu\text{m}$  and scan depth of up to 2.4 mm. Scanning duration depends on the scanning protocol and ranges from approximately 1 second to greater than 1 minute. Some of the devices incorporate an eye motion tracking system to reduce motion artifacts and averaging of repetitive images to reduce inherent noise level and improve image quality.

Various scanning patterns are offered by the available devices, with the most common scanning pattern for the ONH being a raster scan, which is composed of rapid succession of parallel frames. Other scanning patterns include a spoke pattern configuration of equally spaced radial scans centered on the ONH or a combination of radial and concentric circles. Many of the devices provide three-dimensional reconstructions of the scanned area (Fig. 10.7.3). (Video 10.7.1.)

Quantitative analysis of the ONH is offered without the need of delineating the ONH margin in most devices. The cup is defined by a plane parallel to the plane connecting the disc margins with a fixed offset that differs among the devices. The parameters provided vary among the devices and commonly include the disc area, cup and neuroretinal rim areas and their ratio, minimal rim width (minimal distance between Bruch's membrane opening and optic nerve head surface)<sup>19</sup> and cup volume (Fig. 10.7.4). Some of the devices include a normative data set that allows comparison and highlights measurements deviating from the normal range.<sup>20,21</sup> OCT measurements are highly reproducible<sup>22,23</sup> and have been shown to provide good discrimination ability between healthy and glaucomatous eyes.<sup>24,25</sup> RNFL thickness is the most commonly used OCT parameter to evaluate glaucoma. RNFL thickness parameters used are RNFL global average, quadrants and clock-hour sectors.<sup>25,26</sup> ONH parameters were shown to be strongly associated with visual field findings, similar to the performance of RNFL measurements<sup>24,27</sup> (see Fig. 10.7.4). SD-OCT also allows for acquisition of enhanced depth images (EDIs) of the ONH, enabling deeper structures, such as the lamina cribrosa, to be visualized (Fig. 10.7.5). An association between lamina morphology and visual field glaucomatous damage has been reported,<sup>28</sup> but in the absence of quantifiable information from the lamina cribrosa in this iteration of OCT, the clinical utility of this scan has yet to be determined.

Several commercial devices offer automated analysis for detection of glaucomatous structural progression. This analysis predominantly uses RNFL measurements, with some devices offering similar tools with ONH measurements. ONH analysis is based on a trend analysis where the rate of change is estimated over the course of follow-up (Fig. 10.7.6). Some



**Fig. 10.7.3** Three-dimensional reconstruction of the optic nerve region of a glaucomatous eye. Indentation of the temporal inferior neuroretinal rim is marked by the red arrow. Retinal nerve fiber layer wedge defect boundaries are marked with white arrows.

devices providing progression report, which combines the progression analysis of OCT parameters with visual field results to allow the assessment of corresponding structural and functional findings.<sup>29</sup>

OCT technology is rapidly evolving with new tools and biomarkers frequently presented. Swept-Source OCT (SS-OCT) is a new iteration of the technology that is becoming available commercially. SS-OCT uses a short cavity swept laser (center wavelength: 1050 nm) with a tunable wavelength of operation. Scanning speeds can reach over 400 000 per second with an axial resolution of 5  $\mu\text{m}$ .<sup>30</sup> The deeper penetration of the SS-OCT signal and the reduced depth dependent signal drop-off observed with other iterations of OCT, enables SS-OCT to evaluate deeper ocular structures, such as the choroid and the lamina cribrosa.

OCT angiography (OCTA) is a recent analysis tool that is increasingly incorporated in the clinical ophthalmological practice.<sup>31</sup> This system allows for detailed visualization of superficial and deep vascular network noninvasively and without the need for dye injection. The utility of this system in glaucoma management is currently being investigated.

Adaptive optics (AO) systems, which correct monochromatic aberrations, normally occurring in the eye, using wavefront sensing and deformable mirrors, are improving the transverse resolution. Research systems of AO coupled with scanning laser ophthalmoscopy or with OCT have been shown to substantially improve image quality and were mostly tested in the context of retinal disease. For ONH analysis, AO systems are capable of improving visualization of the lamina cribrosa microstructures, such as the pores and beams, as well as the retinal fiber bundles<sup>32,33</sup> (Fig. 10.7.7).

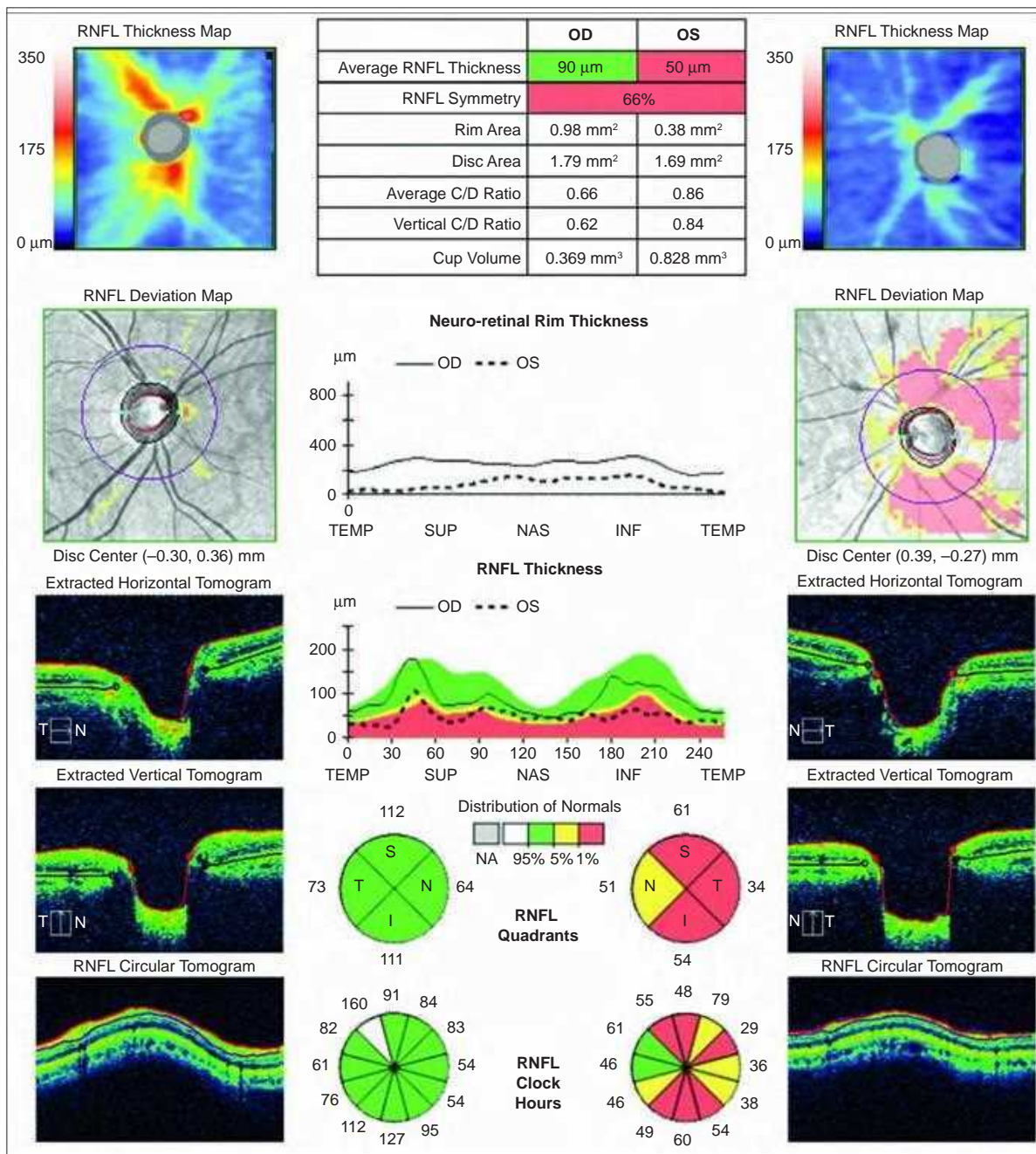
Other novel OCT systems for ONH examination undergoing research include polarization-sensitive OCT, which generates images with tissue-specific contrast based on properties that alter polarization state; and visible-light OCT, which uses wideband light source enabling high-resolution images, in vivo oximetry and spectrometry.<sup>34,35</sup>

## CONCLUSIONS

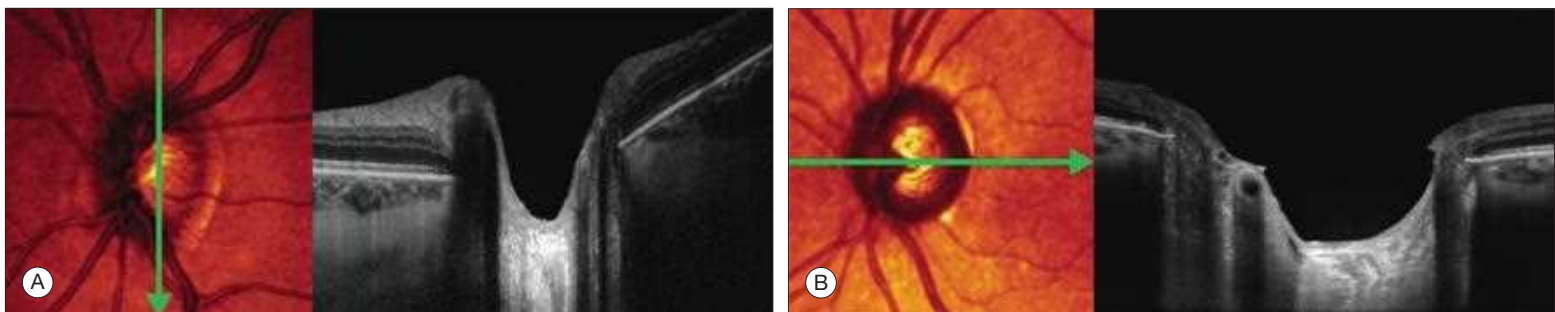
The ONH has been the cornerstone of clinical glaucoma diagnosis for a very long time. The ability to obtain detailed visualization and quantification of ONH structures through the use of ophthalmic imaging further strengthens its role in glaucoma diagnosis and progression detection.



See clip:  
10.7.1

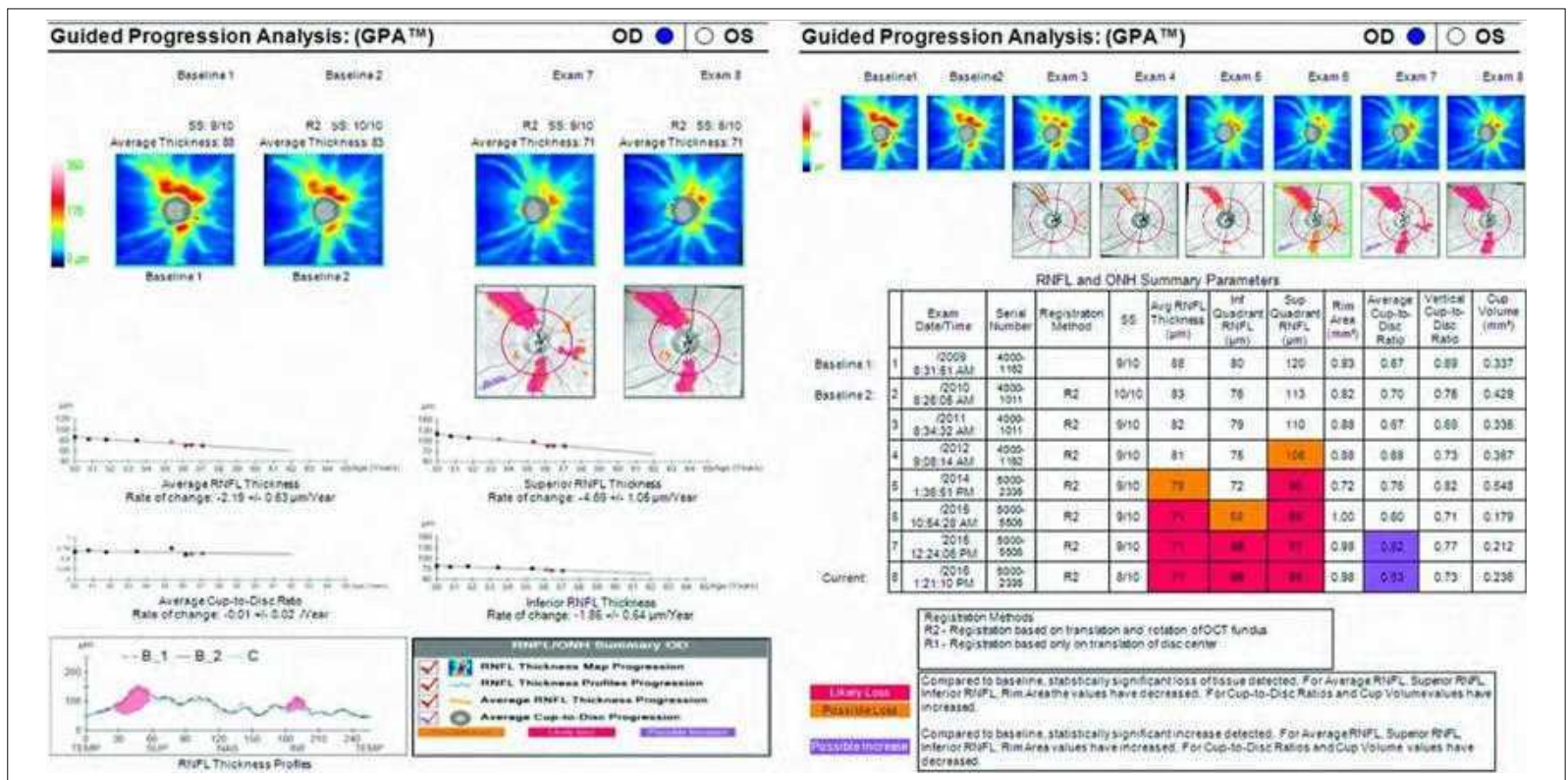


**Fig. 10.7.4** Optical coherence tomography report of the optic nerve head scan of healthy (right eye) and glaucomatous (left eye) eyes. Color-coded retinal nerve fiber layer thickness map (top) shows in the healthy eye (left) a central optic nerve head cup (light gray area) with typical thickening of the retinal nerve fiber layer (RNFL) adjacent to the optic nerve head poles (red and yellow areas). Cross-sections through the optic nerve head and surrounding circle appear at the bottom of the column. The en face image of the scanned region with the delineation of the disc and cup margins and the circumpapillary scan location is presented at the center of the left column. The glaucomatous eye (right) shows markedly enlarged cupping (top right) with nearly complete obliteration of the normally thicker RNFL superiorly and inferiorly. The RNFL damage is highlighted by the red and yellow clusters in the RNFL Deviation Map (center right). Quantitative measurements of the optic nerve head structures appear at the top of the middle column with the Average RNFL Thickness parameter within normal range for the right eye (green background) and outside normal range for the left eye (red background). RNFL symmetry between the eyes was also marked as outside normal range. RNFL thickness measurements for quadrants and clock-hours appear at the bottom of the center column, with their corresponding comparison with normative data ranges. Thickness profiles for both eyes along the optic nerve head margin (neuroretinal rim thickness) and surrounding it appear at the center of the center column.

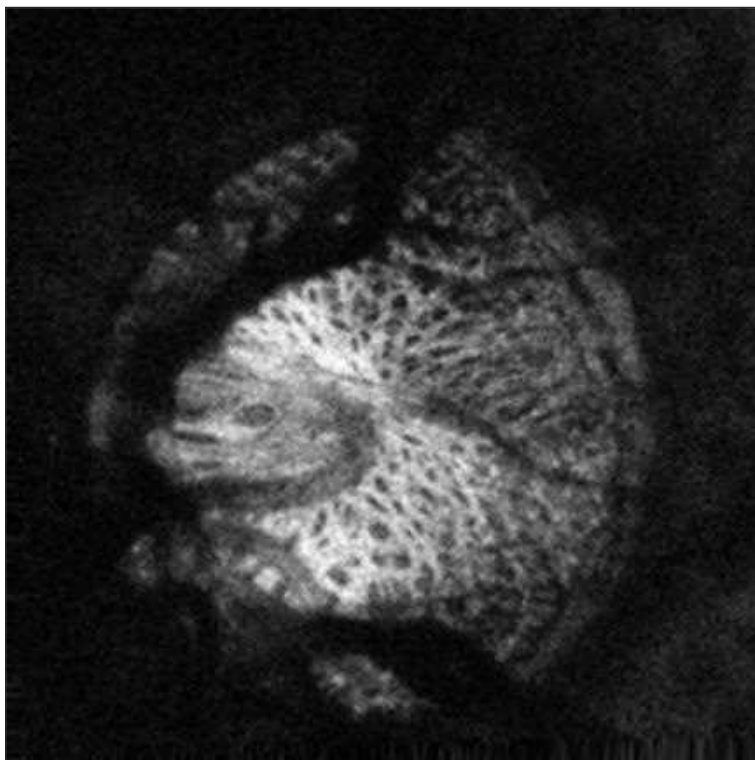


**Fig. 10.7.5** Enhanced depth imaging B-scan with spectral domain optical coherence tomography at the location marked by the green line. (A) Vertical B-scan of an eye without glaucoma. (B) Horizontal scan of an eye with glaucomatous optic neuropathy. Structures deep within the optic nerve head, such as the lamina cribrosa (bright white area within the optic nerve head) can be detected by using this scanning method.





**Fig. 10.7.6** Optical coherence tomography glaucoma progression analysis (GPA) of the optic nerve head report of the right eye. The left page shows the two baselines used for determining the analysis of events of progression (probably loss or likely loss) and determining the rate of change of the average, superior, and inferior RNFL and the average cup-to-disc-ratio. The deviation maps of the baselines and last two visits are shown as well as a summary of the events (bottom right of the page). The second page (right) of the GPA report shows the deviation map of every visit selected and its change and a table summarizing the RNFL and ONH parameters at every visit. If there is significant change the value is flagged with yellow (possible loss) or red (likely loss).



**Fig. 10.7.7** En face view of the lamina cribrosa using adaptive optics scanning line ophthalmoscopy technology. The microstructures of the lamina cribrosa such as pores and beams can be appreciated and measured using this advance of the technology.

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# Optic Nerve Blood Flow Measurement

## 10.8

Josh C. Gross, Alon Harris, Andrew Koustenis, Brent Siesky

**Definition:** Methods of assessing optic nerve blood flow in health and disease.

### Key Features

- Optic nerve anatomy.
- Optic nerve physiology.
- Clinical studies on optic nerve blood flow.
- Systemic vascular diseases and glaucoma.

### Associated Features

- Technologies for imaging optic nerve blood flow.
- Ocular blood flow and visual function.
- Pharmacology.

## INTRODUCTION

A substantial number of patients with glaucoma (perhaps up to 30%) have low/normal intraocular pressure (IOP) at the time of initial diagnosis, and the lowering of IOP does not always prevent or arrest the disease. This indicates that risk factors other than IOP alone contribute to the pathogenesis of optic nerve (ON) damage, especially in certain demographic groups. Ischemia contributing to the loss of ON axons, a concept recognized for more than 100 years, is among the foremost non-IOP risk factor with preliminary supporting data. Over the past several decades, it has become increasingly clear that vascular compromise plays a significant role in some individuals with glaucoma. Some clinical features that suggest an underlying vascular problem include localized rim notching or focal ischemic glaucoma (Fig. 10.8.1), peripapillary vasoconstriction (Fig. 10.8.2), optic disc hemorrhage, senile sclerotic optic discs with peripapillary choroidal sclerosis, and decreased ocular perfusion pressure.<sup>1,2</sup>

The precise role that ON blood flow plays in the loss of axons in glaucoma is not clear. Pallor and gross visual field loss but little cupping of

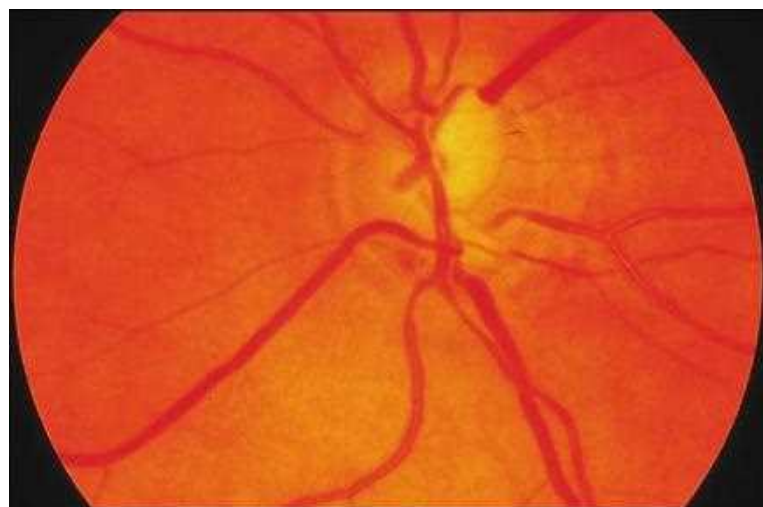
the optic disc can be seen after an acute cessation of flow in a short posterior ciliary artery (PCA) in giant cell arteritis. Furthermore, focal ischemia (which presumably arises from infarction of a small ciliary vessel in the prelaminar region) produces localized disc cupping and pallor, and a corresponding, well-defined (frequently small) visual field defect. However, to date, well-established large clinical data demonstrating specific vascular contributions in glaucoma pathology, especially vascular tissues associated with the ON, are lacking.

## APPLIED ANATOMY

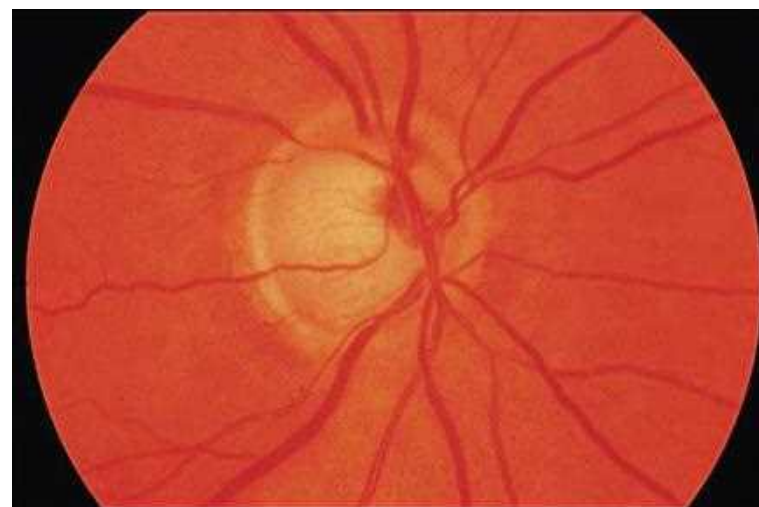
The ophthalmic artery (OA) is the first branch of the internal carotid artery and gives off 2–4 posterior ciliary arteries (PCAs), which divide into 10–20 short PCAs that pierce the sclera and enter the globe around the ON. The number and route of short PCAs are variable in this region, but in general, they supply the posterior choroid and anterior ON either directly or indirectly via the arterial circle of Zinn–Haller, which, when present, is formed by the anastomosis of the medial and lateral short PCAs and circumscribes the anterior ON within the sclera.<sup>3–5</sup> The central retinal artery (CRA) enters the ON about 8–12 mm behind the globe and passes along the central axis of the nerve giving off few, if any, branches to the neural tissue. Venous drainage of the anterior ON is through the central retinal vein and into the superior ophthalmic vein.

The anterior optic nerve head (ONH) (prelaminar, laminar, and postlaminar neural tissues) is supplied by branches from the short PCAs, and the nerve fiber layer of the superficial retina receives arteriolar branches from the CRA. The capillaries of the anterior CRA (retinal and ciliary) and the ONH have tight junctions, are not fenestrated, and form a rich anastomotic plexus.<sup>6</sup> Histological examination of glaucomatous optic nerves have demonstrated a reduction in the number of capillaries consistent with the degree of neural loss, and recent optical coherence tomography angiography (OCTA) performed in patients with glaucoma has shown peripapillary capillary loss corresponding with visual field defects.<sup>7</sup>

The peripapillary choroidal circulation may contribute occasional small arterioles to the perfusion of the prelaminar and laminar ONH,<sup>6</sup> although watershed zones in the region of the ON that arise from the presence of the various interindividual segmental distributions of the various PCAs and the short PCAs may be a factor in the development of ON ischemia.<sup>8</sup>



**Fig. 10.8.1 Focal Ischemic Optic Disc Appearance (Left Eye).** Localized loss of the superotemporal neuroretinal rim in a 54-year-old woman, who has migraine and Raynaud's phenomenon.



**Fig. 10.8.2 Peripapillary Vasoconstriction in Glaucoma (Right Eye).** Marked narrowing of a branch of the inferotemporal retinal artery (at the 6 o'clock position) as it crosses the optic disc boundary adjacent to the inferior temporal vein.

Therefore, watershed zones are dependent on an individual’s anatomy, but most commonly pass through the temporal optic disc and peripapillary choroid.<sup>8</sup>

PHYSIOLOGY

Blood flow in the anterior ON relies on such factors as ocular perfusion pressure (OPP) (mean arterial blood pressure minus IOP), resistance to flow as determined by the vascular caliber in the arterioles and capillaries, and, more recently, the concept of translaminal pressure difference (IOP minus retrolaminar tissue pressure).<sup>9</sup> Vascular caliber is influenced by local mechanical, metabolic, and endothelial factors. The ability to keep local tissue flow and metabolic demand constant throughout changes in the local environment is called *autoregulation*.<sup>9</sup> Moderate changes in IOP, systemic blood pressure, and changing oxygen (O<sub>2</sub>) and carbon dioxide (CO<sub>2</sub>) conditions have little effect on anterior ON blood flow. However, if autoregulation is impaired, changes in OPP and intracranial pressure may reduce ON perfusion. In fact, patients with normal-pressure glaucoma and primary open-angle glaucoma have been found to have impaired ON and retinal autoregulation. Large population-based studies have shown that decreased OPP is a risk factor for the prevalence, incidence, and progression of glaucoma.<sup>2</sup> The difficulty in imaging specific ocular tissues currently limits our ability to connect all of these pieces of the vascular puzzle; however, advances in mathematical modeling are helping to illuminate the balance between ocular pressures and autoregulation to determine their role in ocular blood flow.<sup>10</sup>

Vascular responses in the ONH are complex and include mechanical, metabolic, and neurovascular influences. Neurovascular coupling, where active neurons directly or indirectly influence blood vessels to increase local blood flow, is mediated by several compounds including nitric oxide, adenosine, and O<sub>2</sub>.<sup>9</sup> Substances produced in response to mechanical forces play a major role in the control of ocular blood flow and include the vasodilators nitric oxide and prostacyclin, and vasoconstrictors, such as angiotensin and the endothelins. Cells that produce these substances have been identified in the choroid, retina, and ON. Repeated endothelin-1 injections into the perineural space of the ON produced chronic ischemia and excavation of the optic disc in animal studies.<sup>11</sup> Additionally, experiments modulating the activity of these substances produced changes in human ONH blood flow,<sup>9</sup> and patients with open-angle or normal-pressure glaucoma show significantly increased endothelin-1 plasma levels.<sup>12</sup> Although autonomic alpha- and beta-receptors have been identified in the ONH, they have not proven to have any functional properties.

EXPERIMENTAL INVESTIGATIONS

Blood flow in the ONH has been quantified in animal work using radiolabeled microsphere and iodoantipyrine methods, which show high flow in the prelaminar and laminar regions.<sup>13,14</sup> In the retina and ON, blood flow is

coupled closely with glucose consumption, as measured by the deoxyglucose uptake technique. In monkeys, IOP that is higher than systolic blood pressure results in complete cessation of blood flow in the prelaminar tissue, and monkey glaucoma models show increased ONH blood flow in the early stages of disease, followed by a linear decrease that strongly correlates with decreased RNFL thickness.<sup>15</sup> Theoretical mathematical models using experimental and clinical data demonstrate that loss of viscoelasticity in the lamina cribrosa caused by disease may lead to increased risk of ONH hemodynamic changes.<sup>16</sup>

CLINICAL STUDIES

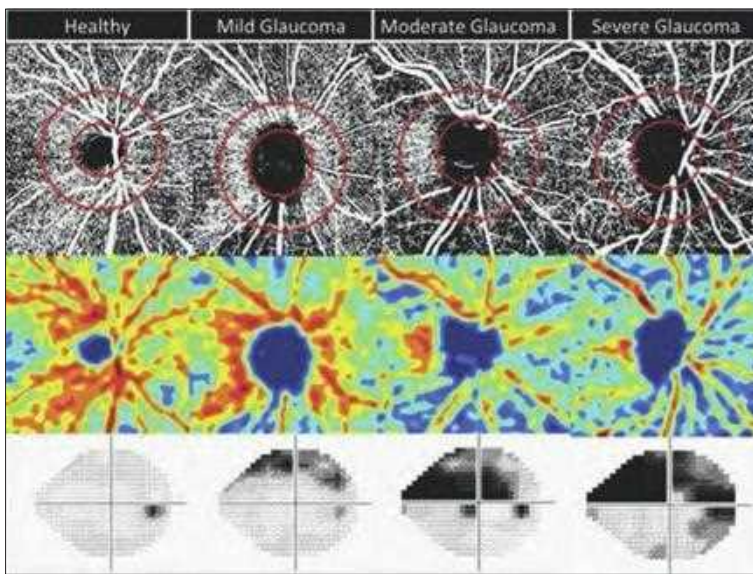
Advances in measurement techniques of ocular blood flow have increased the fundamental knowledge of optic nerve perfusion and helped characterize its role in glaucoma. The anatomical vascular regions of particular interest in glaucoma include retrobulbar vessels, the capillary plexus of the superficial retinal fiber layer, pre- and intralaminar ONH, and the peripapillary choroid. It is important to acknowledge that currently no single examination technique can assess all relevant vascular beds involved in glaucoma.

Imaging of ocular and ONH blood flow has historically presented many challenges, and therefore, many modalities focus on areas accessible by laser, ultrasound, or other principles to assess some measure of ocular vascularity as shown in Table 10.8.1. Fluorescein angiography (FA) and indocyanine green angiography (ICGA) allow for qualitative study of the retinal, choroidal, and optic disc circulations, and abnormalities have been described in patients with glaucoma.<sup>17</sup> Because of poor image acquisition of the radial peripapillary capillary plexus, this technique is not commonly used.<sup>18</sup> Color Doppler imaging (CDI) using color-coded ultrasound Doppler has been utilized to measure the retrobulbar circulation with good results, and studies have found that reductions in velocities and increases in resistivity occur in all vascular beds in both high-pressure and normal-pressure open-angle glaucoma.<sup>19,20</sup> However, CDI does not have the capability to measure absolute volume flow and requires a skilled examiner. Laser Doppler flowmeter, which uses an infrared laser to analyze erythrocyte movement in the anterior ONH and peripapillary retina,<sup>21</sup> has shown diminished blood flow velocities in and around the ONH in patients with glaucoma,<sup>22</sup> and recently, strong correlations between retinal blood flow and structural changes were found in patients of African descent.<sup>23</sup> Nevertheless, there are some limitations, such as lengthy data analysis, arbitrary units of blood flow, and discontinued production. Doppler optical coherence tomography (OCT) incorporates the concepts of OCT with the ability to measure total retinal blood flow in absolute units (μL/min), and studies in patients with glaucoma have shown reduced total retinal blood flow associated with disease progression and visual field loss.<sup>24</sup> However, although absolute blood flow measurements are achieved, this modality finds limitations in measuring capillary flow in the retina and ONH and currently lacks robust longitudinal data.

TABLE 10.8.1 Comparisons of Ocular Vascular Imaging Modalities

Modality	Principle of Operation	Advantages	Disadvantages	Comments
Split-Spectrum Amplitude-Decorrelation Angiography (SSADA OCTA)	• Utilizes the reflected amplitude of an infrared laser to find the decorrelation between consecutive B scans	• Reduction of artifacts from saccadic eye movements • High signal-to-noise ratio and vessel continuity on imaging • Vessel quantification in terms of density and flow index	• Slightly compromised resolution (18 μm, compared to 5 μm without SSADA) • Difficulty imaging deeper ONH capillaries due to emergence of retinal vessels	• A high signal-to-noise ratio for imaging is achieved through bandwidth segmentation
Doppler OCT (Fourier Domain)	• Utilizes the Doppler shift to calculate velocity based on the incident light angle	• Blood flow velocity can be obtained in larger vessels	• Blood flow in small vessels is hard to measure • Detection depends on the incidence angle of the laser beam	• Blood flow velocity is obtained
Optical Microangiography (OMAG) OCT	• Utilizes a Hilbert transformation to assess scattering light reflections as either static or in motion	• Highly sensitive capillary images • Can detect blood flow as slow as 4 μm/s	• Artifacts may occur from bulk motion	• Sensitive to bulk tissue/fluid motion
Color Doppler Imaging	• Utilizes the Doppler shift principle and reflected sound waves to assess blood flow velocities	• Vessel selective, reproducible, universal units of measure • Resistive indices calculated from velocities	• Measures blood velocity, not volumetric flow	• Widely utilized, strong pilot data shows relationship of parameters to POAG outcomes
Laser Doppler Flowmetry	• Calculates temporal laser speckle fluctuations reflecting from blood cells	• Resolution to 10 μm	• Sensitive to illumination changes • Wide variation in modalities	• Useful for anterior ONH and peripapillary retina
Retinal Oximetry	• Utilizes reflected light in retinal vessels to determine the ratio of optical densities of oxyhemoglobin and deoxyhemoglobin	• Noninvasive direct measurement of retinal oxygenation	• Need for standardization • Lack of longitudinal studies	• May indicate metabolic status





**Fig. 10.8.3 Optical Coherence Tomography Angiography (OCTA) Images With Corresponding Visual Fields.** Correlation between vessel densities measured with OCTA and visual field results, in both healthy controls and patients with glaucoma. Patients with glaucoma of several degrees have progressive peripapillary vessel deficits that correspond to greater relative visual field loss. This demonstrates a relationship between structural changes and functional changes. (Used with permission from Yarmohammadi A, Zangwill LM, Diniz-Filho A, et al. Relationship between optical coherence tomography angiography vessel density and severity of visual field loss in glaucoma. *Ophthalmology* 2016 Dec;123(12):2498–508.)

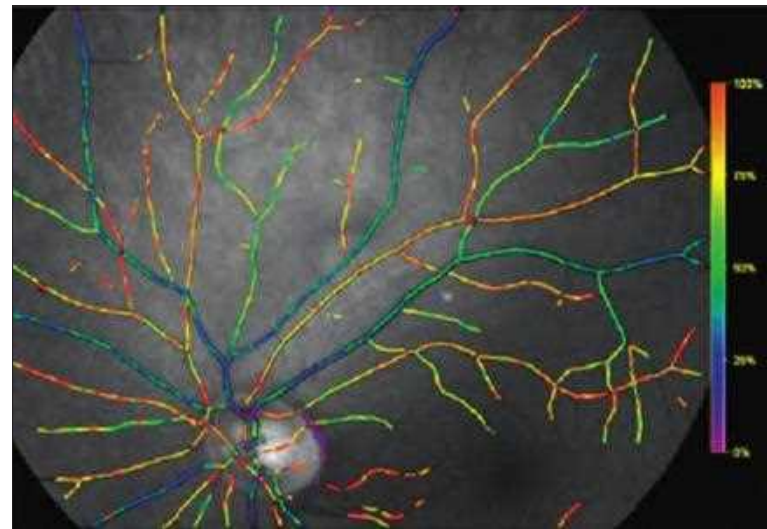
## OPTICAL COHERENCE TOMOGRAPHY ANGIOGRAPHY

OCTA is a novel and noninvasive imaging modality that builds on existing OCT technology and offers the promise of highly specialized outcomes of ON vascularity. OCTA utilizes the differences in amplitude between subsequent beams of reflected infrared light to compute the quantity of blood flow (in dimensionless units), providing vessel density in the retina and optic nerve. These calculations are used to generate high-resolution images as fine as 18  $\mu\text{m}$  and provide simultaneous structural and vascular assessments.<sup>25</sup> Currently, two algorithms are being commercially utilized: split-spectrum amplitude-decorrelation angiography and optical microangiography OCT. OCTA has been utilized to investigate blood flow in segmented layers of the peripapillary retina, and studies have suggested that OCTA may be able to segment the optic disc vasculature, including deep into the lamina cribrosa. A cross-sectional study utilizing OCTA demonstrated a correlation between decreased peripapillary vessel density and corresponding visual field deficits,<sup>7</sup> as demonstrated in Fig. 10.8.3. Additional cross-sectional studies have shown the correlation of visual field deficits to be stronger with vessel density deficits than with retinal nerve fiber layer thinning in patients with glaucoma.<sup>26</sup> Studies have suggested an association between the radial peripapillary capillary plexus and RNFL thickness and visual function.<sup>27,28</sup> Huang et al. also demonstrated the depth resolved impact of glaucoma on macular vascular density, showing that the superficial vascular complex is affected, whereas the intermediate and deep vascular complexes are not.<sup>29</sup>

Although these findings are interesting and reveal that OCTA can differentiate between healthy subjects and those with glaucoma of various degrees of severity, there is a lack of OCTA-based longitudinal studies in glaucoma populations. Furthermore, currently, visualization of the deep optic disc with vasculature OCTA is poor because of shadow interference from the emerging central retinal vessels and their branches,<sup>30</sup> and its inability to assess microvascular leakage in the retina.<sup>31</sup> Currently, OCTA does not have the capability to provide comprehensive assessment of all relevant vascular beds in glaucoma, and apparent reductions in ON vascularity may only represent a consequence of ischemic insult in downstream vascular beds.

## RETINAL OXIMETRY

All but one of the methodologies listed in Table 10.8.1 measure ocular blood flow parameters, which may serve only as a surrogate assessment of tissue metabolic status. Retinal oximetry provides an assessment of ocular



**Fig. 10.8.4 Retinal Oximetry.** Color overlay of oxygen saturation in the retinal vessels.

tissue metabolic status by measuring light absorption in the retinal vessels and by calculating oxygen saturation and is a step toward understanding the true impact of ischemia on the retinal photoreceptor ganglion cells. Retinal oximetry is a highly reproducible technique,<sup>32</sup> that requires the modification of a fundus camera or similar device and the application of algorithms to record oxygen levels within arteries and veins, the difference of which is informative about tissue oxygenation and metabolism (Fig. 10.8.4). Studies of patients with glaucoma (open-angle, normal-pressure) demonstrated higher baseline mean sulfur dioxide ( $\text{SO}_2$ ) levels in retinal veins and decreased arteriovenous  $\text{SO}_2$  difference compared with the levels in healthy patients.<sup>33,34</sup> In addition, correlations between worsening rim area, RNFL thickness, and visual field defects with increased  $\text{SO}_2$  in retinal venules and decreased arteriovenous  $\text{SO}_2$  difference have been found.<sup>35</sup> As with OCTA, longitudinal studies using retinal oximetry are lacking, thereby limiting our understanding of oxygen utilization in glaucoma conversion and progression.

## Ocular Blood Flow and Visual Field Loss

The number and size of optic disc FA filling defects has been shown to increase with the severity of visual field loss in glaucoma. Using confocal scanning angiography, Melamed et al. reported a good correlation between the optic disc filling abnormalities and the visual field defect location in 75% of the 65 glaucomatous eyes studied.<sup>36</sup> Several longitudinal studies utilizing CDI now demonstrate a correlation between decreased retrobulbar blood flow velocities, higher resistivity indexes, and visual field loss, including a 4-year study with 112 patients with primary open-angle glaucoma by Moore et al., who found that lower baseline blood flow velocities predicted visual field loss.<sup>19</sup> Additionally, cross-sectional studies using OCTA have shown correlations between decreased macular and peripapillary capillary density and visual field loss in patients with glaucoma.<sup>7,27,29</sup>

## Systemic Vascular Disease and Glaucoma

It has been recognized for many years that patients with glaucoma have a higher prevalence of concomitant vascular disease compared with the rest of the population. This has been reported as particularly true in normal-pressure (tension) glaucoma. Systemic vascular disease includes the ocular vasculature, with susceptible ocular microvasculature potentially at the forefront of vascular damage. The more common systemic vascular conditions reported include cardiac disease (angina), systemic hypertension and hypotension, small vessel disease (as occurs in atherosclerosis and diabetes mellitus), and cerebrovascular disease.<sup>37,38</sup> In addition, the presence of systemic vasospastic conditions, such as Raynaud's phenomenon and migraine, are relatively common in normal-pressure glaucoma. Studies show that spontaneous and/or medically induced significant nocturnal systemic hypotension ("dippers"), especially deficits of at least 10 mm Hg compared with daytime blood pressure, predicted visual field deficits and subsequent glaucoma progression.<sup>39</sup> Increased erythrocyte aggregation and decreased erythrocyte elongation index (deformability) have been reported in patients with open-angle glaucoma, the latter of which has been shown to be significantly correlated with RNFL thickness.<sup>40</sup>

Furthermore, stronger correlations in blood flow abnormalities with glaucomatous structural damage in patients of African descent compared with those of European descent suggests possible complexity of vascular etiology across ethnicities.<sup>23,41</sup>

The concept of vasospasm has often been described in the glaucoma literature, particularly for normal-pressure open-angle glaucoma.<sup>38</sup> An abnormal vascular endothelial response (with normal anatomy) to common everyday stimuli, such as cold, stress, mechanical force, and anxiety, is implicated. Many patients exhibit a Raynaud's phenomenon-like peripheral circulation, with reduced blood flow to the fingers after immersion of the hand in cold water. This is supported by abnormal blood flow regulation, specifically impaired vasodilation in patients with normal-pressure glaucoma,<sup>42</sup> as demonstrated by impaired retinal vein vasodilation and increased retinal artery constriction.<sup>43</sup> Thickening of the intima and media of the carotid vessels in subjects with normal-pressure glaucoma has also been shown.<sup>44</sup> Migraine and silent myocardial ischemia appear to be more prevalent, and elevated systemic levels of endothelin-1 have been reported in normal-pressure glaucoma. A possible explanation for endothelin -1 contribution to ONH ischemia may be the presence of fenestrated capillaries at the prelaminar ONH, which allow for the passage of endothelin -1 and subsequent vasoconstriction of ONH vasculature.<sup>44</sup>

Therefore, for each individual patient with glaucoma, it is important that care providers review an accurate history of systemic diseases, particularly cardiovascular problems, as well as that of all systemic medications taken. Many cardiovascular drugs have potential effects within the eye, including systemic beta-blockers and calcium channel blockers (which have an ocular hypotensive effect). Obtaining accurate systemic and medication histories is important at the time of diagnosis, and it is essential that this information is regularly updated.

## PHARMACOLOGY

When reduced ocular and ON blood flows contribute significantly to the pathogenesis of axonal loss, modification of blood flow might provide protection from ischemia-induced neuronal damage; however, currently there are no treatments for vascular improvement in glaucoma. Topical carbonic anhydrase inhibitors in combination with beta-blockers increase retrobulbar, choroidal, and retinal blood flows in patients with high-pressure and normal-pressure glaucoma.<sup>45</sup> The use of calcium channel blockers for systemic hypertension may be useful in the treatment of normal-pressure glaucoma,<sup>46</sup> although some studies have shown evidence that these drugs may promote glaucoma progression.<sup>47</sup> In some patients, improvement in ocular blood flow and contrast sensitivity is seen with calcium-channel blockers or inhaled CO<sub>2</sub> in short-term investigations. Additionally, patients with normal-pressure glaucoma experienced a smaller deterioration rate of visual field sensitivity after 2 years of oral brovincamine, a relatively

selective cerebral vasodilator with weak calcium antagonist action.<sup>48</sup> Medical and surgical reduction of IOP may, in some patients with glaucoma, improve ocular blood flow as well.<sup>49,50</sup>

Advances in imaging modalities and efforts to establish longitudinal data, especially in ON tissue beds, may allow for improved and individualized glaucoma management planning, resulting in better patient outcomes.

## STATEMENT OF DISCLOSURE

None of the listed authors has any competing interests with submission of this manuscript. Dr. Alon Harris would like to disclose that he receives remuneration from Stemnion, Biolight, Nano Retina, AdOM, Science-Based Health, Isarna Therapeutics, and Ono Pharmaceuticals for serving as a consultant. Dr. Harris also holds an ownership interest in AdOM, Nano Retina, and Oxymap. All relationships listed above are pursuant to Indiana University's policy on outside activities. None of the other authors listed have any financial disclosures.

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# Ocular Hypertension

Jason D. Rupp, Michael A. Kass

# 10.9

**Definition:** Although there is no absolute number separating normal intraocular pressure (IOP) from abnormal IOP, ocular hypertension is a condition in which IOP is above the usual range but without any evidence of structural or functional optic nerve damage.

## Key Features

- IOP greater than 21 mm Hg without evidence of secondary causes.
- No evidence of optic neuropathy or nerve fiber layer loss.
- No visual field loss.
- Open angles on gonioscopy.

## INTRODUCTION

Intraocular pressure (IOP) is the only modifiable risk factor for primary open-angle glaucoma (POAG), and patients with ocular hypertension (OHT) are at greater risk for developing the disease. Predictive factors for the conversion of OHT to POAG can be used to guide the clinician in determining how to individualize management for patients with OHT, including the frequency of examinations and the potential benefit of early treatment.

## EPIDEMIOLOGY AND PATHOGENESIS

OHT is estimated to affect from 4.5%–9.4% of middle-aged and older adults in the United States.<sup>1</sup> The prevalence of OHT varies among different ethnic groups. The Afro-Caribbean population in the Barbados Eye Study was found to have one of the highest reported prevalence rates of OHT (12.6%).<sup>2</sup> In contrast, other studies found the prevalence of OHT was 1.1% in southern India<sup>3</sup> and 0.9% in Japan.<sup>4</sup> The prevalence rate of OHT increases substantially with age. In the Framingham Eye Study, 6.2% of white participants under age 65 years had an IOP greater than 21 mm Hg, compared with 8.7% in those over age 75 years.<sup>1</sup>

## Predictive Factors for Conversion of OHT to POAG

The Ocular Hypertension Treatment Study (OHTS) provided valuable data about progression from OHT to POAG. The predictive factors from the OHTS are discussed below.

## Central Corneal Thickness

The OHTS trial showed that baseline central corneal thickness (CCT) was a powerful predictor of the development of POAG among OHT participants.<sup>5</sup> In OHTS, eyes with a CCT of 555  $\mu$ m or less had a threefold greater risk of progression to glaucoma at 5 years compared with participants who had a CCT of greater than 588  $\mu$ m. Fig. 10.9.1 demonstrates the percentage of the observation group that developed POAG, determined on the basis of baseline IOP and CCT.<sup>5-7</sup>

## Intraocular Pressure

Higher IOP is a predictive factor of progression from OHT to POAG. The relative risk is 1.1 for each 1 mm Hg increase in baseline IOP within the range of the study.

## Age

Older participants had a greater risk of conversion to glaucoma.

## Pattern Standard Deviation

A greater baseline pattern standard deviation (PSD) on standard automated perimetry correlated with increased risk of progression from OHT to POAG.

## Optic Nerve

Even when patients with OHT had no clinically apparent glaucomatous structural damage, a larger cup-to-disc ratio was a risk factor for progression.

## Optic Disc Hemorrhage

In a multivariate analysis, the occurrence of an optic disc hemorrhage increased the risk of developing glaucoma 2.6-fold.<sup>8,9</sup>

## Other Predictive Factors

Race was found to be significant in the univariate analysis, but not in the multivariate analysis of the OHTS when cup-to-disc ratio and CCT were included. However, many studies support the finding that POAG is 3–4 times more prevalent in black versus white populations.<sup>10-12</sup> Although family history was not found to be a significant predictor for progression in the OHTS, other studies have shown it to play a key role in the susceptibility to POAG.<sup>13,14</sup> Genetic studies have not yet found risk alleles or genes with enough of an effect to warrant routine clinical testing.<sup>15</sup>

## DIAGNOSIS

Thorough medical and ocular histories must rule out any secondary causes of elevated IOP, such as corticosteroid use or trauma. A complete ophthalmic examination with the following key components is necessary:

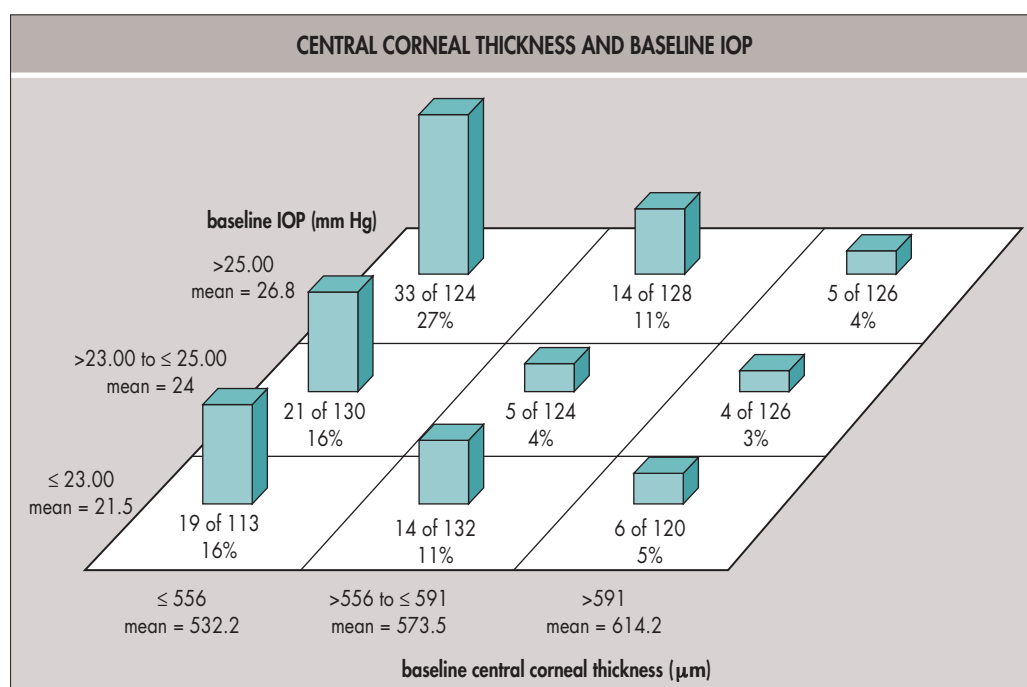
- *Tonometry*—IOP greater than 21 mm Hg.
- *Ophthalmoscopy*—normal optic nerve with no evidence of glaucomatous cupping or nerve fiber layer (NFL) loss.
- *Standard automated perimetry*—no evidence of visual defects.
- *Pachymetry*—measurements should be performed over the central cornea in an area without pathology.
- *Gonioscopy*—open angles with no evidence of pathology.
- *OCT*—definitive longitudinal studies have not been performed to establish diagnostic thresholds for distinguishing between OHT and POAG, but there is evidence that a thin NFL correlates with high risk OHT.<sup>16-18</sup> OCT can also detect loss of macular ganglion cells.<sup>19</sup>

Other tests that may be beneficial include the following:

- Corneal hysteresis.
- Heidelberg Retina Tomography.
- GDX-scanning laser polarimetry (Laser Diagnostic Technologies, San Diego, CA).

## DIFFERENTIAL DIAGNOSIS

The differential diagnosis for OHT includes undiagnosed POAG as well as secondary causes of OHT, such as topical or systemic corticosteroid use, angle recession, and angle-closure glaucoma.



**Fig. 10.9.1** Graph demonstrating the effect of central corneal thickness and baseline intraocular pressure on progression to glaucoma in patients with ocular hypertension. These results were derived from an analysis of pooled data from the Ocular Hypertension Treatment Study and the European Glaucoma Prevention Study. (Reproduced from data, Ocular Hypertension Treatment Study Group and European Glaucoma Prevention Study Group. Validated prediction model for the development of primary open-angle glaucoma in individuals with ocular hypertension. *Ophthalmology* 2007;114:10–19, copyright 2007, with permission from the American Academy of Ophthalmology.)

## TREATMENT

The OHTS trial provided predictive factors (CCT, PSD, age, cup-to-disc ratio, disc hemorrhage, and IOP) that should be considered when deciding whether to treat OHT and confirmed the safety and efficacy of treating OHT with topical medications. Specifically, it determined that ocular hypotensive medication reduced the rate of progression of OHT to POAG by 50% at 10 years. The absolute reduction in POAG incidence was greatest in participants in the highest tertile of baseline risk (from 42%–19%).<sup>20</sup>

Treatment of OHT can be considered in high-risk patients after taking into account patient preference, age, and health status. Patients at low risk of conversion can be followed up yearly, typically without treatment, as long as they are monitored for signs of early disease.<sup>21–23</sup> With this treatment plan, regular follow-up examinations and testing are critical. Some physicians may prefer to monitor all patients with OHT, initiating medication only after early damage is detected. It is important to involve the patient in the decision making so that an individualized treatment plan can be created.

Patients can be stratified by risk calculators derived from the OHTS and European Glaucoma Prevention Study data.<sup>24</sup> Cost-effectiveness analysis using OHTS data supports treating patients with OHT if there is at least a 2% annual risk of development of POAG.<sup>25,26</sup> Although the calculator may help guide the clinician in determining patient management, it should not supersede clinical judgment.<sup>27,28</sup>

## COURSE AND OUTCOME

The majority of patients with OHT do well over long periods of follow-up. The accepted average rate for progression from OHT to POAG is 1%–2% per year, but subgroups with higher risk do exist. In eyes with OHT that did not reach an endpoint for POAG, the rate of change of mean deviation was slow (–0.05 dB/yr), whereas eyes that converted to POAG progressed at a faster rate (–0.26 dB/yr).<sup>29</sup> Although data from the OHTS suggest that visual field change in early glaucoma is most commonly localized, a significant number of individuals will show diffuse changes that may go undetected if only pattern deviation analyses are used.<sup>29,30</sup> The earliest changes of POAG, however, were most commonly structural, highlighting the importance of clinical examination, optic disc photography, and imaging of the optic nerve and NFL.

In general, high-risk patients who are treated are likely to have good outcomes. For patients who are monitored without treatment and who progress, early detection of damage and treatment may slow further progression.

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# Primary Open-Angle Glaucoma

James C. Tan, Paul L. Kaufman

# 10.10

**Definition:** Age-related optic neuropathy characterized by progressive optic nerve cupping, visual deficit, and gonioscopically open angles.

## Key Features

- Glaucomatous optic disc cupping and retinal nerve fiber loss.
- Corresponding visual field abnormality.
- Open anterior chamber angles.
- Intraocular pressure as a major and only modifiable risk factor, applicable at every pressure level but with higher pressures posing greater risk.
- Progressive, age-related condition.

## Associated Features

- Corneal thickness.
- Chronic disease.
- Visual impairment.

## DEFINITION AND CLASSIFICATION

The term *glaucoma* describes a progressive optic neuropathy with characteristic optic disc cupping and corresponding visual deficit. The condition has as its basis gradual loss of retinal ganglion cells (Fig. 10.10.1) and axons traversing the retina and the optic nerve (Fig. 10.10.2) to the brain. Intraocular pressure (IOP) is a major modifiable risk factor. Glaucoma is progressive; left unchecked, it may cause blindness.

Glaucoma is classified as *primary* if elevated IOP is of unknown etiology and *secondary* where an etiological factor is identifiable. Conventionally, the term *primary open-angle glaucoma* (POAG) has been applied to adult primary chronic glaucoma, in which the anterior chamber drainage angle is open and IOP elevated for no apparent reason. Overall prevalence of POAG in the United States is about 1%, with this varying ethnically,

wherein the rates among African American and Hispanic Americans are reported to exceed 4%.<sup>1,3</sup> These rates increase with increasing age in all ethnicities.

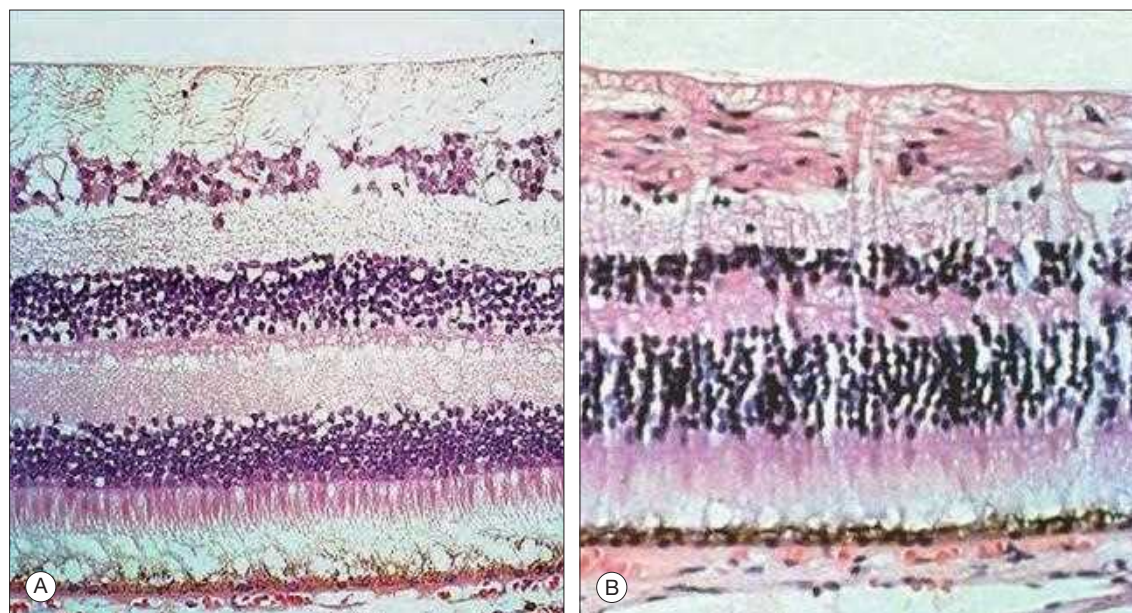
Two other entities are closely considered with POAG. People with ocular hypertension have open angles and elevated IOP (>21 mm Hg) that has apparently not caused nerve damage. They are at heightened risk of developing glaucoma. People with so-called normal-tension glaucoma (NTG) have primary chronic glaucoma and open anterior chamber drainage angles but IOP within normal statistical limits (<22 mm Hg). NTG is now classified as part of the POAG spectrum. Neither ocular hypertension nor NTG is rare<sup>4,5</sup>; ocular hypertension is more prevalent than POAG, whereas at least 30% of those with POAG have NTG.

This chapter will discuss the risk factors for POAG, the nature of progressive visual loss in the disease, and the broad principles of diagnosis and treatment.

## INTRAOCULAR PRESSURE, RISK FACTORS, AND ASPECTS OF MOLECULAR PATHOGENESIS

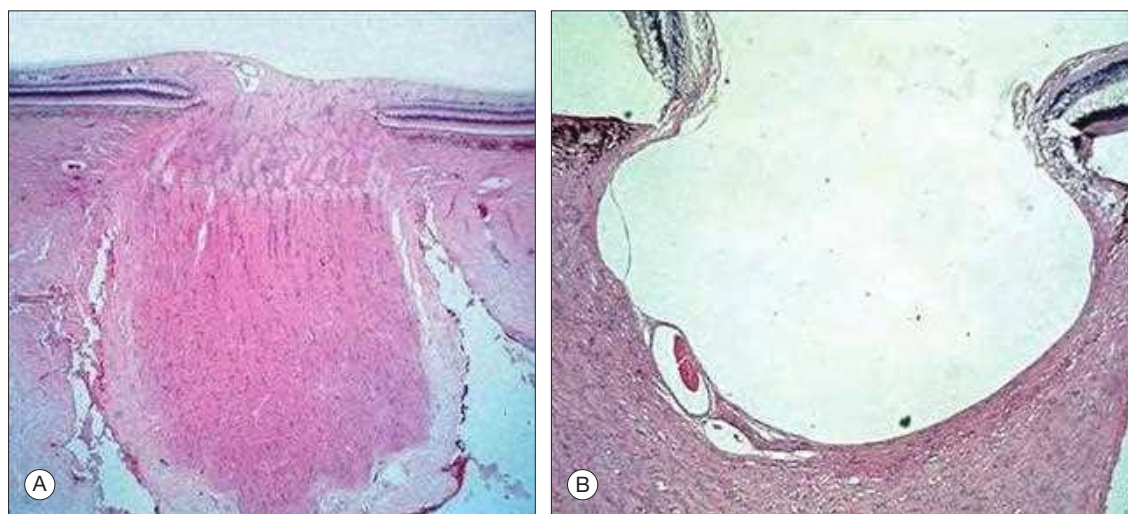
Many epidemiological, clinical, histopathological, and experimental studies support the role of IOP in glaucoma pathogenesis.<sup>6,7</sup> However, what constitutes glaucoma-inducing IOP is not always clear in patients. The traditional cutoff for “normal” IOP of 21 mm Hg has its source in a German population survey in the 1950s.<sup>8</sup> This analysis assumed that the distribution of IOP is normal, but it is, in fact, skewed toward higher IOP.<sup>6</sup> The right-skew increases with age and varies with race. This statistical quirk means that the proportion of people with IOP exceeding 21 mm Hg and having glaucoma is less than initially predicted, and many will be diagnosed with ocular hypertension. We now realize that glaucoma-related pathological IOP has a continuous distribution and does not obey a strict cutoff.

Eyes with ocular hypertension are at increased risk of POAG. The risk of developing POAG is up to six times higher in those with ocular hypertension than in those without any risk factors for glaucoma.<sup>9</sup> The risk of developing POAG in ocular hypertension in the Ocular Hypertension



**Fig. 10.10.1 Histopathology of Human Retina Showing the Effect of Glaucoma.**

(A) Normal retina seen in cross-section. (B) Glaucomatous retina in which the retinal nerve fiber layer is thinned and ganglion cell bodies are sparser. (Photos courtesy Dr. Morton E. Smith.)



**Fig. 10.10.2 Histopathological Correlation of Glaucomatous Optic Disc Cupping.**

(A) Normal human optic nerve with a small cup. Axons of the thick retinal nerve fiber layer turn posteriorly to form the neuroretinal rim of the optic disc. The lamina cribrosa of the anterior optic nerve is transversely orientated in continuity with flanking sclera. (B) Glaucomatous optic nerve with a markedly thinned retinal nerve fiber layer and neuroretinal rim, large cup, and posteriorly bowed lamina cribrosa. (Photos courtesy Dr. Morton E. Smith.)

Treatment Study was 9.5% over 5 years.<sup>10</sup> In a standard clinic setting this may be observed as 1%–2% per year<sup>11,12</sup> or about 10% per decade.<sup>13</sup> This risk rises with IOP, increasing significantly at pressures over 24 mm Hg, and especially over 30 mm Hg.<sup>6,10,11,14,15</sup> POAG risk is further influenced by other factors, such as age, ethnicity, and central corneal thickness (see later).

The entity NTG is prevalent in east Asia, comprising over 80% of open-angle glaucoma.<sup>16,17</sup> The matching prevalence in Western countries is 30%–55%, based on isolated IOP readings in population studies,<sup>2,4,18</sup> although it is reported to be as high as 75%–82% in Hispanic Americans in Arizona,<sup>19</sup> Los Angeles Latinos,<sup>1</sup> and Australian Blue Mountains Caucasians.<sup>5</sup> Underdiagnosis of glaucoma<sup>1,4,5</sup> is not surprising given the traditional focus on IOP for glaucoma case-finding. Although IOP may not seem that high in NTG, it is still too high for these eyes,<sup>16</sup> and disease progression may be slowed by reducing IOP.<sup>20,21</sup>

Higher-than-normal IOP fluctuation occurs in POAG (including NTG) and may be evident as IOP peaks at certain times of day or with certain postures.<sup>22–25</sup> A further consideration is that the natural history of IOP in any individual is typically unknown; that is, in an eye with POAG we know little of the past course IOP has taken to become elevated, and we cannot predict its future course. We also do not know if IOP in some NTG persons has risen from an even lower baseline over time. A rise of IOP in POAG is not measureable over 6 years, but it is in pseudo-exfoliation glaucoma,<sup>22</sup> which is not surprising given the more pronounced IOP elevation and disease progression of the latter.<sup>22,26,27</sup> It does suggest, however, that a presumed IOP rise in POAG occurs gradually, perhaps over a decade or more.

Pathological IOP elevation in POAG is attributed to increased resistance to aqueous humor outflow.<sup>28</sup> In POAG, aberrant plaque-like accumulations of fine fibrils associate with elastic microfibrils of the trabecular meshwork,<sup>29–32</sup> a contractile and richly elastic drainage tissue that is an important site of aqueous outflow resistance. Nevertheless, only modest IOP lowering is yielded by surgically bypassing the trabecular meshwork,<sup>33</sup> suggesting that pathogenic roles of other drainage sites such as the intrascleral channels and uveoscleral pathway ought to be considered. Cellular and molecular mechanisms regulate these pathways and determine IOP.<sup>34</sup> An important POAG disease biomarker of still unknown origin is the aqueous level of transforming growth factor beta (TGFβ) that is consistently elevated in POAG eyes across diverse populations.<sup>35–42</sup> Elevated TGFβ causes trabecular meshwork stiffening and altered contractility that can increase outflow resistance.<sup>43</sup> New classes of pharmaceutical agents targeting trabecular contractility are presently in the development pipeline for POAG therapy.

Besides IOP, the strongest independent risk factor for developing POAG is age, with subjects aged greater than 60 years many times more likely to develop glaucoma than those in their 40s.<sup>1,3,5,11,19,44</sup> Glaucoma is more prevalent in people of Hispanic and African descent,<sup>1,3,44</sup> with the latter typically younger and having higher IOP and more advanced optic neuropathy at initial diagnosis compared with Caucasians. Their disease is also more refractory to treatment and has a worse prognosis.<sup>45</sup> IOP fluctuation itself is considered by many to be a risk factor for disease progression.<sup>23,24,46–52</sup>

Other significant risk factors are genetic predisposition and a positive family history. A further independent and important risk factor is thin

central corneas, which may be related to structural factors conferring on the optic nerve susceptibility to damage.<sup>10,53</sup> Thin central corneas may also cause IOP underestimation.<sup>10,54</sup> Myopia, diabetes, systemic hypertension, and vascular conditions, such as migraine and vasospasm, are also considered risk factors for POAG, although the evidence is more ambiguous.

Large epidemiological and randomized control studies from recent decades have yielded vital quantitative data on the link between risk factors and glaucoma.<sup>55</sup> In the future, such information may be useful for estimating the actuarial risk of glaucoma in individuals, providing an extra tool for case-finding, diagnosis, and treatment.

## DIAGNOSIS

Diagnosing POAG requires evaluation of IOP; the anterior chamber angle by gonioscopy; optic disc and related structures, such as the retinal nerve fiber and ganglion cell layer; and visual field.

IOP has a normal diurnal variation that is more exaggerated with disease.<sup>56</sup> IOP is usually measured by Goldmann applanation tonometry. In measuring IOP, clinicians should be aware of extremes of corneal thickness,<sup>57</sup> wherein IOP is overestimated in thick corneas and underestimated in thin corneas because Goldmann tonometry assumes a central corneal thickness of 550 microns. This is important to consider in individuals who have had laser refractive surgery or who carry a diagnosis of NTG or ocular hypertension.<sup>10</sup>

The optic disc is evaluated for glaucomatous cupping (Fig. 10.10.3). In practice, it can be difficult to separate normal optic discs from glaucomatous optic discs on the basis of appearance. The reason is that the range of normal disc morphology overlaps with that of glaucoma, especially with early disease.<sup>58</sup> Optic disc stereophotography and retinal nerve fiber layer observation by red-free funduscopy or photography are traditional methods for assessing structural abnormality or change, with disc photography still commonly used. Newer imaging technologies, such as optical coherence tomography, have special analytical algorithms to help identify glaucomatous damage to the retinal nerve fiber layer and ganglion cell complex.

Evidence of reproducible visual field abnormality on standard “white-on-white” perimetry is enough to corroborate the suspicion of a glaucomatous-appearing optic disc. The visual field defect should correspond to the region of perceived optic disc abnormality. Although white-on-white visual field defects may not be the earliest sign of visual deficit in glaucoma (see next section), perimetry remains essential to diagnosing glaucoma.

## NATURE OF PROGRESSIVE VISUAL LOSS

Observing visual field change over time can inform on how POAG progresses. Progression may be considered in four phases: preperimetric (occult), threshold, critical,<sup>59</sup> and compatible with blindness.

### Preperimetric Glaucoma

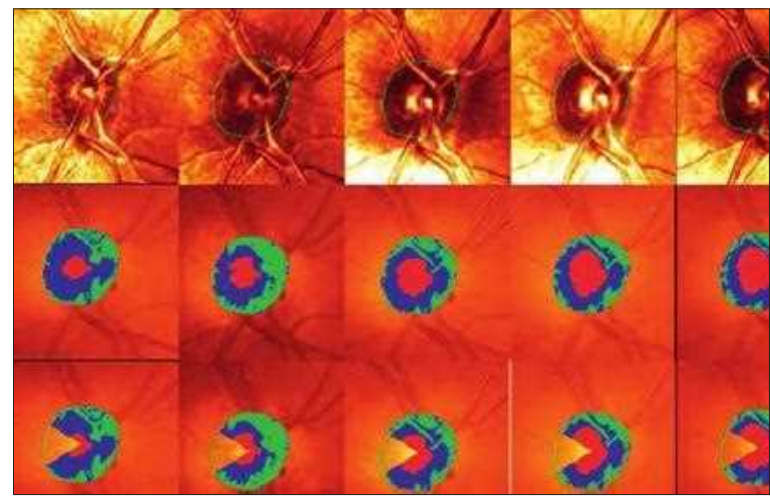
Initially, disease is subclinical during a prolonged occult period in which white-on-white visual fields—the standard for diagnosis—remain normal. Any decreased visual sensitivity during this time is still too subtle to be





**Fig. 10.10.3 Progressive Glaucomatous Optic Neuropathy.** (A) Glaucomatous optic disc. (B) The same optic disc 3 years later. There is increased cupping associated with localized rim thinning inferiorly.

detected by perimetry because for this to happen, sensitivity must be decreased enough to consistently remain below the age-matched normal population visual threshold of detection. Perimetric signs, if present, are nonspecific and include blind spot change, isopter shrinkage on kinetic perimetry, and increased regional variability.<sup>60-62</sup> Other parameters of visual function, such as sensitivity to contrast, color (blue-yellow perimetry), motion, and the spatial frequency doubling illusion (frequency doubling perimetry), may already be abnormal. Despite visual fields being well preserved, significant retinal ganglion cell loss, progressive disc cupping (Fig. 10.10.4) and retinal nerve fiber layer thinning may already be present.<sup>63-66</sup>



**Fig. 10.10.4 Longitudinal Scanning Laser Tomography Images of the Optic Nerve in an Eye With Ocular Hypertension.** There is progressive and widespread neuroretinal rim loss over time so that the optic cup is enlarged concentrically. (Top row) Topography images. (Second row) Color-coding indicates the neuroretinal rim (blue and green) and optic cup (red). (Third row) Image analysis indicates parts of the rim (blue-green) and corresponding cup (red) that are significantly altered over time. This pathological change affected over three-quarters of the rim circumference despite visual fields remaining normal. (From Tan JC, Hitchings RA. Approach for identifying glaucomatous optic nerve progression by scanning laser tomography. *Invest Ophthalmol Vis Sci* 2003;44:2621-6.)

## Threshold and Conversion

The term *conversion* refers to persistent visual field defects developing in previously normal visual fields. It describes the appearance of visual field abnormality over time in those suspected to have glaucoma. Normal fields “convert” when visual sensitivity in one or more regions decreases to persistently lie outside normal limits. This is often gradual, although these early visual field defects may appear transiently or abruptly because they are just at the threshold of detection.<sup>59</sup> They may disappear after treatment, only to reappear later, and it could be years before they become consistently present.

At conversion the earliest visual field defects involve small regions in the arcuate and central 30° of the visual field, and nasal steps.<sup>60-62</sup> Inferior arcuate defects are mainly nasal, but superior arcuate defects are more central and nearer fixation. Conversion does not imply a sudden appearance of glaucoma but rather that previously preperimetric disease has worsened to become detectable.

## Critical Phase

When the earliest consistent visual field defects appear, disease is no longer early as ~50% of ganglion cells and axons may already be lost.<sup>63,64,67</sup> Despite treatment many eyes may show visual deterioration. In unilateral glaucoma, there is a 26% risk of visual field abnormality developing in the fellow eye within 5 years.<sup>67</sup> Without adequate treatment the risk of vision deteriorating to cause functional impairment within a decade is significant.<sup>68,69</sup>

Scotomata frequently evolve by deepening, but enlarging arcuate defects and the appearing of new defects are also common.<sup>70</sup> Change over time usually follows a linear or curvilinear course, but it may also seem episodic and more stepwise. Bigger and denser scotomata tend to deteriorate faster.<sup>71</sup> The upper and lower visual field hemispheres show differing susceptibilities to developing abnormality, but over a decade, roughly a third of eyes with only one hemisphere affected initially will develop bi-hemispheric abnormality.<sup>59,70</sup> Because upper hemispheric involvement tends to be more central,<sup>72</sup> the visual impact of such abnormality is expected to be greater. Simultaneous bi-hemispheric involvement carries a poor prognosis; without adequate treatment, up to half these eyes will suffer absolute visual field loss over a decade.<sup>44</sup>

## Blindness

Blindness may occur despite treatment. Studies show the following: Despite treatment, the risk over 20 years of developing unilateral and bilateral blindness is 27% and 9%, respectively<sup>73</sup>; the cumulative rate of



glaucoma blindness despite treatment is 19% over 22 years<sup>74</sup>; despite IOP being controlled below 22 mm Hg, the probability of retaining useful vision declined by 31% over 15 years, with half of visual disability attributable to glaucoma.<sup>69</sup> This high incidence of blindness is seen in both developed and developing countries.

Glaucoma affects 60–70 million people worldwide and is the leading cause of irreversible blindness.<sup>75,76</sup> It is estimated that three quarters of people with glaucoma have the open-angle variant, and of these, almost 10% are bilaterally blind.<sup>75</sup> POAG is the most prevalent form of glaucoma in the United States, where it is the leading cause of blindness in African Americans and Hispanic Americans and the third leading cause in Caucasians.<sup>75,77</sup> The prevalence of glaucoma blindness markedly increases with age. Glaucoma blindness is higher in African Americans compared with Caucasians, with African Americans going blind 10 years earlier, on average.<sup>78</sup> Sometimes severe visual impairment is already present at diagnosis. In the Olmstead County Community Study in Minnesota, 10% of subjects were at least unilaterally blind at diagnosis, and of these, 2% were bilaterally blind. The 20-year cumulative risk of glaucoma-related unilateral blindness was 26% and bilateral blindness was 9%.<sup>68</sup>

## TREATMENT AND MONITORING

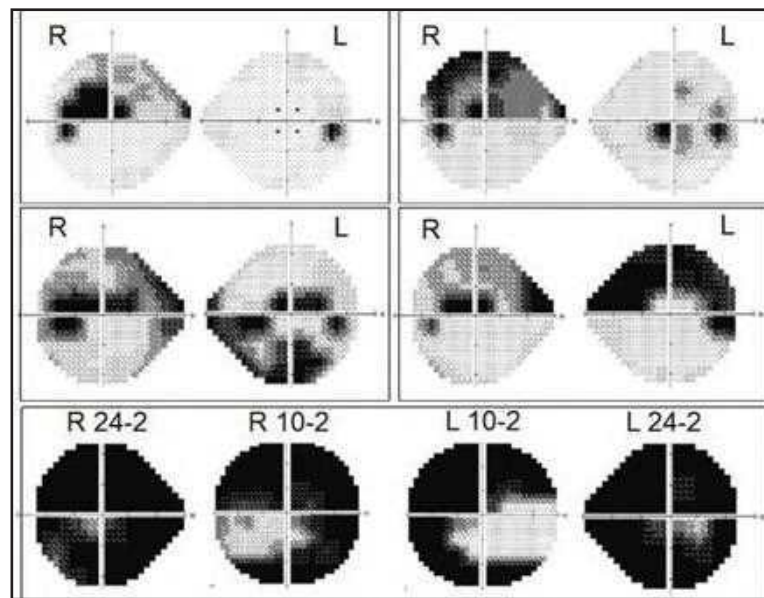
IOP is the only risk factor that can be manipulated to stop or slow glaucoma progression. Rigorous IOP-lowering can help control POAG.<sup>20,21,79–84</sup> This is commonly achieved with medication, laser, surgery, or some combination thereof. Currently, it is not known how other risk factors influence the disease or how these risk factors may be altered. Patients with ocular hypertension at high risk of conversion may benefit from closer monitoring or treatment to modify risk.<sup>83</sup> Clinicians are forced initially to guess a level of IOP—known as “target pressure”—which will stop or slow further damage.<sup>82</sup> Once target pressure is achieved, the level of IOP still needs to be monitored because it may change over time, fluctuate, or not be low enough.<sup>84</sup> Isolated clinic measurements do not necessarily predict the peak and range of IOP variation that affects the likelihood of glaucoma progression. The possibility of higher IOP may be verified by checking IOP at different times of the day, although this does not fully capture nocturnal variations, and there remains a need for new technologies to monitor IOP continuously.

Treatment needs to be individualized because the IOP level needed to control disease varies widely among individuals. There is no universal formula to tell how much IOP needs to be reduced. There is need for clinical judgment, aided by reliable clinical measurements, where available. Patients with moderate or advanced disease especially with fixation-threatening visual loss (Fig. 10.10.5) may benefit from earlier surgery and more aggressive IOP lowering.<sup>85</sup> Lowering IOP, however, has limits, as determined by treatment side effects and possibility of hypotony, especially after surgery.

The real guide for long-term clinical management is not IOP but the course taken by the optic neuropathy. It is standard practice to sequentially examine the visual field and optic disc to ascertain progression. But reliably detecting progression using subjective and qualitative methods is not easy,<sup>86</sup> especially when trying to identify smaller amounts of disease-induced change. It is important to determine if perceived change from testing is real and reproducible and not caused by test variability. It is hoped that newer objective, quantitative, and potentially more reliable vision (e.g., multifocal visual evoked potential) and imaging tests (see Fig. 10.10.4) will help in this regard.

POAG is a chronic disease, and patients are more likely to comply with treatments if they understand the nature of the disease and the need for ongoing treatment and monitoring. Noncompliance with medical treatment is a significant barrier to effective control of the disease, being reported in 30%–80% of patients.<sup>87–89</sup> One reason for noncompliance is that glaucoma treatments may cause symptoms, whereas the disease may otherwise be asymptomatic. Older patients are especially susceptible to the systemic side effects of glaucoma medications (e.g., beta-blockers). It is useful to involve patients' families as supports, where possible.

Timely and effective treatment is critical to preventing visual disability resulting from POAG. It is vital that the clinician develop some estimate of the rate of progression, its likely threat to central fixation, and lifetime risk of functional visual compromise. Factors that may influence prognosis, such as race, age, or family history, ought to be taken into account, as should other issues common to chronic disease such as the coexistence of other illness, life expectancy, quality of life, and the cost and side effects of long-term treatments.



**Fig. 10.10.5** Examples of Visual Fields in Which Paracentral Field Locations Are Affected and Fixation Is Threatened or Involved. Each of five visual field pairs is enclosed within a box. (First row, left box) Scotoma in the right (R) eye extends from the blind spot affecting both superior paracentral locations. Paracentral perimetric locations are indicated by blue spots in the left eye (L) visual field, which is normal. Field damage is clearly asymmetric. (First row, right box) The right eye has developed a superior altitudinal defect with deeper defects in paracentral locations. Paracentral defects in the left eye have first developed inferiorly, which is somewhat less common. (Second row, left box) Fixation threat associated with bi-hemispheric field involvement carries a poor prognosis. (Second row, right box) The left eye has a dense superior arcuate defect with paracentral sparing that is helping compensate for paracentral loss in the right eye. It is critical to therapeutically preserve paracentral vision in the left eye. (Third row) Both eyes had residual central islands. Three of four paracentral locations were affected with fixation split as seen in the corresponding 10-2 fields.

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# Normal-Tension Glaucoma

Louis R. Pasquale

# 10.11

**Definition:** A progressive excavation of optic nerve head tissue despite recorded intraocular pressures that are typically tolerated by most patients.

## Key Features

- Preponderance of untreated intraocular pressure readings that are only slightly higher compared with patients without glaucoma.
- Glaucomatous cupping with loss of prelaminar neural tissue accompanied by variable amounts of laminar displacement posteriorly and under the neuroretinal rim.
- Visual field loss patterns conforming to retinal nerve fiber layer loss.
- Open angles on gonioscopy.
- No history of eye disease with raised intraocular pressure.

## Associated Features

- Vascular endothelial cell dysfunction.
- Headache with or without features of migraine.
- Optic disc hemorrhage.

## INTRODUCTION

With the relaxation of intraocular pressure (IOP) criteria for primary open-angle glaucoma (POAG), it is now recognized that a significant percent of glaucoma cases present with IOP 21 mm Hg or less. In fact, there is considerable overlap in disease features between cases that present with IOP above and below the arbitrary IOP cutoff of 21 mm Hg. Normal tension glaucoma (NTG) is a potentially blinding disease, where the optic nerve sustains load-bearing failure in the face of measured IOPs that should be tolerable but nonetheless lead to excavation and erosion of the neuroretinal rim tissues.

## EPIDEMIOLOGY AND PATHOGENESIS

In the landmark Barbados Eye Study, 47.8% of incident open-angle glaucoma cases had a baseline IOP 21 mm Hg or less.<sup>1</sup> In analytical epidemiological studies performed in the Nurses Health Study and Health Professionals Follow-up Study, approximately 30% of incident POAG cases had known maximum IOP 21 mm Hg or less.<sup>2</sup> Interestingly, in a Korean population-based study only 38 of 10,096 subjects had IOP greater than 21 mm Hg (0.4%), and therefore almost all of the incident POAG cases could be designated as NTG by using the arbitrary definition of idiopathic optic nerve head excavation associated with known maximum IOP less than 22 mm Hg.<sup>3</sup>

A contemporary view of disease pathogenesis is that load-bearing sclera fails leading to backward bowing of the lamina cribrosa, although concomitant primary neuronal/glial cell support failure cannot be ruled out. This backward bowing produces an axonopathy that ultimately manifests clinically as cupping and characteristic visual field loss. This optic nerve head vulnerability is created by a combination of inherent connective tissue weakness, genetic factors, vascular mechanisms, autoimmune deviations, and inflammatory insults.

One genetic region that contributes to optic nerve vulnerability in NTG is *CDKN2B-AS*,<sup>4,5</sup> but exactly how gene variants in this region contribute to optic nerve degeneration is unclear. A meta-analysis of seven candidate gene association studies suggest that two common polymorphisms in *OPA1* are associated with NTG.<sup>6</sup> Haploinsufficiency in *OPA1* produces

mitochondrial dysfunction and causes a mendelian form of dominant optic atrophy.

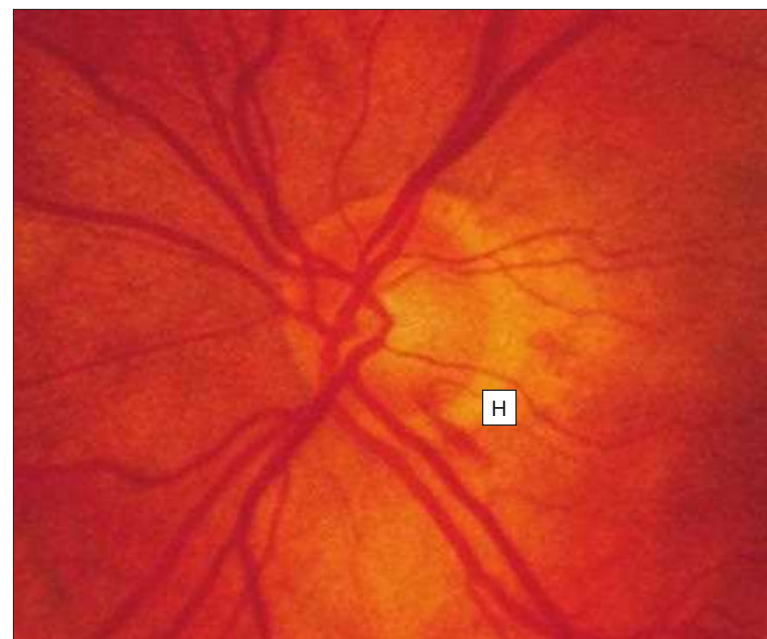
Vascular mechanisms may involve nocturnal hypotension, vascular dysregulation, and autonomic dysfunction. Evidence for an immune deviation comes from work showing an abundance of serum paraproteins and autoantibodies in NTG versus controls.<sup>7</sup> Furthermore, the discovery of rare optineurin (*OPTN*) variants in familial POAG that includes patients with known maximum IOP less than 22 mm Hg, implicates impaired tumor necrosis factor alpha signaling in NTG.<sup>8</sup>

## OCULAR MANIFESTATIONS

No characteristic ocular features distinguish NTG from POAG that develops in association with higher IOP levels. However, NTG has some notable ocular features. The IOP may be slightly higher in the more severely affected eye, although the difference may only be 1–2 mm Hg.<sup>9,10</sup> In a study from South Korea, the preponderance of diurnal IOP measurements in untreated NTG were less than 22 mm Hg.<sup>11</sup>

Patients with NTG are more likely to exhibit optic disc hemorrhages compared with those with POAG with higher IOP.<sup>12</sup> Disc hemorrhage represents an important biomarker for disease progression in NTG,<sup>13</sup> but this is also true for OAG across the IOP spectrum (Fig. 10.11.1). The optic nerve head rim tissue can be focally eroded or exhibit diffuse thinning accompanied by extensive peripapillary atrophy, suggesting that distinct NTG endophenotypes do exist.<sup>11</sup> Determining whether macula or deep optic nerve head ocular coherence tomography will reveal distinct structural biomarkers associated with these NTG endophenotypes is currently a topic of active clinical research.

The visual field is more likely to show defects close to fixation, although this feature can be seen in glaucoma patients with IOP greater than 21 mm Hg.<sup>14</sup> Overall rates of visual field progression in untreated NTG vary considerably from –0.2 to greater than –2 dB per year on the Total Deviation plot.<sup>15</sup>



**Fig. 10.11.1** Optic disc of a patient who has normal-tension glaucoma. Note disc hemorrhage (H).

Over a period of 4–5 years, up to 50% of patients with untreated NTG show demonstrable progression.<sup>15</sup>

## DIAGNOSIS

Typically, patients are asymptomatic on presentation but will occasionally present with acute paracentral vision loss. It is critical to obtain past ocular, medical, and surgical histories (both ocular and nonocular) on all patients with new glaucoma. Past ocular history may reveal a history of uveitic glaucoma that could contribute to the appearance of a glaucomatous optic nerve at normal IOP. History of current and past medication use is also important, as pointed out in the differential diagnosis section below. For instance, a history of past steroid use may suggest prior steroid-induced glaucoma as a cause of apparent NTG. Vision and IOP are ophthalmic vital signs, and they are typically normal in NTG patients. There are no agreed-upon IOP criteria for NTG, although most recent publications require an IOP less than 22 mm Hg.

Confirmation of the diagnosis requires the following:

- Slit-lamp examination to rule out signs consistent with secondary glaucomas, such as prior pigment dispersion syndrome.<sup>16</sup>
- Gonioscopy to ensure the angle is not occludable.
- Fundus examination to detect signs of excavation of the cup and erosion of the neuroretinal rim while excluding signs of nonglaucomatous optic neuropathy, such as pallor out of portion to cupping<sup>17</sup> or chorioretinal lesions that either produce<sup>18,19</sup> or appear in a distribution that could mimic glaucomatous visual field defects.<sup>20</sup>
- Confirmation that the visual field defect conforms to the retinal nerve fiber layer territory.

Currently, ambulatory blood pressure measurements have no role in diagnosing NTG. Patients with pallor, cupping, or visual field defects respecting the vertical meridian should be considered for neuroimaging. In select instances, neuroimaging may also be indicated in younger patients or in those with a history of rapid visual field progression. Widespread use of neuroimaging to screen for intracranial pathology in patients with NTG should be discouraged. Occasionally, visual symptoms out of proportion to Snellen acuity (e.g., profound nyctalopia) or visual field loss not explained by the optic nerve head appearance may trigger a search for retinal disease, such as retinitis pigmentosa.<sup>21</sup>

## DIFFERENTIAL DIAGNOSIS

The differential diagnosis of NTG is fairly extensive and summarized in [Box 10.11.1](#).

Many patients with NTG are discovered to have IOP greater than 21 mm Hg on more extensive IOP profiling. In another scenario, a patient with “progressive NTG” may have had a history of IOP greater than 21 mm Hg in the distant past, but often those records are unavailable. Careful history or examination in apparent NTG cases may reveal prior episodes of elevated IOP that likely produced glaucomatous optic neuropathy that is now nonprogressive.

“Myopic glaucoma” is emerging as a challenging condition that can be considered a form of open-angle glaucoma often associated with IOP less than 22 mm Hg. These patients can present in young adulthood,<sup>22</sup> and they have different IOP profiles versus NTG associated with focal disc notching.<sup>11</sup> The optic nerve can exhibit a variety of dysmorphic features, including peripapillary atrophy, tilt, and torsion.<sup>23</sup> Myopic glaucomatous optic neuropathy can be progressive and seems to be IOP sensitive.<sup>24</sup>

A variety of optic neuropathies can be misconstrued as NTG. Conversely, NTG can be incorrectly labeled as nonglaucomatous optic neuropathy. Dominant optic atrophy typically affects the maculopapillary bundle early on, producing temporal wedge cupping as opposed to vertical elongation of the cup.<sup>25</sup> NTG can be misconstrued as nonarteritic anterior ischemic optic neuropathy (AION) because of seemingly rapid onset altitudinal visual field loss, but a large cup volume and insidious progression can solidify a diagnosis of open-angle glaucoma at normal IOP. Conversely, arteritic AION commonly produces glaucoma-like cupping.<sup>26</sup> Superior segmental optic nerve hypoplasia (SSONH) typically is associated with a maternal history of type 1 diabetes mellitus and presents with stationary dense inferior visual field defects,<sup>27</sup> although coexistent SSONH and progressive NTG have been reported.<sup>28</sup> Documented recurrent intrathecal hypotension caused by malfunctioning ventriculo-extracranial shunts was associated with “NTG” (focal notching, disc hemorrhage, and superior paracentral scotoma were present) in a 27-year-old with a history of pinealoblastoma.<sup>29</sup> Last but not least, anterior visual pathway lesions can produce

### BOX 10.11.1 Differential Diagnosis of Normal-Tension Glaucoma

- High-tension glaucoma possibly misclassified as NTG:
  - More extensive intraocular pressure (IOP) profiling reveals elevated IOP greater than 21 mm Hg
  - Prior secondary glaucoma that has resolved like corticosteroid-induced or uveitic glaucoma
  - Prior high-tension glaucoma with progression despite IOP in the “normal range”
- Myopic optic nerve/retinal degeneration with varying degrees of optic nerve tilt and torsion
- Nonglaucomatous optic neuropathy:
  - Dominant optic atrophy
  - Prior nonarteritic or arteritic anterior ischemic optic neuropathy
  - Superior segmental optic nerve hypoplasia
  - Anterior visual pathway lesions
- Optic neuropathy related to documented low intracranial pressure
- Retinal based nerve fiber layer dropout:
  - Branch retinal artery occlusion
  - Toxoplasmosis
  - Cotton-wool spot
- Deep chorioretinal pathology mimicking nerve fiber pattern of visual field loss
  - Retinitis pigmentosa
  - Hydroxychloroquine toxicity
  - Cancer-associated retinopathy
- Drug-induced nerve fiber layer dropout
  - Methanol toxicity
  - Ethambutol toxicity
  - Vigabratin use
  - Others

cupping.<sup>30</sup> If these conditions are caught early, it can save lives and reverse visual field loss.

Retinal pathology, such as cotton-wool spots and toxoplasma lesions, has been reported to produce nerve fiber dropout. Because the retinal arterioles supply the superficial retina, a branch retinal artery occlusion can produce visual field loss mimicking glaucomatous defects.<sup>31</sup> Finally, deep chorioretinal pathology that produces photoreceptor dropout in a nerve fiber pattern can produce visual field loss that mimics glaucoma.

It is important to be cognizant of the wide range of agents that can produce toxic optic neuropathy when encountering a patient with cupping, pallor, and normal IOP.<sup>32</sup> Intentional or accidental methanol exposure produces profound visual loss related to an optic neuropathy characterized by acute disc swelling followed by cupping and atrophy.<sup>33</sup> An idiosyncratic response to the antituberculosis drug ethambutol can produce an optic neuropathy with propensity to involve the maculopapillary bundles.<sup>34</sup> Vigabratin is a gamma-aminobutyric acid (GABA) transaminase inhibitor used to treat epilepsy in children and adults that has direct retinal ganglion cell toxicity.<sup>35</sup> Interestingly, a genome-wide search revealed that aspects of the GABA metabolism pathway was associated with NTG.<sup>36</sup>

## SYSTEMIC ASSOCIATIONS

The stereotypical NTG patient is a thin woman with poorly perfused distal extremities and migraines, and this view is supported by clinic-based<sup>37,38</sup> and population-based studies,<sup>39,40</sup> although more research is needed to confirm these associations. Several studies indicate the presence of nail bed extravascular hemorrhages<sup>41,42</sup> and impaired flow-mediated vasodilation in NTG,<sup>43</sup> but these findings also apply to patients with open-angle glaucoma and IOP greater than 21 mm Hg. Impaired flow-mediated vasodilation is demonstrated by impaired brachial artery dilation in response to peripheral limb ischemia and is an indicator of poor communication between the vascular endothelium and the adjacent smooth muscle. A pharmacological interventional study highlighted this impaired communication—the brachial artery of patients with untreated NTG had impaired dilation in response to the universal vasodilator acetylcholine.<sup>44</sup> Overall, the lack of consensus on systemic disease or biomarkers for NTG should discourage nondirected workups to explain glaucomatous optic neuropathy occurring at normal IOP because these workups are typically negative and tend to waste resources.

## TREATMENT

The decision to treat NTG depends on the patient's age, disease severity at presentation, and level of IOP. It may be justified to observe an older patient with mild visual field loss and IOP in the low teens, especially because it is possible that the disease will progress slowly.<sup>15</sup> However, a young patient with significant visual loss involving fixation needs treatment, especially if the IOP is in the upper teens and/or there is a history of migraine as the latter was a risk factor for disease progression in the untreated arm of the Collaborative Normal Tension Glaucoma Treatment Study.<sup>14</sup>

### Lower Intraocular Pressure

There is no agreed-upon formula for setting target IOP goals in NTG. Randomized clinical evidence suggests that reduction of IOP by approximately 30% can slow disease progression in NTG.<sup>45,46</sup> The Low Pressure Glaucoma Treatment Study indicated that brimonidine was more effective than timolol in slowing disease progression in NTG,<sup>47</sup> suggesting that the former agent should be considered in the medical regimen, even though it is a drug with an unfavorable side-effect profile. The Early Manifest Glaucoma Treatment study indicated that laser trabeculoplasty plus topical beta-blocker did slow disease progression in the subset of patients with open-angle NTG.<sup>48</sup> Topical beta-blockers are not contraindicated in NTG, but they should be avoided at bedtime in all patients with glaucoma because they are ineffective when administered at this time. Adjustment of the target IOP should be guided by the degree of structural and functional progression and perhaps by the presence of disc hemorrhages, given that they are predictors of disease progression. Despite the expanded pharmacological regimen and repeatability of laser trabeculoplasty, trabeculectomy with mitomycin C is often needed because many patients with NTG progress despite IOP in the mid- to low teens. Cases series suggest that achievement of single-digit IOPs can slow disease progression in these cases.<sup>49,50</sup> There is little role for minimally invasive glaucoma surgery or glaucoma drainage devices to achieve these IOP levels.

Besides lowering of IOP, there is no proven nonophthalmic strategy to slow disease progression, and the existing data suggest that there is no proven strategy to halt disease progression entirely. Perhaps it is reasonable to suggest that systemic hypertension medicines be taken closer to dinner as opposed to bedtime, thus avoiding a nocturnal dip in blood pressure. It is unclear if lifestyle changes, such as altering sleep patterns, exercise, diet, or supplement use, will alter the natural history of NTG,

although there may be very good reason to adopt some of these behaviors. There is certainly a need to identify and validate new neuroprotection targets for NTG.

## COURSE AND OUTCOME

Predictors of disease progression include female gender, migraine, and disc hemorrhage.<sup>14</sup> Hospital-based data from Japan suggests that the 20-year rate of unilateral blindness from treated NTG was 10%, whereas the 20-year rate of bilateral blindness was only 1.4%.<sup>51</sup> Both patients and eye care providers should take some comfort in the latter statistic, but it should not serve to minimize the tremendous impact this disease has on vision and on activities of daily living.

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# Angle-Closure Glaucoma

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10.12

**Definition:** A group of glaucomas characterized by elevated intraocular pressure as a result of mechanical obstruction of the trabecular meshwork by either apposition of the peripheral iris to the trabecular meshwork or by synechial angle closure.

## Key Features

- May be acute, subacute, or chronic.
- Acute angle closure may result in sudden pain, blurred vision, photophobia, colored halos around lights, ocular injection, headache, nausea, and vomiting.
- Subacute angle closure may be symptomatic with headaches, often mistaken for migraine, or may be asymptomatic.
- Chronic angle closure is generally asymptomatic.

## INTRODUCTION

Angle-closure glaucoma (ACG) was probably the first glaucoma to be recognized, when St. Yves, in 1722, described its symptoms, signs, and prognosis. It was not until 1923, however, when Raeder proposed that glaucoma be classified into two main types, one with a shallow anterior chamber and the other with a normal or deep chamber, that ACG was distinguished from open-angle glaucoma (OAG).

Population-based surveys of the prevalence of eye diseases in Europe<sup>1</sup> and the United States<sup>2-4</sup> suggest a much greater rate of OAG compared with ACG. Hence, little was published about the epidemiology of ACG, until recent epidemiological studies in Asia reported that Inuit,<sup>5,6</sup> Mongolians,<sup>7</sup> and Chinese<sup>8,9</sup> had significantly higher rates of ACG. It is now confirmed that not only is ACG more common than originally thought but that it is also associated with a much higher visual morbidity than OAG. ACG, if recognized and treated early, results in a good visual prognosis. Visual morbidity can be prevented if ACG is detected early; hence, early detection is key.

## EPIDEMIOLOGY AND PATHOGENESIS

### Prevalence

The prevalence of primary angle-closure glaucoma (PACG) in whites is reported to be 0.6% in Italy and 0.5% in Wales<sup>10</sup> in the 40+-year age group, and 0.1% in the 55+-year age group in Sweden.<sup>11</sup> The prevalence in Inuit is some 20–40 times higher.<sup>5,6,12,13</sup> The prevalence in East Asia and Southeast Asia has been reported to range from 1.4% to 4.3%, depending on the age group.<sup>7,9,14</sup>

Recent estimates based on various population-based studies of the prevalence of ACG suggest that in 2010, approximately 60.5 million people were affected by glaucoma (44.7 million with OAG and 15.7 million with ACG). This number is projected to increase to 79.6 million by 2020.<sup>15</sup> Of these, 26% will have ACG. The prevalence of ACG in 2010 among those 40 years and older was estimated to be 1.26% in China and 1.20% in Southeast Asia compared with 0.25% in Europe and 0.16% in Africa. Given the high prevalence of ACG in Asia,<sup>16,17</sup> Asians are predicted to represent 87% of those with ACG. Women will comprise 69.5% of cases of ACG because of the higher prevalence of the disease among women<sup>18</sup> and their greater longevity.

The World Health Organization currently ranks glaucoma as the second most common cause of blindness.<sup>19</sup> By 2010, bilateral blindness was estimated to be present in 3.9 million people with ACG. This is estimated to rise to 5.3 million people in 2020. The number of people blinded by ACG is nearly equal to the number blinded by OAG because of the higher morbidity of the former disease.

## Incidence

The incidence of acute PACG varies widely among different ethnic groups, from 4.7 (per 100 000 per year in the population 30 years and older) in Finland<sup>20</sup> to 11.4 in Japan,<sup>21</sup> and 12.2 in Singapore.<sup>18</sup>

## Risk Factors

1. Demographic factors:
  - a. Age (>60 years).
  - b. Female gender.
  - c. Chinese ethnic origin.<sup>22</sup>
  - d. Family history (especially first-degree relatives, because ocular anatomic features are inherited).
2. Anatomical factors<sup>23-27</sup>:
  - a. Shallow anterior chamber depth, especially peripherally.
  - b. Thick/anteriorly positioned/increased anterior curvature of lens.
  - c. Short axial length.
  - d. Small diameter/increased curvature of cornea.
  - e. Novel anterior-segment optical coherence tomography features.<sup>28-30</sup>
    - i. Anterior chamber angle characteristics:
      - Smaller trabecular-iris space area.
      - Smaller anterior chamber depth.
      - Increased lens vault.
    - ii. Iris characteristics:
      - Smaller curvature of the iris.
      - Increased iris thickness.
3. Precipitating factors:
  - a. Dim illumination (including extremes of temperature causing people to stay indoors).<sup>18,31-33</sup>
  - b. Drugs.
    - i. Anticholinergic agents (topical, e.g., atropine, cyclopentolate, and tropicamide; or systemic, e.g., antihistamine, antipsychotic [especially antidepressants], antiparkinsonian, atropine, and gastrointestinal spasmolytic drugs).
    - ii. Adrenergic agents (topical, e.g., epinephrine and phenylephrine; or systemic, e.g., vasoconstrictors, central nervous system stimulants, bronchodilators, appetite depressants, and hallucinogenic agents).
  - c. Emotional stress, excruciating pain (possibly due to mydriasis secondary to increased sympathetic tone).

ACG may be broadly subdivided into:

1. Primary ACG—no cause other than anatomical predisposition is identified.
2. Secondary ACG—angle closure is the result of a specific pathological condition that may arise in any part of the eye (e.g., neovascular glaucoma and anterior uveitis).

The traditional classification of ACG (Box 10.12.1) evolved from clinical observations and is based on symptoms that are subjective and may be highly variable. The lack of standardization and the frequent overlap in clinical presentation make it difficult for comparison in epidemiological studies. Furthermore, this form of classification does not offer any insight

### BOX 10.12.1 Traditional Classification of Angle-Closure Glaucoma (Based on Clinical Presentation and Symptomatology)

#### Acute

- Sudden onset of IOP elevation resulting from total angle closure, accompanied by symptoms of severe, usually unilateral, ocular pain, red eye, blurred vision, halos, headache (ipsilateral frontal), nausea, and vomiting

#### Subacute/Intermittent

- An episode of sudden IOP elevation that is spontaneously aborted so that symptoms are mild or even absent. Such subacute IOP elevations may be recurrent and therefore termed *intermittent angle closure*. Intermittent episodes can result in progressive PAS formation.

#### Chronic

- Chronic IOP elevation caused by the presence of PAS that permanently close the anterior chamber angle. Symptoms are usually absent. *Creeping angle closure* refers to chronic closure of angle where the root of the iris slowly creeps, or is pushed, into the depths of the narrow angle until it gradually smothers the outflow channels.<sup>23</sup>

#### Latent

- Evidence that an open but narrow angle can and does close under certain circumstances. Asymptomatic, but PAS is often found on gonioscopy.

IOP, intraocular pressure; PAS, peripheral anterior synechiae.

### BOX 10.12.2 Classification Based on Natural History

#### Primary Angle Closure Suspect (PACS)

- An eye in which appositional contact between the peripheral iris and posterior trabecular meshwork is present or considered possible, in the absence of elevated IOP, PAS, disc, or VF changes. Epidemiologically, this has been defined as an angle in which 180–270° of the posterior trabecular meshwork cannot be seen gonioscopically.

#### Primary Angle Closure (PAC)

- PACS with statistically raised IOP and/or primary PAS, without disc or VF changes.

#### Primary Angle-Closure Glaucoma (PACG)

- PAC with glaucomatous optic neuropathy and corresponding VF loss.

IOP, intraocular pressure; PAS, peripheral anterior synechiae; VF, visual field. Adapted from Foster PJ, Buhrmann RR, Quigley HA, et al. The definition and classification of glaucoma in prevalence surveys. *Br J Ophthalmol* 2002;86:238–42.

as to the natural history of the disease or the presence or absence of glaucomatous optic neuropathy and is therefore not useful for visual prognostication. Hence, the International Society of Ophthalmic Epidemiology developed a classification that is based on the natural history of the disease (Box 10.12.2).<sup>34</sup>

This classification is evidence based and is therefore more objective. These definitions have been widely used in the classification of subjects in research and have been adopted in the Asia Pacific Glaucoma Guidelines. However, it does not identify the pathophysiological mechanism that is responsible for angle closure and hence does not facilitate the clinician in choosing an appropriate treatment. A classification devised by Ritch and colleagues<sup>35</sup> is useful for this purpose and should be used in parallel (Box 10.12.3; Figs. 10.12.1 to 10.12.7).

## Pupillary Block

Pupillary block represents the most common mechanism underlying angle closure. In pupillary block, iridolenticular contact at the pupil limits the flow of aqueous from its site of production at the nonpigmented ciliary epithelium to the anterior chamber, resulting in a pressure gradient between the posterior and anterior chambers that further pushes the iris anteriorly. Anterior bowing of the peripheral iris narrows the angle and may then cause iridotrabecular apposition and angle closure. Laser iridectomy re-establishes aqueous flow from the posterior to the anterior chamber and

### BOX 10.12.3 Classification Based on Anatomic Levels of Obstruction to Aqueous Flow (Pathophysiology of Angle-Closure Glaucoma)

Apposition of the iris to the trabecular meshwork in angle-closure glaucoma may be caused by forces acting at four anatomical levels:

#### Iris

- Pupillary block (see Fig. 10.12.1)
- <sup>a</sup>Nonpupillary block/angle crowding mechanisms—e.g., thick peripheral iris roll (see Fig. 10.12.2)
- Contraction of fibrovascular membrane in neovascular glaucoma
- Contraction of fibrin in angle secondary to anterior uveitis or hyphema
- Endothelial proliferation (iridocorneoendothelial syndromes)
- Epithelial downgrowth

#### Ciliary Body

- Plateau iris configuration (forward rotation of the ciliary body or anterior position of ciliary processes) (see Fig. 10.12.3)
- Iridociliary cysts (pseudo-plateau iris) (see Fig. 10.12.4)

#### Lens

- Phacomorphic glaucoma (thick lens) (see Fig. 10.12.5)
- Phakotopic glaucoma (anteriorly positioned lens)
- Subluxed lens (e.g., pseudo-exfoliation syndrome, traumatic) (see Fig. 10.12.6)

#### Vectors Posterior to Lens

- Aqueous misdirection (malignant glaucoma) (see Fig. 10.12.7)
- *Serous or hemorrhagic choroidal detachment or effusion*
- *Space-occupying lesion (gas bubble, vitreous substitutes, tumor)*
- *Retrolenticular tissue contracture (retinopathy of prematurity, persistent hyperplastic primary vitreous)*

<sup>a</sup>Nonpupillary block/angle crowding mechanisms have been included here as an addition to Ritch's classification.

Secondary causes of angle closure are shown in italics.

relieves the pressure gradient, thereby allowing the iris to flatten and the angle to widen.

## Nonpupillary Block Mechanisms

The variable efficacy of laser iridectomy in many cases of angle closure as well as ultrasound biomicroscopy imaging suggests that pupillary block may not be the only mechanism responsible. The role of angle crowding, for example, that caused by a thick peripheral iris roll, has been increasingly recognized in many cases of angle closure. This has been added to Ritch's classification, for the sake of completeness. In many such cases, the peripheral iris stroma is thick. Upon pupil dilatation, the peripheral iris bunches up. If the angle is already narrow, this thick peripheral iris roll may become apposed to the trabecular meshwork and result in angle closure.

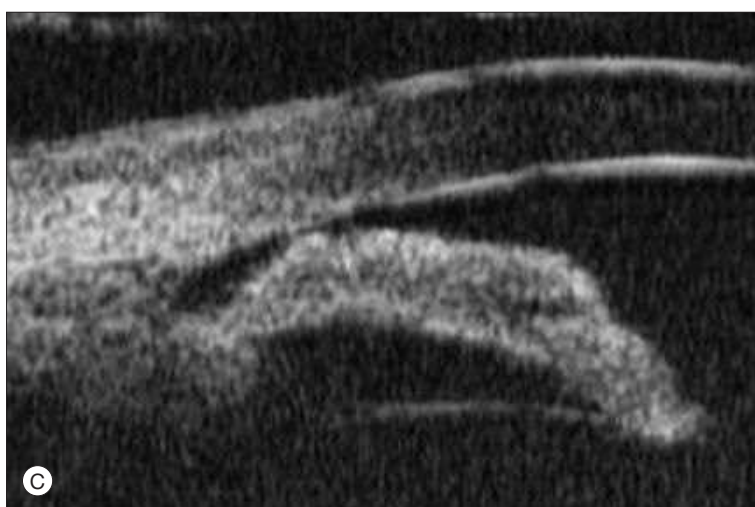
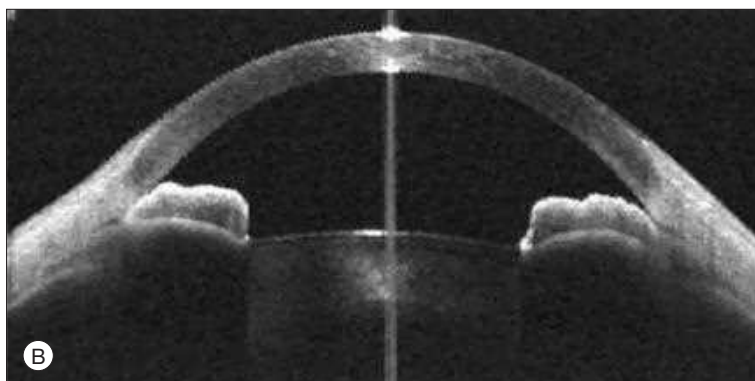
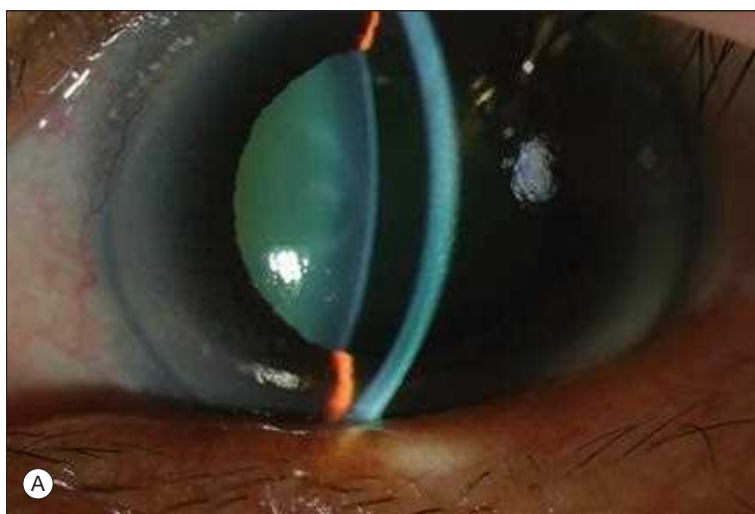
## Plateau Iris Configuration

On gonioscopy, the iris assumes a steep approach at its insertion before flattening centrally. The peripheral iris is forced into the angle by anterior rotation of the ciliary body or anteriorly positioned ciliary processes. The development of angle closure either spontaneously or after pupil dilatation in an eye with plateau iris configuration, in the presence of a patent laser iridectomy, is termed *plateau iris syndrome*. Disorders of the ciliary body, such as iridociliary cysts or tumors, may result in a similar plateau iris configuration. This is termed *pseudo-plateau iris*.

## Aqueous Misdirection

This condition, also called *malignant glaucoma* or *ciliary block glaucoma*, is characterized by shallowing or flattening of the anterior chamber, accompanied by a rise in intraocular pressure (IOP). It is typically seen in the post-operative period but can arise spontaneously. It is believed that aqueous passes posteriorly to the posterior segment instead of anteriorly to the posterior chamber because of obstruction to flow caused by the anterior rotation of ciliary processes resulting in their apposition to the lens equator in the phakic eye, or against the anterior hyaloid in the aphakic eye. The

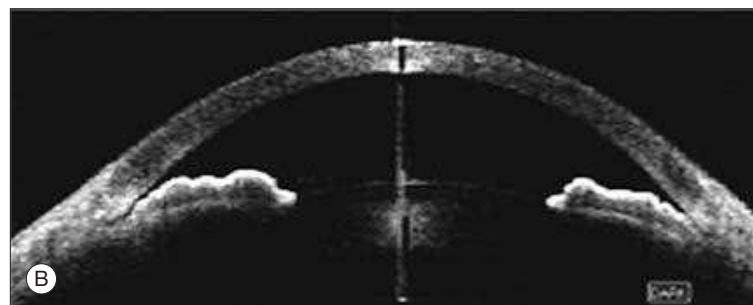
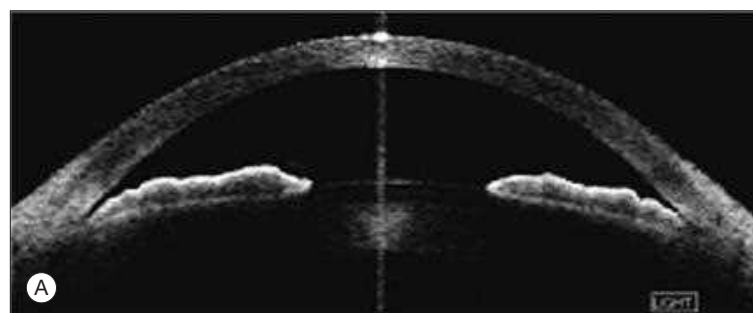




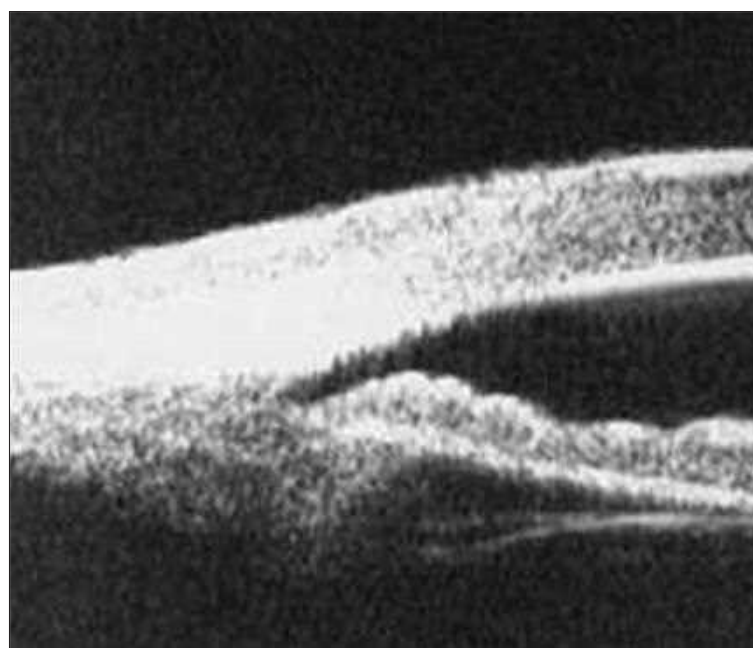
**Fig. 10.12.1 Pupillary Block.** (A) Photograph of eye with pupillary block. (B) Anterior segment optical coherence tomography image. (C) Ultrasound biomicroscopy image.

accumulation of aqueous in the posterior segment causes an anterior displacement of the lens–iris diaphragm. Laxity of the lens zonules allowing this forward movement has also been suggested to play a role in the development of this condition.

The term “malignant” was used originally to describe its poor response to conventional miotic treatment. Early recognition of aqueous misdirection is important in reducing its morbidity. Management involves prompt medical treatment with topical cycloplegic agents, such as atropine, which increases zonular tension and pulls the lens posteriorly. Atropine 1% may be given 2–4 times a day for weeks to months or even years. Topical beta-blockers, alpha-2-agonists, and carbonic anhydrase inhibitors may be used to decrease aqueous production and lower the IOP. Hyperosmotic agents may also be used to decrease the vitreous volume. If the condition persists beyond 5 days despite adequate medical therapy, laser or surgical intervention must be considered. Neodymium:yttrium–aluminum–garnet (Nd:YAG) laser has been demonstrated to be effective in the pseudo-phakic and aphakic eye by disrupting the anterior hyaloid face, especially peripherally. Aspiration of the anterior vitreous, anterior pars plana vitrectomy, or



**Fig. 10.12.2 Peripheral Iris Roll.** Anterior segment optical coherence tomography images of the same eye taken in (A) light and (B) dark conditions.



**Fig. 10.12.3 Plateau Iris Configuration.** Ultrasound biomicroscopy image.

lens extraction with a posterior capsulotomy may be performed; however, disruption of the hyaloid face is key to the success of this procedure. A prophylactic laser iridectomy should also be considered for the fellow eye, as there is a significant risk that aqueous misdirection may occur following intraocular surgery in that eye.

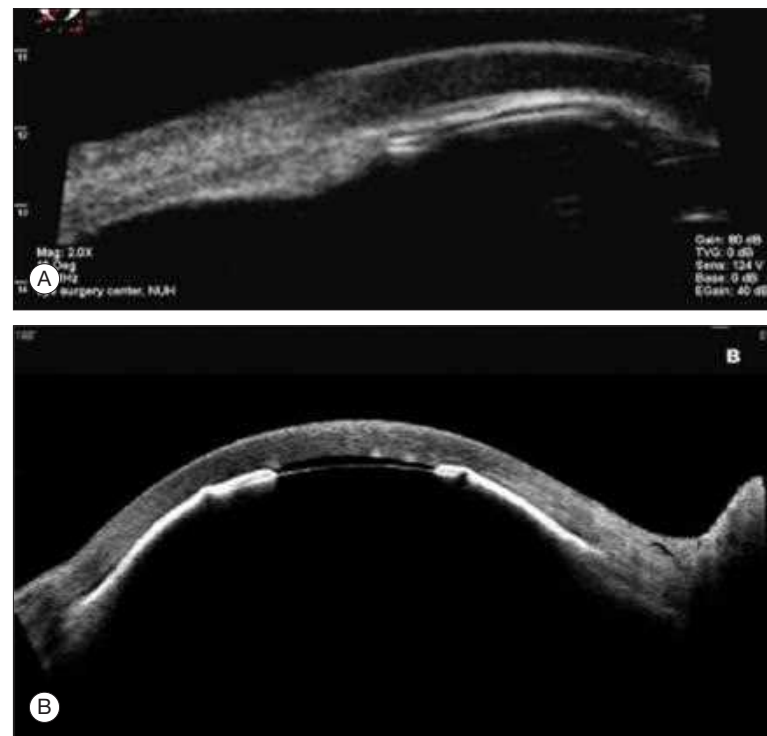
## DIAGNOSIS

### External Examination

The majority of people with PACG do not experience any symptoms.<sup>3,7</sup> Characteristic findings in a patient presenting during an acute angle-closure attack include conjunctival hyperemia, a hazy cornea with corresponding decreased visual acuity (Fig. 10.12.8), and a mid-dilated nonreactive or sluggish pupil. The pupil is mid-dilated because of ischemic paralysis of the iris sphincter muscles occurring as a result of the greatly elevated IOP. With infarction of these muscles, the pupil does not return to its normal appearance, even when the IOP has been lowered, and iris whorling may become evident. Digital palpation of the eye through a closed eyelid reveals a firm (often rock-hard) eye. The patient may also experience bradycardia or arrhythmia.



**Fig. 10.12.4 Iridociliary Cysts.** (A) Ultrasound biomicroscopy image. (B) Anterior segment optical coherence tomography image (arrowhead).



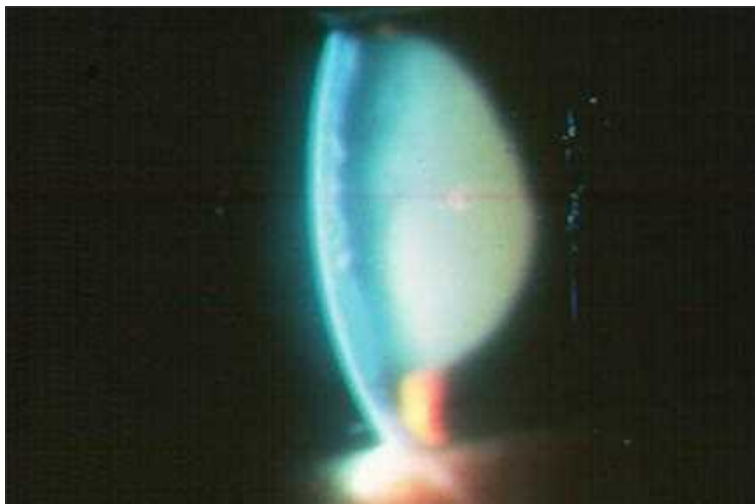
**Fig. 10.12.7 Malignant Glaucoma.** (A) Ultrasound biomicroscopy image. (B) Anterior segment optical coherence tomography image.



**Fig. 10.12.5 Phacomorphic glaucoma.**



**Fig. 10.12.8 Acute angle-closure glaucoma.**



**Fig. 10.12.6 Anteriorly subluxed lens.**

## Penlight Examination

When a slit lamp or gonioscope is unavailable, a penlight may be used to estimate the anterior chamber depth. This test is performed by shining the penlight from the temporal side of the eye. A flat iris with a deep anterior chamber would allow the nasal iris to be illuminated, whereas an iris that is convex with a correspondingly shallow anterior chamber would block the illumination, causing the nasal iris to be in shadow.

## Slit-Lamp Examination

In acute angle closure, the cornea usually appears hazy because of epithelial and stromal edema secondary to the acute rise in IOP with mid-dilated pupil and peripherally shallow anterior chamber. Iris bombé is usually present as a result of pupillary block. Iris whorling (sectoral infarction of the iris sphincter leading to torsion of the iris), patchy iris stromal atrophy (Fig. 10.12.9), and lens glaucomflecken (Fig. 10.12.10) (small gray-white anterior subcapsular or capsular opacities in the pupillary zone resulting from infarction of lens fibers) may also be evident if the patient has had an acute rise in IOP previously.

Both central and peripheral anterior chamber depth (ACD) may be assessed at the slit lamp. Although the central ACD only weakly correlates with the angle width,<sup>36</sup> peripheral ACD estimation appears to perform well





**Fig. 10.12.9** Iris whorling and atrophy.



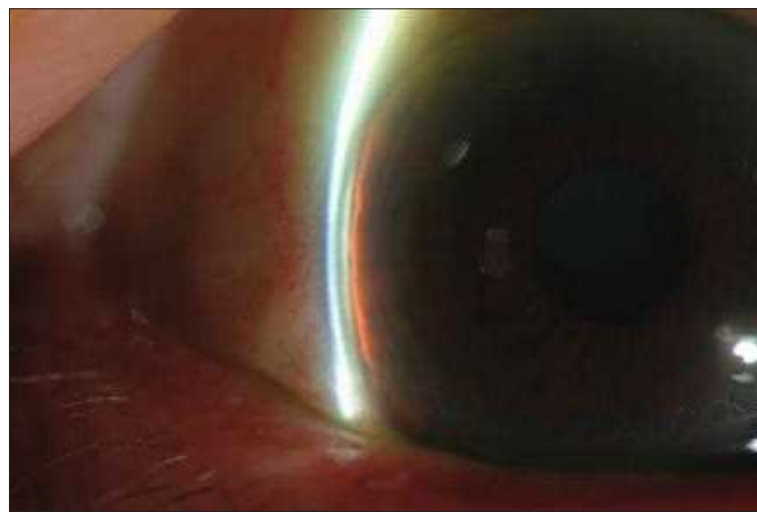
**Fig. 10.12.10** Glaucomflecken.

in the detection of occludable angles.<sup>37</sup> The van Herick technique<sup>38</sup> (Fig. 10.12.11) is useful for estimating the peripheral ACD. In this technique, the illumination column is offset from the axis of the microscope by 60°. The brightest, narrowest possible vertical beam of light is directed at the temporal limbus, perpendicular to the ocular surface. Viewed from the nasal aspect, the peripheral ACD is compared with the adjacent corneal thickness that is illuminated by the light beam. The angle may be occludable if the peripheral ACD is less than one fourth of the corneal thickness. The limbal chamber depth method of grading the peripheral anterior chamber is a recent modification of the van Herick test.<sup>39</sup> Instead of the four grades used in the van Herick method, it has seven grades that are expressed as a percentage fraction of the thickness of the adjacent cornea: 0%, 5%, 15%, 25%, 40%, 75%, and 100%. The limbal chamber depth method has been demonstrated to perform better in the detection of established PACG and is now widely used in epidemiological research.

Slit-lamp examination should also include a thorough check for the presence of any inflammation, hyphema, and cataract or subluxed lens. IOP is often severely elevated (often >40 mm Hg). Careful examination of the optic disc should also be performed to detect any evidence of glaucomatous optic neuropathy.

## Gonioscopy

Careful gonioscopic examination of the angle is vital to make the diagnosis of angle closure. This is best performed using first a two-mirror goniolens



**Fig. 10.12.11** Van Herick technique.

(e.g., Goldmann) to avoid artifactual distortion of the angle caused by inadvertent pressure on the cornea, followed by a four-mirror goniolens (e.g., Sussman, Zeiss) that allows indentation gonioscopy to reveal whether any closure is caused by peripheral anterior synechiae (PAS) or is merely appositional. Gonioscopy should be performed in a dark room using a 1-mm light beam reduced to a very narrow slit, and care should be taken to avoid any light falling on the pupil, which might otherwise cause pupil constriction and angle widening. The vertical light beam should be offset horizontally for the assessment of the superior and inferior angles, and the horizontal beam should be offset vertically for the nasal and temporal angles. Assessment of the angles should be carried out at  $\times 25$  magnification. Although currently the reference standard for angle assessment, gonioscopy remains a subjective technique that depends on the experience of the clinician as well as conditions of illumination.

Various grading systems, including Scheie, Shaffer, and Spaeth, have been proposed for the recording of gonioscopic findings. These gonioscopic grades provide an index of the likelihood of angle closure.<sup>40</sup> With the Scheie grading system, there is a high risk of angle closure in eyes that are graded III (only anterior TM and Schwalbe's line visible) or IV (only Schwalbe's line visible). Shaffer grades I (angle width 0–10°) and II (10–20°) are associated with risk of angle closure, while an angle with a Spaeth grade of B20s (iris insertion behind Schwalbe's line, angle width 20°, steep peripheral iris contour) may be potentially occludable. “Biometry gonioscopy,” where a reticule in the eyepiece of the slit lamp is used to measure the distance from the iris insertion to Schwalbe's line, has also been suggested as a more reproducible and objective method of gonioscopy.

## Other Imaging Techniques

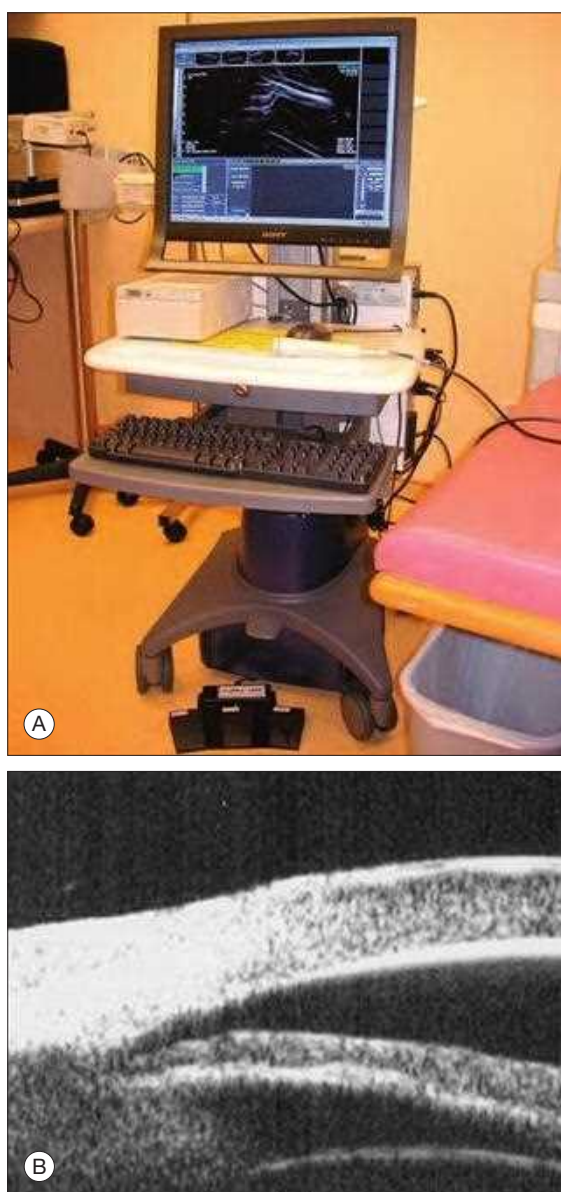
### Ultrasound Biomicroscopy

Ultrasound biomicroscopy (UBM) (Fig. 10.12.12) allows dynamic high-resolution imaging of the anterior segment structures, including the anterior chamber angle, the iris, iris–lens interaction, and ciliary body. Thus it can help elucidate the underlying mechanism of angle closure in most cases, including plateau iris syndrome and iridociliary cysts, thereby allowing the appropriate treatment to be given. It is also useful in demonstrating angle occludability when performed in a dark room. The major disadvantages of UBM are that it is a time-consuming procedure, and it requires a skilled operator and contact with the patient's eye. Its high cost also limits its availability.

### Anterior-Segment Optical Coherence Tomography

Time-domain anterior segment optical coherence tomography (AS-OCT) (Fig. 10.12.13) using light of wavelength 1310 nm has enabled high-speed imaging of the anterior segment structures. It is an easy technique to master and does not require contact with the patient's eye. A comparison with gonioscopy has found that it may be superior in its ability to detect angle occludability.<sup>41</sup> It suggests that gonioscopy (which uses visible light) may be underestimating angle occludability, even when performed in ideal darkroom conditions. AS-OCT has also been reported to be similar to UBM in quantitative anterior chamber angle measurement and detection of narrow angles.<sup>42</sup> More recently, the use of swept-source AS-OCT has the





**Fig. 10.12.12 Ultrasound Biomicroscopy.** (A) Ultrasound biomicroscopy (UBM) device. (B) UBM image of the anterior chamber angle.

added advantage of higher resolution, faster scanning speed, 360° imaging of the anterior chamber angles (Fig. 10.12.14A–B).<sup>43</sup>

### Provocative Tests

Historically, provocative tests were used to attempt to trigger angle closure in primary angle-closure suspects (PACS) to identify patients for whom treatment is then recommended. These included the darkroom prone test and pharmacological pupil dilatation. However, these tests may not be easily reversible and are associated with high false-positive and false-negative rates. They are therefore seldom practiced now.

## DIFFERENTIAL DIAGNOSIS

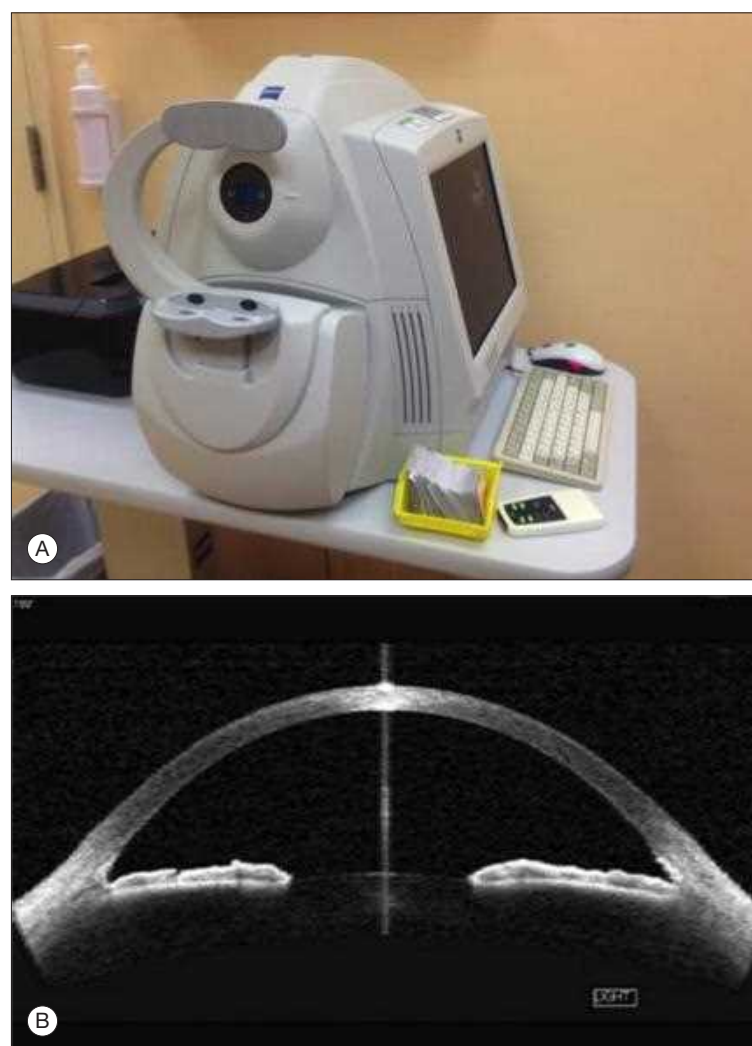
Differential diagnosis includes the following:

- Secondary ACG (shown in *italics* in Box 10.12.3).
- Other causes of headache (e.g., migraine or cluster headache).

## MANAGEMENT OF ACUTE ANGLE CLOSURE

Acute angle closure is an ophthalmological emergency. Measures should be taken within minutes to hours to lower the IOP and break the attack, followed by identification of the mechanism of angle closure and appropriate treatment to widen the angle.

Corneal indentation with a four-mirror gonioscope or cotton-tipped applicator may be attempted at 30-second intervals to force open an area of appositionally closed trabecular meshwork that will allow some aqueous



**Fig. 10.12.13 Anterior-segment optical coherence tomography (AS-OCT).** (A) AS-OCT device (Carl Zeiss Meditec). (B) AS-OCT image of anterior chamber.

to exit the eye.<sup>44</sup> However, this technique may cause pain and momentary further increases in IOP. Hence, it may not be suitable in all cases.

Recent studies suggest that laser iridoplasty may be a useful alternative to conventional systemic medication as a first-line treatment in the management of acute angle closure, especially when certain medications are contraindicated, for example, in patients with pre-existing asthma, or cardiac or renal disease.<sup>45,46</sup>

### After 1 to 2 Hours

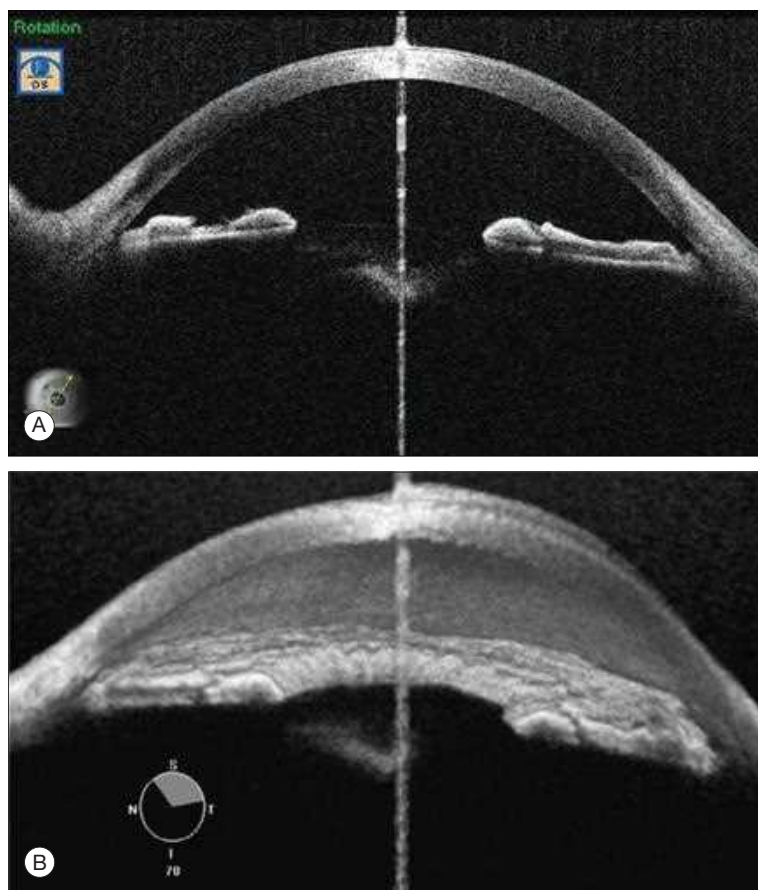
- If the attack is broken and corneal edema resolves, perform laser iridectomy. Laser iridoplasty should be performed in addition in cases of plateau iris syndrome, and can also be considered where the angle remains narrow despite a patent laser iridectomy.
- If the attack is not broken but the cornea is clear, laser iridectomy should be performed.
- If the attack is not broken and the cornea is still hazy, laser iridoplasty is performed first, followed by laser iridectomy later when corneal edema resolves.<sup>47–49</sup>

Laser iridectomy is the definitive treatment in ACG and results in significant angle opening in the majority of cases.<sup>50</sup>

Anterior chamber paracentesis has also been suggested as an alternative to break the attack if all else fails, especially if laser is unavailable.<sup>51</sup>

### Later

If the attack is still not broken, consider surgery (lens extraction if the lens is the causative factor, or surgical peripheral iridectomy). The fellow eye should be evaluated by gonioscopy for risk of angle occludability and treated with prophylactic laser iridectomy (Box 10.12.4)<sup>52,53</sup>, if necessary. Topical corticosteroids should be continued four times a day for about 5–7



**Fig. 10.12.14** Swept-source anterior-segment optical coherence tomography (AS-OCT). (A) Cross-sectional AS-OCT image (CASIA SS-1000, Tomey, Japan). (B) Swept source 3D AS-OCT image.

days after laser iridectomy, and antiglaucoma medications discontinued when IOP returns to normal.

## Even Later

A repeat gonioscopic examination should be carried out after laser iridectomy has been successfully performed to assess if the eye is still at risk of angle closure as well as to document the presence and extent of PAS. Once it is deemed safe to dilate the pupil, a dilated ocular examination should also be performed to assess the optic nerve status and to exclude any secondary causes of angle closure that may need further treatment.

The IOP should be monitored closely in the first 12 months after the attack to detect any asymptomatic rise in IOP early.

## MANAGEMENT OF CHRONIC ANGLE-CLOSURE GLAUCOMA

In the case of a patient presenting with elevated IOP, in the presence of partially or totally occluded angles with PAS and glaucomatous optic neuropathy, medical treatment (see below) to lower IOP should be commenced. Laser iridectomy and laser iridoplasty may be considered, although the effects of laser iridoplasty in the presence of extensive synechial closure may be questionable. Gonioscopy should be repeated to assess angle width and the extent of PAS. If IOP continues to be inadequately controlled or if there is any evidence of progression in optic nerve or visual field damage, then the decision to go on to surgical treatment (see below) should be taken.

## MANAGEMENT OF ANGLE-CLOSURE GLAUCOMA

### Medical Treatment

In acute angle closure, topical beta-blockers, alpha-2-agonists, and carbonic anhydrase inhibitors may be used to lower the IOP to a level where corneal edema resolves, allowing laser iridectomy to be performed. Topical pilocarpine (2% or 4%) can also be used in the acute setting to constrict

## BOX 10.12.4 Laser Iridectomy

### Indications

- AC
- ACG
- ACS, especially if:
  - AC in fellow eye
  - Family history of ACG
  - Need for repeated dilated examinations
  - Poor access to regular ophthalmic care

### Procedure

1. Before laser:
  - Instill topical 2% or 4% pilocarpine and alpha-2-agonist and/or oral acetazolamide 30–60 minutes prior to the procedure. This helps to reduce the occurrence of postlaser IOP spike
  - Topical anesthesia
2. Laser:
  - Abraham/Wise iridectomy lens with coupling fluid
  - Choose iris crypt or an area of thin iris. Avoid level of tear meniscus formed by lid and globe. Aim at peripheral iris, avoiding cornea arcus.
  - Nd:YAG 2–5 mJ (use minimum energy), 1–3 pulses/burst
  - Argon laser 700–1100 mW, 50  $\mu$ m spot size, 100 ms, 10–20 burns can be used prior to Nd:YAG laser in a thick iris to photocoagulate and thin the iris stroma, thereby also reducing the risk of iris bleeding<sup>58</sup>
  - Endpoint—iris pigment plume, lens visible through iridectomy, LI size of about 150–200  $\mu$ m.<sup>59</sup> Brown Asian irides are thicker than blue ones and probably require a larger iridectomy
3. After laser:
  - Check IOP 1 hour after laser to exclude any IOP spike

### Complications

- Corneal endothelial burns (with argon)
- Iris hemorrhage from site of LI (with Nd:YAG)—applying pressure on the globe with the laser lens is usually sufficient to stop the hemorrhage
- IOP spike
- AC inflammation with closure of iridectomy, formation of posterior synechiae, or raised IOP
- Cataract formation
- Corneal endothelial decompensation, malignant glaucoma, retinal damage, cystoid macular edema (all rare)

AC, Angle closure; ACG, angle-closure glaucoma; ACS, angle-closure suspect; IOP, intraocular pressure; LI, laser iridectomy.

the pupil in an attempt to pull the peripheral iris away from the trabecular meshwork to re-establish aqueous outflow. Pupil constriction also helps to stretch the iris so that laser iridectomy may be performed more easily through a thinner iris. Pilocarpine is effective in inducing miosis only when iris ischemia is relieved (i.e., when IOP falls to <50 mm Hg). Pilocarpine should, however, be avoided in cases where it may exacerbate pupillary block, such as in pseudo-exfoliation, phacomorphic glaucoma, and aqueous misdirection, that is, where angle closure is secondary to lens-induced or retrolenticular mechanisms. Intravenous/oral acetazolamide 5–10 mg/kg (alternatives: hyperosmotic agents, e.g., intravenous 20% mannitol 1–2 g/kg, oral 50% glycerol 1–1.5 g/kg [contraindicated in diabetics], oral isosorbide 1.5–2.0 g/kg) may also be given to lower IOP for as long as not medically contraindicated. Topical corticosteroids are added to relieve ocular congestion and inflammation.

Once the patient has been treated with laser iridectomy (and laser iridoplasty, where indicated), long-term medical treatment can be used if IOP control remains suboptimal. Recent studies have demonstrated that prostaglandins, such as latanoprost, bimatoprost, and travoprost, are also effective in lowering IOP in chronic PACG, even in the presence of 360° of PAS.<sup>45,53–59</sup> Their delayed onset of action, however, precludes their use in the acute setting.

## Laser Treatment

A summary of the indications, procedure, and complications of laser iridectomy is given in Box 10.12.4 (Fig. 10.12.15) and of laser iridoplasty in Box 10.12.5 (Fig. 10.12.16).



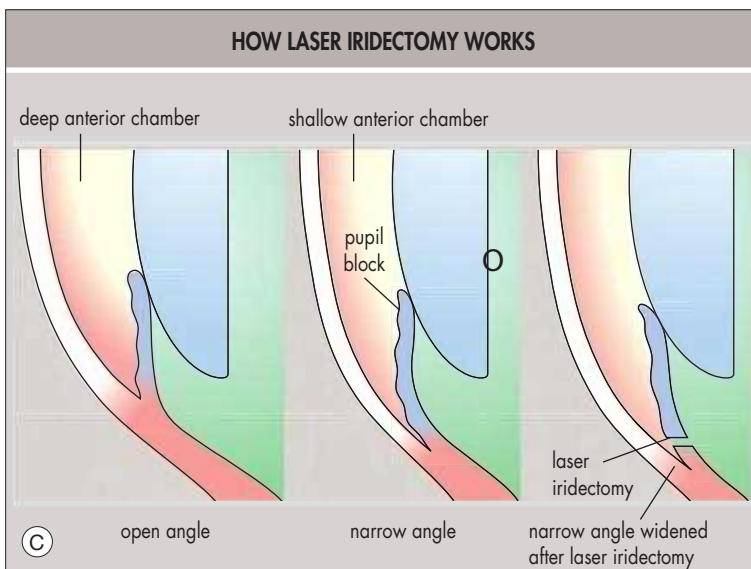
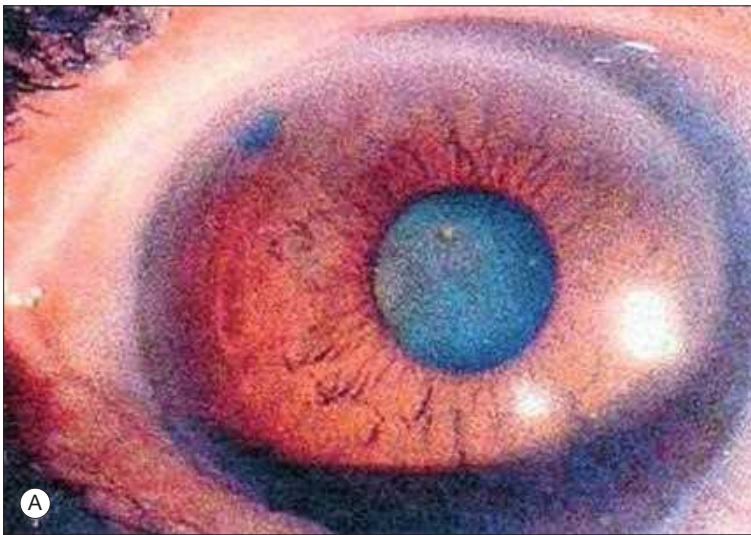


Fig. 10.12.15 Laser iridectomy.

The long-term efficacy of laser iridoplasty has not been well established.

## Surgical Treatment

The main aims and indications for surgical treatment for angle closure are given in Box 10.12.6.

### Surgical Iridectomy

Since the advent of laser iridectomy, surgical peripheral iridectomy is now seldom performed. However, it may still be useful occasionally where the cornea fails to clear sufficiently for laser iridectomy to be performed, or in the case of a patient who is unable to cooperate with the laser procedure.

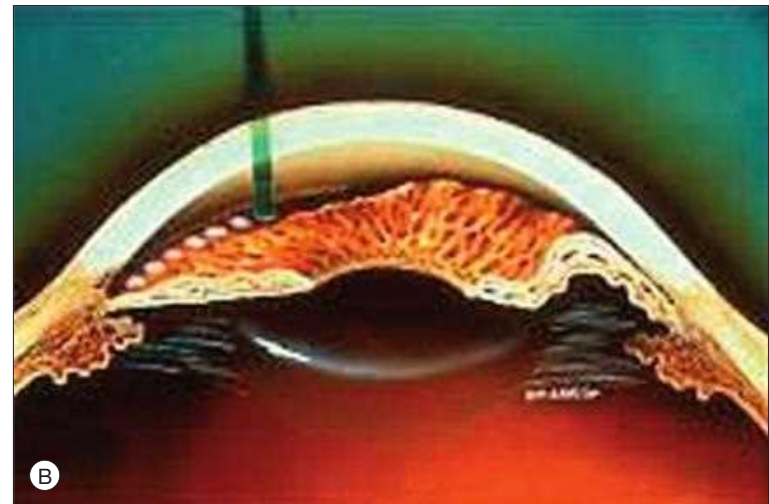
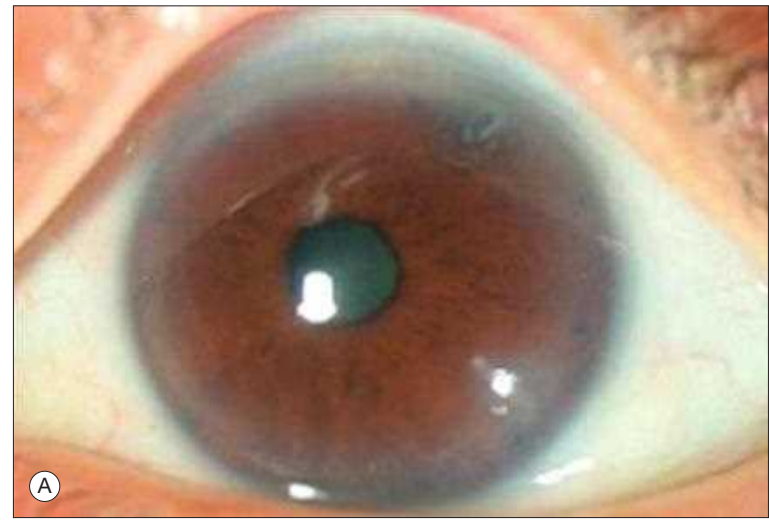


Fig. 10.12.16 Laser iridoplasty (performed in addition to laser iridectomy).

### BOX 10.12.5 Laser Iridoplasty

#### Indications

- Angle still occludable after laser iridectomy (e.g., plateau iris)
- In acute angle closure, to help break the attack where medical therapy has failed or is contraindicated
- To facilitate access to trabecular meshwork for laser trabeculoplasty

#### Procedure

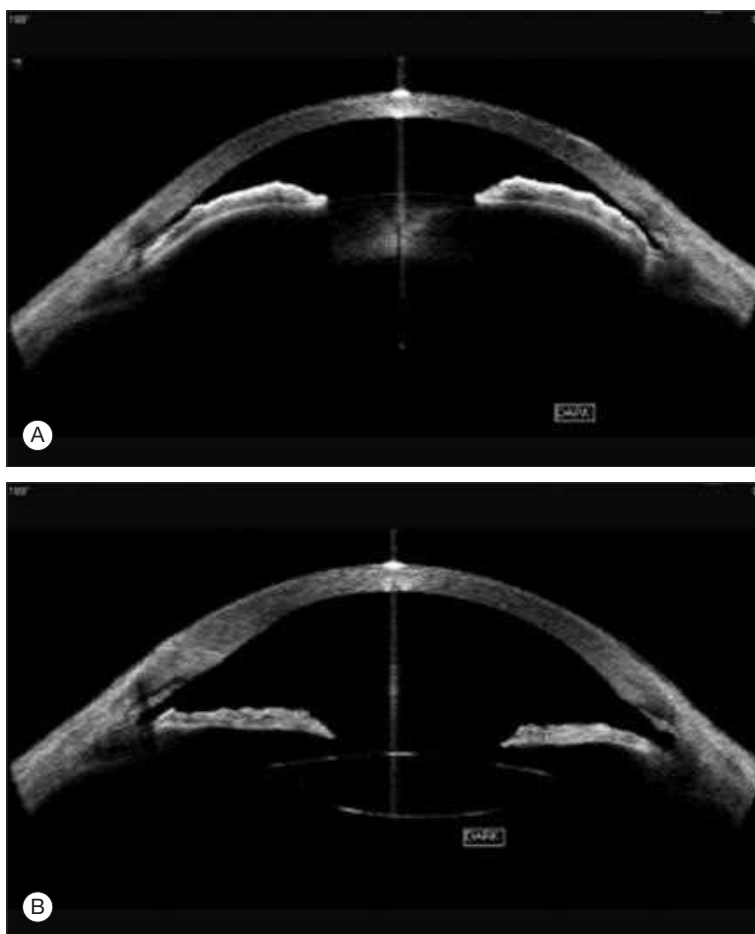
1. Before laser:
  - As for laser iridectomy
2. Laser:
  - Abraham/Wise/Goldmann three-mirror lens
  - Aim at iris as peripheral as possible, outside of any cornea arcus
  - Argon green or blue-green, or diode 200–500 mW, 100–500  $\mu$ m spot size, 0.2–0.5 seconds, single row of 6–10 burns per quadrant over 180–360°
  - Endpoint—iris stromal contraction accompanied by progressive peripheral anterior chamber deepening with increasing number of burns
3. After laser:
  - As for laser iridectomy. Topical corticosteroids four times/day for 7 days.

#### Complications

- Corneal endothelial burns
- Iritis
- Intraocular pressure spike
- Peripheral anterior and/or posterior synechiae

A 2–3 mm partial-thickness incision (to about two thirds of the corneal thickness) is made, usually in the superotemporal peripheral cornea or at the limbus after a limited conjunctival peritomy. The anterior chamber is then entered with the blade held vertically. A toothed forceps is used to hold the prolapsed iris, and Vannas scissors are used to excise it. Neither





**Fig. 10.12.17** Pre-phacoemulsification (A) versus postphacoemulsification (B) with intraocular lens implant. Anterior-segment optical coherence tomography images.

### BOX 10.12.6 The Main Aims and Indications for Surgical Treatment in Angle Closure

#### Main Aims

- To decrease IOP and reduce risk of optic nerve damage
- To prevent progressive angle closure
- To reduce risk of acute angle closure

#### Indications

- Inadequate control of IOP, with progression of optic nerve or visual field damage, despite medical and laser treatment
- Poor compliance or intolerance to medical treatment
- Inability to cooperate with laser treatment
- Worsening angle closure and/or PAS
- Presence of significant cataract impairing vision

IOP, Intraocular pressure; PAS, peripheral anterior synechiae.

forceps nor scissors enter the anterior chamber, thus avoiding any risk of damage to the lens or other structures. The edges of the incision are then stroked to encourage the iris to retract into the anterior chamber, and the corneal incision is closed with one or two 10-0 nylon sutures.

### Lens Extraction

Removal of the lens, especially if there is any evidence of cataract, may be helpful in cases where either the lens thickness or anterior position is thought to be the main mechanism underlying the acute episode of angle closure (Fig. 10.12.17). However, care must be taken during surgery because these eyes are usually associated with high IOP, shallow anterior chambers, cloudy cornea, decreased corneal endothelial cell counts, floppy iris resulting from previous ischemia, posterior synechiae, bulky lens, lax lens zonules, and a high risk of malignant glaucoma. Reports of phacoemulsification combined with goniosynechialysis, in the presence of peripheral anterior synechial closure, have been encouraging.<sup>60,61</sup> A recent randomized controlled trial demonstrated that there could be a role for early lens extraction in eyes where the lens is a significant component of angle closure.<sup>62</sup>

### Goniosynechialysis

This is usually performed in combination with lens extraction, and involves mechanical stripping of PAS away from the trabecular meshwork using viscoelastics or an irrigation cyclodialysis spatula.<sup>60,61</sup>

### Trabeculectomy

Trabeculectomy is performed similarly as for OAG, with the exception that a surgical peripheral iridectomy should always be performed at the time of trabeculectomy. In addition, the use of antimetabolites should be considered. Trabeculectomy, alone or in combination with lens extraction, should be considered after the acute attack of angle closure, if the IOP control remains suboptimal despite medical and laser treatment, especially in more advanced cases of ACG that are associated with PAS, optic nerve, or visual field damage. In acutely inflamed eyes, trabeculectomy has been reported to have low success rates.<sup>63</sup>

### Glaucoma Drainage Implant

This may be considered in chronic ACG where trabeculectomy has failed to control the IOP or in eyes that are deemed to be at high risk of failure with trabeculectomy.

### Cyclodestructive Procedures

Cyclodestructive procedures, such as transscleral cyclophotocoagulation, are used for ACG eyes with end-stage disease that have poor visual potential, especially if they are symptomatic because of high IOP.

### Micropulse Laser

A recent advancement, in the form of micropulse laser treatment to the eye via trans-pars plana treatment with a modified contact probe is currently available for use. Compared with conventional cyclodestructive procedures, this new form of micropulse laser therapy has been reported to be better tolerated because there are no severe complications, such as hypotony, loss of vision, and phthisis bulbi.<sup>64</sup>

Caution must be exercised when performing surgery in eyes with ACG because of the increased risk of malignant glaucoma.<sup>65</sup> In addition, the use of topical corticosteroids after laser treatment or surgery in these patients may be associated with corticosteroid-induced IOP elevation following an attack of ACG.<sup>66</sup>

## PROGNOSIS

Angle closure is associated with good visual prognosis, provided it is detected early and the appropriate treatment given. Of the cases presenting with acute primary angle closure (PAC), 42%–72% can be satisfactorily treated with laser iridectomy alone,<sup>67,68</sup> and 60%–75% of such patients recover without optic disc or visual field damage, if the IOP is promptly and adequately controlled.<sup>69</sup> However, a longer duration of the angle-closure attack or a history of intermittent angle-closure episodes is often associated with the need for additional medical or even surgical therapy.<sup>70–72</sup> The presence of a significant amount of PAS, a higher presenting IOP, and a larger cup-to-disc ratio on presentation are other predictors of inadequate IOP control despite a patent laser iridectomy.<sup>73–75</sup> Most patients who develop a rise in IOP after laser iridectomy do so within the first 6 months.<sup>72</sup> Once glaucomatous optic neuropathy and visual field damage have developed, 94%–100% may require further surgical treatment to control IOP.<sup>76</sup>

In patients presenting with unilateral acute PAC, prophylactic laser iridectomy in the fellow eye also appears to be safe and effective in preventing acute PAC in 100% and in preventing long-term rise in IOP in 89%.<sup>77</sup> However, the fact that a small proportion of fellow eyes did develop a pressure rise despite the presence of a patent laser iridectomy emphasizes the importance of long-term monitoring.

There has been a paucity of longitudinal studies looking at the rate of progression from PACS to PAC and PACG. One population-based study in Greenland<sup>78</sup> reported an incidence of PAC (in subjects who progressed from PACS) of 16% over 10 years, and Thomas et al.<sup>79</sup> reported that 22% of PACS developed PAC after 5 years, and 28% of PAC subjects went on to develop PACG<sup>80</sup> over a similar period. However, more research needs to be done to understand the natural history of this disease better.

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# Glaucoma Associated With (Pseudo)-Exfoliation Syndrome

10.13

Robert Ritch, Bryan S. Lee, Thomas W. Samuelson

**Definition:** Exfoliation syndrome (also referred to as *pseudo-exfoliation syndrome*) is a systemic disorder with multiple ocular associations, the most important of which is glaucoma secondary to the deposition of whitish, fibrillar material on and within the structures of the anterior segment.

## Key Features

- Exfoliation material is most often seen on the anterior lens capsule and pupillary border of the iris. It can be seen in the angle and on the cornea.
- Most commonly associated with open-angle configuration and increased angle pigmentation, but also a common cause of narrow and closed angles.
- Intraocular pressure can be normal to markedly elevated.

## Associated Features

- Increased irregular angle pigmentation, pigment on Schwalbe's line, and Sampaolesi's line (strongly indicates diagnosis) on peripheral corneal shelf.
- Pigment dispersion in anterior chamber after pupillary dilation, often with an associated rise in IOP.
- Zonular laxity and fragmentation predisposing to both lens and in-the-bag IOL subluxation, surgical complications, and anterior chamber shallowing.
- Iris sphincter region transillumination defects, relative pupillary miosis, and often poor dilation, especially during phacoemulsification.
- Defective blood–aqueous barrier.

## INTRODUCTION

Exfoliation (or pseudo-exfoliation) syndrome (referred to herein as *exfoliation syndrome* [XFS]), is an ocular manifestation of an age-related systemic disorder of the extracellular matrix characterized by the production and progressive accumulation of a fibrillar extracellular material in many ocular and systemic tissues. XFS appears to be a disease of elastic tissue microfibrils. It is the most identifiable cause of secondary open-angle glaucoma worldwide, comprising the majority of cases in some countries.<sup>1</sup>

First described in 1917 by Lindberg in Finland, the importance of XFS and the differences from primary open-angle glaucoma (POAG) were largely overlooked until the twenty-first century. The diagnosis was largely missed because of failure to examine the lens after pupillary dilation and because of failure to recognize its importance. It is a disease with specific genetic, cell biological, and pathophysiological mechanisms and is related to other glaucomas only in the sense that it causes high-tension glaucoma as a result of blockage and dysfunction of the trabecular meshwork. Rapidly increasing research has revealed new findings in genetics, biochemistry, and cellular pathophysiology, opening the door to the development of new approaches to treatment. XFS is now regarded as potentially preventable and eventually reversible or even curable.<sup>2,3</sup>

The incidence of XFS increases steadily with age in all populations. It presents unilaterally in about two thirds of cases, and 50% of uninvolved fellow eyes will develop it in 15 years. Exfoliation material is found in the conjunctiva and iris in the uninvolved eye, but why it does not develop

clinically bilaterally is a question of renewed importance. Its prognosis has been described as worse than that of POAG, with greater intraocular pressure (IOP) and visual field loss at the time of presentation, poorer response to therapy, greater need for surgery, and greater progression to blindness. About one third of patients with XFS will develop secondary glaucoma.<sup>4,5</sup>

## EPIDEMIOLOGY AND GENETICS

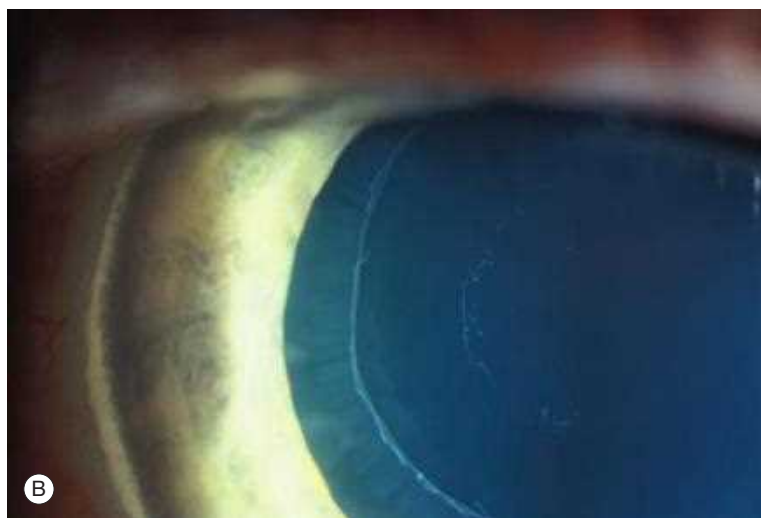
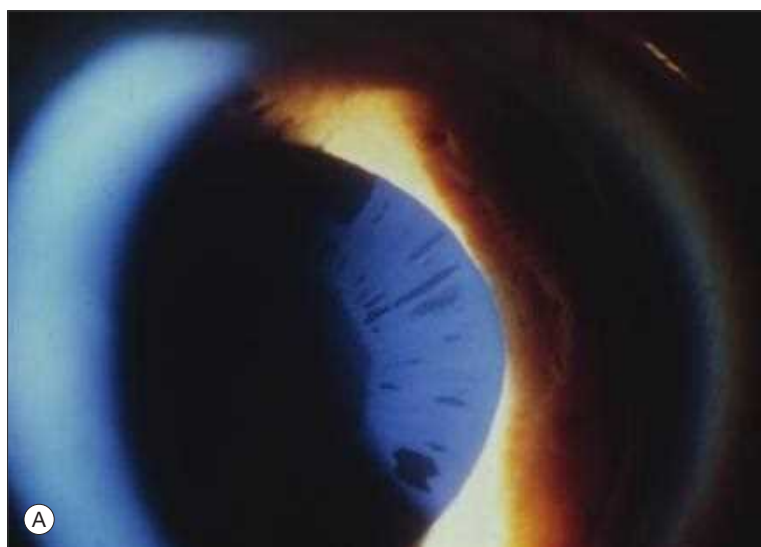
Formerly thought to be primarily a disease found in Scandinavian countries, XFS exists worldwide, with widely varying prevalence rates. It is common in Scandinavia, Celtic populations, across the Mediterranean, and in the Middle East and South Asia, but its prevalence tapers off and is uncommon in China. It has been described as being common among South African Bantu, Ethiopians, Navahos, and other groups.

The prevalence of XFS in patients with glaucoma is significantly higher than in age-matched nonglaucomatous populations. Approximately 25%–50% of patients with XFS have or will develop elevated IOP, and one third of these will develop glaucoma. There is approximately six times the odds of finding elevated IOP in eyes without XFS. It has been estimated (Lindberg Society) that clinically detectable XFS affects approximately 60–80 million people, or nearly 20% of the world's population with open-angle glaucoma.<sup>1,5-10</sup>

In 2007, Thorleifsson et al. reported that single nucleotide polymorphisms (SNPs) in the lysyl oxidase-like protein 1 (LOXL1) gene conferred a risk for exfoliation glaucoma (XFG) but not POAG in patients from Iceland and Sweden.<sup>11</sup> A single nucleotide polymorphism (SNP) in the first intron tagged susceptibility to XFG and was equally present in XFS. Actual XFG was associated with haplotypes formed by two nonsynonymous SNPs in the first exon of LOXL1. Association studies of these two SNPs showed that the highest risk haplotype conferred a 700-fold greater risk of XFS than the lowest risk haplotype. The two higher-risk haplotypes explained over 99% of XFG in Caucasians. However, the normal population without XFS also has a high prevalence of these haplotypes, including populations in which XFS is rare. The SNPs are associated, but not causative. The LOXL1 protein is involved in cross-linking of elastin fibers in the extracellular matrix.<sup>12</sup> In 2015, a significant association between *CACNA1A*, a gene involved in calcium transport, and XFS was reported.<sup>13</sup> Calcium is necessary for LOXL1 binding to the extracellular matrix. In 2017, five new susceptibility genes and a protective locus were reported.<sup>14,15</sup> It remains to be discovered how these are related, but further work may provide ways to genetically regulate LOXL1 production. Gene–environment interactions, including caffeine intake, ultraviolet radiation, and latitude of birth, and early life also appear to influence the manifestation of XFS in addition to racial and ethnic variations.<sup>7,16</sup>

## CLINICAL PRESENTATION AND OCULAR MANIFESTATIONS

XFS is diagnosed by the presence of typical whitish, fibrillogranular exfoliation material (XFM) on the anterior lens surface or pupillary border (Fig. 10.13.1). This consists of three zones: a central disc, an intermediate clear zone, and a peripheral granular zone. The XFM is produced primarily by the iris pigment epithelium, ciliary pigment epithelium, and anterior peripheral pre-equatorial lens epithelium. The formation of the central disc is unclear, and it is not clinically present in about 20% of patients. In the other two zones, XFM initially consists of an even coating but is scraped by the iris border during routine dilation and constriction of the



**Fig. 10.13.1 Deposition of Exfoliation Material (XFM) Deposition on the Anterior Lens Capsule.** (A) Early in the disease, clefts form in the XFM as a result of iris rubbing over the lens. (B) In the mature phase, a central disc of XFM is seen with a relatively clear intermediate zone as a result of iris chaffing and a peripheral zone of granular deposits.

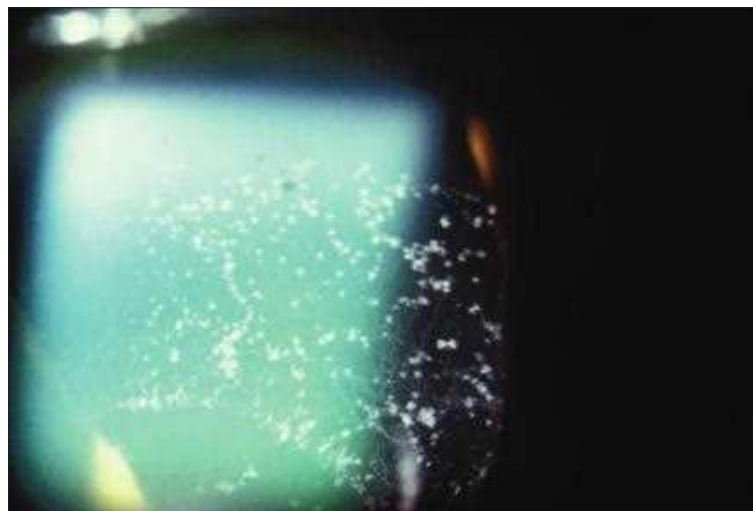


**Fig. 10.13.2** Iris pigment being released from ruptured cells of the pigment ruff during pupillary dilation.

iris. This results in the appearance of clefts in the material beginning at the site at which the iris touches the lens and continuing until this zone is denuded of XFM. At the same time, the XFM on the lens acts like sandpaper, causing rupture of iris pigment epithelial cells at the ruff and surrounding sphincter region, with concomitant pigment dispersion into the anterior chamber, leading to iris transillumination defects, loss of the ruff, and trabecular hyperpigmentation (Figs. 10.13.2 and 10.13.3).<sup>2,8-10</sup>



**Fig 10.13.3** Classic angle features of exfoliation syndrome showing irregular moderately dense pigmentation of the trabecular meshwork, pigment on Schwalbe's line, and a Sampaolesi's line



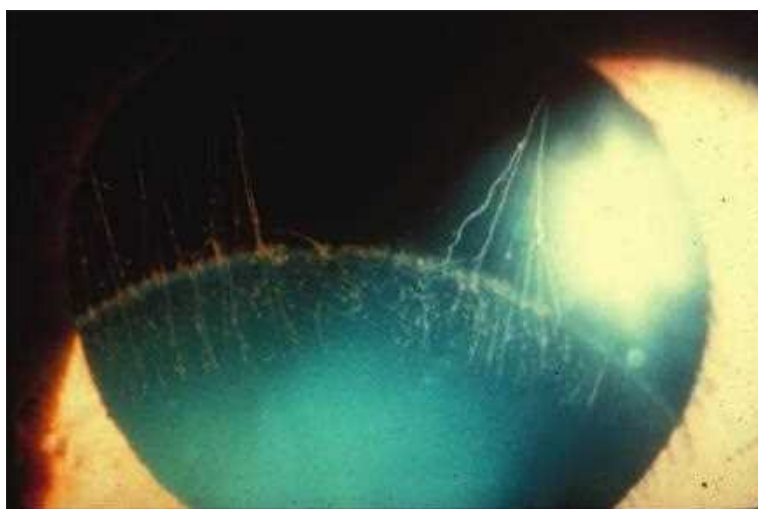
**Fig 10.13.4** Exfoliation material on vitreous strands in a patient with a ruptured posterior capsule.

An early sign of XFS is the development of radial, nongranular striae in the middle third of the lens capsule behind the iris (pregranular exfoliation). XFM can be identified on the ciliary body, zonules, corneal endothelium, and the angle. In patients with pseudo-phakia or aphakia, XFM on these structures and on vitreous strands (Fig. 10.13.4) often helps confirm the diagnosis. Because of the zonular fragmentation and instability inherent in this syndrome,<sup>17</sup> patients occasionally demonstrate phacodonesis or frank subluxation or dislocation of the natural or implanted lens (Fig. 10.13.5). XFS is the most common cause of subluxed intraocular lenses (IOLs).<sup>18</sup> Capsular phimosis may be a precursor to impending IOL subluxation.

Increased pigmentation in the angle is characteristic and may also occasionally be found on the corneal endothelium. XFS has been associated with nonguttate endothelial loss and subsequent corneal decompensation. Peripupillary iris transillumination defects (TIDs) are common, as opposed to the midperipheral radial TIDs of pigment dispersion syndrome (PDS). The angle deposition of pigment is often patchy and unevenly distributed in XFS, contrasting with the homogeneous dense angle pigment seen in PDS. A Sampaolesi's line, most often in the inferior angle, is frequently seen. Other suggestive signs are atrophy of the iris sphincter, poor dilation of the iris, anisocoria, a ground-glass appearance of the lens capsule, and heterochromia, in which the more involved side is lighter.

Pigment dispersion after pupillary dilation may be profuse. Marked IOP increases can occur, and IOP should be measured routinely in all patients after dilation. It should be stressed that all patients should be examined for pigment in the anterior chamber and XFM on the lens after dilation, as this is the only way to make the diagnosis, and failure to do this has led to marked underdiagnosis in the past. Dispersed pigment in the anterior chamber should prompt a careful search for XFM on the lens. Additionally, if pigment liberation is profuse, IOP should be checked an hour later. In patients known to have XFS and an IOP rise after dilation, apraclonidine or brimonidine given prior to dilation can ameliorate this condition.





**Fig 10.13.5** Spontaneously dislocated lens with only fragments of the zonules remaining.

Cataracts are etiologically related to XFS, virtually always being in the same eye when clinically unilateral. Antioxidant activity is reduced in the aqueous humor. Ischemia and oxidative damage correlate with the severity of IOP and glaucoma.<sup>19</sup> Zonules are fragmented and degenerated, contributing to an increased rate of complications at the time of cataract surgery.<sup>17</sup> Zonular laxity, allowing thickening, and anterior movement of the lens, combined with sphincter muscle fibrosis, iris stiffness, and cataract formation are a prominent cause of angle closure.<sup>9</sup> Other reported ocular associations include retinal vein occlusion, ocular surface disease, and macular degeneration.<sup>20</sup>

## GLAUCOMA IN EXFOLIATION SYNDROME

XFG is defined as glaucomatous optic neuropathy in patients with XFS. Blockage of aqueous outflow occurs by a combination of pigment and XFM in the intertrabecular spaces, juxtacanalicular meshwork, and beneath the endothelium of Schlemm's canal. Patients with XFS should be considered glaucoma suspects and monitored at least yearly, with a complete ophthalmic examination, IOP, visual field testing, and nerve fiber layer quantification, and more frequently if there is concern for or evidence of significant disease. Of the patients with XFS, 30%–40% eventually develop glaucoma.<sup>10</sup> XFS is more aggressive than POAG, and failure of medical treatment is more common. In some patients, the condition may have been stable for years but may get out of control and require further intervention.

Medical management of XFG is similar to that of POAG and consists of the use of all current classes of IOP-lowering pharmaceuticals. Prostaglandin analogues are those most frequently initially used. Pilocarpine increases trabecular outflow, which is beneficial in eyes with XFS. Not only does it lower IOP but should slow the progression of the disease by limiting pupillary movement. Unfortunately, pilocarpine has almost disappeared from use in glaucoma on the basis that it is considered a four-times-daily drug; because many patients have nuclear sclerosis, miotics may cause dim vision and long-term use may lead to the development of posterior synechiae. However, we have found that 2% pilocarpine at bedtime can provide sufficient limitation of pupillary mobility without causing these side effects. It produces a 3-mm nonreactive pupil, preventing the liberation of XFM and pigment by eliminating iridolenticular friction, and buildup of granular XMF at the pupillary border and on the center of the lens often occurs. Miotics may also exacerbate pupillary block, but generally not at this low dose. Conversely, if the angle is shallow as a result of zonular laxity, anticholinergic agents often paradoxically deepen the angle in XFS by tightening the cilio–zonular complex.

Argon or selective laser trabeculoplasty can be performed in XFS if the angle is open enough to allow laser application. Argon laser trabeculoplasty has been reported to have a higher success rate in XFS than in POAG and therefore is often used earlier in the management of XFS cases. Selective laser trabeculoplasty has been reported equally or less effective but can be attempted prior to argon treatment because it can be repeated.

If IOP is not adequately controlled with medical or laser treatment, surgical intervention should be considered. The results of trabeculectomy

are favorable, with no significant difference in the postoperative complication rate than in POAG. Newer and less invasive procedures, such as Trabectome or trabeculotomy have shown promise in XFG because they can eliminate trabecular blockage. Newer microinvasive glaucoma surgery procedures, such as XEN or CyPass, should equal their effect in POAG.<sup>21,22</sup>

Combined cataract and glaucoma surgery is common in patients with XFS, and several important considerations must be made in these cases. First, the zonular attachments in XFS are weakened and formerly this resulted in a 5–7 times greater incidence of lens subluxation, zonular dialysis, and vitreous loss. This has been significantly reduced by improved techniques of phacoemulsification and the use of iris and anterior capsular hooks, when necessary. Poor dilation is the single most important predictor for vitreous loss in cataract surgery among these patients. Capsular tension rings (CTRs) may be useful in decreasing zonular and capsular instability, as well as for improving IOL centration and decreasing capsular phimosis. Spontaneous dislocation of the capsular bag and its IOL has been reported with increasing frequency, and it is not yet known whether a CTR will prevent this late postoperative complication. In some cases, it may be necessary to place the IOL into the ciliary sulcus, preferably with optic capture within the capsule. Profound capsular instability may necessitate suture fixation of the lens to the iris or sclera. Other observations made in eyes with XFS include a greater risk for perioperative IOP spikes, posterior synechiae formation, and cellular precipitates on the IOL.

If the lens is unstable, it may be best to perform supracapsular phacoemulsification by aggressive hydrodissection of the lens from the capsular bag. A pars plana approach may be considered if the lens appears to be very unstable. Nonetheless, with a gentle and methodical surgical technique, the results of cataract surgery in patients with XFS can be quite good. If XFG is well controlled and there is no evidence of advanced visual field or nerve damage, clear cornea cataract surgery alone can produce improved IOP control.

With the use of modern surgical equipment and techniques, successful outcomes for the management of cataract and glaucoma in patients with XFS are increasing. Future research will pave the way for a better understanding of the pathogenesis and management of this disease.

## SYSTEMIC MANIFESTATIONS

XFS is associated with deposition of abnormal fibrillary material on both ocular and nonocular tissues. The first studies by Streeten and Schlötzer-Schrehardt in 1992 revealed XFM-like material in the heart, lungs, liver, kidneys, and meninges, closely associated with connective tissue, vascular wall cells, and muscle cells.<sup>10</sup> The most common systemic association of XFS is with ischemic disease, reflected in cardiovascular abnormalities and oxidative damage. It has been associated with cerebrovascular and cardiovascular disease, including hypertension, angina, coronary artery disease, arterial endothelial dysfunction, aortic aneurysm, and renal artery stenosis.<sup>23–26</sup>

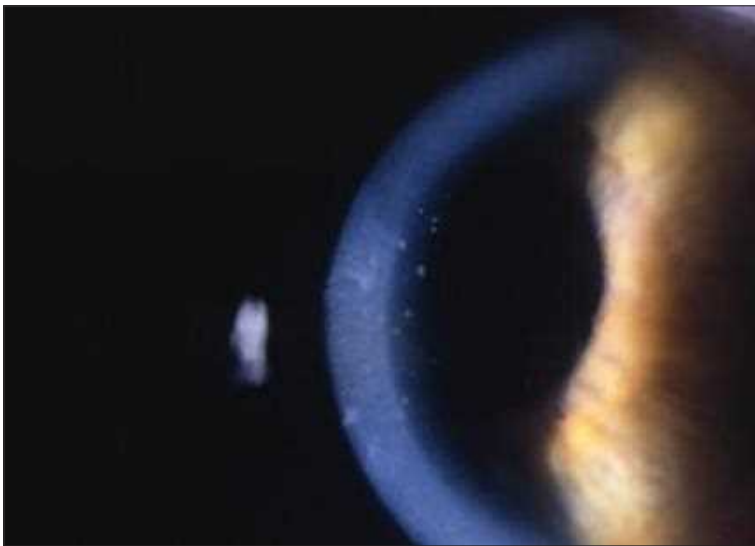
More recently, it has been associated with elastic tissue disorders, specifically chronic obstructive pulmonary disease, inguinal hernia, and pelvic organ prolapse. Associated hearing loss has been strongly associated with XFS.<sup>27</sup> This is truly a protean disease. Nevertheless, there has been no report of increased mortality in patients with XFS. The role of homocysteine and folic acid in etiology has yet to be elucidated.

## DIFFERENTIAL DIAGNOSIS

The differential diagnosis for XFS includes:

- Pigment dispersion syndrome.
- Capsular delamination (true exfoliation).
- Primary amyloidosis.

PDS is more often clinically bilateral, is more common in young men with myopia than in young women, and displays characteristic TIDs and uniform angle pigmentation. True exfoliation is a splitting of the anterior lens capsule without deposition of XFS material. It can occur on rare occasions secondary to heat, trauma, irradiation, or inflammation. Another rare condition that may produce fibrillar material deposition on the lens surface, different from XFM, is primary familial amyloidosis. Most commonly, XFG is misdiagnosed as POAG because of failure to recognize the characteristic clinical signs. XFS may also be confused with iritis if the material deposited on the corneal endothelium is confused with keratic precipitates (Fig. 10.13.6).



**Fig 10.13.6** Exfoliation material on the cornea mimicking keratic precipitates.

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# Pigmentary Glaucoma

Andrew M. Williams, Kelly W. Muir

# 10.14

**Definition:** A form of open-angle glaucoma characterized by dispersion of pigment granules from the iris pigment epithelium, with deposition throughout the anterior segment, including the trabecular meshwork.

## Key Features

- Pigment deposition on the corneal endothelium (Krukenberg's spindle).
- Midperipheral, spoke-like iris transillumination defects.
- Heavy, homogeneous pigmentation of the trabecular meshwork.

## Associated Features

- Presence of key features but without glaucoma is called *pigment dispersion syndrome* (PDS).
- Patients with PDS have a 35%–50% lifetime risk of progressing to pigmentary glaucoma.
- Typical patient is a young man with myopia.
- Predominantly in white patients.
- "Reverse" pupillary block mechanism.

## INTRODUCTION

In 1949, Sugar and Barbour described a patient with pigment dispersion in the anterior chamber and glaucoma and coined the term *pigmentary glaucoma*.<sup>1</sup> Although once thought to be a rare form of open-angle glaucoma, it has been estimated to account for 0.5%–5% of the glaucoma population in the United States.<sup>2</sup> A several-fold larger number of individuals have the typical pigment dispersion without glaucoma, which is referred to as *pigment dispersion syndrome* (PDS).

The mechanism of the pigment dispersion (Box 10.14.1) was suggested by Campbell in 1979 as friction between the iris pigment epithelium and packets of lens zonules, which results from a posterior bowing of the peripheral iris.<sup>3</sup> This iris configuration is seen most commonly in young men with myopia and is felt to result from a reverse pupillary block.<sup>4</sup> The probability of converting from PDS to pigmentary glaucoma has been estimated at about 15% at 15 years,<sup>5</sup> or 35%–50% over the course of a lifetime.<sup>6–9</sup>

### BOX 10.14.1 Stages of Pigmentary Glaucoma

- Pigment dispersion syndrome (PDS)
  - Active or inactive pigment dispersion with stable IOP
- Pigmentary glaucoma (develops in 35%–50% of PDS cases)
  - Clinically reversible stage:
    - Pigment accumulation in the trabecular meshwork
    - Trabecular endothelial phagocytosis
    - Endothelial cell autolysis and migration
  - Clinically irreversible stage:
    - Trabecular meshwork denudation and degeneration
    - Trabecular meshwork collapse and sclerosis

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## EPIDEMIOLOGY AND PATHOGENESIS

The prevalence of PDS is uncertain, as variable degrees of phenotypic expression may lead to underdiagnosis. Estimates range from 10–100 per 100 000, with one group finding a rate as high as 2% in a population undergoing glaucoma screening.<sup>10</sup> Although the PDS is found in roughly equal numbers of men and women, pigmentary glaucoma is more common in men, who have a 3:1 predominance. The glaucoma also tends to occur earlier in men (age at onset 35 years) than in women (46 years), with a tendency in both genders for the condition to decrease in severity or disappear by the sixth to seventh decades of life.<sup>7,11</sup> Patients usually have myopia, and there is a strong preponderance of white patients.

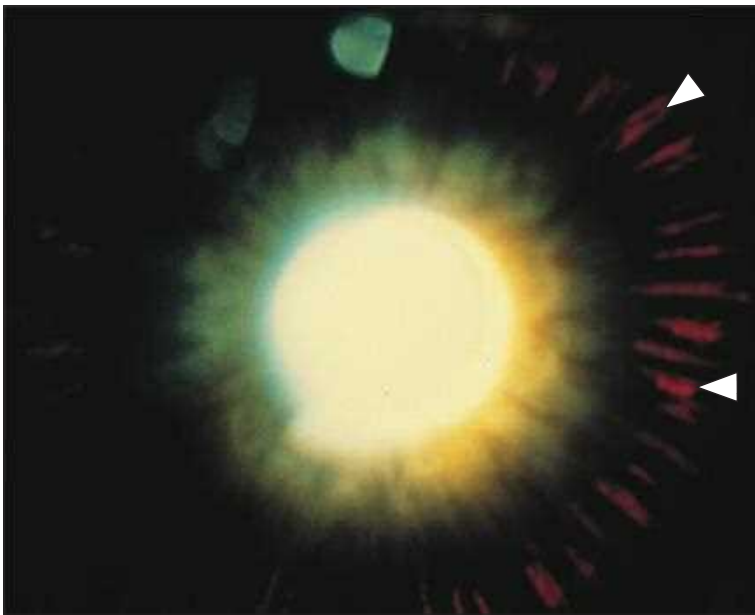
PDS has a complex genetic pattern. One study of four families linked the condition to the long arm of chromosome 7 (7q35–q36) with autosomal dominant inheritance.<sup>12</sup> Although other genetic loci have been evaluated, no single causal gene has been identified. Research in mice has established causal mutations in melanosomal proteins, but the inheritance of PDS likely involves multiple genes that have variable expressivity and penetrance.<sup>13,14</sup>

The configuration of the eye is believed to be responsible for the forces that lead to the iridozonular friction and pigment dispersion. The eyes are larger than average in size, explaining the preponderance of men and those with myopia, and the anterior chamber is deep, which may explain the spontaneous improvement in older patients, as lens changes lead to a shallowing of the chamber. Other anatomical features associated with pigment dispersion are a flatter corneal curvature than in age-matched controls with myopia,<sup>15</sup> a more posterior insertion of the iris into the ciliary body,<sup>16</sup> and a relatively larger iris.<sup>17</sup>

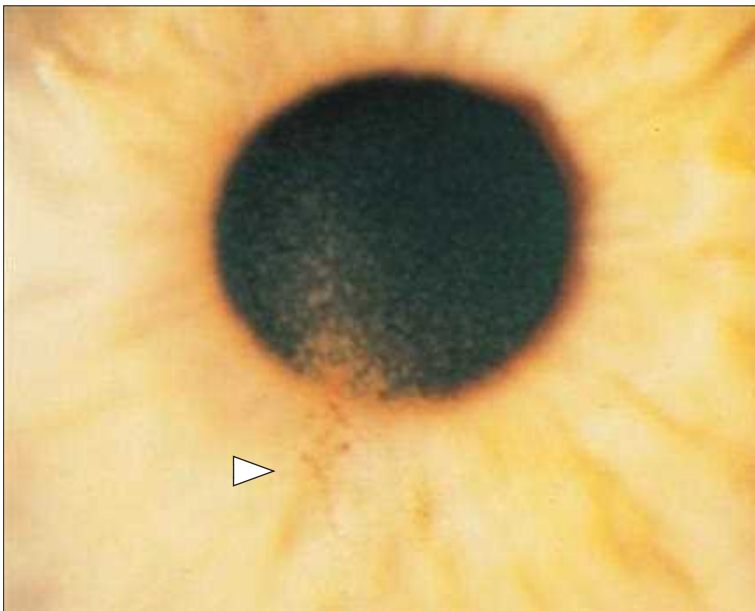
In addition to the above-noted anatomical features, which favor iridozonular friction, histopathological observations of the iris of patients with PDS and pigmentary glaucoma have revealed focal atrophy, hypopigmentation, and apparent delayed melanogenesis of the iris pigment epithelium.<sup>18</sup> It may be, therefore, that both the mechanical iridozonular friction and a developmental abnormality of the iris pigment epithelium are necessary to produce the liberation of pigment granules in these patients.

The concept of reverse pupillary block is critical to an understanding of the mechanisms that lead to pigmentary glaucoma. The configuration of the eye in these patients appears to favor a "pumping" action of the iris, in which eye movement, as with blinking, causes the peripheral iris to act as a bellows in forcing aqueous from the posterior to the anterior chamber. This results in a reverse pressure gradient, that is, higher in the anterior than posterior chamber. The iris then acts as a one-way valve against the lens, preventing aqueous from returning to the posterior chamber. The increased pressure in the anterior chamber leads to posterior bowing of the midperipheral iris and consequently to the rubbing of the iris pigment epithelium against packets of lens zonules, with liberation of pigment granules into the aqueous. Once released into the aqueous, some of the pigment granules then lodge in the trabecular meshwork and obstruct aqueous outflow, resulting in elevated intraocular pressure (IOP).<sup>19</sup> Support for the concept of reverse pupillary block is seen in ultrasound biomicroscopy studies, in which prevention of blinking eliminates the posterior bowing.<sup>20</sup>

Histopathological examinations show that the trabecular endothelial cells engulf the pigment, which results in cell injury and death from phagocytic overload.<sup>21</sup> Macrophages carry off the pigment and debris, leaving the denuded collagen beams to collapse and fuse, with obliteration of the outflow channels. This may explain why treatments directed at increasing trabecular outflow, such as laser trabeculoplasty, are more effective in the earlier stages of pigmentary glaucoma than later in the course.



**Fig. 10.14.1 Transillumination Defects.** The radial, midperipheral, spoke-like iris transillumination defects, typical of patients with pigmentary glaucoma, correspond anatomically to packets of lens zonules.



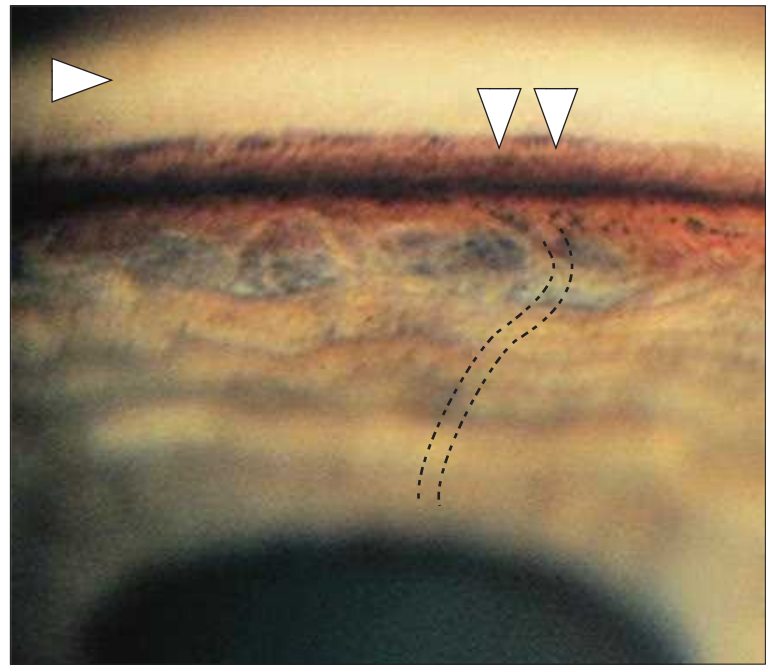
**Fig. 10.14.2 Krukenberg's Spindle.** Vertical, spindle-shaped deposition on central corneal endothelium in patient with pigmentary glaucoma.

## OCULAR MANIFESTATIONS

Contact between the iris and packets of lens zonules leads to characteristic midperipheral, spoke-like iris transillumination defects. This typically appears first in the inferior quadrant, but may be seen for 360° in advanced cases (Fig. 10.14.1). With elimination of the iridozonular friction, as a result of either treatment or age, the transillumination defects gradually fill in and disappear. Characteristically, the dispersed pigment granules deposit on ocular structures in the anterior segment. One of the most common manifestations is a vertical, spindle-shaped deposition on the central corneal endothelium, referred to as *Krukenberg's spindle* (Fig. 10.14.2). Pigment granules may also accumulate in the radial and circumferential iris ridges. But the most classic finding, and the final mechanism of IOP elevation, is the dense, homogeneous pigmentation of the trabecular meshwork (Fig. 10.14.3).

## DIFFERENTIAL DIAGNOSIS

There are several additional forms of glaucoma that may have variable amounts of pigment dispersion in the anterior chamber and which must be distinguished from pigmentary glaucoma, including *pseudo-exfoliation syndrome*, glaucoma in pseudo-phakia, in which the iris rubs against the



**Fig. 10.14.3 Gonioscopic Appearance in Pigmentary Glaucoma.** A wide, open angle with heavy, homogeneous trabecular meshwork pigmentation is a consistent feature of pigmentary glaucoma.

optic or haptic of a posterior chamber intraocular lens, some forms of uveitis, trauma, ocular melanosis and melanoma, and chronic open-angle glaucoma with increased pigment dispersion.

## TREATMENT

Treatment options for pigmentary glaucoma include medical management, laser therapy, and surgery. Initial treatment is typically medical. In particular, prostaglandins have been found to lower IOP more significantly than beta-blockers in patients with pigmentary glaucoma and are therefore usually considered first-line therapy.<sup>22</sup>

Selective laser trabeculoplasty (SLT) is effective in treating pigmentary glaucoma, especially in the early stages of the disease. Interestingly, one recent study suggests that its long-term efficacy is less certain, with an 85% success rate at 12 months but only a 14% success rate at 48 months after treatment.<sup>23</sup> Additionally, caution must be used with SLT because patients with heavily pigmented trabecular meshwork may have significant post-laser treatment IOP elevations.<sup>24</sup> Treating 180° versus 360° of the meshwork and/or using lower power may reduce the risk of post-laser treatment IOP elevation.

The use of laser peripheral iridectomy (LPI) in the setting of pigment dispersion with open angles is controversial. Although LPI does appear to flatten the iris configuration, several studies have found that this has no benefit in reducing disease progression compared with control groups,<sup>25,26</sup> perhaps as a result of pigment liberation from the iridectomy. Interestingly, one study did find support for LPI for eyes with PDS that are at high-risk for converting to pigmentary glaucoma.<sup>27</sup> A 2016 Cochrane review of five randomized-controlled trials found insufficient evidence to make a recommendation for or against LPI in PDS or pigmentary glaucoma.<sup>28</sup>

Incisional surgery is considered when more conservative measures fail to control the disease. Trabeculectomy is an effective, well-established procedure in this population.<sup>29</sup> Most recently, minimally invasive glaucoma surgery (MIGS) have been examined as a treatment modality for pigmentary glaucoma. Early data suggest that ab interno trabeculectomy may be similarly effective for pigmentary glaucoma compared with primary open-angle glaucoma.<sup>30</sup> In contrast, trabecular microbypass stent failed in all three included cases of pigmentary glaucoma in a recent retrospective study, all of whom experienced significant postoperative IOP elevation and required trabeculectomy.<sup>31</sup> With paucity of available data, it is unclear at present what role MIGS has in management of pigmentary glaucoma.

## COURSE AND OUTCOME

Individuals with PDS must be monitored closely as glaucoma suspects because of the risk of conversion to pigmentary glaucoma, which can have a relatively aggressive nature. Although the disease does have a tendency

to “burn out” in later life, the stakes are high in the patient with pigmentary glaucoma because of its early onset. Therefore, aggressive treatment is often required to ensure that these individuals will get through the active decades of the glaucoma with their sight intact.

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# Neovascular Glaucoma

Malik Y. Kahook

10.15

**Definition:** A secondary glaucoma resulting from neovascularization of the anterior segment, including the iris and angle, often associated with and/or secondary to retinal ischemia.

**Key Features**

- Neovascularization of the iris, angle, and anterior chamber.
- Elevated intraocular pressure.
- Peripheral anterior synechiae.

**Associated Features**

- Decreased vision.
- Ectropion uveae.
- Anterior chamber inflammation.
- Cupping of the optic nerve.
- Corneal edema, depending on acuteness.
- Conjunctival congestion.
- Retinal disease with ischemia, inflammation, or tumor.

**INTRODUCTION**

Neovascular glaucoma (NVG) occurs when new vessels proliferate onto the iris surface and over the anterior chamber angle structures, namely, the trabecular meshwork. Retinal ischemia with retinal capillary nonperfusion and subsequent secretion of vasoproliferative factors are the events that lead to neovascularization and glaucoma in most cases. The evolution of NVG usually follows an ordered sequence, beginning with new vessel formation and ending with fibrovascular membranes migrating over the drainage angle, potentially leading to end-stage glaucoma. There is a high likelihood of profound vision loss once intraocular pressure (IOP) increases, making early diagnosis key to preserving ocular function. Medications, laser treatment, and incisional surgery have been the mainstay of treatment. Recently, treatment modalities targeting the vasoproliferative factors directly have emerged, potentially improving outcomes.

**EPIDEMIOLOGY AND PATHOGENESIS**

Coats described the occurrence of iris neovascularization in connection with central retinal vein obstruction (CRVO) in 1906.<sup>1</sup> Weiss et al. coined the term *neovascular glaucoma* in 1963, basing the diagnosis on the presence of new vessels on the iris leading to increased IOP.<sup>2</sup> Diabetic retinopathy and CRVO are the most common pathological processes involved in the development of ocular neovascularization (Box 10.15.1). Thirty-six percent of all cases of NVG arise from CRVO, 32% from proliferative diabetic retinopathy, and 13% from carotid artery occlusive disease.<sup>3</sup> The common denominator in all of these diseases is ocular tissue hypoxia.

The concept of an angiogenic factor stimulating new vessel proliferation as a consequence of hypoxia has long been theorized. Recent advances in molecular biology identified vascular endothelial growth factor (VEGF) as a leading protein involved in the neovascular cascade. Tolentino et al. showed that injection of recombinant human VEGF is sufficient to produce neovascularization in a nonhuman primate model.<sup>4</sup> Tripathi et al. found elevated VEGF levels in the aqueous humor of patients with neovascular glaucoma.<sup>5</sup> Sample analysis detected VEGF in all 12 samples from patients with NVG, 15 of 28 of patients with primary open-angle glaucoma, and 4 of 20 aqueous humor samples from patients with cataract. Mean VEGF concentration in the aqueous humor of patients with NVG was 40 and 113

**BOX 10.15.1 Causes of Iris Neovascularization**

**Retinal Ischemia**

- Diabetic retinopathy
- Central retinal vein occlusion
- Central retinal artery occlusion
- Retinal detachment
- Sick cell retinopathy
- Retinoschisis
- Carotid artery occlusion

**Inflammatory**

- Chronic uveitis
- Endophthalmitis
- Vogt–Koyanagi–Harada syndrome
- Sympathetic ophthalmia

**Tumors**

- Choroidal/iris melanoma
- Ocular lymphoma
- Retinoblastoma

**Irradiation**

- External beam radiation
- Charged particle therapy
- Plaque therapy

**BOX 10.15.2 Stages of Neovascular Glaucoma**

**Stage I: Rubeosis Iridis**

- Normal IOP
- NVI with or without NVA
- Vascular tufts at pupillary margin

**Stage II: Open-Angle Glaucoma**

- Elevated IOP
- Increased NVI and NVA
- No synechial angle closure

**Stage III: Angle-Closure Glaucoma**

- Elevated IOP
- Reduced visual acuity
- Synechial angle closure

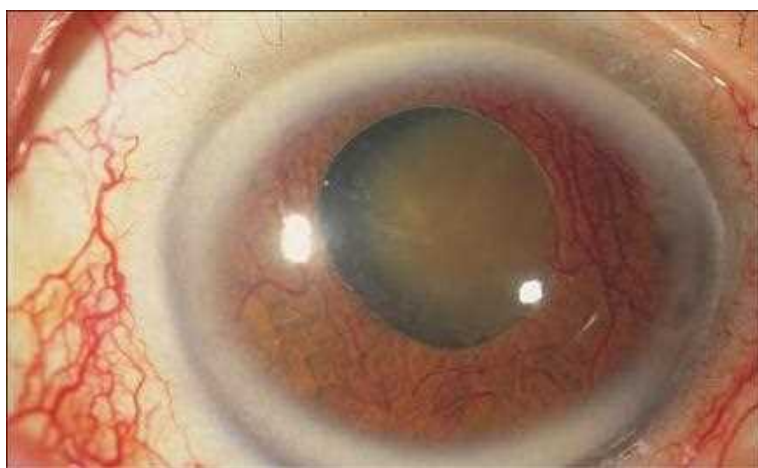
IOP, intraocular pressure; NVA, neovascularization of the angle; NVI, neovascularization of the iris.

times higher than that of patients with POAG and cataract, respectively. Recently, anti-VEGF medications have been shown to dramatically reduce ocular neovascularization when injected in the vitreous of patients with macular degeneration and NVG.<sup>6,7</sup>

Although ischemia is believed to be a primary instigator of angiogenesis, other factors play a role in abnormal vessel formation. Inflammation and hypoxia often coexist in the microenvironment leading to new vessel formation. These links remain incompletely understood and only recently have they been partially elucidated. Inflammatory mediators, such as angiopoietin-1 and angiopoietin-2, are now known to play a role in new vessel formation and remodeling, along with their role in inflammation.<sup>8</sup> Furthermore, intravitreal triamcinolone, a potent anti-inflammatory agent, has shown modest efficacy in decreasing iris neovascularization.<sup>9</sup> Theoretically, corticosteroids decrease neovascularization by interrupting the inflammatory cascade that contributes to the neovascular drive.

**OCULAR MANIFESTATIONS**

Neovascular glaucoma can be divided into three stages (Box 10.15.2). Stage 1 consists of vascular proliferation at the pupillary margin. Neovascularization of the iris may be difficult to detect at this point. Slit-lamp biomicroscopy reveals fine, tortuous, randomly oriented tufts of vessels on the



**Fig. 10.15.1 Neovascularization of the Iris.** Note the florid neovascular proliferation at the pupillary margin, which grows in random orientation on the iris surface.



**Fig. 10.15.2 Neovascularization of the Angle.** Gonioscopic view of new vessels that cover the trabecular meshwork and impart a characteristic red flush.

surface of the iris, near the pupillary margin. These tufts may be obscured in dark irides and more obvious in lighter irides. Neovascularization characteristically progresses from the pupillary margin toward the angle (Fig. 10.15.1) of undilated pupils, but angle neovascularization in the absence of pupillary involvement may occur. Repeated gonioscopy is indicated in eyes at high risk for the development of NVG. As vascular proliferation develops, biomicroscopy of the anterior chamber shows cells and flare. Gonioscopy reveals new vessels that grow from the circumferential artery of the ciliary body onto the surface of the iris and onto the surface of the wall of the angle.

The vessels cross the angle recess and grow forward over the ciliary body band and scleral spur onto the trabecular meshwork, which imparts a characteristic red flush (Fig. 10.15.2). Early in the course of anterior segment neovascularization the IOP often is normal. The new blood vessels arborize to form a fibrovascular membrane (invisible on gonioscopy) that gives rise to a secondary open-angle glaucoma representing the second stage of NVG. Stage II of NVG is characterized by contraction of the fibrovascular membrane, which pulls the peripheral iris over the trabecular meshwork and results in variable degrees of synechial angle closure. Ectropion uveae and hyphema occur frequently. Ectropion uveae results from radial traction along the surface of the iris, which pulls the posterior pigmented layer of the iris around the pupillary margin onto the anterior iris surface. It is at this stage that patients may present with the dramatic onset of pain secondary to elevated IOP. Patients typically experience severely reduced visual acuity accompanied by corneal edema and anterior chamber inflammation. Stage III findings are similar to stage II findings, with the exception that synechial angle closure is present.

## DIAGNOSIS

The medical history is crucial in evaluating patients for the development of NVG. Diabetes mellitus, hypertension, arteriosclerosis, and a previous history of vision loss indicative of CRVO, central retinal artery obstruction (CRAO), or retinal detachment are important. Recent ocular surgery may increase the risk in predisposed individuals. It is imperative that a

### BOX 10.15.3 Differential Diagnosis of Neovascular Glaucoma

- Uveitic glaucoma
- Acute angle-closure glaucoma
- Chronic angle-closure glaucoma
- Iridocorneal endothelial syndrome
- Fuchs' heterochromic iridocyclitis

posterior segment examination be performed in all patients to identify concomitant retinal disease. The diagnosis of NVG is made on the basis of clinical examination findings. Careful slit-lamp and gonioscopic examinations are usually sufficient to make the diagnosis. An undilated pupil is helpful. The goal is to establish the diagnosis well before angle structures become involved and elevated IOP or synechial angle closure occurs.

Involvement of the anterior chamber angle sometimes occurs before the appearance of neovascularization of the iris. These vessels typically run on the iris surface, follow a nonradial course, and may cross the scleral spur. Thus, gonioscopy must be performed on every patient at risk for the development of NVG. In most instances, however, small tufts of neovascularization are noted first at the pupillary margin. This tendency for initial involvement of the pupillary margin appears to result from aqueous flow dynamics, whereby angiogenic factors produced in the posterior segment have the most contact with the pupillary margin.

Occasionally, early neovascularization may be missed when the new vessels are fine and thin, the iris is darkly pigmented, or pressure from the gonioscopy lens reduces the caliber of the new vessels and renders them clinically unapparent. Frequent follow-up of patients at high risk for NVG enables early detection of new vessels in difficult cases. Fluorescein angiography (FA) of the iris may be used to demonstrate the presence of new vessels before they become visible clinically with slit-lamp biomicroscopy. FA of the retinal circulation, if corneal clarity and pupillary dilation allows, is an important adjunct. Peripheral sweeps and wide field angiography are especially helpful in detecting peripheral retinal capillary nonperfusion as well as detecting posterior-segment neovascularization.

The b-wave to a-wave amplitude ratio of the bright-flash, dark-adapted electroretinography may help predict which eyes will develop NVG following CRVO.<sup>10</sup> This ratio was found to be less than 1.0 (average 0.84) in eyes that developed NVG after ischemic CRVO. In contrast, the b-wave to a-wave amplitude ratio was always greater than 1.0 in eyes that did not develop NVG following CRVO.

## DIFFERENTIAL DIAGNOSIS

The differential diagnosis of NVG is summarized in Box 10.15.3. The diagnosis of NVG is often made easy by the appearance of iris neovascularization in the presence of retinal pathology. However, occasional cases are less obvious with subtle neovascularization and little or no visible retinal pathology. In these cases, the treating physician should be familiar with other disease processes infrequently linked to rubeosis iridis and high IOP. Uveitic glaucoma can mimic NVG with high pressure and dilated iris vessels. Fuchs' heterochromic iridocyclitis can present with high IOP and abnormal vessels in the anterior chamber angle. Finally, end-stage NVG can look identical to chronic angle-closure glaucoma with angle closure because of diffuse anterior synechiae.

## TREATMENT

The key to successful management of NVG is early diagnosis. Recognition of neovascularization of the iris is crucial so that preventive treatment can be initiated before the anterior chamber angle is closed by peripheral anterior synechiae. Once the florid, intractable final stage is established, the eye is likely blind, with very high IOP and painful bullous keratopathy. If the NVG is secondary to carotid artery or other systemic disease, it is important to evaluate and treat the primary systemic condition.

Panretinal photocoagulation (PRP) remains the first line of therapy in almost all cases of NVG. Prompt application of PRP has been shown to achieve regression of anterior and posterior segment neovascularization and to reduce the risk of developing neovascularization of the iris in eyes that have retinal vascular disease.<sup>11</sup> In the open-angle glaucoma stage and early angle-closure glaucoma stage, PRP may reverse or mitigate IOP elevation. For eyes that have advanced synechial angle closure of the anterior chamber with some potentially useful vision, PRP may eliminate



the stimulus for neovascularization, which prepares the eye for filtering surgery and the prevention of further visual loss.

Panretinal cryotherapy is an alternative to PRP in eyes that have cloudy media and in eyes for which complete PRP fails to halt the progression of neovascularization.<sup>12</sup> It is rarely employed, given its high rate of complications. Goniophotocoagulation may be used as an adjunct to PRP to reduce neovascularization in the angle before it is closed by synechiae, but generally the effects are only temporary.<sup>13</sup> The treatment of NVG is directed by the visual potential. Any usable vision, even 20/400 (6/120) or less in a monocular patient, is worth preserving.

The role of glaucoma filtering surgery in NVG is to prevent pressure-induced injury to the optic nerve and, theoretically, to improve vascular perfusion. Before glaucoma surgery, every attempt is made to reduce or eliminate the stimulus for angiogenesis using PRP. By allowing the maximal amount of time between PRP and glaucoma surgery, the risk of intraoperative and postoperative bleeding and severe intraocular inflammation is reduced. The importance of complete preoperative PRP to the success of glaucoma filtering surgery in patients who have NVG cannot be overstressed.

Of special importance is the use of intraoperative cautery to achieve hemostasis and to avoid bleeding. Direct cauterization of the peripheral iris before iridectomy may reduce the risk of bleeding. Variable success rates have been reported after conventional filtering surgery in patients who have NVG. Allen et al.<sup>14</sup> reported IOP control in 67% of patients who had NVG and underwent trabeculectomy or posterior lip sclerectomy after PRP. Tsai et al.<sup>15</sup> reported a high risk of long-term failure with 5-fluorouracil filtering surgery; 12 of 34 patients with NVG (35%) lost light perception vision, and eight patients (24%) developed phthisis bulbi over a 5-year follow-up period. Younger age ( $\leq 50$  years) and type I diabetes mellitus are significant risk factors for early surgical failure. Skuta et al.<sup>16</sup> described the use of mitomycin C with trabeculectomy in patients who had NVG.

Glaucoma drainage implants are also used for the primary surgical treatment of NVG. Seton procedures place the effective sclerostomy inside the anterior chamber away from the angle, which maintains a patent fistula between the anterior chamber and an equatorial bleb. Sidoti et al.<sup>17</sup> cited life-table success rates of 79% and 56% at 12 and 18 months, respectively, following Baerveldt glaucoma implantation surgery for NVG. Success was defined as a final IOP of 6–21 mm Hg (0.8–2.8 kilopascals [kPa]) without additional glaucoma surgery or devastating complications. Loss of light perception occurred in 31% of patients. Cox model regression survival analysis demonstrated young patient age and poorer preoperative visual acuity as significant predictors of surgical failure. Another study that evaluated the use of the single-plate Molteno valve implantation for NVG reported success rates of 62% at 1 year, 52.9% at 2 years, 43.1% at 3 years, 30.8% at 4 years, and 10.3% at 5 years; loss of light perception was seen in 29 of 60 eyes (48%), and phthisis bulbi developed in 11 eyes (18%).<sup>18</sup>

Noninvasive techniques are employed to achieve patient comfort if the eye has no visual potential. Topically administered corticosteroids and cycloplegics may relieve ocular discomfort. Topical beta-adrenergic blockers, alpha-adrenergic agonists, and carbonic anhydrase inhibitors may be used to reduce aqueous production. Miotic therapy is avoided because it may aggravate intraocular inflammation and pain. Once the anterior chamber angle is closed, medical therapy alone may not provide long-term IOP control, and surgical intervention becomes necessary. Cyclocryotherapy had been advocated in the treatment of elevated IOP in NVG. Although the IOP can be controlled in a high percentage of patients who undergo the procedure, the long-term visual outcome is dismal; loss of light perception occurs in 58.5% of patients. In addition, the high incidence of major complications, which include anterior segment necrosis and phthisis bulbi (34%), means that its use in eyes that have visual potential is limited.<sup>19</sup> Other modalities of therapy to control IOP include diode and neodymium:yttrium–aluminum–garnet transscleral cyclophotocoagulation. Schuman et al.<sup>20</sup> reported a 39% success rate using the latter in patients who had advanced NVG. As laser treatment has evolved, the standard cyclodestructive modality has become diode laser cyclophotocoagulation of the ciliary body. This technique is typically performed transsclerally with an 810 nm diode laser equipped with a semidisposable G-probe. The pain and inflammation of this procedure is typically less than that seen with prior, more destructive versions. More targeted techniques using an endoscope in the operating room setting have also been used to adequately lower IOP.<sup>21</sup>

In painful eyes that have poor visual potential, cycloablation, retrobulbar alcohol injection, and enucleation may help achieve comfort.

## COURSE AND OUTCOME

The natural course of NVG is uniformly one of complete loss of vision and the development of intractable, severe pain. The high degree of ocular morbidity and mortality in patients who have NVG emphasizes the severity of the underlying systemic conditions associated with diabetic retinopathy and CRVO, the main causes of this disorder. Usually, NVG occurs in patients burdened with serious systemic disease. Krupin et al.<sup>22</sup> and Mermoud et al.<sup>18</sup> cited mortality rates of 22% and 15% in patients who have NVG. Diabetes mellitus was the underlying cause of NVG in the majority of patients reported by the Diabetes Control and Complication Research Group,<sup>23</sup> which highlights the importance of effective blood sugar control in patients who have diabetic retinopathy. The risk of progression of mild diabetic retinopathy and the development of proliferative diabetic retinopathy is reduced to half in patients using effective blood sugar control.

NVG does not invariably follow the development of neovascularization of the iris. When such neovascularization is detected, it behooves the clinician to monitor patients carefully with repeated slit-lamp examinations and undilated gonioscopy. Neovascularization of the iris has been reported to develop in 50% of patients who have proliferative diabetic retinopathy and in 60% of those who have the ischemic type of CRVO. It is imperative that PRP be applied promptly to ischemic retina to eliminate the stimulus for further neovascularization.

Visual loss in NVG is common and may be attributed to a combination of causes, including severe ocular ischemia with progression of the underlying retinal disease, glaucomatous optic nerve damage, cataract formation, corneal decompensation, and phthisis bulbi. The most common cause of surgical failure in patients who have NVG is related to progression of the underlying retinal disease, not to uncontrolled IOP.<sup>15,17,22</sup> The ultimate solution for patients who have NVG lies in the development of new modalities of treatment designed to prevent the initiation of neovascularization. Murata et al.<sup>24</sup> recently showed that thiazolidinediones, a novel class of drugs that can be used to improve insulin resistance in type II diabetes, inhibit angiogenic responses to VEGF in vitro. Current research to develop pharmacological therapies targeted at the inhibition of angiogenic factors offers hope for the preservation of vision in patients at risk.

## EMERGING TREATMENTS

It is clear that the best way to treat NVG is to prevent it from occurring in the first place. Having failed to prevent its occurrence, NVG is best dealt with when diagnosed early and treated aggressively. Current therapeutic options, such as laser and incisional surgery, carry with them the high risk of loss of visual field or visual acuity and, in the case of drainage devices and trabeculectomy, a high risk of infection. Newer treatment modalities should offer more precise targeting of the angiogenic mediators.

Antiangiogenic medications are promising as new methods for treating NVG. Bevacizumab (Avastin, Genentech) has been investigated as a potential adjunct in the treatment of NVG.<sup>7</sup> VEGF is a potent mitogen specific for vascular endothelial cells and is upregulated under conditions of retinal ischemia and NVG.<sup>25,26</sup> A downregulation in the production of VEGF through the use of inhibitors should limit neovascularization in diseases that lead to retinal ischemia.<sup>27</sup> Multiple case series publications have highlighted the regression of neovascularization of both the iris and angle after injections of VEGF inhibitors.<sup>7,26–33</sup> Kahook et al.<sup>7</sup> described the case of a patient who was treated with the anti-VEGF bevacizumab after having failed IOP control with transscleral CPC and PRP. A rapid decrease in IOP was noted, and the patient experienced symptomatic improvement within 48 hours. Other similar case reports found matching results after use of bevacizumab for NVG.<sup>29,30</sup>

Iliev et al.<sup>31</sup> described the use of intravitreal bevacizumab (IVB; 1.25 mg/0.05 mL) in a series of six consecutive patients with NVI and refractory NVG. They noted marked regression of anterior segment neovascularization and rapid relief of symptoms. IOP was significantly reduced in three patients, and in the remaining three patients, IOP was controlled after the addition of CPC and PRP. Oshima et al.<sup>32</sup> described IVB treatment of seven eyes with NVI caused by PDR and reported that NVI regressed within 1 week. With the use of iris FA, Grisanti et al.<sup>33</sup> studied the effects of IVB on NVI and noted a decrease in iris FA leakage as early as one day after injection.

Gheith et al.<sup>34</sup> presented a case series of six patients with NVG, each of whom received 1.25 mg/0.05 mL IVB, followed by PRP 1 week later. All patients had a complete regression of iris and angle neovascularization. Those authors noted that topical medications failed to control IOP in the patients who developed peripheral anterior synechiae, and they also

highlighted the need for continued monitoring of patients because of the long-term risk of recurrence of neovascularization seen in some patients. It should be noted that Bakri et al.<sup>35</sup> found the vitreous half-life of 1.25 mg IVB was 4.32 days in a rabbit eye. Recurrence of neovascularization is to be expected if the hypoxic drive remains in place from an ischemic retina. It is clear within our university based practice that anti-VEGF injections (bevacizumab, ranibizumab, or aflibercept) are becoming a standard of care for patients presenting with NVG and have improved comfort and visual outcomes when combined with PRP and CPC and/or prior to performing incisional surgery, such as trabeculectomy and glaucoma drainage device implantation.

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# Inflammatory and Corticosteroid-Induced Glaucoma

10.16

Ridia Lim, Ivan Goldberg

**Definition:** Characteristic glaucomatous optic neuropathy associated with ocular inflammation and/or exposure to corticosteroids.

## Key Features

- Optic disc pallor and cupping and nerve fiber bundle perimetric defect(s), with evidence of inflammation involving one or more ocular tissues and/or past or continuing exposure to corticosteroids.
- Pre-existing glaucoma or a tendency to angle-closure may pre-exist and may contribute to pathophysiology.

## Associated Features

- Variably raised and/or fluctuating intraocular pressure (IOP).
- Mechanisms for IOP rise may vary over time and require continuous reassessment to focus treatment effectively.
- Use of corticosteroids may lead to IOP rise; treatments that exacerbate inflammation (miotics) should be avoided.
- Specific treatment for the cause of any uveitis is important. Nonspecific treatments of uveitis include corticosteroids, nonsteroidal anti-inflammatory drugs, immunosuppressives, and newer biological agents.
- Inflammatory glaucomas should be treated with ocular hypotensive medications (primarily aqueous suppressants), laser therapies, and augmented filtering surgery.
- Hypotony is a risk with drainage surgery, especially if there has been previous cyclodestruction.

## INTRODUCTION

Ocular inflammation and/or corticosteroid use can cause glaucomatous damage by elevating intraocular pressure (IOP) and/or by ischemia or infiltration of the optic nerve head.

To be effective, management needs to include precise detection of inflammation, treatment of the inflammation *and* its underlying cause (if possible), elucidation of the mechanism(s) of any IOP elevation, and its effective control.

Symptoms and signs may vary from marked to none; clinical course may be acute, subacute, unpredictably relapsing, or chronic. Management of the inflammation and any glaucoma is often challenging, especially as the mechanism(s) for raised IOP may change. This demands ongoing re-evaluation of mechanism(s) raising IOP and changes to treatment.

Raised IOP complicates about 20% of clinic-based uveitis cases; about 40% of these later have abnormal perimetry.<sup>1</sup> It is more common with anterior uveitides than with intermediate or posterior uveitides.

## PATHOPHYSIOLOGY

The relationship between IOP and inflammation is complex. IOP depends on the comparative rates of aqueous production and outflow (trabecular and uveoscleral). All of these, as well as aqueous circulation, can be altered by inflammation, by its effects on the ocular tissues involved, and by treatment, particularly corticosteroids. To identify the different processes that may change over time, repeated careful history and examination are required.

### BOX 10.16.1 Possible Causes of Raised Intraocular Pressure

- Secondary open-angle glaucoma
  - Trabecular meshwork obstruction
  - Schlemm's canal and episcleral venous outflow obstruction
  - Corticosteroid-induced elevation of intraocular pressure
  - Permanent, direct trabecular meshwork tissue damage
  - Post-trabecular outflow damage
  - Hypersecretion
- Pre-existing primary open-angle glaucoma
- Secondary angle-closure glaucoma
  - Peripheral anterior synechiae
  - Posterior synechiae
- Pre-existing disposition to primary angle-closure glaucoma
- Combined-mechanism glaucoma

Development of glaucomatous optic neuropathy depends on disease chronicity and susceptibility to corticosteroids, as well as to dose and duration, patient age, and optic nerve susceptibility to damage. Some eyes have multimechanism glaucoma. Although elevated IOP is a risk factor for uveitic glaucoma, IOP may not be elevated, and raised IOP (uveitic “ocular hypertension”) does not universally lead to glaucoma.

## MECHANISMS OF ELEVATED IOP

See Box 10.16.1.

### Secondary Open-Angle Glaucoma

*Trabecular meshwork obstruction* is the most common mechanism<sup>2</sup> and may occur after the following:

- White blood cell accumulation (macrophages and activated T lymphocytes) or their aggregations—seen gonioscopically as small pale yellow or gray precipitates or later as fine peripheral anterior synechiae and angle-closure glaucoma.
- Inflammatory debris, such as proteins, fibrin or even normal serum components after blood–aqueous barrier (BAB) breakdown—IOP may rise from increased aqueous viscosity. Altered vascular permeability may persist indefinitely, with a subtle aqueous flare-up being the clinical clue. This may predispose to recurrent inflammations by increasing intraocular concentrations of such substances as prostaglandins.
- Rarely, other solid components contribute to the blockage, for example, in Schwartz's syndrome (rhegmatogenous retinal detachment, uveitis and glaucoma, rod outer segments can block trabeculum).<sup>3</sup>
- Swelling of trabecular lamellae and endothelial cells with narrowing of trabecular pores and dysfunction.
- Overwhelming the trabecular endothelial phagocytic and pathway-clearing processes by a severe inflammation.
- If trabecular endothelial cell loss or damage becomes irreversible, permanent reduction in conventional outflow ensues.
- Direct trabecular damage from keratitis or the toxic effects of corneal stromal destruction. Keratitis without uveitis rarely elevates IOP.

These various mechanisms may potentiate one another.

Schlemm's canal and episcleral venous outflow obstruction can be caused by similar physical and chemical means or by raised episcleral venous pressure—particularly with scleritis, episcleritis, and keratitis.

Corticosteroids induce IOP elevation in susceptible patients by reducing trabecular outflow facility through changes to the mechanical structure of the trabecular meshwork, extracellular matrix trabecular deposits, and reduction of trabecular endothelial functional and phagocytic activity.<sup>4</sup> This is possible with topical, other local (dermal or inhalational), depot (subconjunctival, sub-Tenon's, intravitreal), or systemic corticosteroids. Following 4–6 weeks of topical corticosteroids, in about 5% of patients IOP will rise by more than 16 mm Hg and in 30%, by 6–15 mm Hg.<sup>5,6</sup> In a minority, IOP rise can be faster and to a greater extent; risk factors for this include primary open-angle glaucoma (POAG), family history of glaucoma, very young or older age, diabetes, connective tissue disease, and myopia.<sup>7</sup> Ninety-two percent of patients with POAG are high corticosteroid responders, with 19% of their children also being high responders.<sup>6</sup> Intravitreal triamcinolone acetonide can increase IOP for months. A 20-mg dose increased IOP above 21 mm Hg in 40% of individuals for up to 9 months; of these, 1% required trabeculectomy.<sup>8</sup> More than 50% of children age less than 10 years respond to dexamethasone.<sup>9</sup> Within 2 years of implanting the intravitreal Retisert implant (0.59 mg fluocinolone acetonide; Bausch & Lomb), which acts for more than 30 months, 60% required IOP-lowering medications, and 32% needed filtering surgery.

Topical corticosteroids vary in their IOP elevation effect (from the strongest effect to the least: dexamethasone 0.1%, prednisolone 1%, fluorometholone 0.1%, medrysone 1%)<sup>7</sup> to reduce steroid response, minimize the strength, frequency, and duration of corticosteroids. If possible, an individual's IOP steroid response should be elucidated *before* using depot corticosteroids.

Monitoring IOP is essential in all patients receiving corticosteroids. Once use of topical corticosteroids has ceased, IOP almost always returns to baseline within 4 weeks.<sup>10</sup> Steroid response is possible even after glaucoma surgery (microinvasive glaucoma surgery [MIGS], deep sclerectomy, or trabeculectomy). In uveitis treatment, steroids show variable effects on IOP, depending on their influence at that time on rates of aqueous inflow, outflow, viscosity, and the BAB (Table 10.16.1).

Permanent direct trabecular meshwork tissue damage can result from the following:

- Anterior and/or limbal scleritis.
- Destructive or degenerative connective tissue diseases.
- Chemical injuries, including those caused by caustic soda, ammonia, formalin, nitrogen mustards, and chloroform.
- Post-trabecular outflow damage from scleritis with vasculitis—lymphocytes surround intrascleral outflow channels, with an anterior uveal perivasculitis.
- Hypersecretion may occur in uveitis but is difficult to quantify—BAB breakdown renders fluorophotometry inaccurate; may contribute to glaucomatocyclitic crises, but flow probably normal.<sup>11</sup>

## Pre-Existing Open-Angle Glaucoma

Elevated IOP in an eye with uveitis does not mean that inflammation is the cause. Other primary or secondary forms of open-angle glaucoma, such as post-traumatic (particularly if unilateral) or pseudo-exfoliative (may be unilateral or bilateral) glaucoma, must be ruled out.

An acute onset and unilaterality suggest uveitis as the cause, whereas an afferent pupil defect with asymmetrical disc cupping and perimetric loss in a patient with a short symptomatic (uveitic) history suggests a chronic underlying glaucomatous process.

**TABLE 10.16.1** Effects of Corticosteroid Therapy on Intraocular Pressure in Ocular Inflammation

Action	Result	Effect on IOP
Decrease trabecular meshwork inflammation	Increased trabecular meshwork outflow	Decrease
Increase blood–aqueous barrier	Decreased aqueous viscosity Increased trabecular meshwork outflow	Decrease
Decrease ciliary body inflammation	Aqueous inflow returned to normal	Increase
Alter trabecular meshwork endothelial cells in corticosteroid responders	Decreased trabecular meshwork outflow	Increase

IOP, Intraocular pressure.

## Secondary Angle-Closure Glaucoma

Peripheral anterior synechiae (PAS) commonly complicate uveitis and, if allowed to progress, may seal the angle partly or completely, thus raising IOP.

PAS may follow organization of inflammatory debris or protracted iridotrabecular contact from an acute secondary angle-closure attack, a flat or shallow anterior chamber after incisional surgery, or an exudative retinal detachment with anterior displacement of the lens–iris diaphragm. Ciliary body rotation anteriorly from uveitis-induced swelling or suprachoroidal exudation can produce the same result. Swelling of the peripheral iris and exudation of proteins and other inflammatory products, such as fibrin into the chamber angle, increase PAS formation.

Neovascularization of the anterior chamber angle with subsequent fibrovascular closure may follow chronic uveitis.

Posterior synechiae form with fibrin, with later fibrovascular organization. Involvement of the entire pupil margin results in a secluded pupil; iris bombé produces a shallow or closed peripheral anterior chamber with normal central depth. PAS follow if this acute secondary angle-closure is not treated promptly with one or more adequate peripheral iridectomies.

With widespread adhesion of iris to anterior lens surface, bombé may not occur evenly or at all. Lens–iris diaphragm forward movement may be the only sign of secondary pupillary block and can be confused with an underlying tendency to primary angle closure. The anterior chamber configuration should be compared with that of the fellow eye to differentiate these mechanisms. Laser iridectomy placement can be crucial. Drainage surgery may be indicated.

In the presence of uveitis, iris bombé, and a closed angle, low or normal IOP signals possible profound aqueous hyposecretion. Successful drainage surgery may precipitate the eye into phthisis bulbi, an increased risk anyway with uveitis.

## Pre-Existing Disposition to Primary Angle Closure

With pre-existing shallow anterior chamber and relative pupillary block, an acute angle-closure crisis may be precipitated by anterior segment edema and inflammation, increased aqueous viscosity, swelling and forward rotation of the ciliary body, and anterior shift of the lens–iris diaphragm. All or some of these factors may accompany uveitis. The depth of the contralateral anterior chamber will confirm this diagnosis.

## Combined-Mechanism Glaucoma

Usually, raised IOP associated with uveitis results from more than one of these mechanisms. The mix may change as the disease and its treatment proceed. Recognizing the responsible mechanism(s) at any time point enables effective antiglaucoma therapy.

## PRINCIPLES OF MANAGEMENT

Both the underlying inflammation and the glaucoma require assessment, diagnosis, and directed treatment. Management demands flexibility as the disease(s), the effects on the eye(s), and the treatment itself may change significantly over time. An open mind and careful examination and re-examination are vital for therapeutic success.

## UVEITIS

### Diagnosis

A careful history with a review of systems and a complete ocular examination followed by targeted investigations should allow accurate diagnosis of the majority of ocular inflammations. Refer to the sections on uveitis, keratitis, and scleritis. Box 10.16.2 lists the conditions that commonly raise IOP.

### Management

Detected ocular and any associated systemic diseases are treated on their merits. Active inflammation should be controlled adequately, and its damaging effects on aqueous circulation and drainage prevented, and elevated IOP controlled (Table 10.16.2). Management in collaboration with uveitis specialists and general physicians is highly recommended, particularly when systemic medication is required.

**BOX 10.16.2 Inflammatory Conditions Commonly Associated With Raised Intraocular Pressure**

- Anterior uveitis
  - HLA-B27–related acute anterior uveitis = 20% (0%)
  - Glaucomatocyclitic crisis (Posner–Schlossman syndrome) = 100% (0%)
  - Phacolytic glaucoma
  - Herpes virus–associated uveitis = 30% (29%)
  - Fuchs’ heterochromic iridocyclitis
  - Juvenile idiopathic arthritis–associated uveitis
  - Chronic anterior uveitis
- Intermediate uveitis (pars planitis)
- Posterior uveitis
  - Peripheral anterior synechiae
  - Sarcoidosis = 34% (39%)
  - Behçet’s disease = 21% (50%)
  - Toxoplasmosis = 12% (36%)
  - Vogt–Koyanagi–Harada syndrome = 16% (34%)
  - Sympathetic ophthalmia
  - Acute retinal necrosis
  - Masquerade syndromes
  - Retinal detachment, uveitis, and glaucoma (Schwartz’s syndrome)

Percentages are cases with raised intraocular pressure (% with abnormal perimetry).

HLA, Human leukocyte antigen.

From Takahashi T, Ohtani S, Miyata K, et al. A clinical evaluation of uveitis-associated secondary glaucoma. *Jpn J Ophthalmol* 2002;46:556–62; and P. McCluskey, personal communication.

**TABLE 10.16.2 Treatment Guidelines for Inflammatory Glaucoma**

1. Treat Underlying Systemic Disease (if present)		
Specific	e.g., Anti-infectives	Specific treatment for toxoplasmosis, toxocariasis, Lyme disease, syphilis, TB
Nonspecific	Anti-inflammatory	Corticosteroids, NSAIDs
	Immunosuppression	Corticosteroid-sparing agents: methotrexate, cyclosporine, mycophenolate, mofetil, azathioprine, cyclophosphamide
	Biologicals	Anti-TNF agents, e.g., infliximab, adalimumab interferon
2. Treat Ocular Inflammation		
Specific	E.g., Intravitreal antibiotics for bacterial endophthalmitis	
Nonspecific	Anti-inflammatory	Topical, depot, intravitreal or systemic corticosteroids, NSAIDs
	Pupillary dilation	Cycloplegic, sympathomimetic agents
3. Treat Elevated IOP		
Medical	Reduce aqueous production Increase uveoscleral outflow	Beta-blockers, alpha-2-adrenergic agonists, carbonic anhydrase inhibitors Prostaglandin analogs
Surgical	Peripheral iridectomy	For pupillary block, if present with recurrence after laser iridectomy(ies)
	Augmented trabeculectomy	If medications are insufficient
	Glaucoma drainage devices	If augmented trabeculectomy fails
	Cyclodestruction: transscleral or endoscopic laser, cryotherapy	For eyes with little visual potential

IOP, Intraocular pressure; NSAIDs, nonsteroidal anti-inflammatory drugs; TB, tuberculosis.

Corticosteroids nonselectively inhibit most inflammatory reactions, irrespective of cause; they do not treat the cause. Corticosteroids aid IOP control by treating trabeculitis and by restoring the BAB; the balance can shift to higher IOP with corticosteroid responsiveness and recovery of aqueous production with resolution of iridocyclitis. Corticosteroids remain the first-line treatment for inflammation.

Nonsteroidal anti-inflammatory drugs (NSAIDs) and immunosuppressive drugs (methotrexate, cyclosporine, mycophenolate mofetil, azathioprine, cyclophosphamide) are indicated alone or in combination with one another or with corticosteroids, if corticosteroids alone have failed to control inflammation or are contraindicated. These steroid-sparing agents are particularly useful in chronic uveitides in corticosteroid-responsive

patients. Biological agents, particularly anti-tumor necrosis factor blockers, are increasingly being incorporated into uveitis treatment.

In addition to anti-inflammatory measures, antibiotics and antifungal agents are necessary when inflammation is secondary to a specific infection (e.g., toxoplasmosis).

### Mydriasis and Cycloplegia

Pupillary dilation with cycloplegics (atropine, homatropine) and sympathomimetics (phenylephrine) prevents formation of posterior synechiae or breaks them, thereby avoiding a secluded pupil. These drugs help control IOP by increasing uveoscleral outflow and by stabilizing the BAB. By decreasing ciliary muscle spasm, they may relieve discomfort.

### GLAUCOMA

In most eyes with acute inflammation, the optic disc is healthy and may withstand elevated IOP levels even into the 30s for weeks or months. Controlling inflammation and protecting the eye from damage to aqueous circulation and drainage mechanisms will normalize IOP. IOP reduction per se may not be required unless levels are thought to be unsafe, disc decompensation appears, other risk factors predispose additionally to retinal vein occlusion, corneal endothelial disease contributes to edema, or recurrent or chronic inflammation provokes long-standing ocular hypertension. Because any type of glaucoma that develops can cause rapid progression of inflammation, this requires careful monitoring.

### Medical Management

Reduction of aqueous production is the cornerstone of medical management of raised IOP with inflammation by using beta-blockers (timolol, betaxolol, carteolol, levobunolol), alpha-2-adrenergic agonists (apraclonidine, brimonidine), and topical or systemic carbonic anhydrase inhibitors (dorzolamide, brinzolamide, acetazolamide, dichlorphenamide, methazolamide). Latanoprost, travoprost, and bimatoprost in uveitis are now accepted and have been used effectively in many uveitic eyes without sequelae.<sup>4</sup> Exacerbation of uveitis and cystoid macular edema were concerns; nonetheless, these agents should be used cautiously. NSAIDs reduce the ocular hypotensive effect of brimonidine and, possibly, latanoprost.<sup>12,13</sup> Prostaglandins should be avoided in herpetic keratouveitis.

Because they enhance posterior synechiae formation by aggravating BAB breakdown, by producing miosis, and by contributing to anterior chamber shallowing, miotics (pilocarpine, carbachol) should be avoided.<sup>14</sup> They may exaggerate discomfort with ciliary muscle spasm and may raise IOP paradoxically by failing to improve trabecular outflow while blocking uveoscleral outflow.

### Surgical Management

Laser peripheral iridectomy (LPI) is indicated if posterior synechiae precipitate a secluded pupil with iris bombé and if medical mydriatic measures fail to break them. To eliminate pupillary block, the iridectomy(ies) must be adequate in size and position. LPI can raise IOP and exaggerate anterior uveitis; it can be difficult technically because of iris congestion. Gentle argon laser flattening (settings: 200–500 mW, 0.2–0.5 s, 200–500 µm spot) or “chipping” pretreatment (settings: 800–1000 mW, 0.02 s, 50 µm spot) may facilitate neodymium:yttrium–aluminum–garnet (Nd:YAG) laser penetration of the iris. Laser openings may close with active inflammation and should be monitored carefully; surgical iridectomy may have to be considered in this situation. In eyes with severe uveitis, particularly in children, a larger surgical iridectomy may be preferable to Nd:YAG iridectomy because it minimizes inflammation and is less likely to cause closure.

Argon laser trabeculoplasty (LT) can exacerbate anterior uveitis and promote PAS formation; it has a poor chance of reducing IOP significantly.<sup>15</sup> It is contraindicated in inflammatory glaucoma. Selective laser trabeculoplasty has not yet been evaluated adequately in these eyes. In corticosteroid-induced glaucoma, it may be effective.

Filtration surgery becomes necessary when medical and laser management, along with treatment of both inflammation and its cause, cannot reduce the IOP below levels that are causing or likely to cause optic disc decompensation and functional damage. Because of increased postoperative inflammation and a greater risk of profound hypotony leading to bleb failure, filtering surgery is less likely to succeed in inflamed eyes than in those with primary open-angle glaucoma.<sup>16</sup> One of the keys to success in all drainage surgery is to control inflammation maximally both before and



after surgery with, for example, intensive topical, local, or even systemic corticosteroids.

Adjunctive antifibrotic agents (intraoperative mitomycin C,<sup>17</sup> postoperative 5-fluorouracil<sup>18</sup>) have improved trabeculectomy success rates appreciably—both in the short term and in the long term. Complication rates increase, however, with these agents, the most serious ones being hypotonous maculopathy and late endophthalmitis from leaks through thin-walled blebs.

Glaucoma drainage devices (GDDs), both valved (Ahmed) and non-valved (Molteno and Baerveldt) have had more success than unaugmented trabeculectomies. GDDs do not achieve the low levels of IOP (7–11 mm Hg) that augmented trabeculectomies often can. In eyes with extensive optic disc damage, a GDD-attained IOP of 14–18 mm Hg may not be sufficiently protective. In eyes with visual potential, a GDD is indicated where augmented trabeculectomies have failed.<sup>19</sup> GDD tubes must be patched with donor sclera or equivalent to minimize the risk of later erosion, especially in uveitic glaucoma. In chronic uveitic glaucoma where aqueous production is borderline and hypotony risk is high, a smaller GDD (single plate Molteno or 250 mm<sup>2</sup> Baerveldt or Ahmed) is preferable to larger devices. Reducing aqueous production by damaging ciliary epithelium (cyclodestruction) by Diode, Nd:YAG or ultrasound energy has been used to lower IOP. Because they may aggravate ocular inflammation and lower IOP unpredictably (with significant risk of secondary phthisis bulbi or failure to control IOP), as well as the albeit small risk of sympathetic ophthalmia, cyclodestruction is recommended where all else has failed and where there is little visual potential.<sup>20</sup> Lower laser power settings are prudent, and lasers delivering lower doses, such as the micropulse laser and endoscopic laser, may be preferable. Drainage surgery after ciliary body destruction in an inflamed eye is a likely setting for hypotony and phthisis bulbi. Deep sclerectomy and newer surgeries, such as MIGS, need further evaluation in uveitic glaucoma.

## SPECIFIC ENTITIES

Table 10.16.2 highlights conditions associated with ocular inflammation and glaucoma etiologically. (Refer to other chapters for more detail.)

### Glaucomatocyclitic Crisis (Posner–Schlossman Syndrome)

In 1948, Posner and Schlossman described nine patients with this entity.<sup>21</sup> Clinical features include episodic, unilateral markedly elevated IOP (usually 40–60 mm Hg), associated with a mild anterior uveitis. Recurrences are always in the same eye. Posterior synechiae and PAS are absent, and the drainage angle remains open. Each attack lasts from a few hours to a month, but usually for 1–3 weeks. Antiglaucoma treatment does not abbreviate the attack, and iridectomy or filtering surgery does not prevent recurrences. Glaucomatous optic neuropathy may occur. Between attacks, there are generally no signs or symptoms of inflammation or glaucoma, and the contralateral eye remains normal. Of unknown etiology, although infection (with cytomegalovirus [CMV], herpesvirus, or *Helicobacter pylori*) has been implicated, this condition has a complex relationship with primary open-angle glaucoma.<sup>22–27</sup>

Management comprises the following:

- Hypotensive measures—apraclonidine or brimonidine seems particularly effective during attacks, with supplementation as required with other aqueous suppressants. The role for prostaglandin derivatives has yet to be established. Rarely, hyperosmotic agents may be needed.
- Anti-inflammatory measures—although there is no evidence that corticosteroids and/or topical NSAIDs shorten the attack or prevent recurrences, many clinicians consider them “useful.” Cycloplegics are not needed.

Intervals between attacks vary from a few days to several years. Some are seasonal. Attacks are rare in older adults, suggesting a self-resolving course. Thus prevention of irreversible disc and field damage is all the more important.

An anterior chamber paracentesis may reveal an infectious etiology for Posner–Schlossman syndrome, which, in turn, may guide specific therapy

directed against that agent, rather than treatment of elevated IOP. Should aqueous polymerase chain reaction (PCR) reveal CMV, for example, treatment with ganciclovir may be curative of the IOP elevation. Topical ganciclovir ointment, in addition to oral valganciclovir, can be of benefit; however, systemic treatment is necessary in the case of CMV infection.<sup>25</sup> Valganciclovir is not benign, and the patient must be monitored closely to detect any treatment toxicity.

### Fuchs’ Uveitis Syndrome (Fuchs’ Heterochromic Iridocyclitis)

More expansive than the one described by Fuchs in 1906,<sup>28</sup> this condition encompasses a chronic, usually unilateral (90%), low-grade panuveitis with rapid cataract formation (commencing as posterior subcapsular) and a high risk of secondary open-angle glaucoma. This entity is differentiated from other inflammatory glaucomas by the lack of posterior synechiae and the rarely more than “moderate” anterior chamber cells and flare; it is asymptomatic. Vitreous cells are common. Characteristically, keratic precipitates are small, round or stellate, and discrete; they cover the entire corneal endothelial surface and fine filaments are often seen between them. Their presence and extent greatly exceeds the inflammation. Rubella has been implicated as the inciting event,<sup>29</sup> as has CMV infection.<sup>25–27</sup> Anterior chamber paracentesis with aqueous PCR is recommended in Fuchs’ heterochromic iridocyclitis, as for Posner–Schlossman syndrome. Should an infectious etiology be present, treatment is described as above for Posner–Schlossman syndrome, specific for the infectious agent. This may eliminate the need for ocular antihypertensive treatment, with IOP normalization. Fuchs’ uveitis syndrome (FUS) and Posner–Schlossman syndrome may be thought of as part of a spectrum of uveitic glaucomas and may share the same infectious etiology.

Unless an infectious etiology for FUS is found, therapy of the uveitis is unnecessary, although a short intensive trial of corticosteroids may help to confirm the diagnosis (by lack of response). When the eye is symptomatic, short bursts of topical corticosteroids may restore comfort, but corticosteroids do not normalize the BAB or achieve total quiescence. The glaucoma is more difficult to control.<sup>30</sup> Initially, a raised IOP may respond to anti-inflammatory treatment, but in two thirds of patients, a chronic IOP rise often resists medications. Argon LTP is “underwhelming” in its effect and is contraindicated by angle changes. Selective laser trabeculoplasty has not been evaluated. Should an augmented trabeculectomy fail, GDDs may prove helpful.

Patients require ongoing monitoring, especially for glaucoma damage and for progressive iris atrophy, which hint at a poor prognosis. Recognition is important; it renders anti-inflammatory therapy unnecessary.

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# Glaucoma Associated With Ocular Trauma

10.17

*Tony K.Y. Lin, David P. Tingey, Bradford J. Shingleton*

**Definition:** Glaucomatous damage to the optic nerve related to elevated intraocular pressure associated with acute or prior ocular trauma.

## Key Features

- Previous blunt or penetrating ocular trauma—glaucoma is more likely to follow blunt trauma.
- Angle recession—the greater the number of clock hours recessed, the more likely glaucoma is to occur, even months, years, or decades after the injury.
- Hyphema—often accompanies angle recession, and may be an acute cause of elevated intraocular pressure, especially in the presence of hemoglobinopathies (e.g., sickle cell disease or trait).

## Associated Features

- Trabecular tears/trabeculitis.
- Angle recession.
- Iridodialysis.
- Pupillary sphincter tears.
- Cyclodialysis.
- Zonular dehiscence.
- Lens damage, subluxation, or dislocation.
- Vitreous hemorrhage—may lead to ghost cell glaucoma.
- Retinal dialysis/retinal tear.

## INTRODUCTION

Glaucoma may occur in traumatized eyes in the period immediately following injury or years or decades later. There exist a plethora of potential causes of glaucoma following ocular trauma. It is important for the evaluating ophthalmologist to be familiar with the various types of glaucoma in this setting as well as their pathogenesis. Recent cohort studies have examined the relationship between glaucoma after ocular injury and several baseline structural and functional ocular characteristics. The risk of developing glaucoma in 3627 patients in the United States Eye Injury Registry with penetrating ocular injury was 2.67%. The development of glaucoma in these patients was independently associated with advancing age, lens injury, poor baseline acuity, and inflammation.<sup>1</sup> In a similar study, 6021 patients who experienced ocular contusion injury were found to have a risk of developing glaucoma of 3.39% at 6 months after their injury. The development of glaucoma was independently associated with the following factors:

- Advancing age.
- Visual acuity worse than 20/200.
- Iris injury.
- Lens injury.
- Angle recession.<sup>2</sup>

Ultrasound biomicroscopy (UBM) was used in conjunction with clinical features to determine early predictors of traumatic glaucoma after closed globe injury prospectively in 40 consecutive eyes.<sup>3</sup> This study found that the best clinical indicators for the development of chronic glaucoma

included degree of trabecular pigmentation, angle recession more than 180°, hyphema, lens displacement, and higher baseline intraocular pressure (IOP). UBM findings that were significant predictors of chronic glaucoma included a wider angle and the absence of cyclodialysis.<sup>3</sup>

In the initial period after an ocular injury, the IOP may be normal, high, or low. There are several mechanisms that explain a low pressure. These mechanisms include aqueous hyposecretion based on ciliary contusion and inflammation, increased egress of aqueous through a cyclodialysis cleft, or loss of integrity of the wall of the globe. The presence of ocular hypotension or normal IOP does not preclude the development of glaucoma at a later date. Whether glaucoma is present initially or at a later date, it is generally a reflection of reduced facility of outflow of aqueous humor.

One may categorize the existence of traumatic glaucoma relative to the time of onset of the glaucoma (immediate or delayed) and the type of trauma that caused the injury. The type of trauma may be divided into blunt force trauma or penetrating trauma. A broader classification would include chemicals, electromagnetic radiation, and surgery as additional causes of trauma that might induce glaucoma. Glaucoma may also occur as a result of the therapeutic modalities employed to treat the initial injury.

## IMMEDIATE OR EARLY-ONSET GLAUCOMA AFTER OCULAR TRAUMA

### Contusion

IOP elevation in the setting of blunt trauma with a notable absence of clinical evidence of tissue damage may be noted on occasion. Gonioscopy is entirely normal with no evidence of angle recession, and there is no evidence of blood or abnormal pigment in the angle. Flare and cells may be evident at the slit lamp. The presumed mechanism of this type of glaucoma is reduced outflow facility as a result of trabecular inflammation. The course of this glaucoma is usually brief and self-limiting, although a trial of topical anti-inflammatory drops in addition to any IOP-lowering agents may hasten improvement and shorten the clinical course.

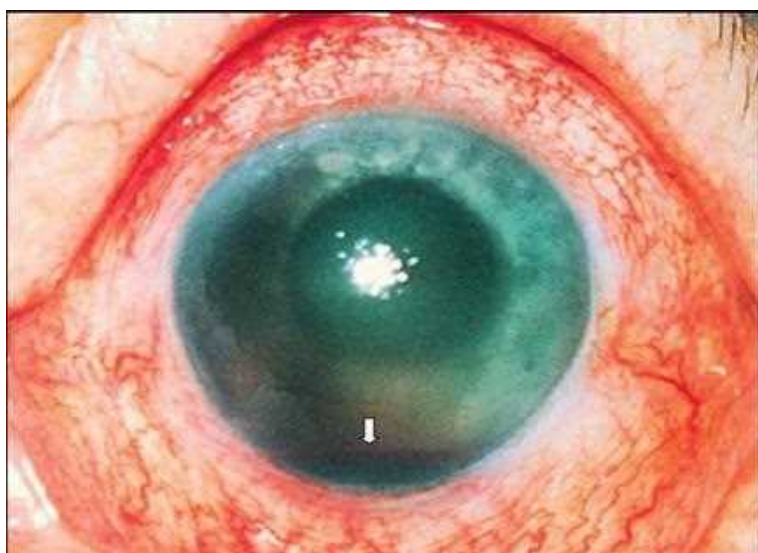
### Trabecular Disruption

Evidence of trauma-related changes to the trabecular meshwork has been documented in a study utilizing gonioscopy performed within the first 48 hours following injury. Documented abnormalities ranged from sharply demarcated hemorrhage into Schlemm's canal and possibly the outer trabecular sheets to full-thickness rupture of the trabecular meshwork for part of its circumference. A trabecular flap may be created with a point of rupture at or just below the insertion of the trabecular sheets at Schwalbe's line. This flap is typically hinged in the region of the scleral spur. Such lesions at the trabecular meshwork may or may not be associated with elevated IOP at the time of injury. Trabecular lesions may scar with time and become increasingly difficult to recognize over time. Although angle recession is associated with the late development of glaucoma, the occurrence of late glaucoma may correlate better with the amount of trabecular disruption observed acutely.<sup>4</sup>

### Hyphema

The presence of hyphema (Fig. 10.17.1) after ocular trauma is an indicator of significant intraocular injury. Cho et al. compared the clinical





**Fig. 10.17.1** Blood layering (arrow) in the anterior chamber (hyphema). (From Schuman JS, Christopoulos V, Dhaliwal D, et al. *Rapid diagnosis in ophthalmology series: lens and glaucoma*. St Louis, MO: Elsevier; 2007.)

characteristics of 18 patients with very poor visual outcome after nonperforating hyphema to 166 patients with better visual outcome after nonperforating hyphema. The presence of posterior segment injuries, anterior segment injuries, poor initial visual acuity, glaucoma, vitreous hemorrhage, and eyelid laceration were all associated with long-term poor visual outcome.<sup>5</sup> Hyphema may produce glaucoma via several mechanisms, including contusion/inflammation of the trabecular meshwork, physical disruption of the meshwork, and plugging of the meshwork by red blood cells (RBCs). In addition, a large clot in the anterior chamber may even produce pupillary block by entirely occluding the pupillary aperture.

Elevation of IOP in association with hyphema may threaten vision as a result of optic nerve damage, compromised blood flow to the posterior segment, or corneal blood staining. IOP elevation occurs in up to 27% of patients acutely; however, this elevation is often mild and self-limiting.<sup>4</sup>

The duration and level of IOP required to damage the optic nerve for a given individual is difficult to determine. Read and Goldberg<sup>6</sup> studied 137 patients with hyphema prospectively and determined that optic atrophy tended to occur with IOPs at or greater than 35 mm Hg with durations varying from 5–14 days. Optic atrophy as a direct result of the trauma itself may be a confounding factor in such studies.

Corneal blood staining occurs more readily in the presence of IOP that is greater than 25 mm Hg and has persisted for at least 6 days in the setting of blood clot apposition to the corneal endothelium.<sup>6</sup> If the corneal endothelial cells are already compromised as a result of the trauma itself or pre-existing disease, the risk of staining with only marginal pressure elevation is even greater.

Sickle cell disease represents a unique challenge in the hyphema patient. Even small amounts of blood in the anterior chamber of such patients may result in severe IOP elevation.<sup>7</sup> Sickled erythrocytes presumably obstruct the outflow apparatus. Optic atrophy has also been reported in such patients with only mild pressure elevation.<sup>7,8</sup> Compromised blood flow to the optic nerve as a result of sickling has been proposed as a mechanism for this. These complications may be seen in patients with either sickle cell disease or trait. In addition, several of the conventional IOP-lowering pharmacological agents may be harmful to patients with sickle cell hemoglobinopathy. Carbonic anhydrase inhibitors may produce systemic acidosis, which enhances sickling. Methazolamide may be a safer choice than acetazolamide in this setting because it causes less systemic acidosis. Both carbonic anhydrase inhibitors and osmotic agents increase hemoconcentration and viscosity because of their diuretic effect. This, in turn, may compromise blood flow in a system already at risk from sickled erythrocytes. Acetazolamide can increase ascorbate in the aqueous humor, and this may worsen the sickling process as well. Epinephrine agents and less specific alpha-agonists, such as apraclonidine, may cause vasoconstriction, which may also compromise ocular blood flow in patients with sickle cell disease. The presence of hyphema in the patient calls for the judicious use of pharmacological agents to control even mild pressure elevation and a lower threshold on the part of the clinician for performing a washout of erythrocytes from the anterior chamber. There are reports of successful use of intracameral tissue plasminogen activator in a patient with sickle cell disease as well as traumatic hyphema and acute glaucoma.<sup>9</sup>

Rebleeding into the anterior chamber can be a devastating complication, which typically occurs between days 2 and 6 after the initial injury. The reported incidence of rebleeding is somewhere between 6% and 33%, as reported by several studies.<sup>6,8,10,11</sup> Markedly elevated IOP and its attendant complications are a particular concern with rebleeding.

Various treatments, such as those using aminocaproic acid, tranexamic acid, corticosteroids, and cycloplegics, are employed to decrease the rate of rebleeding in patients with hyphema. Aminocaproic acid and tranexamic acid are antifibrinolytic agents that decrease the rate of rebleeding; however, studies on these two agents have not shown any significant benefit to best vision or final visual acuity after traumatic hyphema.<sup>8,11–14</sup> Aminocaproic acid use is associated with significant side effects, including nausea, vomiting, gastrointestinal upset, increased systemic thrombosis risks, and systemic hypotension.<sup>11</sup> The side-effect profile of tranexamic acid is similar but with fewer gastrointestinal side effects.<sup>11,12</sup> These findings, as well as the relatively low incidence of rebleeding overall, may account for the limited use of antifibrinolytic agents by clinicians.

Corticosteroids have been used to reduce the incidence of rebleeding as well.<sup>15,16</sup> The rationale behind this is the reduction of inflammation, stabilization of blood–ocular barrier, or direct inhibition of fibrinolysis, thus preventing secondary rebleeding. However, studies examining either oral corticosteroids<sup>13,17</sup> or topical corticosteroids<sup>18,19</sup> failed to find significant differences in the time to resolution of primary hemorrhage or rates of rebleeding.

Cycloplegics and miotics have both been studied with inconclusive findings because of low rates of rebleeding.<sup>18,20</sup> Other lesser known treatment modalities, such as use of conjugated estrogen and aspirin, have been shown to have no benefit.<sup>21,22</sup>

Acute IOP elevation in the setting of hyphema may be treated with conventional pharmacological agents, with the exception of miotic agents and prostaglandin agents. Both these agents may exacerbate any pre-existing inflammation, and so they are not generally used as first-line agents. Cycloplegic agents and topical corticosteroids are often employed in the treatment of any associated inflammation after hyphema. The potential for either topical or systemic corticosteroids to produce IOP elevation with more chronic use must be kept in mind.

If the IOP remains elevated at a level that threatens the optic nerve or the cornea in spite of medical therapy, then surgical intervention may be necessary. Many surgical procedures including anterior chamber washout,<sup>23</sup> mechanical clot expression,<sup>24</sup> delivery of the clot with a cryoprobe,<sup>25</sup> automated hyphemectomy,<sup>26</sup> and ultrasonic emulsification and aspiration of the clot,<sup>27</sup> have been reported in the literature. Trabecular gonioaspiration has been reported as a successful way of managing pressure elevation resulting from blood obstructing the trabecular meshwork in patients with the sickle cell trait.<sup>28</sup> Adjunctive procedures may include peripheral iridectomy to relieve clot-induced pupillary block.<sup>29</sup> Trabeculectomy has been used to achieve pressure normalization.<sup>30,31</sup> Cyclodiathermy to control recurrent bleeding has also been described.<sup>32</sup>

Paracentesis and anterior chamber washout is the simplest and safest procedure for blood cell evacuation. This can be performed by simple irrigation or by manual coaxial irrigation and aspiration. Removal of the entire clot may not be necessary. This technique also spares the conjunctiva for future filtration surgery if it becomes required.

## Massive Choroidal Hemorrhage

This is a rare cause of acute IOP elevation after ocular trauma. At the slit lamp, a shallow anterior chamber, both axially and peripherally, will be seen in association with a reduced red reflex or a frank retrolenticular mass. Indirect ophthalmoscopy reveals choroidal elevation. Obstruction of the trabecular meshwork from secondary angle closure is the most common reason for IOP elevation in this setting, although other mechanisms from associated other effects of the trauma, such as hyphema, inflammation, and so on, may also play a role.

Initial treatment consists of topical IOP-lowering agents as well as oral carbonic anhydrase inhibitors and a systemic hyperosmotic agent, if needed. Miotics should be avoided because they will further make the anterior chamber shallow. Cycloplegics may be effective in deepening the anterior chamber. Oral corticosteroids may be helpful in reducing inflammation and stabilizing compromised choroidal vasculature.

Certain situations, such as persistent angle closure with IOP elevation, lens–cornea apposition, and “kissing” choroidals with retinal apposition may warrant surgical drainage of the blood in the suprachoroidal space. It is advisable to wait several days, if possible, for the blood clot to become liquefied in the suprachoroidal space before intervening.

Chronic synechial closure of the angle may be a sequela of massive suprachoroidal hemorrhage. This may require intervention in the form of chronic medical therapy, laser iridoplasty, surgical goniosynecholysis, conventional filtration surgery, or cycloablation, depending on the circumstance.

Massive choroidal detachment with intraretinal dissection is a rarely seen occurrence after trauma in the setting of age-related macular degeneration. This results in a “Y-suture” apposition of posterior segment tissues pushing the lens–iris diaphragm forward and leading to angle closure.<sup>33</sup> IOP rises dramatically, and vision is often reduced to no light perception. Medical or surgical therapy rarely restores vision.

## Chemical Trauma

Alkali burns produce tissue saponification, resulting in severe damage to the ocular structures. Acid burns are often self-limiting as a result of tissue coagulation. Glaucoma is more often associated with alkali burns.

Glaucoma as a result of alkali burns may be immediate or delayed. In 1946, Hughes<sup>34</sup> documented several cases of elevated IOP with delayed onset after an alkali burn. Several papers in the 1960s documented acute pressure elevation after alkali burn.<sup>35,36</sup> The angle was gonioscopically open in these cases.

The nature of the acute IOP rise has been studied in rabbits by Chiang et al.<sup>37</sup> These authors demonstrated a dicrotic rise in IOP following the application of sodium hydroxide. In the rabbit model, there was an immediate rise of 40 mm Hg in IOP, followed by a gradual decline in pressure to 20 mm Hg above normal in 10 minutes. The IOP again rose gradually reaching 40 mm Hg above normal at 1 hour. The IOP was 20 mm Hg above normal at 3 hours after the alkali application.

The mechanism of IOP rise in rabbits following alkali application was elucidated by Paterson and Pfister.<sup>38</sup> They implicated tissue shrinkage involving the outer coats of the eye in the initial pressure spike. Lid contraction and extraocular muscle spasm were not thought to play an important role in pathogenesis. Prostaglandin release as part of the inflammatory cascade was thought to be the greatest contributor to the second hypertensive phase. The authors also postulated that blockage of the trabecular meshwork with inflammatory debris might also play a later role in the rise of IOP.

The potential for acute IOP elevation in the setting of alkali burn as documented in the animal model points to the importance of attempting to document IOP as early as possible after injury. In addition to the conventional therapies directed at the anterior segment consequences of an alkali burn, treatment of any IOP elevation is important. Arguably, treatment with IOP-lowering agents on a prophylactic basis is a reasonable consideration, particularly in severe burns, given the propensity for these burns to produce rapid and severe IOP elevation.

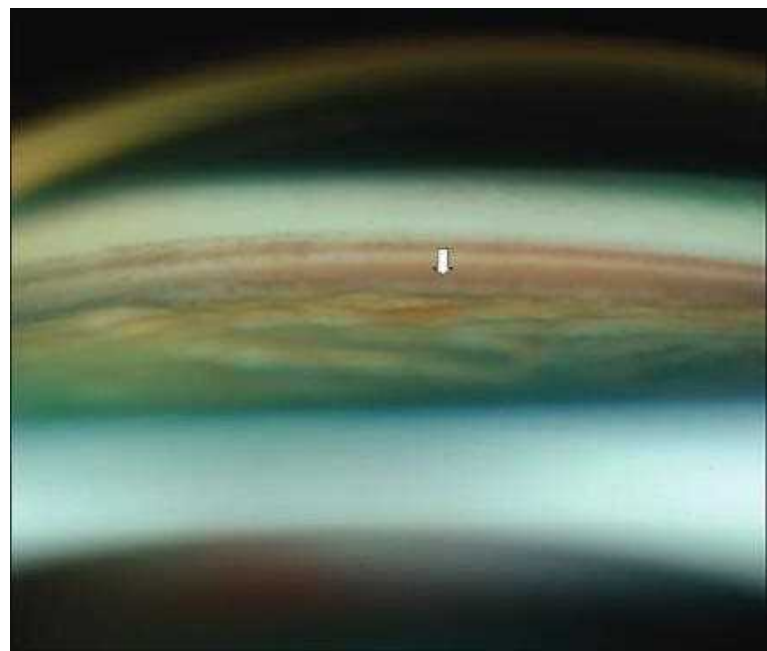
When the decision to treat with IOP-lowering agents is made, topical beta-blockers, alpha-agonists, and carbonic anhydrase inhibitors are all appropriate, as well as systemic treatment with carbonic anhydrase inhibitors and hyperosmotic agents, as needed. Miotics and topical prostaglandin analogues are generally avoided because of the inflammatory nature of this condition. Anti-inflammatory medications and adequate cycloplegia are also important. Anterior chamber paracentesis with aspiration of aqueous humor may be required if the IOP is extremely high during the initial hypertensive phase. This reduces the IOP and removes inflammatory mediators, debris, and alkali directly from the anterior chamber.

After the initial alkali burn, glaucoma may appear or reappear. Ongoing inflammation with secondary peripheral anterior synechiae (PAS) and angle closure is the most common mechanism. In their study looking at the incidence of glaucoma in eyes with severe chemical burn, before and after keratoprosthesis, Cade et al. found that 21 of 28 eyes in this group had preoperative evidence of glaucoma, nine of these eyes developed glaucoma progression after keratoprosthesis implantation, and two more eyes developed glaucoma postoperatively.<sup>39</sup> The treatment of this late-onset glaucoma includes conventional medical and surgical therapies.

## LATE-ONSET GLAUCOMA AFTER OCULAR TRAUMA

### Angle Recession

The first pathological description of angle recession resulting from blunt trauma was described by Collins<sup>40</sup> in 1892. In 1949, D’Ombrain<sup>41</sup> described chronic posttraumatic glaucoma, which he attributed to a proliferative



**Fig. 10.17.2** Tear between the longitudinal and circular muscles of the ciliary body presenting as a widening (arrow) of the ciliary band (angle recession). (From Schuman JS, Christopoulos V, Dhaliwal D, et al. *Rapid diagnosis in ophthalmology series: lens and glaucoma*. St Louis, MO: Elsevier; 2007.)

lesion scarring the trabecular meshwork. No observation of pathological deepening of the anterior chamber angle was made. The pathological entity of angle recession and the clinical phenomenon of unilateral chronic glaucoma were linked by Wolff and Zimmerman in 1962.<sup>42</sup>

Anatomical recession of the anterior chamber angle (Fig. 10.17.2) is common after blunt trauma. The incidence of angle recession after traumatic hyphema ranges from 71%–100%, as indicated by several reports.<sup>43–46</sup> Glaucoma is relatively uncommon after angle recession, being found in 7%–9% of eyes.<sup>43,45,47</sup> Attempts have been made to correlate the degree of angle recession with the likelihood of developing glaucoma. Alper<sup>48</sup> believed that the risk of glaucoma developing was highest if more than 240° of the angle appeared recessed. In a population-based survey, Salmon et al. performed gonioscopy on 987 inhabitants of a small South African village. These authors found a cumulative lifetime prevalence of angle recession in the community of 14.6%. The prevalence of glaucoma in individuals with angle recession was 5.5% (8 of 146). Of 87 eyes with 360° of angle recession, only seven (8%) had glaucoma.<sup>49</sup>

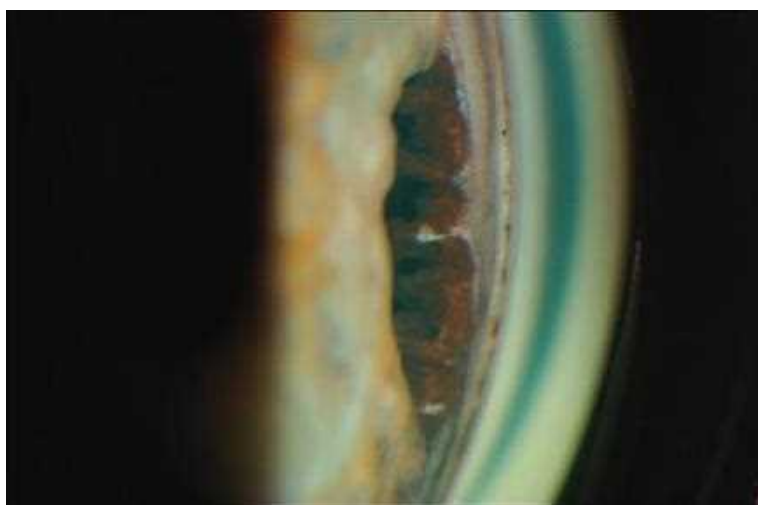
The elevation of IOP from angle recession demonstrates a bimodal pattern with glaucoma occurring either within the first year or after 10 years as described by Blanton.<sup>43</sup> This author found that the earlier-onset group often had less angle recession, and the IOP rise was transient in some patients. Other authors have found recession greater than 270° more common in the early-onset group.<sup>4</sup>

Angle recession is defined pathologically as a separation between the longitudinal and circular fibers of the ciliary body muscle.<sup>42</sup> The longitudinal muscles remain attached to the scleral spur, and there is a posterior displacement of the iris root. Iridodialysis (Fig. 10.17.3) and cyclodialysis may also be observed. Lenticular changes, including subluxation, dislocation, or cataract, may occur. Late evaluation of the angle may show a broad ciliary band with a fusiform appearance attributed to atrophy of the inner circular portion of the ciliary muscle. Variable degrees of fibrosis and hyalinization of the trabecular meshwork may occur. Peripheral synechiae may also be present.

Elevated IOP immediately after injury may result from extensive angle recession, although it may also be due to other causes, as cited earlier in this chapter. The clinical presentation of glaucoma secondary to angle recession is variable and depends somewhat on the time of presentation relative to the initial injury. Often angle-recession glaucoma presents years after the initial event as a chronic unilateral glaucoma. In a pathological review of 100 eyes enucleated for unilateral glaucoma, Miles and Boniuk<sup>50</sup> found angle deformity as the principal cause for the glaucoma in 11 eyes. None of these deformities had been recognized clinically. Eight of these 11 patients gave a history of previous trauma to the eye, ranging from 6 months to 24 years before the onset of glaucoma.

Unilateral glaucoma is typically secondary, and a history of previous trauma should always be sought. Examination will often reveal clues,





**Fig. 10.17.3** Tear in the root of the iris (iridodialysis). (From Schuman JS, Christopoulos V, Dhaliwal D, et al. *Rapid diagnosis in ophthalmology series: lens and glaucoma*. St Louis, MO: Elsevier; 2007.)

including a deeper anterior chamber on the affected side, tears of the iris sphincter or root, thinning of the iris stroma, or abnormal clumps of pigmentation on the iris. As a result of pigmentary changes, the iris color may differ between the two eyes. Tonjum<sup>51</sup> has demonstrated a paralyzed or paretic pupillary sphincter in the same sector as the chamber angle deformity in acutely injured eyes. This pupillary change may recover over time. The lens may be abnormally mobile or frankly dislocated. There may be clues to previous injury in the posterior segment, including pigment in the vitreous, macular edema, retinal pigment epithelial hyperplasia, choroidal or retinal scars, or frank retinal detachment.

Gonioscopy is key in establishing a diagnosis of angle recession. The cardinal features of angle recession on gonioscopy include an exposed ciliary body face that appears wider than usual and an iris root that appears to be posteriorly displaced. Uveal processes are disrupted, and the scleral spur may appear abnormally pale or white. Comparison of the angle appearance between contralateral eyes is helpful in detecting more subtle degrees of angle recession. The technique of bilateral simultaneous Koeppel gonioscopy is most helpful in this regard. An additional gonioscopic finding is the presence of a gray-white membrane covering the angle recess which may be observed even years after the initial injury.<sup>48</sup>

Elevated IOP in angle recession is a result of significant injury to the trabecular meshwork as opposed to the more evident tear into the ciliary body. The facility of outflow, as measured by tonography, is reduced and correlates with the degree of angle recession and glaucoma.<sup>44</sup> Herschler<sup>4</sup> was able to document a high incidence of visible damage to the trabecular meshwork and Schlemm's canal in eyes undergoing gonioscopy within 48 hours of injury. These trabecular lesions decreased over time while the ciliary body tears persisted. An underlying predisposition to the development of glaucoma in some injured patients may exist. Spaeth<sup>52</sup> studied 13 patients in whom unilateral angle-recession glaucoma had developed and found that approximately 50% of these patients had evidence of frank or probable glaucoma in the fellow eye.

Angle-recession glaucoma is a secondary chronic open-angle glaucoma that is generally amenable to standard topical medications used to treat the glaucomas. Laser trabeculoplasty may be attempted provided the initial IOP is not too high.<sup>53,54</sup> Argon laser trabeculoplasty was used in one study, but it failed to lower IOP.<sup>53</sup> The use of selective laser trabeculoplasty has not been well studied and is also likely to be ineffective. Neodymium:yttrium-aluminum-garnet (Nd:YAG) laser trabeculopuncture met with some success in a small series of 11 Japanese patients with angle-recession glaucoma.<sup>55</sup> Filtration surgery is certainly an option in these patients, provided the conjunctiva is not extensively scarred by the injury itself or by related ocular surgeries, such as retinal detachment repair. Trabeculectomy may be less successful in posttraumatic angle-recession glaucoma. Mermoud et al. found the success rate of trabeculectomy for angle-recession glaucoma to be 43% in 35 consecutive patients compared with a success rate of 74% in 35 consecutive matched patients with primary open-angle glaucoma (POAG). These authors advocated the routine use of antimetabolites in such cases.<sup>56</sup> These results were also supported by a retrospective analysis of 87 drainage procedures performed over an 8-year period during which trabeculectomy with antimetabolite outperformed trabeculectomy without antimetabolite and Molteno implantation.<sup>57</sup> The

effectiveness of using mitomycin C in filtering surgery for angle-recession glaucoma was demonstrated in a retrospective review of 43 consecutive procedures. Cumulative probability of success was 85% at 1 year and 81% at 2 years.<sup>58</sup> Additionally, tube shunt surgery or cyclodestruction represent additional available therapeutic modalities, as indicated. A prospective case series examined 38 patients who received a Molteno implant with a mean follow-up of 10.9 years. IOP of 21 mm Hg or less (with or without hypotensive medication) occurred with a probability of 0.80 at 5 years and 0.72 at 10 years.<sup>59</sup>

More recently, de Kierk and Au reported successful treatment of angle-recession glaucoma with the i-Stent in two patients.<sup>60</sup>

## Peripheral Anterior Synechiae

PAS are a product of apposition of iris to the angle structures or peripheral cornea in the setting of inflammation. Ocular trauma can provide these conditions on occasion. Organization of blood and inflammatory debris in the angle can occur after hyphema. Penetrating trauma may shallow the chamber for extended periods, resulting in extensive synechial closure of the angle. Endothelialization of the angle has been observed after blunt trauma, and this can pull the angle closed. Epithelial or fibrous downgrowth after penetrating trauma will produce angle closure. Massive choroidal hemorrhage after trauma will push the angle closed and sets up an inflammatory cascade, often leaving the angle closed after the hemorrhage has resolved. The potential for synechial closure necessitates careful and repeated gonioscopy after a traumatic event.

Treatment of synechial closure can often be directed at attempting to reopen the angle, particularly if the intervention occurs early rather than late. Iridogonioplasty with the argon laser may be sufficient to pull the iris away from the angle. Failing this, surgical goniosynechialysis may be effective in reopening the angle for filtration. If the angle is permanently closed, with ensuing high IOP, therapy is directed at lowering the pressure with more conventional medical and surgical methods.

## Ghost Cell (Hemolytic) Glaucoma

Campbell et al. initially described ghost cell glaucoma by demonstrating that after vitreous hemorrhage, fresh RBCs degenerated into ghost cells in the vitreous usually within 1 or 2 weeks.<sup>61</sup> If there is hyaloid face disruption, the ghost cells gain access to the anterior chamber. Ghost cells differ from normal RBCs in that they are rigid and do not pass through the meshwork easily. These cells obstruct outflow and produce an elevation of IOP.

An early review of ghost cell glaucoma by Campbell examined the clinical characteristics of 14 patients, all of whom had a traumatic ghost cell glaucoma.<sup>62</sup> A common clinical course of severe trauma resulting in anterior chamber and vitreous hemorrhage was followed by clearing of the anterior chamber blood; however, the fresh RBCs in the vitreous gradually converted to ghost cells. These cells had a characteristic ochre color and were found both in the posterior and anterior segments. Occasionally, ghost cells would layer out in the anterior chamber creating a "pseudo-hypopyon." Ghost cell glaucoma occurred anywhere from 2 weeks to 3 months after the trauma but was most common 1 month after the injury. The IOP was usually very elevated, ranging from 30–50 mm Hg.

Histopathological examination of one eye demonstrated ghost cells in the anterior chamber with a relatively normal-looking angle. Macrophages laden with RBC debris were evident in the vitreous cavity as well as free ghost cells in the vitreous cavity. The anterior hyaloid face was disrupted, allowing passage of the ghost cells into the anterior chamber. Phase contrast microscopy demonstrated a crenated shrunken appearance of the ghost cells, with Heinz bodies demonstrating denatured hemoglobin present in the cytoplasm of some of the ghost cells.<sup>62</sup>

Standard glaucoma medical therapy is initially employed to treat ghost cell glaucoma, although Campbell found that less than half of patients are controlled by medical therapy alone.<sup>62</sup> Initial surgical intervention involves washing the ghost cells out of the anterior chamber. If this is unsuccessful, a pars plana vitrectomy may be necessary to ensure complete removal of the cellular load from the eye.

## Lens-Induced Glaucoma

These comprise a group of glaucomas that share the lens as a common pathway in their pathogenesis. Lens-induced glaucomas can be further subdivided by their angle configuration with secondary angle-closure



glaucoma caused by lens dislocation/ectopia lentis and phacomorphic glaucoma and secondary open-angle glaucoma caused by phacolytic, phacoantigenic, and lens particle glaucoma.

### Lens Dislocation

Trauma of a sufficient magnitude may disrupt the zonules resulting in subluxation or dislocation of the lens. Pupillary block with angle closure may result from forward advancement of the lens. Pupillary block may also be the result of vitreous blocking the papillary aperture if the lens has dislocated posteriorly.

The onset of angle-closure glaucoma with pupillary block may present acutely with a painful red eye, corneal edema, and severely elevated IOP, mimicking acute angle-closure glaucoma with primary pupillary block. The chamber will appear shallow both axially and peripherally with iris convexity. The angle will appear closed on gonioscopy. A previous history of trauma and an axially deep chamber in the fellow eye with a wide open angle on gonioscopy all point to traumatic lens subluxation. In a Chinese study of 526 cases presenting as primary acute-angle closure, 5.89% of cases were found to be secondary to lens subluxation. Previous history or signs of trauma were often neglected.<sup>63</sup> Phacodonesis may be appreciated at the slit lamp. With lens dislocation vitreous blocking, the pupil may be appreciated at the slit lamp. Evidence of lens dislocation may also be seen on ophthalmoscopy. Secondary glaucoma as a result of traumatic lens dislocation was found to occur in 88% of 106 patients in a review from China.<sup>64</sup>

Treatment of this form of glaucoma is directed at relieving the pupillary block with laser iridectomy or surgical iridectomy. Lensectomy may be required for reasons of visual rehabilitation or if the lens continues to compromise the angle or cornea after iridectomy/iridectomy because of persistent extreme anterior displacement.

### Phacomorphic Glaucoma

Phacomorphic glaucoma may be caused by a mature cataract as a result of pupillary block or direct angle compromise from mass effect. Similarly, an intumescent cataract that occurs from lens swelling can precipitate acute secondary angle-closure glaucoma acutely through the same mechanisms. Unilateral intumescent cataract with chamber depth asymmetry may result from previous ocular trauma.

Pupillary block may be relieved by laser iridectomy or surgical iridectomy. Cataract surgery is indicated to remove the underlying cause of this problem and restore vision. If chronic angle closure exists laser iridoplasty or surgical goniosynecholysis at the time of cataract surgery may be beneficial.

### Phacolytic Glaucoma

Phacolytic glaucoma is seen in the setting of a hypermature cataract. Leakage of high-molecular-weight proteins through an intact lens capsule elicit an immune response of macrophages and other inflammatory debris, which compromises outflow facility.<sup>65</sup> Treatment is the surgical removal of the hypermature cataract.

### Phacoantigenic Glaucoma

This is a rare secondary lens-induced glaucoma, previously known as *phacoanaphylaxis*. Phacoanaphylaxis is no longer used because it incorrectly implies an allergic reaction. Phacoantigenic glaucoma is a granulomatous inflammation to retained lens proteins in the eye as a result of sensitization of the immune system after cataract surgery or penetrating injury. The resulting inflammation obstructs outflow facility. Use of topical corticosteroids and IOP control comprise the initial therapy. Persistent inflammation will require the surgical removal of all residual lens protein.<sup>65,66</sup>

### Lens Particle Glaucoma

Lens particle glaucoma is a result of obstruction of the trabecular meshwork from lens fragments that have been liberated from the lens as a result of surgical or traumatic disruption of the lens capsule. These lens fragments are evident on slit-lamp examination. Treatment is directed at removal of the lens and any associated free fragments.<sup>65,66</sup>

## Delayed Closure of a Cyclodialysis Cleft

Cyclodialysis clefts represent separation between the scleral spur and the ciliary muscle. These clefts can occur as a result of trauma or surgical intervention. A cyclodialysis cleft is associated with hypotony as a result of increased egress of aqueous humor through this alternative pathway as well as decreased aqueous production. A cyclodialysis cleft can close

spontaneously or as a result of intentional intervention. When closure of the cleft occurs, the IOP may rise dramatically. Goldmann<sup>67</sup> postulated that the reduction in flow of aqueous humor across the conventional trabecular pathway during a cyclodialysis cleft results in a reduced permeability of the trabecular meshwork, which is manifest as dramatically elevated IOP after closure of the cleft.

Closure of a cyclodialysis cleft will often produce acutely elevated IOP with associated subjective symptoms, including decreased vision, ocular discomfort, and even systemic effects, such as nausea and vomiting. Corneal edema, a formed anterior chamber, and an open angle will be present. A previous history of trauma or a previously documented cleft with associated signs and symptoms of hypotony may be elicited. When closure of the cleft is a concern, reopening the cleft with miotics and phenylephrine may be effective in reopening the cleft and lowering IOP. Repeating gonioscopy after this maneuver will assist in confirming the diagnosis.

## Epithelial Downgrowth

Epithelial cells may proliferate abnormally in the anterior chamber of the eye either as a result of their introduction into the eye after penetrating trauma, or they may grow into the anterior chamber as a result of a patent fistula allowing communication between the external surface of the eye and the anterior chamber. Subsequent proliferation of these abnormally located epithelial cells can produce glaucoma as either a result of an epithelial sheet-like proliferation over the meshwork or subsequent angle closure from PAS as the epithelial sheets contract and pull the peripheral iris into the angle. This rare occurrence has a poor prognosis and is difficult to treat.

## Retained Intraocular Foreign Body

A retained foreign body may be associated with several types of glaucoma. Loss of integrity of the globe as a result of penetration may produce a shallow or flat anterior chamber. This, in association with attendant inflammation, can result in secondary angle-closure glaucoma with extensive PAS. As discussed in our previous section, penetration may introduce epithelial cells or create a fistula resulting in epithelial downgrowth and associated glaucoma. Frank disruption of the lens capsule may produce a lens particle glaucoma. Cataract formation may produce a phacomorphic glaucoma or a phacolytic glaucoma if the cataract becomes hypermature. Siderotic glaucoma may occur as a late manifestation of a retained iron-containing foreign body. This can present long after the initial trauma with associated heterochromia, mydriasis, and a rust-like discoloration of the anterior subcapsular surface of the lens and the posterior corneal surface. The existence of an occult foreign body should be suspected in this setting. A distant history of a foreign body striking the eye may be elicited. There may be clues on examination pointing to an occult foreign body, including unilateral cataract or a small lenticular capsular rupture, chronic inflammation, unilateral glaucoma, discrete areas of iris transillumination, or a corneal or scleral wound.

Dilated fundus examination may allow easy visualization of the retained foreign body. Occasionally, a foreign body is located in the anterior chamber and is found on gonioscopy. Some patients may have signs of chalcosis or siderosis, as outlined previously.

If the media are not clear enough to allow funduscopic examination, additional studies, including plain film radiography, computed tomography, and ultrasonography, are helpful in confirming the diagnosis. Reduced retinal function may also be evident with a reduction electroretinographic activity.

## Rhegmatogenous Retinal Detachment

The presence of rhegmatogenous retinal detachment often increases uveal-scleral outflow via the retinal tear resulting in a reduction in IOP relative to the fellow eye.<sup>68</sup> Ocular hypertension may occur in 5%–10% of patients with rhegmatogenous retinal detachment.<sup>69</sup> Possible reasons for this include pre-existing POAG, associated inflammation, or Schwartz's syndrome.<sup>70</sup> Schwartz's syndrome was initially described in 11 cases of rhegmatogenous retinal detachment associated with glaucoma. Five of these 11 cases were associated with previous ocular trauma.<sup>71</sup>

Matsuo et al.<sup>72</sup> elucidated the pathogenesis of this glaucoma after demonstrating photoreceptors in the aqueous humor by performing transmission electron microscopy on the aqueous humor of seven patients with this syndrome.

Unilateral glaucoma in the presence of rhegmatogenous retinal detachment is an unusual presentation and emphasizes the importance of careful fundusoscopic examination in all cases of unilateral glaucoma.

Repair of the retinal detachment promptly returns the intraocular pressure to normal, provided there are no associated ocular abnormalities, such as angle recession, likely contributing to chronic elevation of intraocular pressure.

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# Glaucoma With Raised Episcleral Venous Pressure

10.18

E. Randy Craven

**Definition:** Glaucoma with elevated intraocular pressure caused by a decrease in aqueous outflow secondary to increased episcleral venous pressure.

**Key Feature**

- Unilateral elevation of intraocular pressure in an eye with prominent episcleral veins.

**Associated Features**

- Blood in Schlemm’s canal.
- Either venous obstruction or arteriovenous abnormalities.

**INTRODUCTION**

Raised episcleral venous pressure can cause open-angle glaucoma by obstructing the outflow of aqueous into the venous drainage system. Raised episcleral venous pressure can come from systemic abnormalities that can be fatal. Therefore, because of the morbidity associated with these causes, one needs to consider beyond the eye when a patient presents with an unilateral red eye and glaucoma.

**EPIDEMIOLOGY AND PATHOGENESIS**

Raising the episcleral venous pressure (ESVP) causes a similar direct rise in the intraocular pressure (IOP).<sup>1</sup> The resultant IOP is determined by the production (F) and facility of outflow (C) of aqueous humor but is one-to-one mm Hg changed by the ESVP (the Goldmann equation):

$$IOP = F/C + ESVP$$

The ESVP can be increased by the body position<sup>2</sup> and venous drainage pressure in the superior/inferior ophthalmic veins, cavernous sinus, petrosal sinuses, and internal and external jugular veins. Thus, any abnormality—including hereditary anomalies—leading to increased venous pressure in the venous drainage system downstream from the eye can lead to elevated IOP.<sup>3</sup>

An idiopathic cause to rise ESVP can lead to elevated IOP and glaucoma.<sup>4</sup> Idiopathic elevation to the ESVP does not appear to feature any extraocular venous abnormalities; color Doppler imaging has not helped to reveal any specific retro-orbital etiology to the cause of this syndrome. These patients tend to be older, without a family history of glaucoma. Unilateral presentation is common, and the right eye is more commonly involved with this syndrome. Venous and arterial abnormalities leading to elevated ESVP are summarized in Table 10.18.1.

**OCULAR MANIFESTATIONS**

Engorged episcleral veins (Fig. 10.18.1) and blood in Schlemm’s canal—best seen via gonioscopy (Fig. 10.18.2)—appear with raised episcleral venous pressure. Neovascularization of the iris can occur if there is associated anterior segment or retinal ischemia.<sup>5</sup> Hemorrhagic choroidal detachments with secondary angle closure may develop.<sup>6</sup> When the venous

TABLE 10.18.1 Venous and Arterial Abnormalities Leading to Elevated Episcleral Venous Pressure

Venous Obstruction	Arteriovenous Abnormality	Tests to Consider	Other Findings
Superior vena cava syndrome		Chest x-ray	Cyanosis
	Dural–cavernous fistula	MRI	
Thyroid ophthalmopathy	Orbital varix	MRI	Proptosis
Sturge–Weber syndrome			Skin/retina
Jugular vein obstruction			Cyanosis
Cavernous sinus thrombosis	Carotid–cavernous fistula	MRI	Pain

MRI, Magnetic resonance imaging.



**Fig. 10.18.1 Prominent Episcleral Veins.** The episcleral vessels are tortuous and appear succulent. The eye lacks the classic ciliary flush seen with iritis or infections.

pressure approaches arterial pressure in patients with arteriovenous abnormalities, the subsequent IOP elevation can be quite high.

Raised ESVP is caused by venous obstruction or arterialization of the veins (arteriovenous abnormalities; see Table 10.18.1). Examination findings may reveal proptosis, which can occur with thyroid eye disease, carotid–cavernous fistulae, or an orbital varix. An orbital varix can have positional proptosis. Carotid–cavernous fistulae can cause pulsatile proptosis. Hemangiomas associated with Sturge–Weber syndrome can involve the skin and retina (“tomato catsup” fundus). Chemosis is common with carotid–cavernous fistulae but can be seen with Sturge–Weber or thyroid ophthalmopathy.

Glaucomatous optic atrophy and visual field loss from raised ESVP can take longer than other forms of acute glaucoma—or not occur—despite very high IOPs. This is especially true in the more acute problems that present with raised ESVP, such as carotid–cavernous fistulae.



**Fig. 10.18.2 Blood in Schlemm's Canal.** Gonioscopy reveals prominent red hue over the trabecular meshwork zone of the angle.

## DIAGNOSIS

The appearance of the episcleral veins in problems with raised episcleral venous pressure is quite characteristic. The appearance of the episcleral vessels (see Fig. 10.18.1) is highly suggestive of the diagnosis. If in doubt, it is possible to measure the venous pressure to confirm or determine the level of the raised venous pressure. Five methods for determining the episcleral venous pressure have been used. The direct method for measuring the episcleral venous pressure can be done by cannulation. This is the most accurate method and reveals the episcleral venous pressure to be 5–12 mm Hg. Noninvasive methods look for a collapse in the vein (partially or totally) while a force is applied to the vein. The remaining four methods use an indirect method in which the pressure required for venous collapse can be determined by a pressure chamber (of Seidel), an air jet, a torsion balance, or an indirect method.<sup>7–8</sup> The pressure chamber or indirect (venometer) methods probably provide the most accurate readings apart from direct cannulation.

## DIFFERENTIAL DIAGNOSIS

Prominent ocular vessels can occur without increased IOP and glaucoma. The specific vessels and pattern of vessels involved differ from that seen with infections, inflammation, or allergies; usually the vessels are finer with a more diffuse hue to the pattern. Ataxia telangiectasia can cause abnormal vessels on the ocular surface but tends to be more localized to a quadrant and smaller vessels.

Scleritis and episcleritis tend to have smaller caliber vessels than with raised ESVP. Additionally, the vessels are more of a crisscross pattern with a network of deep vessels along with radial vessels and overall more diffuse involvement of the vessels. Intraocular tumors can cause prominent scleral vessels (Reese's sign). Conditions with scleral thinning, such as that seen after repeated ciliary body destructive procedures, can lead to a more prominent view of the normal veins.

## SYSTEMIC ASSOCIATIONS

Carotid-cavernous fistulae occur most often after significant trauma. Pulsating exophthalmos, blurred vision, pain, chemosis, and audible shunts

can be heard with a stethoscope. These tend to develop rather suddenly. Dural-cavernous fistulae occur commonly in middle-aged women with a more gradual onset. Superior vena cava syndrome occurs in the presence of bronchogenic carcinomas. Cavernous sinus thrombosis occurs from infections spreading from the middle ear, sinuses, or the face. Significant congestive heart failure can lead to elevated venous pressure; many findings are present, including peripheral edema and pulmonary congestion.

## TREATMENT

When elevated IOP occurs because of the elevated ESVP, it is possible to lower the IOP to the level of the ESVP but not much lower. Aggressive filtering surgery with an avascular bleb can work, but it can, therefore, be very difficult to drop the IOP satisfactorily without treating the primary cause of the raised ESVP. Treatment of fistulae can involve neuroradiological intervention or neurosurgical intervention. Dural-cavernous fistulae are low flow and can spontaneously close, whereas the carotid-cavernous fistulae tend to need intervention. Dural-cavernous fistulae are usually watched and can resolve by the patient sleeping with the head elevated or sitting for a period.

Treatment of other medical problems leading to raised ESVP should be attempted if possible. Medications that suppress the aqueous production are good first-line medication choices. Beta-blockers and carbonic anhydrase inhibitors are commonly used agents. Alpha-agonists, because of their vasoconstrictive effects on the arteries leading into the eye, are also a good first choice for medications.

Laser trabeculoplasty provides little help in most cases. Some surgeons feel nonpenetrating procedures may be a safer form of filtration surgery, and some surgeons prefer valves.<sup>9</sup> Preoperative mannitol and other pressure-lowering medications should be given. Because of the prominent vessels, a releasable suture should be considered with trabeculectomy.

## COURSE AND OUTCOME

Once the problem that caused the raised episcleral venous pressure is treated, the IOP is easier to control. If it is not possible to lower the episcleral venous pressure, such as in Sturge-Weber syndrome, the glaucoma is chronic and progressive until the IOP is controlled.

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# Malignant Glaucoma

Nishat P. Alvi, Louis B. Cantor, Joshua W. Evans

10.19

**Definition:** Malignant glaucoma is a rare form of glaucoma, also known as “aqueous misdirection,” that develops primarily in patients with primary angle closure and is characterized by elevated intraocular pressure with a shallow or flat anterior chamber despite a patent iridectomy.

## Key Features

- Shallowing or flattening of both the central and peripheral anterior chamber despite patent iridectomy.
- Almost always associated with markedly elevated intraocular pressure.
- Chronic angle-closure glaucoma.
- Worsened by miotics.
- Relieved by cycloplegics and mydriatics.
- Usually occurs after intraocular surgery.
- Involves some degree of aqueous misdirection into the vitreous cavity.
- Supraciliary or suprachoroidal effusion, if present, is very small.

## Associated Features

- May occur after laser or medical therapy of glaucoma.
- Intraocular pressure may be within the normal range.

## INTRODUCTION

Aqueous misdirection glaucoma, also known as malignant glaucoma, is a rare form of glaucoma that typically follows intraocular surgery in patients with primary angle closure and primary angle-closure glaucoma (PACG). It occurs after routine cataract surgery, after the administration of miotics in eyes with or without a prior surgical history, after ciliary body swelling, or less commonly spontaneously.<sup>1</sup> It may be difficult to make an accurate diagnosis, particularly in the early stages.

## EPIDEMIOLOGY AND PATHOGENESIS

Aqueous misdirection occurs in approximately 2%–4% of patients who undergo surgery for angle-closure glaucoma, especially if some of the angle is closed preoperatively. If the angle is open or has been opened prophylactically via a laser iridectomy before the development of an angle-closure attack, aqueous misdirection seems less likely to occur after subsequent surgery.<sup>1</sup> This condition also may occur after the cessation of topical cycloplegic therapy, the initiation of topical miotic therapy, laser iridectomy, laser capsulectomy, laser cyclophotocoagulation, cataract extraction, pars plana vitrectomy, seton implantation, central retinal vein occlusion, or argon laser suture lysis, or in eyes that have hyperopia, short axial lengths, or nanophthalmos.<sup>2,3</sup>

The pathogenesis of aqueous misdirection is thought to be multifactorial. Shaffer and Hoskins suggested that there is posterior misdirection of aqueous flow by a relatively impermeable hyaloid membrane into or behind the vitreous body; the subsequent increase in vitreous volume results in a shallower anterior chamber and an increase in intraocular pressure (IOP).<sup>4</sup> Epstein and coauthors demonstrated vitreous hydration as a basic etiology for malignant glaucoma.<sup>5</sup> Quigley and colleagues suggested that choroidal thickening may predispose to angle-closure glaucoma. These changes in the choroid may result in forward rotation of the ciliary body and choroid



**Fig. 10.19.1 Aqueous Misdirection.** Note the flat anterior chamber despite a patent iridectomy.

that predisposes to malignant glaucoma.<sup>6</sup> Events that incite aqueous misdirection include a short eye, a small, crowded anterior segment, angle closure, swelling and inflammation of the ciliary processes, and anterior rotation of the ciliary body and movement of the lens–iris diaphragm forward as a result of the use of miotics. It is notable that the vast majority of reported cases of aqueous misdirection occur in the white populations rather than the Asian population even though PACG is more prevalent in Southeast Asia and China. This may potentially indicate a different etiology of angle closure in white versus Asian populations.<sup>7–9</sup>

## OCULAR MANIFESTATIONS

A red, painful eye develops immediately (or days or even months) after intraocular surgery, typically for acute angle-closure glaucoma. Its development often corresponds to the cessation of cycloplegic therapy or the institution of miotic drops. Slit-lamp examination (Fig. 10.19.1) characteristically reveals a shallow or flat anterior chamber, both centrally and peripherally (with asymmetry with respect to the fellow eye), and no iris bombé. A high index of suspicion is necessary to make the appropriate diagnosis, since initially the IOP may not be elevated much. The key is that the IOP is elevated and the anterior chamber is *axially* shallow. Furthermore, if an attempt is made to reform the anterior chamber postoperatively through the paracentesis site using a viscoelastic substance, a great deal of posterior resistance may be noted, the anterior chamber may not deepen as much as in a hypotonic eye that does not have malignant glaucoma, and the IOP may rise substantially.

## DIAGNOSIS

The diagnosis of malignant glaucoma is based clinically on the previously mentioned ocular manifestations, and it is made only after ruling out pupillary block, suprachoroidal hemorrhage, serous choroidal effusions, or other causes of a flat anterior chamber. High-resolution ultrasound biomicroscopy can be useful to confirm the diagnosis.<sup>10</sup> It reveals anterior rotation of the ciliary body against the peripheral iris and forward displacement of the posterior chamber intraocular lens, as well as a shallow central anterior chamber, all of which are reversible.

TABLE 10.19.1 Differential Diagnosis of Aqueous Misdirection

Criterion	Malignant Glaucoma	Pupillary Block	Suprachoroidal Hemorrhage	Serous Choroidal Effusions
Intraocular pressure	Normal or elevated	Elevated	Normal or elevated	Low
Anterior chamber depth	Shallow; flat centrally and peripherally	Shallow; flat peripherally but deeper centrally	Shallow; flat centrally and peripherally	Shallow; flat centrally and peripherally
Relief by iridectomy	No	Yes	No	No
Ophthalmoscopy	Choroid and retina flat	Choroid and retina flat	Bullous dark brown or dark red choroidal elevations	Bullous light brown choroidal elevations
Ultrasound biomicroscopy	Anterior rotation of ciliary body and lens with ciliary processes flat against iris, pointing directly anteriorly	Iris bombé with lens in normal position	–	–
B-scan ultrasound	–	–	Smooth, thick, dome-shaped movement with little after-movement	Smooth, thick, dome-shaped membrane with little after-movement
			Heterogeneous low-medium reflective echoes	Echolucent suprachoroidal space, high reflective choroidal thickening
Onset	Intraoperative or early postoperative period Occasionally months to years later	Early postoperative period	Intraoperative or early postoperative period associated with pain, nausea/vomiting	Intraoperative or early postoperative period

DIFFERENTIAL DIAGNOSIS

The most difficult entity to distinguish from malignant glaucoma is pupillary block. Pupillary block should be suspected if iris bombé is present and if the anterior chamber is relatively deeper centrally and shallow to flat peripherally. In contrast, with malignant glaucoma, the anterior chamber is uniformly shallow or flat both centrally and peripherally. Next, the presence or absence of a patent iridectomy must be established. If an iridectomy is not present or not patent, a peripheral iridectomy should be performed. Pupillary block is confirmed if the anterior chamber deepens with an iridectomy. If no relief occurs with iridectomy and ophthalmoscopy or B-scan ultrasonography rules out suprachoroidal hemorrhage or serous choroidal effusion, a diagnosis of malignant glaucoma is made. The distinguishing features of these entities are summarized in Table 10.19.1.

TREATMENT

Medical

The first line of therapy is medical and involves the use of cycloplegics and mydriatics, particularly atropine, as proposed by Chandler and Grant more than 50 years ago.<sup>11,12</sup> Atropine 1% 2–3 times a day is given to move the lens–iris diaphragm posteriorly and relax the ciliary muscle, changing the relationship between the ciliary processes and the vitreous face. Phenylephrine 2.5%, cyclopentolate 1%, and tropicamide 1% may be given every 5 minutes times three as a cycloplegic burst in the office. To decrease aqueous production, topical beta-blockers, oral or topical carbonic anhydrase inhibitors, and α-agonists are used. Osmotic agents such as isosorbide 1.5 mg/kg orally or mannitol 2 g/kg intravenously over a 45-minute period can be used to shrink the vitreous volume. No oral foods or liquids should be given 2 hours before or after the administration of a hyperosmotic agent to avoid reduction in the osmotic effect. The patient is maintained on atropine for a prolonged period with a very slow taper because of the high risk of recurrence. Miotic agents are contraindicated, as they may cause or contribute to malignant glaucoma. Medical therapy is successful in approximately 50% of cases within 4–5 days.<sup>7,11,12</sup>

Laser

The second line of treatment is laser therapy. Neodymium:yttrium–aluminum–garnet (Nd:YAG) laser may be used in aphakic and pseudophakic patients to create a large peripheral iridectomy and capsulectomy with hyaloid rupture to release the trapped aqueous from the vitreous and re-establish normal aqueous flow.<sup>3,13,14</sup> Several openings are made peripherally—that is, not directly behind the lens optic, if an intraocular lens is present.<sup>3,13,15</sup> The placement of the iridectomies should be peripheral, because the underlying etiology is an abnormal relationship between the hyaloid and the ciliary processes.<sup>3,13,14</sup> Peripheral placement will enable anterior migration of the aqueous and maximize the likelihood of resolution of the malignant glaucoma. In addition, transscleral laser cyclophotocoagulation can be used to shrink the ciliary processes and induce posterior rotation of the ciliary processes.<sup>16</sup> Alternatively, direct argon laser treatment can be applied to the ciliary processes through a laser peripheral iridectomy.<sup>15</sup>

If there is corneal–lenticular contact there is the risk of corneal decompensation, therefore the chamber should be reformed by the injection of a viscoelastic substance via a 30-gauge cannula through the original paracentesis at the slit lamp following Nd:YAG laser hyaloidectomy.<sup>1</sup>

Surgery

When medical or laser therapy fails, surgery must be performed. In pseudophakic eyes, vitrectomy surgery is successful in resolving malignant glaucoma in 65%–90% of patients compared to only 25%–50% of phakic patients.<sup>17,18</sup> In phakic eyes, definitive management usually requires phacoemulsification with intraocular lens (IOL) combined with pars plana vitrectomy. The combination of vitrectomy–iridectomy–zonulectomy with phacoemulsification in phakic eyes or without in pseudophakic eyes has shown lower relapse rates compared to vitrectomy alone (*Clinical Management of Malignant Glaucoma*). In pseudophakic eyes, a limited anterior vitrectomy–zonulectomy–iridectomy from either an anterior or pars plana approach can be curative. The key is allowing direct aqueous communication between the anterior chamber and vitreous cavity (Zarnowski) to disrupt the vicious cycle of malignant glaucoma.<sup>17,19–21</sup>

Fellow Eye

There is a high risk of malignant glaucoma in the fellow eye. If a narrow angle is present in the fellow eye, a laser peripheral iridectomy is performed before any other surgical procedures. The risk may be reduced in the fellow eye if the angle remains open and the IOP is normal. Failure to provide prompt therapy to the fellow eye has been reported to result in bilateral blindness. Lens extraction can be considered as a primary procedure before glaucoma surgery.<sup>3</sup> In fact, combined vitrectomy and phacoemulsification with IOL is advocated in high-risk cases.<sup>22</sup>

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# Glaucomas Secondary to Abnormalities of the Cornea, Iris, Retina, and Intraocular Tumors

10.20

*Elliott M. Kanner, James C. Tsai*

**Definition:** A diverse group of secondary glaucomas, either open or closed angle, caused by specific abnormalities of the anterior and/or posterior segment. The open-angle varieties include ghost cell hemolytic glaucoma and Schwartz's syndrome. The closed-angle glaucomas include the iridocorneal endothelial syndromes, Axenfeld-Rieger syndrome, epithelial downgrowth and fibrous ingrowth (proliferation), aniridia, and intraocular tumors. Other conditions feature either mixed or nonspecific mechanisms of elevated intraocular pressure, such as the postcorneal transplant and postalkali injury glaucomas.

## Key Features

- Iris abnormalities.
- Previous intraocular surgery.
- Rhegmatogenous retinal detachment.
- Elevated intraocular pressure.
- Ocular tumors.

## GHOST CELL HEMOLYTIC GLAUCOMA

### INTRODUCTION

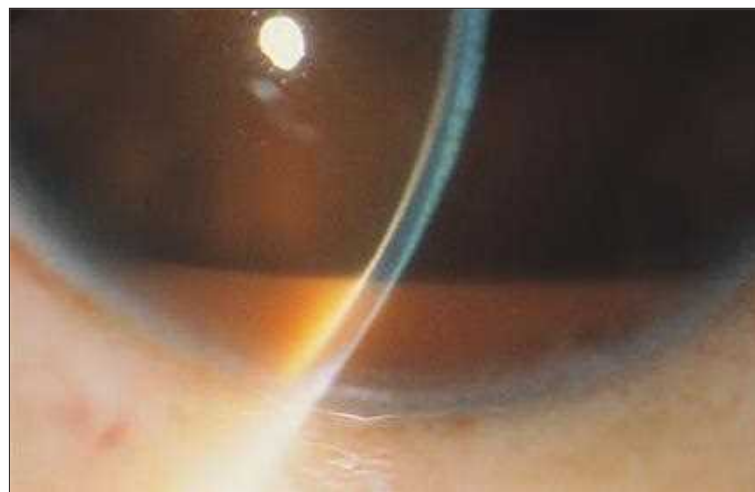
Lysed red blood cells (RBCs) from vitreous hemorrhage can accumulate in the eye if not properly cleared. Remnants of these partially degraded cells contain very little hemoglobin and are referred to as ghost cells, which can cause blockage of the trabecular meshwork. These denatured erythrocytes develop within 2–4 weeks of a vitreous hemorrhage. Any traumatic event that leads to hemorrhage in the vitreous cavity<sup>1</sup> or, rarely, in the anterior chamber, may result in the formation of ghost cell glaucoma.

### EPIDEMIOLOGY AND PATHOGENESIS

The membrane remnants (ghost cells) have lost their intracellular hemoglobin and appear as khaki-colored cells that are less flexible than normal red blood cells. This loss of pliability results in obstruction of the normal trabecular meshwork pathways and subsequent development of secondary glaucoma. For the remnant RBCs to gain access to the anterior chamber, the hyaloid face or posterior lens capsule must be disrupted (which may occur after surgery).

### OCULAR MANIFESTATIONS

The usual history is a chronic vitreous hemorrhage resulting in a sudden onset of elevated intraocular pressure (IOP). The IOP level may be sufficient to cause corneal edema. The anterior chamber is filled with circulating, small, tan-colored cells that layer in the inferior anterior chamber angle (Fig. 10.20.1). The cellular reaction appears out of proportion to the aqueous flare, and the conjunctiva tends not to be inflamed unless the IOP is elevated markedly. On gonioscopy, the angle appears normal except for the presence of ghost cells layered over the inferior trabecular meshwork.



**Fig. 10.20.1** Ghost Cell Glaucoma. Layered ghost cells in the inferior anterior chamber angle.

### PATHOLOGY

Ghost cells lose their hemoglobin through permeable cell membranes. The cells are nonpliable, having lost their natural biconcavity, and are unable to exit through the trabecular meshwork efficiently. Heinz bodies (denatured hemoglobin) can be found in the cytoplasm.<sup>1</sup>

### TREATMENT

The initial treatment is antiglaucoma medical therapy, followed by intraocular surgery in eyes that are nonresponsive to medical treatment. Irrigation of the anterior chamber and pars plana vitrectomy are the initial surgeries of choice to eliminate the source of degenerative red blood cells. If this proves unsuccessful, glaucoma filtration surgery may be required.

## SCHWARTZ'S SYNDROME

The first description of chronic open-angle glaucoma secondary to rhegmatogenous retinal detachment was presented in 1973 by Schwartz.<sup>2</sup> These patients presented with retinal detachments and increased IOP. The elevated IOP resolved following repair of the retinal detachment. All patients had an apparent anterior chamber inflammatory response.

In 1977 Phelps and Burton surveyed 817 patients who underwent retinal detachment repair.<sup>3</sup> They found 18 patients (2.2%) who fit the criteria for Schwartz's syndrome. At that time, several mechanistic theories were proposed. Schwartz postulated that the associated iridocyclitis causes a trabeculitis that decreases aqueous outflow.<sup>2</sup> Matsuo et al. detected photoreceptor outer segments in the anterior chambers of seven patients who had retinal detachments, a discovery that suggested a connection between the subretinal space and the anterior chamber in this condition.<sup>4</sup>

In 1989, Lambrou et al. injected rod outer segments into the anterior chambers of cats in vivo, which resulted in an average rise in IOP

of 10 mm Hg (1.33 kPa).<sup>5</sup> Electron microscopy revealed occlusion of the intratrabecular spaces by the rod outer segments, with little evidence of inflammatory activity. An interesting observation was that the injected rod outer segments mimicked cells in the anterior chamber,<sup>6</sup> which may represent what Schwartz described as iridocyclitis in his original article.<sup>7</sup>

Davidorf described four cases of retinal detachment with elevated IOP and heavy pigmentation of the trabecular meshwork.<sup>7</sup> The IOP decreased after successful reattachment of the retina in these cases. Regardless of the presumed pathophysiology of Schwartz's syndrome, treatment consists of repair of the retinal detachment. The blocked trabecular meshwork causes an increase in IOP that is resistant to medical therapy. The anterior chamber "inflammation" does not typically respond to conventional medical treatment.

## IRIDOCORNEAL ENDOTHELIAL SYNDROME

### INTRODUCTION

Since the initials ICE fit both the term *iridocorneal endothelial* syndrome and the first letter of each of the three component entities, Yanoff suggested the term *ICE syndrome* in 1979 for this spectrum of clinical and histopathological abnormalities.<sup>8</sup> That term is now the one most commonly used. Historically, the component entities were classified as the iris nevus (Cogan–Reese), Chandler's, and essential (progressive) iris atrophy syndromes.

Collectively, ICE syndrome describes a group of disorders characterized by abnormal corneal endothelium that is responsible for variable degrees of iris atrophy, secondary angle-closure glaucoma in association with characteristic peripheral anterior synechiae (PAS), and corneal edema.

### EPIDEMIOLOGY AND PATHOGENESIS

The condition is sporadic and unilateral but with subclinical irregularities of the corneal endothelium commonly noted in the fellow eye. The syndrome affects individuals between 20 and 50 years of age and occurs more often in women. Glaucoma is present in approximately half of all cases.<sup>9</sup> In a study of 37 cases of ICE syndrome, approximately half (21 cases) were Chandler's syndrome; the other two clinical variations each accounted for about one fourth of all cases.<sup>10</sup> Gonioscopic examination of the angle may not reveal anatomic closure, though the "open appearing angle" may still be functionally closed by the endothelial membrane.

### OCULAR MANIFESTATIONS

Patients present with differing degrees of pain, decreased vision, and abnormal iris appearance. The vision may be decreased from corneal edema, which may be worse in the morning and improve later in the day. Microcystic corneal edema may be present without elevated IOP, especially in the case of Chandler's syndrome. In the advanced stages of the syndrome, symptoms of blurred vision and pain may persist throughout the day. Patients also may present with a chief complaint of an irregular shape or position of the pupil (corectopia), or they may describe a dark spot in the eye, which may represent hole formation (pseudopolyopia) or stromal atrophy of the iris. Various degrees of iris atrophy characterize each of the specific clinical entities.

#### Progressive (Essential) Iris Atrophy

This variation is characterized by severe iris atrophy that results in heterochromia, marked corectopia, ectropion uveae, and pseudopolyopia (hole formation). Iridal hole formation is the hallmark finding of progressive iris atrophy (Fig. 10.20.2).

#### Chandler's Syndrome

This variation shows minimal or no iris stromal atrophy, but mild corectopia may be present. The corneal edema and angle findings are the predominant and typical features (Fig. 10.20.3).

#### Iris–Nevus Syndrome (Cogan–Reese Syndrome)

The extent of iris atrophy tends to be variable and less severe. Tan, pedunculated nodules may appear on the anterior iris surface. The entire spectrum of corneal and other iris defects may occur in this variant.



Fig. 10.20.2 Hole Formation in Progressive Iris Atrophy.

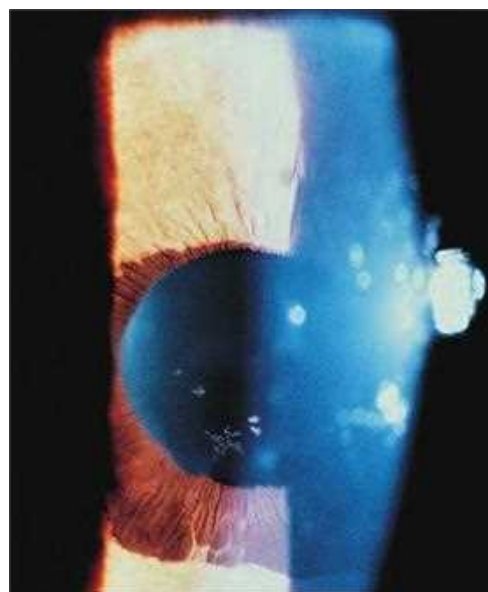
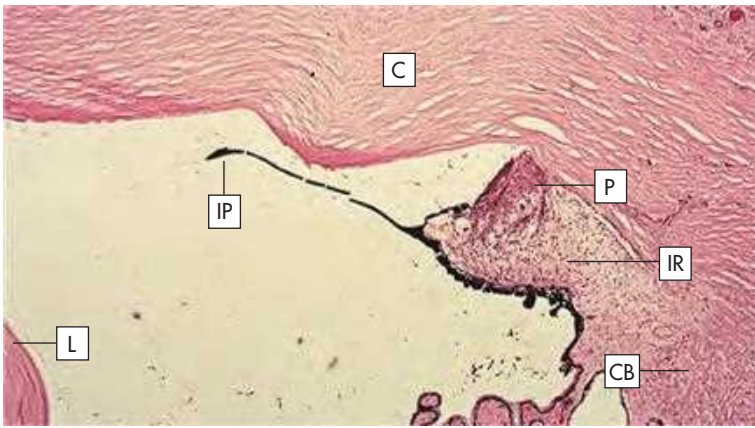


Fig. 10.20.3 Corneal Edema and Iris Findings Are Typical of Chandler's Syndrome.

### PATHOLOGY

The common pathological feature is the appearance of the corneal endothelium, which appears as a fine, hammered silver material, similar to the guttae seen in Fuchs' corneal endothelial dystrophy.<sup>11</sup> Descemet's membrane is normal, but the endothelial cells are abnormal. These endothelial cells take on characteristics of epithelial cells. With electron microscopy, this endothelial layer varies in thickness from a single layer to multiple layers (while normal endothelial cells are invariably a monolayer).<sup>12,13</sup> The endothelial cell layer can vary in thickness in different areas. The cells appear to have the potential to move, as demonstrated by filopodial cytoplasmic processes and cytoplasmic actin. The morphology of the endothelium suggests a widespread state of high metabolic activity.<sup>14,15</sup> These changes and endothelial dysfunction result directly in the corneal edema. The anterior chamber angle may also show high PAS that extend beyond Schwalbe's line. The high PAS are caused by contraction of the endothelial cell layer and surrounding tissues, which extend from the peripheral cornea over the trabecular meshwork and iris. These membranes can contract and cause progressive angle closure. As noted earlier, secondary glaucoma with an open angle may also occur when the endothelial membrane covers the trabecular meshwork without observable evidence of synechiae formation.

The extent of iris abnormalities differentiates the specific clinical variations. When the endothelial cell layer contracts over the iris, this distorts the iris directly, causing holes (Fig. 10.20.4).<sup>16</sup> Hole formation may be associated with ischemia of the iris, as suggested by fluorescein angiography. In Cogan–Reese syndrome, the pigmented, pedunculated nodules seen



**Fig. 10.20.4 Iridocorneal Endothelial Syndrome.** Histological section of an eye that had essential (progressive) iris atrophy shows a peripheral synechia (P), various degrees of degeneration and loss of the central iris stroma, and total loss of the central iris pigment epithelium (IP). (C, Cornea; CB, ciliary body; IR, iris root; L, lens.) (With permission from Yanoff M, Fine BS. Ocular pathology. London: Mosby; 1996.)

are composed of underlying iris stroma pinched off by abnormal cellular membrane.<sup>17</sup>

A viral cause has been postulated for the pathophysiological mechanism of ICE syndrome. Epstein-Barr and herpes simplex viruses have been found serologically in ICE patients.<sup>12,18</sup> Lymphocytes were found on a sample of the corneal endothelium of an ICE patient, suggesting chronic inflammation.

## TREATMENT

A diagnosis of ICE syndrome must be considered in younger patients who have unilateral angle-closure glaucoma and can be confirmed by specular or confocal microscopy. Aqueous suppressant medications tend to be effective in controlling the IOP, whereas prostaglandin analogs and other outflow-associated medications are less effective. Corneal edema may often be controlled using hypertonic saline solutions. Reduction of the elevated IOP may lessen the degree of corneal edema. If the IOP level remains uncontrolled despite medical treatment, filtration surgery may be indicated, though late surgical failures have been reported secondary to endothelialization of the fistular opening.<sup>19,20</sup> These endothelial obstructions of the fistula may be reopened successfully using the neodymium:yttrium-aluminum-garnet (Nd:YAG) laser. In a study of 83 patients who had ICE syndrome, the success rates of initial trabeculectomy operations at 1 and 3 years were both 58%,<sup>20</sup> and those of second and third operations at 1-year intervals were both 58%.<sup>13</sup> Glaucoma tube shunt procedures are indicated for cases refractory to the previously mentioned treatments and more recently have been used as the primary procedure.<sup>21</sup>

## AXENFELD-RIEGER SYNDROME

Axenfeld-Rieger (A-R) syndrome represents a rare spectrum of developmental disorders involving abnormalities of both ocular and extraocular structures derived from the neural crest.<sup>22</sup> The term *anterior cleavage syndrome* was used in the past,<sup>23</sup> but it incorrectly reflects the development in this syndrome. All clinical variations of this syndrome are now referred to as Axenfeld-Rieger syndrome (rather than the individual component syndromes).

## EPIDEMIOLOGY AND PATHOGENESIS

A-R syndrome involves the anterior segment bilaterally and is associated with secondary glaucoma due to arrested angle development in about 50% of cases. A-R syndrome is a rare, autosomal dominant inherited disorder. Shields<sup>24</sup> postulated that the developmental arrest late in gestation results in primordial endothelium being retained over parts of the iris and anterior chamber angle. Contraction of this layer causes iris stromal thinning, corectopia, and hole formation. With contraction, the anterior uvea is hindered from posterior migration, which results in a high insertion of the iris into the anterior chamber angle.<sup>22</sup> Several mutations are associated with A-R, including *PITX2*, *FOXC1*, and *PAX6*.<sup>25</sup> The affected anterior segment structures are primarily of neural crest derivation. The most common extraocular defects involve dentition and facial bones.

## OCULAR MANIFESTATIONS

The typical abnormality of the cornea is an anteriorly displaced Schwalbe's line (posterior embryotoxon) that appears as a white ring on the posterior cornea near the limbus. The ring tends to be more common temporally and rarely involves all 360°. An anteriorly displaced Schwalbe's line occurs in 8%–15%<sup>26,27</sup> of the general population and may not always be present with A-R syndrome. On gonioscopy, thread-like PAS extending to the posterior embryotoxon may obscure the angle. Iris defects ranging from stromal thinning to actual hole formation, corectopia, and ectropion uveae may occur.

## SYSTEMIC ASSOCIATIONS

Developmental defects associated with A-R syndrome most commonly involve dentition and facial bones. Microdontia (peg-like incisors), hypodontia (decreased number of evenly spaced teeth), and anodontia (focal absence of teeth) are noted most commonly.<sup>23,27</sup> The facial abnormalities include maxillary hypoplasia and a protruding lower lid. Telecanthus, hypertelorism, and primary empty-sella syndrome have also been documented with A-R syndrome.<sup>22,28,29</sup>

## PATHOLOGY

The peripheral cornea characteristically exhibits an anteriorly displaced Schwalbe's line. This posterior embryotoxon shows a cellular monolayer with basement membrane that covers dense collagen.<sup>22,27</sup> The iridocorneal strands tend to be iris stroma mixed with the aforementioned cellular monolayer. This cellular membrane also may extend over the iris surface, which distorts the iris, creates iris stromal thinning, and results in actual hole formation and corectopia as it contracts.

## TREATMENT

Topical medications that decrease aqueous flow (beta-blockers, carbonic anhydrase inhibitors, and short-term use of  $\alpha$ -agonists) are more effective than outflow facilitators (prostaglandin analogs, pilocarpine). Surgical intervention may be goniotomy or trabeculectomy.<sup>30,31</sup> The procedure of choice in A-R syndrome is usually trabeculectomy with the adjunctive use of antimetabolites.<sup>32,33</sup> If the initial surgical treatment fails, glaucoma tube shunt procedures may be utilized.<sup>34</sup>

## EPITHELIAL DOWNGROWTH AND FIBROUS INGROWTH (PROLIFERATION)

### INTRODUCTION

Unlike ICE syndrome, epithelial downgrowth/fibrous ingrowth results from the access of epithelial/fibrous cells into the anterior chamber. Epithelial/fibrous cells entering through an insufficiently closed wound usually cause these conditions.<sup>35</sup> Fortunately, with advancements in microsurgical techniques (e.g., improved wound closure), the incidence of these entities has been reduced greatly.

## EPIDEMIOLOGY AND PATHOGENESIS

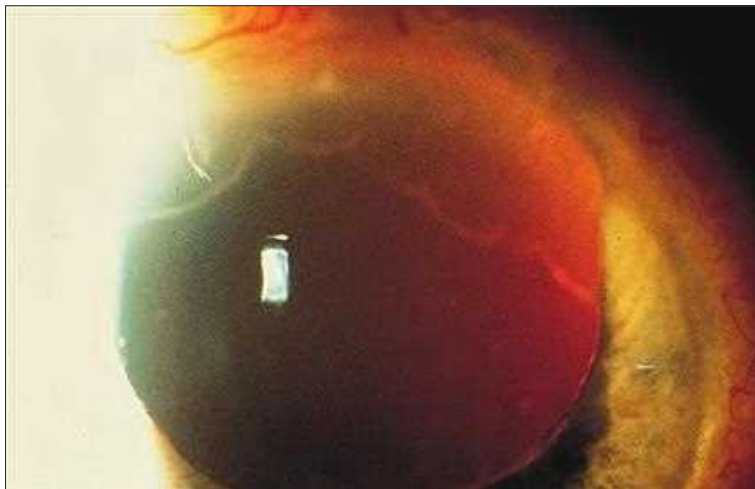
The incidence of epithelial downgrowth and fibrous ingrowth has declined greatly over the years with the advent of small-incision surgery. The prevalence of epithelial downgrowth occurred in the range of 0.12%–0.6% following intracapsular cataract surgery.<sup>36–38</sup> While previously more common after cataract surgery, epithelial downgrowth is now more commonly seen after penetrating keratoplasty,<sup>39–41</sup> ocular trauma, and glaucoma filtration surgery.<sup>42,43</sup> Fibrous ingrowth is more prevalent than epithelial downgrowth, progresses more slowly, and is often self-limited. Epithelial downgrowth and fibrous ingrowth can occur simultaneously.<sup>36</sup> Prolonged ocular inflammation is a major risk factor for epithelial and fibrous proliferation.<sup>44</sup> Other risk factors appear to be wound dehiscence, delayed closure of the wound postoperatively, and stripping of Descemet's layer.<sup>45,46</sup>

Normal postoperative healing of the corneal scleral wound requires invasion of connective tissue to the inner margin of the wound and formation of a fibrous plug. By the second week, the inner wound is usually covered by endothelium. Contact inhibition stops the movement of endothelium.<sup>47,48</sup> When the endothelium fails to close this defect, epithelial and





**Fig. 10.20.5** Translucent, Nonvascular, Anterior Chamber Epithelial Cyst.



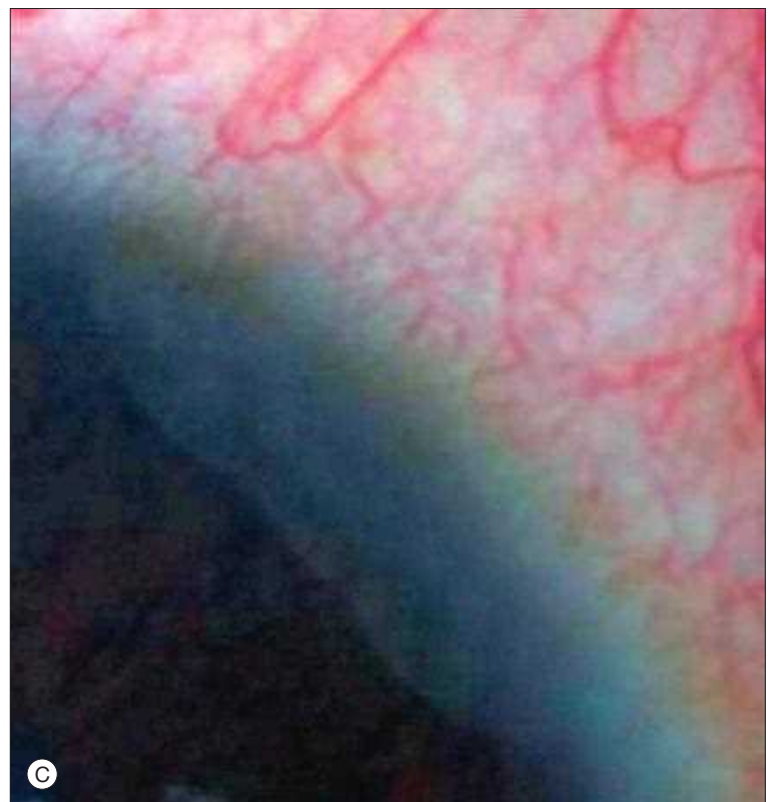
**Fig. 10.20.6** Grayish, Sheet-Like Epithelial Ingrowth With Rolled Edges.

fibrous proliferation can occur. Thus an abnormality in the corneal endothelium is also a risk factor. Posterior limbal incisions may be more commonly associated with fibrous ingrowth, whereas anterior limbal incisions may be associated with epithelial downgrowth.<sup>44</sup> Small incisional cataract surgery has minimized the importance of such distinctions. Other proposed risk factors for fibrous and epithelial proliferation are fornix-based conjunctival flaps, intraocular use of surgical instruments on the conjunctiva,<sup>49</sup> and use of intracameral anticoagulant therapy.<sup>50</sup>

## OCULAR MANIFESTATIONS

Epithelial proliferation may be present in three forms: “pearl” tumors of the iris, epithelial cysts, and epithelial ingrowth. Epithelial cysts and epithelial ingrowth often cause secondary glaucoma. Epithelial cysts appear as translucent, nonvascular anterior chamber cysts that originate from surgical or traumatic wounds (Fig. 10.20.5). Epithelial ingrowth presents as a grayish, sheet-like growth with rolled edges on the posterior surface of the cornea (Fig. 10.20.6), trabecular meshwork, iris, and ciliary body. It is often associated with wound incarceration, wound gape, ocular inflammation, band keratopathy,<sup>41,51</sup> and corneal edema. The degree of ingrowth can be very specifically detected by the characteristic whitening on application of the argon laser (Fig. 10.20.7).<sup>52</sup> Specular and confocal microscopy provide other means of diagnosis by direct visualization of epithelial cells.<sup>53</sup>

Unlike epithelial proliferation, fibrous ingrowth is slow to progress and may be self-limited. A common cause of corneal graft failure, fibrous ingrowth appears as a thick, gray-white, vascular, retrocorneal membrane with an irregular scalloped border reminiscent of woven cloth.<sup>54</sup> The ingrowth often involves the angle, which results in the formation of PAS and the destruction of the trabecular meshwork. The resultant secondary angle-closure glaucoma is a frequent complication and is often difficult to control medically.



**Fig. 10.20.7** Epithelial Iris Cyst and Downgrowth. (A) Scanning electron microscopy shows a sheet of epithelium that covers the trabecular meshwork, anterior face of the ciliary body, anterior iris, and pupillary margin. (B) Epithelium lines the posterior cornea, anterior chamber angle, and peripheral iris and extends onto the vitreous posteriorly in a surgically aphakic eye. (C) Detection of epithelial downgrowth by application of argon laser to the iris. (A–B, With permission from Yanoff M, Fine BS. Ocular pathology. London: Mosby; 1996.)

**BOX 10.20.1 Management Options of Noncystic/Diffuse Epithelial Proliferation**

- Freezing the involved corneal surface to close the wound gape or fistula
- Swabbing the involved corneal surface with absolute ethanol
- Resecting the posterior membrane<sup>60</sup>
- Intracameral injection of 5-fluorouracil<sup>161</sup>

**PATHOLOGY**

Epithelial downgrowth consists of a multilayered membrane composed of nonkeratinized, stratified, squamous epithelium that has surface microvilli; wide intercellular borders with occasional hemidesmosomes attached to a subepithelial connective tissue layer; and epithelial cells of uneven sizes and shapes.<sup>55,56</sup> This epithelial sheet lacks blood vessels and shows multiple tonofilaments at its leading edge (see Fig. 10.20.7).<sup>57</sup> The underlying structures in contact with the epithelial sheet undergo disorganization and destruction.

**TREATMENT**

Management of epithelial cysts includes observation until complications are observed. Numerous approaches have been used to excise epithelial cysts, but currently a wide excision of the intact cyst is preferred. If the cyst is adherent to any intraocular structures, it may be collapsed by aspiration before excision.<sup>58</sup> Photocoagulation of epithelial cysts, a less invasive procedure than surgical removal, has been performed successfully.<sup>59</sup> Photocoagulation is less effective when the cyst is nonpigmented or adherent to underlying structures. The management options for noncystic/diffuse epithelial proliferation are listed in Box 10.20.1.

Management of glaucoma is a difficult challenge and has a high failure rate using traditional filtration surgery techniques. Glaucoma drainage tube implants have been shown to be the most effective procedure, with both fibrous and epithelial ingrowth.<sup>34,62</sup> Cycloablation is used only when other treatment modalities fail.

**ANIRIDIA****INTRODUCTION**

Aniridia is a rare, bilateral, hereditary absence of the iris. The condition rarely occurs in its pure form and usually presents with a rudimentary stump of iris.

**EPIDEMIOLOGY AND PATHOGENESIS**

Aniridia is seen in approximately 1.8/100 000 live births.<sup>63</sup> Three phenotypes are recognized, of which autosomal dominant aniridia is the most common; it is present in approximately 85% of all cases and is not associated with any other systemic manifestations. The second type is congenital sporadic aniridia, found in association with Wilms' tumor (nephroblastoma), genitourinary anomalies, and intellectual disability (Miller's syndrome). The second type has been labeled WAGR syndrome (for Wilms' tumor, aniridia, genitourinary anomalies, retardation), is linked with partial deletions of the short arm of chromosome 11 (11p13), and accounts for approximately 13% of all aniridias. Autosomal recessive aniridia is the third genetic type; it is seen in approximately 2% of all cases and is associated with cerebellar ataxia and mental retardation (Gillespie's syndrome).<sup>64</sup> Hereditary aniridia is associated with the *PAX6* gene.<sup>65</sup>

Different theories have been developed to explain the pathogenesis of aniridia. Some researchers consider it a subtype of coloboma. In addition, some aniridias are associated with hypoplastic discs and the absence of iris musculature, on the basis of which investigators have proposed mesodermal and neuroectodermal theories, respectively. Glaucoma develops in about 50% of patients who have aniridia.<sup>66</sup> Glaucoma is rare in newborns; it is usually seen after the second decade of life, as anatomic changes occur in the angle secondary to contracture of peripheral iris strands.<sup>67</sup> These iris strands bridge the space between the iris stump and trabecular meshwork, resulting in angle-closure glaucoma. In addition, goniodysgenesis is noted in some cases.

**OCULAR MANIFESTATIONS**

The clinical manifestations of aniridia include photophobia related to the extent of iris involvement. Pendular nystagmus, decreased vision, amblyopia, and strabismus are seen secondary to foveal and optic nerve head hypoplasia. Bilateral ptosis also may occur in aniridia. With gonioscopy, the iris appears as a rudimentary stump with fibers that bridge the angle. This rudimentary iris leaflet appears to be pulled forward by iris strands, which results in posterior synechiae formation and subsequent angle-closure glaucoma. In addition to the anterior segment changes, findings in the posterior segment may include foveal and optic nerve head hypoplasia and choroidal coloboma. Lenticular changes include cataract, ectopia lentis, microphakia, and persistent pupillary membranes. Microcornea<sup>68</sup> and corneal opacifications also have been observed in aniridic patients. The corneal opacification is often associated with a fine, vascular network and pannus formation.<sup>69</sup>

**SYSTEMIC ASSOCIATIONS**

Wilms' tumor (nephroblastoma) is found in association with aniridia in Miller's syndrome; 25%–33% of patients who have sporadic aniridia develop Wilms' tumor. In addition to Wilms' tumor, severe mental retardation, genitourinary anomalies, craniofacial dysmorphism, and hemihypertrophy can occur.<sup>62</sup> In Gillespie's syndrome, intellectual disability and cerebellar ataxia are seen.

**PATHOLOGY**

Arrestment of the neuroectodermal tissue is the most striking histopathological feature of this condition. With histological examination, a small stump of iris that lacks iris musculature may be observed. The iris remnant appears continuous with the trabecular meshwork. Glaucoma in Miller's syndrome may develop secondary to angle anomalies, which include dysgenesis of the trabecular meshwork and Schlemm's canal.<sup>63</sup>

**TREATMENT**

Glaucoma and its surgical complications are the main causes of blindness in patients with aniridia. Surgery is often required by age 20 for IOP control.<sup>63,70,71</sup> A prophylactic modified goniotomy has been advocated to prevent this secondary glaucoma in certain young patients with aniridia.<sup>72,73</sup>

**TUMORS AND GLAUCOMA****INTRODUCTION**

A variety of intratumors may cause unilateral glaucoma; the most common ones associated with glaucoma include primary melanomas, metastases, and retinoblastomas. The mechanism of glaucoma development varies with the location, type, and size of the tumor. Choroidal melanomas and other choroidal and retinal tumors close the angle by a mass effect by shifting the lens–iris diaphragm forward with angle closure. Inflammation caused by necrotic tumors can cause posterior synechiae, which can exacerbate this angle closure through a pupillary block mechanism. Neovascularization can be caused by choroidal melanomas, medulloepitheliomas, and retinoblastomas. Liberated tumor cells can also obstruct aqueous outflow.

**EPIDEMIOLOGY AND PATHOGENESIS**

In 1987, Shields et al.<sup>74</sup> studied 2704 eyes that had intraocular tumors, of which 5% were found to have IOP elevation secondary to the tumor. The most common tumor in adults to result in glaucoma was malignant uveal melanoma.<sup>75–79</sup> Direct infiltration of the angle was the most common cause of increased IOP. The trabecular meshwork can also be obstructed by pigment, tumor, or inflammatory cells. Shields et al.<sup>74</sup> found glaucoma in 7 of 102 eyes that had iris melanoma. Iris melanocytomas are rare and have a predisposition to release pigment into the anterior chamber, which causes a secondary open-angle glaucoma.<sup>80</sup> Ciliary body melanomas may present with increased IOP secondary to a variety of mechanisms.<sup>76</sup>

Shields et al.<sup>74</sup> reported that 16 of 96 eyes that had ciliary body melanomas also had associated glaucoma. Medulloepithelioma (diktyoma) is a tumor of the nonpigmented ciliary epithelium and usually presents in childhood as a cystic or solid tumor, and in one study, about 50% of these eyes presented with glaucoma, with neovascularization as the most common



cause of glaucoma.<sup>76</sup> Mechanical displacement of the angle, direct invasion of the angle, and one case of recurrent hyphema also caused glaucoma.<sup>77</sup>

Retinoblastoma is the most common malignant intraocular tumor of childhood. Approximately 1 in 14 000–20 000 newborns have retinoblastoma, and 30%–35% of cases occur bilaterally, with no sex or race predisposition. Glaucoma secondary to retinoblastoma has an incidence of 2%–22%.<sup>74,81</sup> Neovascular glaucoma secondary to retinal ischemia is the most common mechanism (73%).<sup>74</sup> The second most common cause of glaucoma in these eyes is anterior displacement of the lens–iris diaphragm.

Metastatic tumors in the uvea are usually posterior. The most common sites of origin are breasts in women and lungs in men.<sup>80</sup> In contrast to iris and ciliary body metastases, metastatic tumors to the choroid show only about a 2% incidence of glaucoma. The main presentation of glaucoma results from a forward shift of the lens–iris diaphragm secondary to non-rhegmatogenous retinal detachment.<sup>81</sup> Glaucoma is associated with 64% of iris metastases and 67% of ciliary body metastases.<sup>74</sup> Elevated IOP is seen in patients with these tumors, usually from localized blockage of the trabecular meshwork by released tumor cells.<sup>81</sup>

## OCULAR MANIFESTATIONS

The clinical presentation of glaucoma that arises from intraocular tumors is dependent on the mechanism of inducement. Glaucoma secondary to tumors may present as secondary angle-closure glaucoma by a posterior-push mechanism or an anterior-pull mechanism. Other mechanisms include those of secondary open-angle glaucoma.

## PATHOLOGY

Iris melanoma usually appears as a well-circumscribed, variably pigmented, fixed, or slow-growing tumor that may eventually invade the trabecular meshwork. The tumor is composed of spindle-shaped cells with occasional epithelioid cells.<sup>81</sup> Ciliary body melanoma appears as a circumscribed mass that replaces the ciliary body. Choroidal melanoma appears as a variably pigmented mass that may result in a secondary nonrhegmatogenous retinal detachment. As the tumor breaches Bruch's membrane it can form the characteristic “mushroom” shape. Melanocytoma appears as a brown or black mass that may be well circumscribed<sup>80</sup> and usually occurs at the optic disc but may arise anywhere in the uvea. Necrotic areas are present within the mass, which may result in fragmentation and liberation of tumor cells into the angle.<sup>81</sup>

Iris and ciliary body metastases usually have poor differentiation, which makes determination of the primary site difficult. Choroidal metastases are ill-defined, relatively elevated, or diffuse lesions, often associated with serous or choroidal retinal detachment. The lesions may present with a brown discoloration secondary to overlying pigment or with a gray to yellow–cream color. Retinoblastoma appears as a chalky white mass within the globe and is composed of neuroblastic cells; areas of calcification and necrosis are common findings. The differentiated tumors are characterized by highly organized Flexner–Wintersteiner rosettes.<sup>80</sup> Medulloepithelioma is an embryonic tumor that usually occurs in the ciliary body. The tumor appears as a yellow–pink solid or cystic mass and may contain rosettes. Medulloepithelioma has two types of presentation: the nonteratoid type is composed of nonpigmented epithelium and the teratoid type shows two different germ layers (i.e., cartilage and skeletal muscle).<sup>81</sup>

## TREATMENT

Malignant ocular tumors are often enucleated as the definitive management. Traditional filtration techniques run the risk that tumor cells may be seeded to extraocular areas even after treatment with radiation. Secondary glaucoma from benign tumors can be managed medically and with traditional filtration surgeries. Proper diagnosis of tumors usually is made clinically. Fluorescein angiography and ultrasonography (e.g., A-scan, B-scan, ultrasound microscopy [UBM]) help in the detection and diagnosis of intraocular tumors. In some patients, a fine-needle biopsy, aqueous aspiration, or biopsy is needed for diagnosis.

## PENETRATING KERATOPLASTY

### INTRODUCTION

Secondary glaucoma is a common complication of penetrating keratoplasty and occurs with increased frequency in aphakic and pseudophakic

### BOX 10.20.2 Mechanisms of Secondary Glaucoma Formation

- Wound distortion of trabecular meshwork
- Fibrous ingrowth
- Postoperative inflammation
- Chronic angle closure
- Viscoelastic
- Corticosteroid induced
- Pre-existing conditions

patients<sup>81</sup> and in repeat corneal grafts. The different mechanisms of secondary glaucoma formation are listed in Box 10.20.2. Distortion of the angle, chronic angle closure, and a predisposition before surgery are the most common causes.

## EPIDEMIOLOGY AND PATHOGENESIS

Improved surgical and storage techniques have resulted in a large increase in the number of corneal transplants being done. Penetrating keratoplasty is one of the most successful of all transplants, with a 1-year survival rate of 80%–90%.<sup>82</sup> Postkeratoplasty glaucoma occurs more frequently in patients affected by pre-existing glaucoma. Aphakic and pseudophakic bullous keratopathies are the most common indications for penetrating keratoplasty, at rates of 20%–70% and 18%–53%, respectively.<sup>83</sup> One study indicated no early or late glaucoma in patients who had penetrating keratoplasty for keratoconus and a less than 2% incidence in patients who had Fuchs' corneal endothelial dystrophy treated with penetrating keratoplasty.<sup>84</sup>

## OCULAR MANIFESTATIONS

Graft clarity is reduced significantly when postkeratoplasty glaucoma is present.<sup>85,86</sup> Glaucoma affects the cornea directly and the visual potential by causing optic neuropathy. In early postkeratoplasty glaucoma, epithelial edema is found along with stromal thinning and compression. Such findings are noted before endothelial damage occurs.<sup>87</sup> Progressive angle closure from peripheral synechiae formation is an early sign of impending glaucoma in postkeratoplasty patients. Some studies have demonstrated the presence of PAS in all eyes with elevated IOP after keratoplasty.<sup>88</sup> A major study in which routine gonioscopy was conducted, however, concluded that progressive synechial closure was a plausible explanation for only 14% of eyes that had elevated IOP.<sup>89</sup>

As topical corticosteroids are the mainstay of rejection treatment in corneal transplants, this can also be a cause of increased IOP in susceptible individuals. The use of potent corticosteroids at frequent intervals was reported to reduce the rates of early IOP elevation.<sup>87</sup> In contrast, certain cases of IOP elevation may be related to corticosteroid responders. Following corticosteroid use, reported rates of secondary IOP are increased from 5%–60%.<sup>88–92</sup> This fact outlines the double-edged sword of corticosteroids: the necessity for postkeratoplasty inflammation and potential for postkeratoplasty glaucoma. As we gain experience with other immunosuppressants and their effects on the eye in uveitis, these agents may play a role as corticosteroid-sparing agents in corneal transplants.

## TREATMENT

Treatment modalities for postkeratoplasty glaucoma include medical therapy, trabeculectomy, glaucoma tube shunt procedures, and cyclodestructive procedures. The initial treatment of choice is medical therapy. However, in the presence of significant synechial closure, drugs that influence outflow facility (i.e., miotics) may have limited action. Similarly, the role of prostaglandin analogs in this type of glaucoma and their influence on graft survival and graft clarity remain uncertain. Dorzolamide has been shown to decrease corneal endothelial function and to increase corneal thickness, and reported cases of graft failure have been attributed to its use.<sup>93</sup>

Glaucoma drainage implants (e.g., Ahmed, Krupin, Molteno, Baerveldt, Schocket) have been useful in controlling IOP among patients who have had difficult previous surgeries.<sup>94</sup> In one study, 29% of patients progressed to failure after Molteno implantation and 20% after insertion of Schocket tube.<sup>95</sup> Long-term studies of glaucoma implants have shown that even in cases with well-controlled glaucoma there is an increase in the failure rate of the corneal graft (75% failure at 2 years, with more than 63% having



well-controlled glaucoma).<sup>96</sup> Placement of the shunt implant through the pars plana may also improve graft survival.

Filtration surgery shows success rates of 27%–80%.<sup>89,95,97–99</sup> Aphakic eyes have a lower success rate than do pseudophakic or phakic eyes. Graft failure at 3 years after trabeculectomy is in the range of 11%–20%.<sup>89,98</sup> Cyclodestructive procedures can lower IOP effectively after penetrating keratoplasty. Laser cyclophotoablation is used in preference to cyclocryotherapy because of its reduced side effects and improved visual result. The reported success rate for laser cyclophotoablation is 50%–100%. Graft failure has been reported with laser cyclophotoablation.<sup>98,100,101</sup>

## ALKALI CHEMICAL TRAUMA

### INTRODUCTION

In the acute setting of a patient who has an alkali burn, glaucoma may be overlooked as a complication. It occurs in the acute and late settings with a possible intermediate period of hypotony secondary to ciliary body damage. Secondary glaucoma occurs more often in association with alkali burns than with acidic burns.

### EPIDEMIOLOGY AND PATHOGENESIS

Alkali can cause severe damage to ocular tissues as a result of the saponification of fatty acids in tissue, which allows deep penetration and damage. In contrast, acidic chemicals have a tendency to coagulate tissue proteins, and the layer of precipitated protein helps buffer and limit the acid's penetration through the cornea. Different mechanisms have been postulated for each phase of IOP elevation. The initial pressure elevation may be secondary to tissue shrinkage of the outer coats of the eye<sup>102</sup> or to prostaglandin release that increases uveal blood flow.<sup>103</sup> The intermediate and late phases show changes in the eye as part of the body's response. In these phases, trabecular damage, PAS, and secondary pupillary block are possible mechanisms for the development of glaucoma.

### OCULAR MANIFESTATIONS

Damage to the cornea may be widespread and progressive. Epithelial disintegration may be followed by stromal ulcerations and perforation. Measurement of IOP in eyes that have extensive corneal damage may be difficult using Goldmann applanation tonometry. A Tono-Pen or pneumotonometer may be more accurate. Gonioscopy may be difficult in these patients because of corneal opacification, in which case ultrasound examination may be necessary to visualize the extent of optic nerve cupping and retinal damage. Later in the disease process, symblepharon formation of the palpebral conjunctiva may obliterate the fornices.

## PATHOLOGY

After exposure to an alkaline chemical, the corneal keratocytes rapidly coagulate to leave devitalized corneal stroma. The bulk of the corneal mucopolysaccharide ground substance also is destroyed, which is followed by collagen fiber swelling. Anterior segment shrinkage or prostaglandin-mediated inflammation may contribute to the IOP elevation. Inflammation will cause PAS, which also contributes. Intraocular lens damage may result in cataract formation, and the associated lens swelling may result in secondary phacomorphic glaucoma.

### TREATMENT

Immediate ocular irrigation is needed to remove the chemical from the corneal surface and fornices. Neutralization of an acid with a base causes thermal reaction, which will worsen injury. The management of increased IOP in the early phase is pharmacological. Miotics and prostaglandin analogs should be used cautiously because they may increase intraocular inflammation. Anti-inflammatory medications and cycloplegics are important during the first week; topical corticosteroids are administered with caution because of their potential effect on corneal stromal melting.<sup>104</sup> Conventional medical and surgical therapies are used for the later phases of IOP elevation associated with chemical trauma.

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# Congenital Glaucoma

James D. Brandt, Stuart W. Tompson, Yao Liu

# 10.21

**Definition:** Glaucoma in children less than 2 years of age can be subdivided into (1) primary congenital glaucoma, which is the result of isolated, abnormal development of the anterior chamber angle structures; and (2) secondary congenital glaucomas, either following infantile cataract surgery or those associated with ocular or systemic syndromes.

## Key Features

- Elevated intraocular pressure.
- Glaucomatous optic atrophy.
- Ocular enlargement (“buphthalmos”).

## Associated Features

- Corneal edema.
- Haab’s striae.
- Photophobia.
- Tearing.
- Amblyopia.

## INTRODUCTION

Although clinicians commonly group together all the various forms of “congenital” glaucoma, primary congenital glaucoma (PCG) is the term properly reserved for glaucoma arising due to an isolated developmental defect of the anterior chamber angle structures. PCG is exceedingly rare, and few ophthalmologists will ever make the initial diagnosis of the disease. Nonetheless, most ophthalmologists will encounter the wide variety of secondary glaucomas seen in this age group, especially following surgery for congenital cataract. In this chapter, the reader is provided with a basic understanding of how the various forms of glaucoma can present in infants and young children along with their differential diagnosis and treatment options.

## EPIDEMIOLOGY AND PATHOGENESIS

### Primary Congenital Glaucoma (PCG)

The incidence of primary congenital glaucoma is between 1 in 10 000 and 1 in 15 000 live births in the heterogeneous population of the United States. In other countries, the published series range from a low of 1 in 30 000 in Northern Ireland<sup>1</sup> to a high of 1 in 2500 in Saudi Arabia<sup>2</sup> and 1 in 1250 among Roma families in Romania.<sup>3</sup> Primary congenital glaucoma is bilateral in up to 80% of larger case series; in North America and Europe it is more common in boys, whereas in Japan it is more common in girls.<sup>4,5</sup> The varied incidence among different populations and the increased incidence in consanguineous populations suggests a strong genetic component to the disease. Most new cases (about 90%) of primary congenital glaucoma are sporadic. However, in the remaining 10% there appears to be a strong familial component; penetrance of the defect ranges from 40%–100%.

The pathophysiology and molecular etiology underlying primary congenital glaucoma remains elusive in most cases. However, five regions of the genome termed GLC3A through GLC3E are strongly associated with the disease. The GLC3A locus (OMIM 231300) harbors the cytochrome P450 1B1 (*CYP1B1*) gene, in which homozygous or compound heterozygous loss-of-function mutations are the most common cause of autosomal

recessive primary congenital glaucoma worldwide, particularly in populations with a high prevalence of consanguinity.<sup>6,7</sup> *CYP1B1* protein is required for normal oxidative homeostasis within the eye, and loss of its enzymatic activity can result in an abnormal ultrastructural organization and function of the trabecular meshwork.<sup>8</sup> At the present time, no pathogenic disease-causing mutations have been identified within the GLC3B (OMIM 600975) and GLC3C (OMIM 613085) regions of the genome, although they have been associated with primary congenital glaucoma.<sup>9,10</sup> At the GLC3D (OMIM 613086) locus, autosomal recessive primary congenital glaucoma disease is caused by homozygous or compound heterozygous loss-of-function mutations in the *LTBP2* gene.<sup>11,12</sup> *LTBP2* is an extracellular matrix protein that has roles in cell adhesion and serves as a structural component of microfibrils to confer tissue elasticity. In the eye, *LTBP2* protein localizes to the trabecular meshwork and the ciliary body, where it is essential for normal development of the anterior chamber.<sup>11</sup> Recently, the dogma that primary congenital glaucoma disease always follows an autosomal recessive inheritance pattern was demonstrated to not always hold true. In approximately 4% of primary congenital glaucoma cases, heterozygous loss-of-function mutations in the gene encoding *TEK* (the GLC3E locus, OMIM 617272) cause autosomal dominant disease with variable expressivity.<sup>13</sup> Mice haploinsufficient for *Tek* develop a severely hypomorphic Schlemm’s canal with a variable number of focal narrowings that directly correlates with increased intraocular pressure (IOP). The stochastic severity of outflow pathway malformation provides an explanation for the variable expressivity observed in human families, such as parent-to-child transmission of unilateral disease, and mutation-carrying family members with later onset disease (juvenile and primary open-angle glaucoma). Currently, the molecular basis of disease remains unsolved for approximately 75% of nonconsanguineous primary congenital glaucoma families, but recent advances in exome and whole genome sequencing should expedite the discovery and characterization of additional primary congenital glaucoma-associating genes.

In the early twentieth century, Barkan postulated that a thin, impermeable membrane covered the anterior chamber angle structures and impeded aqueous humor outflow.<sup>14</sup> This hypothesized structure explained why goniotomy, the operation he developed, was so successful in cases of infantile glaucoma. Barkan’s membrane, as the structure became known, has never been confirmed on light or electron microscopy, despite numerous attempts. Some observers have described a compaction of trabecular meshwork that might appear clinically as a continuous membrane.<sup>15</sup> A broad spectrum of anterior chamber “cleavage” disorders<sup>16</sup> often are associated with infantile glaucoma, which suggests that the principal defect in primary congenital glaucoma is a failure of one or more steps in the normal development of the anterior chamber angle.

### Glaucoma Following Cataract Surgery

Taken as a group, the secondary congenital glaucomas of childhood are far more commonly encountered than primary congenital glaucoma. Most common are the early and later onset forms of glaucoma following cataract surgery (GFCS) in infancy. More than half of children who have undergone lens extraction eventually develop ocular hypertension or glaucoma.<sup>17</sup> The Infant Aphakia Treatment Study reported a 12% incidence of glaucoma-related adverse events at 1 year, which increased to 18% by 5-year follow-up.<sup>18,19</sup>

The underlying cause of childhood glaucoma following cataract extraction remains unknown but is almost certainly multifactorial. Rabiah reported that in a case series of 570 eyes with a minimum of 5 years of follow-up, patients who underwent cataract surgery earlier in life, and those with microcornea, had a much higher risk of glaucoma.<sup>20</sup> Mataftsi and colleagues performed an individual patient meta-analysis on 470 patients

and found a similar incidence of glaucoma (17% at a median of 4.3-year follow-up) and an increased risk of glaucoma with younger age.<sup>21</sup> These findings concurred with results from the Infant Aphakia Treatment Study, which also found an increased risk of glaucoma in patients who underwent additional procedures after cataract surgery.<sup>12</sup> It remains unknown whether primary intraocular lens implantation (versus aphakia) is protective.<sup>19</sup> Walton examined 65 children, most of whom presented with glaucoma two or more years after lensectomy.<sup>22</sup> Preoperative gonioscopy revealed no consistent angle defect, but postoperative gonioscopy revealed a near constant (96%) filtration-angle deformity he characterized as blockage of the posterior trabecular meshwork with pigment and synechiae. Many clinicians familiar with this scenario believe that retained lens material is one risk factor for glaucoma that follows pediatric cataract extraction; another is the presence of a small cornea.<sup>19,20</sup> Parks and colleagues described a secondary glaucoma risk of 15% in their cohort of 174 eyes<sup>23</sup>; only 2.9% of eyes that had normal corneal diameters developed glaucoma, whereas 32% of eyes that had corneal diameters <10 mm developed the disease. The presence of both a cataract and a small cornea almost certainly indicates an abnormality that occurred during ocular development; perhaps cataract surgery unmasks a marginally functional and mal-developed anterior chamber angle and sets the stage for later glaucoma.

## Secondary Glaucomas Associated With Ocular Anomalies or Systemic Syndromes

Among the secondary glaucomas of childhood, the underlying pathophysiology is as varied as that in adults; age at presentation provides some clues as to the mechanism. Presentation at birth or shortly thereafter indicates a profound developmental abnormality of the anterior chamber angle. Presentation later in life usually suggests a different process. For example, patients with aniridia who present with obvious glaucoma at birth or early childhood have visibly abnormal anterior chamber angle structures; whereas when glaucoma presents later in life in patients with aniridia, the previously functional trabecular meshwork appears occluded by anterior migration and rotation of the rudimentary iris stump.<sup>24</sup> In patients with Sturge–Weber syndrome or its variants, presentation at birth is associated with a gonioscopic appearance of the anterior chamber angle that cannot be differentiated from that of primary congenital glaucoma. However, in those patients with glaucoma presenting later in life, elevated episcleral venous pressure is thought to be the cause.

Secondary angle closure may be caused by forward pressure from a process in the posterior segment, such as persistent fetal vasculature, retinopathy of prematurity, or retinoblastoma. Synechial angle closure, caused by chronic inflammation or neovascularization, is seen in a variety of settings. Primary angle closure that results from iris bombé is not generally seen in children except in cases of spherophakia, but when the pupil becomes secluded by an inflammatory or neovascular membrane or vitreous, iris bombé and subsequent angle closure may occur.

Secondary open-angle glaucomas also occur in young children. Both corticosteroid-induced and chronic uveitic glaucomas have been well described.<sup>25</sup> Open-angle glaucoma may develop long after blunt trauma to the eye has occurred<sup>26</sup> and may also follow the spontaneous bleeding of juvenile xanthogranuloma.<sup>27</sup>

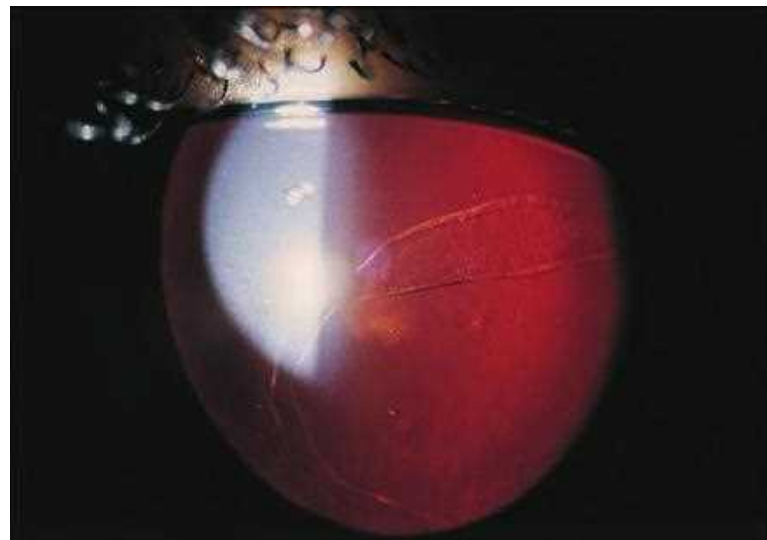
## OCULAR MANIFESTATIONS

The typical infant with congenital glaucoma is usually referred initially to an ophthalmologist because of clinically apparent corneal edema (Fig. 10.21.1). Corneal edema may be subtle—especially in bilateral cases—or may be profound, with an enlarged corneal diameter and globe, breaks in Descemet's membrane (Haab's striae), and sometimes even acute hydrops. Often the commonly described triad of epiphora, blepharospasm, and photophobia has been present for some time but was dismissed until more alarming corneal edema became apparent. The epiphora of congenital glaucoma is often misattributed to congenital nasolacrimal duct obstruction, which is found in 5%–6% of unselected newborns.

The hallmark of all forms of glaucoma in infants and young children is ocular enlargement, which occurs because the immature and growing collagen that constitutes the cornea and sclera in the young eye responds to increased IOP by stretching. All parts of the globe may stretch in response to elevated IOP until 3 to 4 years of age, and glaucoma-related axial myopia may be seen until the early teen years. Measurement of axial length by ultrasound can be very useful in the diagnosis and monitoring of the pediatric glaucomas, particularly in unilateral or asymmetrical cases. With



**Fig. 10.21.1 Clinical Appearance of Primary Congenital Glaucoma.** This 8-month-old boy presented with an acute (3-day) history of corneal edema in the right eye. Note the enlarged corneas in both eyes and the epiphora. Intraocular pressure at examination under anesthetic was >35 mm Hg (>4.7 kPa) in the right eye. Trabeculotomy ab externo was carried out bilaterally.



**Fig. 10.21.2 Haab's Striae.** A retroillumination view of the right eye of the infant shown in Fig. 10.21.1 at 5 years of age. Haab's striae are seen just adjacent to the visual axis. The child is now 21 years old and has a best-corrected visual acuity of 20/50 (6/15) in the right eye, and 20/20 (6/6) in the left eye despite aggressive amblyopia treatment.

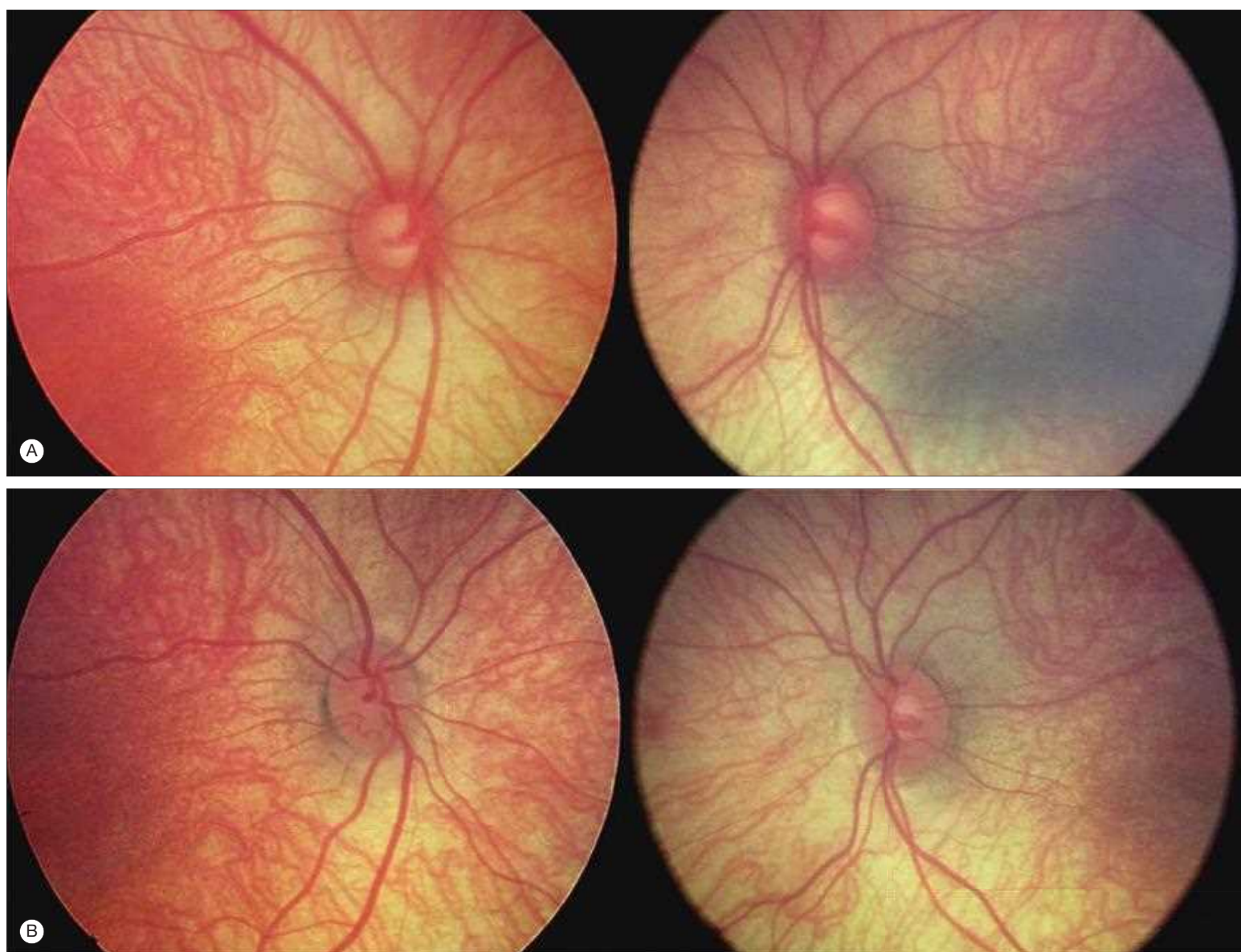
successful treatment, axial length often returns to a near-normal growth curve.<sup>28,29</sup>

Clinically, ocular enlargement is most easily discerned by an increase in corneal diameter. A variety of published series provide some guidelines as to normal measures of corneal diameter;<sup>30,31</sup> in general, the horizontal corneal diameter in the normal neonate is in the range of 10.0–10.5 mm and increases from 0.5 to 1.0 mm during the first year of life. In an infant in whom glaucoma is suspected, a horizontal corneal diameter >12 mm gives a high index of suspicion for the disease, as does asymmetry in corneal diameters of more than 1 mm.

As the cornea stretches and distends, Descemet's membrane and the overlying corneal endothelium may fracture and rip, which results in breaks presenting as profound corneal edema (see Fig. 10.21.1) and acute hydrops, in severe cases. As the endothelial cells migrate over the breaks and lay down new basement membrane, ridges develop along the separated edges of Descemet's membrane, resulting in the formation of the double striae first recognized by Haab<sup>32</sup> in 1899 (Fig. 10.21.2). In children above 2 years of age, corneal enlargement is usually not the predominant sign that glaucoma is present. In these children, decreased visual acuity or strabismus noted at the pediatrician's office or progressive unilateral myopia noted in an optometrist's office prompts the referral and the correct diagnosis.

The hallmark of all forms of glaucoma, and the principal cause of irreversible visual loss, is damage to the optic nerve. Early descriptions of infantile glaucoma stated that optic nerve cupping occurred late in the disease process.<sup>33</sup> It is now apparent not only that cupping may occur rapidly in infants but also that this cupping is reversible with surgical





**Fig. 10.21.3 Reversal of Optic Disc Cupping After Successful Treatment of Primary Congenital Glaucoma.** (A) Significant cupping in a 1-year-old child at the initial examination under anesthesia. (B) The same optic nerves 6 months after uncomplicated 360° trabeculotomy; note the dramatic reversal of optic disc cupping.

treatment and normalization of IOP.<sup>34</sup> Mochizuki and coworkers described a series of patients in whom optic disc cupping reversal was documented with digital photography; planimetry revealed that the scleral canal shrinks in size as the entire globe shrinks circumferentially.<sup>35</sup> Reversibility of optic nerve cupping is one of the hallmarks of successful treatment of glaucoma in infants and young children (Fig. 10.21.3). However, glaucomatous visual field defects and retinal nerve fiber layer thinning persist despite cupping reversal.<sup>36</sup> The short-term resilience of the infant optic nerve should be considered by the surgeon who contemplates incisional surgery based only on borderline anterior segment findings; if the optic nerve is normal, a repeat examination under anesthesia in a few weeks may spare the child an unnecessary intraocular procedure.

## DIAGNOSIS AND ANCILLARY TESTING

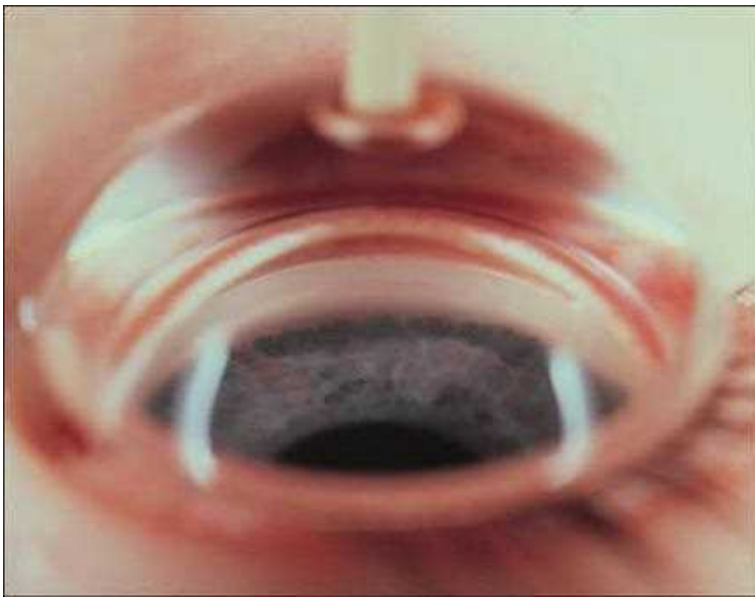
The diagnosis of glaucoma in infants is clinical. In most cases, particularly when the disease presents unilaterally or asymmetrically, the diagnosis is made in the office using a penlight (see Fig. 10.21.1). With some practice, IOP can be measured in the office in a conscious, swaddled infant using a Tono-Pen, handheld Goldmann (Perkins) tonometer, or Icare Rebound tonometer. Usually, the IOP in normal infants is in the range of 11–14 mm Hg (1.5–1.9 kPa) using these devices. The office measurement of an IOP greater than 20 mm Hg (2.7 kPa) in a calm, resting infant is suspicious for glaucoma when other signs and symptoms suggest the disease, as is an asymmetry of more than 5 mm Hg (6.7 kPa) in suspected unilateral or asymmetrical cases. Measurements of IOP undertaken while a child cries and resists efforts to hold the eye open are highly unreliable, since the Valsalva maneuver and lid squeezing can result in IOP readings

of 30–40 mm Hg (4.0–5.3 kPa), even in normal infants. In toddlers and older children, the Icare Rebound tonometer can be helpful in evaluating IOP and avoiding general anesthesia, but the device tends toward slightly higher values than Goldmann tonometry.<sup>37</sup> The recent recognition that central corneal thickness (CCT) can be an important confounder of accurate tonometry has led to investigations of CCT in children.<sup>38–40</sup> Variations in CCT may actually represent additional aspects of certain pediatric glaucoma syndromes such as aniridia.<sup>41</sup> The growing realization that tonometry is far less accurate in adults and children than previously appreciated underscores that the diagnosis of glaucoma in children should not be made solely on the basis of IOP measurement but on a constellation of findings. In addition, studies have shown that parents can learn to take accurate IOP measurements at home using Icare Rebound tonometry.<sup>42</sup>

Examination of the optic nerve is attempted whenever possible, as the presence of obvious glaucomatous cupping confirms the diagnosis. Shaffer and colleagues noted a cup-to-disc (C/D) ratio greater than 0.3 in 68% of 126 eyes affected by primary congenital glaucoma, whereas a C/D ratio greater than 0.3 was found in less than 2.6% of normal newborns.<sup>33</sup> Asymmetry in the C/D ratio between the two optic nerves—especially when the asymmetry corresponds with other findings—is strongly suggestive of glaucoma.<sup>43</sup> The optic nerve may also be monitored using optical coherence tomography (OCT) measurements of the retinal nerve fiber layer, and normative values in children have been found to be comparable to those in young adults.<sup>44</sup>

A Koeppel infant diagnostic lens that does not have a central depression employs a lid-retention flange to prevent the infant from squeezing out the contact lens. Once in place, good visualization of the disc is possible using a direct ophthalmoscope, even with a relatively small pupil. With dilation,





**Fig. 10.21.4 Gonioscopic Appearance of the Anterior Chamber Angle in Primary Congenital Glaucoma.** When viewed through a Koepple diagnostic lens, the iris is seen to insert anteriorly, and the peripheral iris is hypoplastic, unpigmented, and has a scalloped appearance. A sheen occurs over the angle structures (which is difficult to photograph) and gives the impression that a membrane coats the surface of the angle, but Barkan's membrane has not been identified histologically.

fundus photography to document the appearance of the optic nerve may be possible. With a Koepple diagnostic infant lens in place, gonioscopy may be performed, even in a conscious infant in the office. Simultaneous gonioscopy of both eyes may be carried out to compare the angle appearance in unilateral or asymmetrical cases. The diagnosis of glaucoma is not made using gonioscopic appearance alone but is based primarily on the other signs and symptoms of the disease. However, gonioscopy may help differentiate among the various forms of glaucoma and, most importantly, provide the surgeon with an idea of whether angle surgery (goniotomy or trabeculotomy) or fistulization surgery (trabeculectomy or drainage implant) should be the first intervention. The gonioscopic appearance of the anterior chamber angle in primary congenital glaucoma is characteristic (Fig. 10.21.4); the iris inserts anteriorly compared to the normal infant angle. The stroma of the peripheral iris is hypoplastic and unpigmented and has a scalloped appearance.

If the diagnosis of glaucoma is confirmed or strongly suspected based on the office examination, an examination under anesthesia (EUA) and definitive surgical treatment is pursued within a few days. Serial EUAs may be needed to monitor young children in whom only a limited exam can be performed in the clinic. However, the increased tolerability of Icare Rebound tonometry can reduce the number of EUAs needed for IOP monitoring.<sup>45</sup> Details of the EUA as well as goniotomy and trabeculotomy are provided in Chapter 10.27.

As noted previously, some forms of primary congenital glaucoma represent heritable disorders, as do many of the secondary or systemically associated glaucomas of childhood. All children who have glaucoma that presents at birth and in early childhood should be referred to a clinical geneticist familiar with ocular disease. In some cases, a subtle syndromic diagnosis may be made that has important implications for the parents' future child-bearing plans. Furthermore, the variable expressivity observed among *CYP1B1* mutations means that the siblings of affected children should be tested as well. If the same mutation is found in the clinically as-yet unaffected sibling, that child must be followed carefully. Due to advances in the molecular diagnosis of some forms of primary congenital glaucoma, it is now possible to offer prenatal screening for some families.<sup>46</sup>

## DIFFERENTIAL DIAGNOSIS

The differential diagnosis of the various signs and symptoms of glaucoma in children is given in Box 10.21.1; this list is by no means exhaustive. Several acquired and genetic disorders may be mistaken as early childhood glaucoma.<sup>47</sup> Corneal cloudiness may have myriad causes. Corneal opacity that results from hereditary dystrophies is usually symmetrical, whereas corneal edema that arises from obstetric trauma is usually unilateral.

Corneal enlargement may result from megalocornea, which is frequently X-linked. In affected children, the anterior chamber angle, IOP,

### BOX 10.21.1 Differential Diagnosis of Ocular Signs and Symptoms in Congenital Glaucoma

#### Corneal Edema or Clouding

- Congenital hereditary endothelial dystrophy
- Mucopolysaccharidoses I, IS, II, III
- Cystinosis
- Sclerocornea
- Rubella keratitis
- Obstetric birth trauma ("forceps injury")
- Chemical injury

#### Epiphora and/or Red Eye

- Nasolacrimal duct obstruction
- Conjunctivitis (viral, chlamydial, bacterial)
- Corneal epithelial defect, abrasion

#### Photophobia

- Conjunctivitis
- Iritis
- Trauma (especially hyphema)

#### Corneal Enlargement

- Axial myopia
- Megalocornea (X-linked or sporadic)
- Microphthalmic fellow eye

and optic nerve are all normal, as are lens thickness and vitreous cavity axial length.<sup>48</sup> Some clinicians consider megalocornea to be a "forme fruste" of primary congenital glaucoma; such children should be followed carefully for later signs of glaucoma. An entirely normal eye may appear enlarged relative to a microphthalmic fellow eye, and in such cases familiarity with the age-appropriate corneal diameters and axial lengths prevents misdiagnosis.

Although the differential diagnosis of a red, tearing eye in a child is quite broad, the many potential infectious, malignant, or inflammatory causes rarely result in a diagnostic dilemma. Congenital nasolacrimal-duct obstruction occurs in 5%–6% of otherwise normal infants and coexists with congenital glaucoma with similar frequency. If epiphora persists after apparently successful treatment of glaucoma in an infant, the nasolacrimal system must be evaluated.

## CLASSIFICATION SCHEMES

In 2013, the Childhood Glaucoma Research Network (CGRN) and the World Glaucoma Association (WGA) arrived at a classification scheme for childhood glaucoma to assist clinicians and to form the basis of an international disease and surgical registry. An abbreviated version is provided in Box 10.21.2.

## PATHOLOGY

Descriptions of the pathology of the anterior chamber angle in primary congenital glaucoma are limited to a small number of specimens. This is because primary congenital glaucoma is rare, few of these infants die of unrelated causes, and incisional angle surgery does not involve the excision of a surgical specimen. Furthermore, eyes enucleated at an advanced stage for blindness and pain may not be representative of the earlier stage of the disease. Nonetheless, several general observations have been made.<sup>4</sup> The iris inserts anteriorly (see Fig. 10.21.4), but the angle is open; the trabecular meshwork appears open and is perforate; and Schlemm's canal usually is present and open. Although Barkan's membrane has not been identified conclusively, specific angle abnormalities have been described associated with mutations in *CYP1B1*.<sup>49</sup>

## TREATMENT

The preferred treatment of the congenital glaucomas is surgical (Table 10.21.1). Medical therapy alone is rarely effective for these conditions. Even topical prostaglandins, which can be administered once a day and may be safer (systemically) than those previously available, have limited efficacy in children,<sup>50,51</sup> and it remains unrealistic to expect more than short-term medication compliance in children who have a lifelong disease that may result in blindness.

Current techniques of surgery on the anterior chamber angle (goniotomy and trabeculotomy) enjoy a high rate of success in primary congenital glaucoma and can be used in selected cases of glaucoma following cataract surgery in which the anterior chamber angle is open.<sup>52</sup> In addition, alternative surgical approaches (trabeculectomy and drainage implant surgery) may be highly effective in the secondary congenital and childhood glaucomas.

The surgical management of all infants affected by glaucoma begins with a detailed EUA. There is an emerging body of literature that suggests excessive general anesthesia poses some risk to the developing infant brain.<sup>53</sup> Although the safety of general anesthesia in young children

is supported by more recent studies,<sup>54,55</sup> it is always best to avoid EUAs performed solely for diagnosis, thus committing the child to a second anesthetic for surgery. The ophthalmologist who undertakes the management of an infant or child who has glaucoma must approach the EUA with experience in pediatric gonioscopy and a flexible surgical plan. Surgical flexibility is particularly crucial in the case of the secondary congenital glaucomas, for which the surgeon must be prepared to alter the surgical plan depending on what is found intraoperatively. For example, in children with glaucoma following cataract surgery, the presence of a synechially closed anterior chamber angle is a contraindication to conventional angle surgery, as goniotomy or trabeculotomy can lead to iridodialysis or severe intraocular bleeding. In such cases, fistulizing surgery such as a trabeculectomy or drainage implant must be considered instead.

In primary congenital glaucoma, either goniotomy or trabeculotomy is the procedure of choice; these are associated with success rates of 90% or greater. Goniotomy requires the presence of a clear cornea for adequate observation of the anterior chamber angle; ab externo trabeculotomy may be performed in the presence of a hazy or opaque cornea. In a prospective trial in which bilaterally affected infants were treated with goniotomy in one eye and trabeculotomy in the other, Anderson found similar success rates for the two procedures.<sup>56</sup> The choice of which procedure to perform is left to the surgeon's discretion.

Circumferential (360°) trabeculotomy has become increasingly popular among pediatric glaucoma surgeons. These techniques involves the insertion of either a suture (e.g., blunted 6–0 polypropylene or nylon) or iTrack illuminated microcatheter device (Ellex Inc. USA, Minneapolis, MN) into the lumen of Schlemm's canal via an ab externo<sup>57</sup> or ab interno<sup>58</sup> approach followed by pulling the suture or catheter into the anterior chamber, transecting the trabecular meshwork, to create a circumferential trabeculotomy. The TRAB 360 device (Sight Sciences, Inc., Menlo Park, CA) is a single-use device that cannulates Schlemm's canal via an ab interno approach under direct gonioscopic visualization and can treat nearly 360° of the angle with two 180° passes. A comparison of 360° versus traditional (approximately 120° using the Harms trabeculotome) trabeculotomy showed significantly lower IOP in the group receiving 360° treatment.<sup>59</sup> However, 360° treatment may not be possible in certain cases due to incomplete Schlemm's canal development.

Trabeculectomy and trabeculectomy combined with trabeculotomy have been proposed as primary treatments for glaucoma in children.<sup>60</sup> However, a trabeculectomy in an infant eye is not without its own set of unique challenges. To raise a partial-thickness flap in a buphthalmic eye is particularly difficult, as is the postoperative adjustment of flap tension through lysis of flap sutures.<sup>61</sup> Hypotony, hyphema, or a flat chamber in an infant may easily result in profound amblyopia before the visual axis is cleared. Most proponents of filtration surgery in infants and young children advocate the intraoperative application of the potent antimetabolite mitomycin C, as there can be an exuberant scarring response, and postoperative injection of 5-fluorouracil is not an option without a general anesthetic. Filtration procedures augmented with antimetabolites result in the formation of thin acellular blebs that impart high susceptibility to late-onset bleb infection and endophthalmitis.<sup>62</sup> The use of fornix-based conjunctival flaps may reduce the risk of infection.<sup>63</sup> Encouraging results have been reported in young children with relatively few complications using this technique.<sup>64</sup>

### BOX 10.21.2 Abbreviated CGRN/WGA<sup>a</sup> Classification of Childhood Glaucoma

#### Definition of Childhood

- Based on national criteria: <18 years of age (USA); ≤16 years of age (UK, Europe)

#### Definition of Glaucoma—2 or More Required

- IOP >21 mm Hg (investigator discretion if EUA data alone)
- Optic disc cupping: a progressive increase in cup-to-disc ratio, cup-disc asymmetry of ≥0.2, or focal rim thinning
- Corneal findings: Haab's striae or diameter: ≥11 mm in newborn, >12 mm in child <1 year of age, >13 mm any age
- Progressive myopia or myopic shift coupled with an increase in ocular dimensions out of keeping with normal growth
- A reproducible visual field defect that is consistent with glaucomatous optic neuropathy with no other observable reason for the visual field defect.

#### Definition of Glaucoma Suspect—at Least 1 Required

- IOP >21 mm Hg on two separate occasions, or
- Suspicious optic disc appearance for glaucoma, i.e., increased cup-to-disc ratio for size of optic disc, or
- Suspicious visual field for glaucoma, or
- Increased corneal diameter or axial length in setting of normal IOP

#### Primary Childhood Glaucoma

- Primary congenital glaucoma (PCG)
- Juvenile open-angle glaucoma (JOAG)

#### Secondary Childhood Glaucoma

- Glaucoma associated with ocular anomalies
- Glaucoma associated with systemic disease or syndrome
- Glaucoma associated with acquired condition
- Glaucoma following congenital cataract surgery

EUA, Examination under anesthesia; IOP, intraocular pressure.

<sup>a</sup>The Childhood Glaucoma Research Network (CGRN)/World Glaucoma Association (WGA) international classification of childhood glaucoma is proposed to serve as a common classification scheme for an international internet-based disease registry as well as future publications and work on children with glaucoma. Further information may be found at <http://www.gl-foundation.org/resources-for-professionals> and <https://wga.one/wga/>.

TABLE 10.21.1 Surgical Management for Congenital Glaucoma

	Angle Surgery—First-Line for Primary Congenital Glaucoma			
	Goniotomy	Trabeculotomy—ab interno or ab externo		
Pro	<ul style="list-style-type: none"><li>• Spares conjunctiva</li></ul>	<ul style="list-style-type: none"><li>• Can perform ab externo even if cornea is very cloudy</li></ul>		
Con	<ul style="list-style-type: none"><li>• Requires clear cornea to view angle structures</li></ul>	<ul style="list-style-type: none"><li>• Conjunctival incision required (ab externo)</li><li>• May be technically challenging</li><li>• Schlemm’s canal may not be present</li></ul>		
	Alternatives to Angle Surgery—Second-Line for Primary Congenital Glaucoma			
	Trabeculectomy With Mitomycin-C—With or Without Trabeculotomy	Glaucoma Drainage Devices	Cyclodestructive Procedures	
			ECP	CPC
Pro	<ul style="list-style-type: none"><li>• Can perform even if cornea is very cloudy</li></ul>	<ul style="list-style-type: none"><li>• Can perform even if cornea is very cloudy</li></ul>	<ul style="list-style-type: none"><li>• Can perform even if cornea is very cloudy</li><li>• Spares conjunctiva</li></ul>	<ul style="list-style-type: none"><li>• Can perform even if cornea is very cloudy</li><li>• Spares conjunctiva</li></ul>
Con	<ul style="list-style-type: none"><li>• Conjunctival incision required</li><li>• Risks of blebitis, endophthalmitis, late bleb leak, exuberant scarring</li><li>• Avoid contact lens wear</li></ul>	<ul style="list-style-type: none"><li>• Conjunctival incision required</li><li>• Risks of strabismus, late endophthalmitis secondary to tube exposure</li></ul>	<ul style="list-style-type: none"><li>• Avoid in phakic patients</li><li>• May need re-treatment</li></ul>	<ul style="list-style-type: none"><li>• Greater risk of phthisis and chronic hypotony</li></ul>
CPC, Transscleral cyclophotocoagulation; ECP, endocyclophotocoagulation.				

CPC, Transscleral cyclophotocoagulation; ECP, endocyclophotocoagulation.

However, the prospect of a lifetime with a 1%–2% annual rate of infectious complications of filtration surgery must be considered when the surgical approach to these difficult cases is chosen.

Use of a glaucoma drainage implant is another alternative to consider in cases of congenital glaucoma for which conventional angle surgery has either failed or is unlikely to succeed.<sup>65</sup> This option is attractive particularly for patients in whom aphakia is managed by daily or extended-wear contact lenses, as the fistula into the eye is diverted posteriorly away from the edge of the contact lens and probably reduces the incidence of contact lens–facilitated endophthalmitis. Several series recently examined the results of the Baerveldt<sup>66–68</sup> and Ahmed<sup>69–71</sup> drainage implants in the pediatric population.<sup>72</sup>

In cases where conventional glaucoma surgery has failed to control IOP, cycloablative procedures such as cyclocryotherapy<sup>73</sup> or laser cyclophotocoagulation<sup>74,75</sup> may lower the IOP profoundly. In eyes in which the anterior segment is disrupted by previous surgery and the underlying disease, endoscopic cyclophotocoagulation may have significant advantage in that the ciliary body can be directly targeted.<sup>76</sup> Cyclodestructive procedures are painful and are always performed under general anesthesia in children. A long-acting retrobulbar block of bupivacaine 0.75% can be used to provide pain control for the first 12 hours after surgery.

Sympathetic ophthalmia has been described following cyclophotocoagulation,<sup>77</sup> and indeed one of the authors (JDB) follows a child in whom the previously normal fellow eye was nearly lost following cyclophotocoagulation of a blind hypertensive eye with Coats' disease.

## COURSE AND OUTCOME

Glaucoma in children may be recognized any time from birth to late childhood. The age of onset has prognostic implications, in that the child who presents with buphthalmos at birth is most likely to have more significant developmental angle anomalies and secondary damage to eye structures. It is these children—along with those who have more profound disorganization of the anterior segment (e.g., Peters' anomaly, sclerocornea, microcornea)—who require a surgical team approach that may involve penetrating keratoplasty, lensectomy, vitrectomy, and drainage implant. Despite aggressive treatment, most of these eyes achieve limited, if any, vision.

Fortunately, the child who has primary congenital glaucoma presenting a few months after birth (and before dense amblyopia or severe structural damage to the cornea or optic nerve has occurred) may expect a good outcome if the disease is detected and treated promptly. Although prognosis varies by subtype, long-term visual outcomes in retrospective studies of

pediatric glaucoma show that nearly 50% have visual acuities better than 20/70 or 20/100.<sup>78,79</sup> Furthermore, the results of various surgical series of goniotomy and trabeculotomy are reviewed in Chapter 10.27; in general, IOP is reduced in more than 90% of cases.

The surgeon who treats the child affected by glaucoma has many effective options for the management of a disease that uniformly resulted in blindness only 50 years ago. However, the goal of glaucoma treatment is more than the achievement of normal IOP—it is the achievement of normal visual function.<sup>78</sup> The child shown in Figs. 10.21.1 and 10.21.2 illustrates this clearly. Despite timely and successful surgical intervention in infancy and aggressive amblyopia treatment over the next 10 years, this patient has reduced vision (due to amblyopia) in one eye and enters adulthood with decreased binocularity. Nonetheless, at present this represents an excellent result. With earlier diagnosis and treatment through advancing knowledge of the molecular biology of this disorder, we are likely to see even better results in the coming decades.

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# When to Treat Glaucoma

Tak Yee Tania Tai, Jody R. Piltz-Seymour

# 10.22

**Definition:** It is appropriate to treat glaucoma when glaucoma damage is detected or progressing or if there is a high degree of confidence that such damage will occur.

## Key Features

- Multiple factors must be considered when deciding whether or not the patient is to be treated for glaucoma.
- The most important factor is confirming that the patient has glaucoma.
- Assessment for glaucoma must include measurements of optic nerve structure and function.
  - Structure:
    - Evaluation of the optic nerve appearance, optic nerve, nerve fiber layer and macular ganglion cell, and inner plexiform layer thickness.
  - Function:
    - Visual field evaluation:
      - For example, HVF 24-2.
      - Perhaps 10-2, 30-2.
- High intraocular pressure alone does not define glaucoma, but it does considerably increase the risk of developing glaucomatous optic neuropathy.
- The decision as to when to treat must depend on the level of confidence of the clinician that the patient has glaucoma and that the patient's glaucomatous damage is likely to progress without intervention.

## INTRODUCTION

The decision to initiate therapy to lower intraocular pressure (IOP) is a serious one that has far-reaching consequences. Once started, therapy generally is continued for the rest of the patient's life. Patients may be subjected to untoward side effects, significant costs, and altered quality of life from the use of glaucoma medications. In addition, the public health impact of treatment is enormous; therapy is expensive and requires regular medical attention.

Determining when to start treatment is a complex decision-making process, which must be individualized for each patient. Any decision to initiate therapy must weigh the patient's risk factors for the development or progression of glaucoma against the risk of side effects and inconveniences of treatment. Although treatment efficacy is measured in terms of lowering IOP, preserving the optic nerve, and stabilizing the field of vision, clinicians must remember that the true goals of glaucoma therapy are preservation of functional vision and optimization of quality of life.

## ANALYSIS OF RISK FACTORS

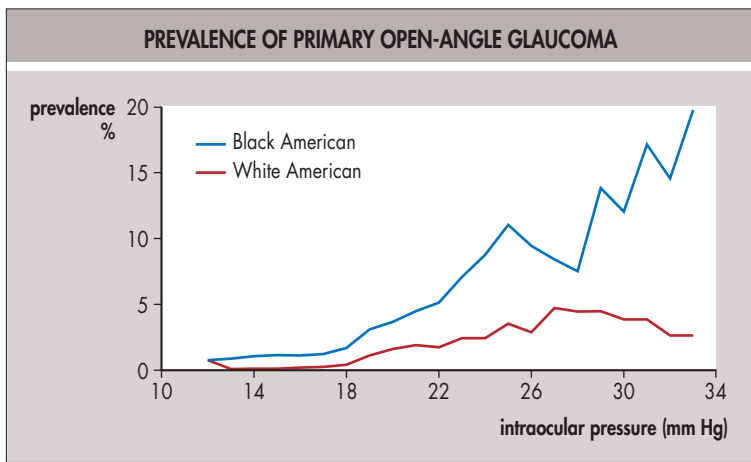
The most important indications of the future risk for glaucomatous damage are the extent of damage already present and the current rate of progression of the disease.<sup>1,2</sup> The extent of damage may be assessed by evaluation of the status of the optic nerve, nerve fiber layer (NFL), and visual field. Stereoscopic evaluation of the optic discs is carried out to search for signs of glaucomatous damage, which include thinning of the neuroretinal rim (particularly at the superior and inferior poles), notching of the rim, disc hemorrhages, asymmetry between the appearance of the optic nerves, and peripapillary atrophy. Documentation with stereo disc photographs help in long-term monitoring. Evaluation of the NFL and optic disc with

imaging technologies, such as optical coherence tomography (OCT), can detect widespread generalized loss or focal arcuate defects in the NFL and macular ganglion cell loss before functional loss is present on automated perimetry. Visual fields are best evaluated by using threshold techniques of the central 24–30°. However, early glaucomatous visual field damage can also occur within the central 10° and can be missed by 24-2 or 30-2 visual field algorithms; thus 10-2 visual fields should also be considered in suspicious eyes to diagnose and monitor glaucoma.<sup>3</sup> Eyes affected by glaucoma exhibit characteristic nerve fiber bundle pattern defects with or without generalized depression (see Chapter 10.5). Not surprisingly, patients at greatest risk of blindness have visual field loss at the time of diagnosis.<sup>2</sup>

Documentation of progressive change of the optic disc, NFL, or visual field is the hallmark of the diagnosis of glaucoma but generally is not possible on initial patient encounters. The rate of progression can be determined only by serial examinations over time. Typically, standard threshold perimetry is performed 1–4 times per year. Stereoscopic nerve head evaluation is also performed at regular intervals, ideally with baseline and possibly interval stereophotographic documentation. Other psychophysical tests may be more sensitive in detecting early functional damage and in confirming progression. Short wavelength automated perimetry (SWAP) may be useful in detecting visual field loss in cases where a glaucomatous retinal NFL defect is strongly suspected, but standard automated perimetry does not detect any visual field abnormalities. SWAP has been reported to detect glaucomatous visual field loss in some patients as early as 5 years before standard achromatic perimetry.<sup>4</sup> Visual field loss in SWAP may also appear simultaneously with, or after, visual field loss in standard automated perimetry. SWAP is more time consuming, has greater variability and fluctuation, and is more affected by lenticular changes compared with standard automated perimetry. Short-duration transient visual evoked potentials (SD-tVEP) have been found to distinguish healthy individuals from patients with glaucoma with high sensitivity and specificity. In discriminating between healthy eyes and eyes with mild glaucoma (mean deviation on visual field of >–6.0), one study found that the sensitivity and specificity of SD-tVEP were 86.7% and 93.3%, respectively.<sup>5</sup>

Serial OCT evaluations of optic nerve, NFL, and ganglion cell complex play an important role in the assessment of the rate of progression over time.<sup>6,7</sup> As the imaging technology continues to evolve, and because it is difficult to compare data from older machines with those from newer machines, there is limited published data for measuring progression with OCT; however, spectral-domain OCT (SD-OCT) has been found to be more sensitive than time-domain OCT (TD-OCT) in detecting retinal NFL abnormalities and changes. SD-OCT glaucoma progression algorithms measure changes using event-based or trend-based analyses. Event-based analysis establishes a threshold for change from baseline and detects progression when a follow-up measurement crosses this threshold. Trend-based analysis establishes a slope of a measured parameter over time and is less susceptible to measurement variability compared with event-based analysis; however, this approach requires a large number of tests before the analysis can be considered reliable.<sup>8</sup> Detection of change is critical because it is believed that the risk of further injury accelerates as the disc injury progresses.

The Ocular Hypertension Treatment Study (OHTS) and the European Glaucoma Prevention Study (EGPS) were two randomized clinical trials designed to determine if lowering IOP reduced or delayed the onset of glaucoma damage.<sup>9</sup> Despite employing different protocols, both studies identified the same risk factors for the development of glaucoma: age, IOP, central corneal thickness (CCT), vertical cup-to-disc ratio (CDR), and the mean deviation of automated perimetry. Other risk factors that have been associated with the development of glaucoma include race, family history of glaucoma, myopia, ocular perfusion pressure, systemic hypertension, systemic hypotension, nocturnal hypotension, vasospasm (associated with



**Fig. 10.22.1** Prevalence of primary open-angle glaucoma in relation to screening intraocular pressure. The curves are smoothed using a running mean with window width of 7 mm Hg. For white American subjects,  $n = 5604$  eyes, and for black American subjects,  $n = 4464$  eyes. (Data from Tielsch JM, Sommer A, Katz J, et al. Racial variations in the prevalence of primary open-angle glaucoma. The Baltimore Eye Survey. *JAMA* 1991;266:369–74.)

cold extremities, migraine headaches, Raynaud's disease), and sleep apnea. Any decision to treat must also take into account psychosocial issues, such as the patient's overall health and predicted life expectancy, current systemic medications, risk of medication side effects, degree of patient understanding of the disease and treatments, level of compliance, and financial impact of treatment.

## RISK FACTORS

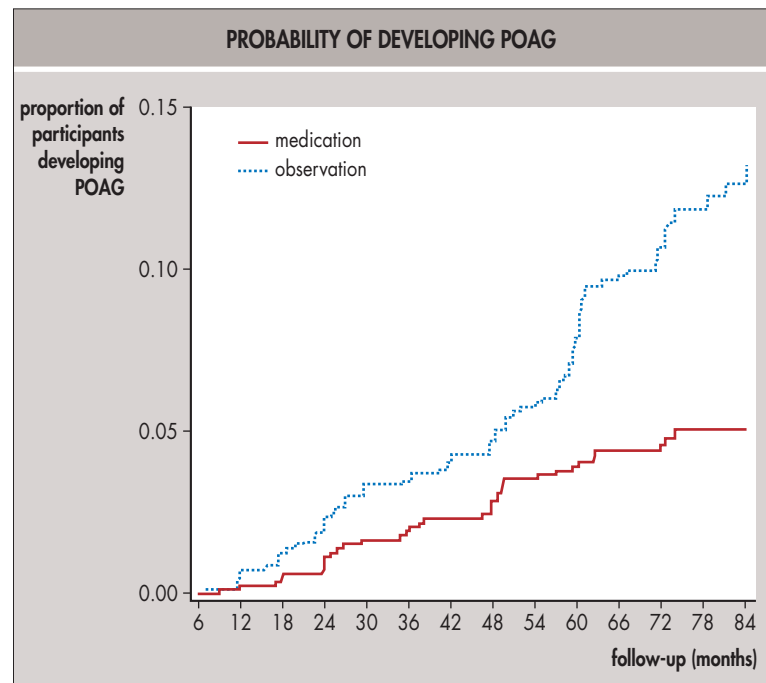
### Intraocular Pressure

IOP is the leading causal risk factor for glaucoma and, at present, the only risk factor for which modulation has been proven to be clinically efficacious. Both the incidence and prevalence of glaucoma increase with increasing IOP (Fig. 10.22.1). Compared with an IOP of 15 mm Hg (2.0 kPa) or lower, the relative risk of glaucomatous optic nerve damage increases 13-fold for an IOP of 22–29 mm Hg (2.9–3.9 kPa), and 40-fold for an IOP >30 mm Hg (>4.0 kPa).<sup>10</sup> However, because the population with lower IOP is vastly greater than that with higher IOP, the majority of patients with glaucoma will not have highly elevated IOP. Asymmetrical or unilateral glaucoma, including secondary glaucoma or angle-closure glaucoma, typically results in worse damage in the eye affected by the higher IOP. Numerous animal models of glaucoma have shown that chronically raised IOP induces glaucomatous optic neuropathy in both primate and nonprimate species.

Multicenter clinical trials have definitively proven that lowering IOP is beneficial in preventing ongoing glaucoma progression in eyes with manifest glaucoma damage. In the Advanced Glaucoma Intervention Study, when IOP was below 18 mm Hg on all visits over 6 years (average IOP of 12 mm Hg), almost no visual field progression ensued; for eyes with IOP <18 mm Hg on fewer than 50% of visits, visual field defect scores worsened by 0.63 units ( $P = 0.083$ ).<sup>11</sup> The Collaborative Normal-Tension Glaucoma Study demonstrated less visual field progression in patients with normal-tension glaucoma in whom treatment successfully reduced the IOP by 30% or more to an average of 11 mm Hg.<sup>12</sup>

The Early Manifest Glaucoma Trial randomized patients with early to moderate glaucomatous damage to treatment with laser trabeculoplasty and betaxolol or observation. Treatment reduced IOP, on average, by 25%, and average duration of follow-up was 6 years. Progression occurred later and less frequently in the treated group than in controls ( $P = 0.007$ ). In a multivariate analysis, progression risk was halved by treatment (hazard ratio [HR] = 0.50; 95% CI 0.35–0.71). The risk of progression decreased by about 10% with each millimeter of mercury that IOP was reduced from baseline to the first follow-up visit (HR = 0.90 per millimeter of mercury decrease; 95% confidence interval [CI] 0.86–0.94).<sup>13</sup>

Great variability occurs among individuals in the susceptibility of the optic nerve to damage from IOP. There is no IOP below which glaucoma never occurs or above which glaucoma always occurs. Of patients who suffer glaucoma, 50% have screening IOPs of <21 mm Hg (<2.8 kPa) and approximately one in six do not have IOP >21 mm Hg (>2.8 kPa) on repeated testing.<sup>8</sup> Although the relative risk of glaucoma is low when IOP is <20 mm Hg (<2.7 kPa), damage may still occur. Even when IOP remains



**Fig. 10.22.2** Kaplan-Meier plot of the cumulative probability of developing primary open-angle glaucoma (POAG) by randomization group. (Reproduced with permission from Kass MA, Heuer DK, Higginbotham EJ, et al. The Ocular Hypertension Treatment Study: a randomized trial determines that topical ocular hypotensive medication delays or prevents the onset of primary open-angle glaucoma. *Arch Ophthalmol* 2002;120:701–13.)

within the normal range, the risk of visual field loss is greater in the eye with the higher IOP.<sup>14</sup> Recent studies have suggested that variability of IOP, both diurnal and day-to-day fluctuations, rather than the absolute level of IOP may be paramount in causing progression of glaucoma.<sup>15</sup>

Ocular hypertension (OHT) is a common disorder that affects 3–6 million people in the United States. In a population over age 70 years, 10% of people suffer from OHT, whereas only 2% have primary open-angle glaucoma. The OHTS—a long-term, multicenter clinical trial sponsored by the National Eye Institute—was designed to determine whether medical reduction of IOP prevents or delays the onset of glaucomatous damage in subjects with OHT.<sup>16,17</sup> It also sought to determine the risk factors involved in the glaucomatous process. More than 1600 subjects were enrolled and followed up for more than 5 years.

Patients were randomized to medical treatment (using any of the topical medications approved by the U.S. Food and Drug Administration) or observation. Goal IOP for subjects in the treatment group was a 20% reduction of IOP and an IOP <24 mm Hg (<3.2 kPa). Patients were monitored by using Humphrey visual fields (program 30-2) and stereoscopic optic disc photographs. The 5-year risk of developing glaucomatous optic disc and/or visual field loss was significantly reduced in the treated group; 9.5% of patients in the observation group developed glaucoma compared with 4.4% of those in the medically treated group (Fig. 10.22.2).<sup>18,19</sup> A later study involving the OHTS cohort initiated glaucoma medications in participants who were initially in the observation group, after a median of 7.5 years of observation without treatment. At the end of 13 years, 16% of the initial treatment group developed primary open-angle glaucoma (POAG), whereas 22% of the later treated group developed POAG. The benefit of treatment was most significant among patients with the highest 5-year risk of developing POAG (>13%), as calculated using the OHTS risk calculator.<sup>19</sup> Thus, in patients at low risk for OHT who agree to regular follow-up, it may be reasonable to delay treatment until early glaucomatous damage is detected.<sup>19</sup>

### Optic Disc Characteristics

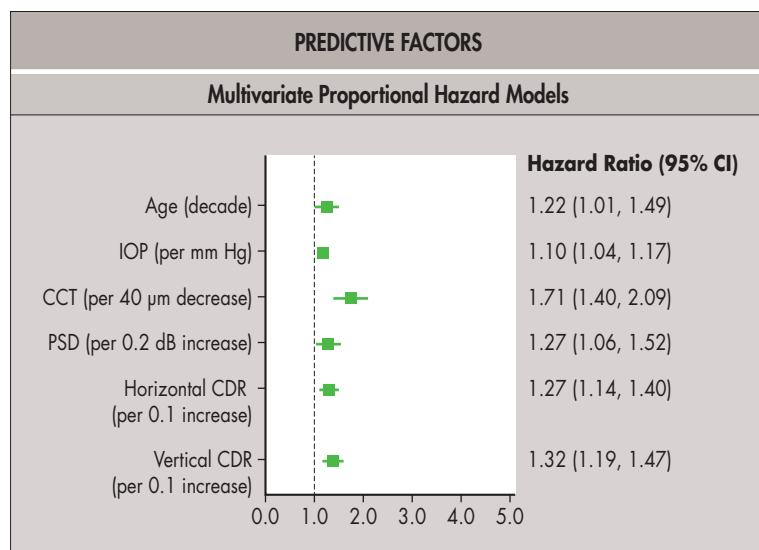
A larger CDR has been shown to be an independent risk factor for the development of glaucoma,<sup>18</sup> although it may also be an indicator of early glaucomatous damage (Fig. 10.22.3). Nonetheless, when a clinician examines a patient for the first time, there is no way to know whether this appearance represents a change from baseline or a stable finding. Although a large CDR may be a normal finding in larger optic nerves, both the OHTS and the EGPS found a strong association between a large CDR and the development of open-angle glaucoma.<sup>9</sup> The Confocal Scanning



Laser Ophthalmoscopy Ancillary Study after the OHTS found that several baseline topographic optic disc measurements, alone or when combined with baseline clinical and demographic factors, were significantly associated with the development of POAG among OHTS participants.<sup>7</sup> SD-OCT has also been shown to be useful in diagnosing preperimetric glaucoma and for detecting glaucomatous progression; OCT has supplanted scanning laser ophthalmoscopy as the preferred imaging modality for glaucoma detection and follow-up.<sup>8</sup> Another important optic disc finding is the presence of a disc hemorrhage, which was observed to result in a 3.7-fold increased risk in the multivariate analysis in the OHTS.<sup>20</sup> Only 16% of these disc hemorrhages were detected by both clinical examination and review of photographs, whereas 84% were detected only by review of photographs, underscoring the importance of disc photos.

### Central Corneal Thickness and Corneal Hysteresis

One of the most surprising findings of the OHTS was the impact of CCT on the development of glaucoma in the OHTS. Overall, participants in the OHTS had thicker corneas than the average population with an average corneal thickness of  $573.0 \pm 39.0$   $\mu\text{m}$ , and a quarter of the OHTS subjects had CCT  $>600$   $\mu\text{m}$ . Black subjects had thinner corneas than white subjects had ( $555.7 \pm 40.0$   $\mu\text{m}$  versus  $579.0 \pm 37.0$   $\mu\text{m}$ ;  $P < 0.0001$ ). The OHTS determined that a thinner CCT measurement was a strong, independent predictive factor for the development of POAG (see Fig. 10.22.3). Participants with a CCT  $<555$   $\mu\text{m}$  had three times the risk of developing POAG compared with patients with CCT  $>588$   $\mu\text{m}$ .<sup>21,22</sup> The risk of developing POAG doubled for every 40  $\mu\text{m}$  decrease in CCT from the overall mean of 573.3  $\mu\text{m}$  in the OHTS and EGPS pooled sample.<sup>9</sup> Other studies have confirmed that a thinner CCT is a risk factor for glaucoma outcomes, such as the presence of advanced glaucoma damage, SWAP visual field defects, and further visual field progression.<sup>21–23</sup>



**Fig. 10.22.3** Baseline risk factors predictive for the development of glaucoma in the Ocular Hypertension Treatment Study (multivariate proportional hazard models). Significant baseline predictive risk factors included central corneal thickness (CCT); cup-to-disc ratio (CDR); intraocular pressure (IOP), Humphrey visual field pattern standard deviation (PSD). (Data from Gordon MO, Beiser JA, Brandt JD, et al. The Ocular Hypertension Treatment Study: baseline factors that predict the onset of primary open-angle glaucoma. Arch Ophthalmol 2002;120:714–20.)

The explanation for the relationship between thinner corneas and glaucoma progression is unclear. It is not yet known whether an increased risk results from underestimation of IOP in patients with thin corneas or whether a thinner CCT is a surrogate for greater susceptibility of the optic nerve to damage.

Corneal hysteresis, the viscous dampening of the cornea which reflects its ability to absorb and dissipate energy, has been a subject of recent study interest. Corneal hysteresis may be lower in patients with glaucoma compared with patients with suspicious-appearing optic discs but normal visual fields or patients with ocular hypertension.<sup>24</sup>

### Age

The risk of having or developing primary open-angle glaucoma increases with increasing age. The prevalence of glaucoma increases from 0.2% in individuals 50–54 years of age to 2% of the population 70–74 years of age (Table 10.22.1).<sup>23</sup> The incidence rates for the development of glaucoma over a 9-year period were also found to increase with age; the Barbados Eye Studies demonstrated a rate of 2.2% in patients 40–49 years of age and 7.9% in those aged 70 years or older.<sup>25,26</sup> Similarly, the prevalence of glaucoma in Latinos  $\geq 80$  years of age was 16 times higher than that in Latinos 40–49 years old.<sup>27</sup> Older age was a statistically significant predictive factor for the development of POAG over a 5-year period in the OHTS<sup>18</sup> (see Fig. 10.22.3). This increased prevalence of glaucoma with increasing age may relate to the longer exposure to elevated IOP, the greater susceptibility of the optic nerves in older adults to sustain damage from elevated IOP, or other physiological factors that are affected by advancing age, such as autoregulation and ophthalmic circulation.

### Race and Ethnicity

The incidence and prevalence of glaucoma varies by race. The Baltimore Eye Survey showed that the prevalence of POAG is 4.3 times greater in black Americans than in other races and that black Americans are 4–8 times more likely to go blind as a result of glaucoma compared with white Americans. In this series, the prevalence of glaucoma was 1.2% among black Americans 40–49 years of age, and 11.3% in those 80+ years of age (see Table 10.22.1).<sup>28</sup> In the OHTS, blacks had a higher incidence of glaucoma compared with other study participants, with an average annual risk of progression to POAG in excess of 2%<sup>16</sup> (see Fig. 10.22.3). However, the OHTS model also suggests that race is not an independent risk factor after adjustment for CCT and CDR.<sup>18,28</sup>

The Barbados Eye Study found a similar prevalence of POAG in the African Caribbean inhabitants of Barbados as was found in black Americans in Baltimore—4.4% of African Caribbean adults versus 0.8% of white Caribbean adults.<sup>25,26</sup> Recent studies have demonstrated a similarly increased risk in Hispanic Americans of primarily Mexican ancestry. The Los Angeles Latino Eye Study estimated the prevalence of POAG to be 4.7% in this population.<sup>27</sup> The Rotterdam study based on the Caucasian population of The Netherlands showed a prevalence of POAG of approximately 1%, similar to the prevalence found in the Baltimore Eye Survey among white Americans.<sup>29</sup>

### Family History

Family history is a well-described risk factor for glaucoma. The Baltimore Eye Survey noted a 3.7-fold increased risk of POAG in individuals who had a sibling affected by POAG and a 2.2-fold increased risk if a parent was

**TABLE 10.22.1** Prevalence of Definite Primary Open-Angle Glaucoma by Age and Race

Family Group	History	Cases		Controls		Odds Ratio (95% CI) <sup>a</sup>	Age–Race Adjusted Odds Ratio (95% CI) <sup>a</sup>
		No.	%	No.	%		
Parents	Positive	9	5.6	206	4.0	1.42 (0.67–2.91)	2.17 (1.07–4.41)
	Negative	152	94.4	4941	96.0		
Siblings	Positive	16	9.9	144	2.8	3.83 (2.14–6.76)	3.69 (2.10–6.48)
	Negative	145	90.1	5003	97.2		
Children	Positive	2	1.2	40	0.8	1.61 (0.40–6.15)	1.12 (0.26–4.86)
	Negative	159	98.8	5107	99.2		
Any first-degree relatives	Positive	26	16.1	371	7.2	2.48 (1.57–3.89)	2.85 (1.82–4.46)
	Negative	135	83.9	4776	92.8		

<sup>a</sup>Age–race adjustment conducted using logistics regression analysis. CI, Confidence interval.

TABLE 10.22.2 Baltimore Eye Survey: Association of Primary Open-Angle Glaucoma With a Family History of Glaucoma

Age (Yr)	Screening Examination (No.)		Cases (No.)		Adjusted Rate/100 (95% CI) <sup>a</sup>	
	White Americans	Black Americans	White Americans	Black Americans	White Americans	Black Americans
40–49	543	632	1	6	0.92 (0–2.72)	1.23 (0.23–2.24)
50–59	618	699	2	25	0.41 (0–0.98)	4.05 (2.47–5.63)
60–69	915	614	7	31	0.88 (0.14–1.62)	5.51 (3.57–7.46)
70–79	631	349	18	27	2.89 (1.44–4.34)	9.15 (5.83–12.48)
≥80	206	101	4	11	2.16 (0.05–4.26)	11.26 (4.52–18.00)
Total	2913	2395	32	100	1.29 (0.80–1.78)	4.74 (3.81–5.67)

<sup>a</sup>Adjusted rate is modified for nonresponse to definitive ophthalmological examination. Difference (Black American – White American) = 5.10 – 1.19 = 3.91% (95% confidence interval, range 3.45%–4.37%). Adapted with permission from Tielsch JM, Sommer A, Katz J, et al. Racial variations in the prevalence of primary open-angle glaucoma. The Baltimore Eye Survey. JAMA 1991;266:369–74.

affected (Table 10.22.2).<sup>30</sup> Distinguishing patients with a history of blinding glaucoma from those with a family history of ocular hypertension or mild glaucoma may help in risk assessment. Patients should be questioned as to whether the family member required surgery or had any significant visual loss from glaucoma.

PRINCIPLES OF INITIATION OF THERAPY

Prior to the initiation of therapy in any patient, it is important to establish a baseline for future comparisons. The IOP of most people who do not have glaucoma varies by <4 mm Hg (<0.5 kPa) over a 24-hour period. Patients with glaucoma have large diurnal variations of IOP, which may change by >10 mm Hg (>1.3 kPa). Many patients have a regular diurnal pattern, most typically with a high IOP upon awakening, but other patterns also occur.

If the IOP is not dangerously high on the initial visit, it may be useful to obtain another IOP measurement on a separate visit or obtain the patient’s diurnal IOP variation prior to starting therapy. It is also important to obtain baseline documentation of optic disc appearance and visual field performance. Discs can be drawn, but stereophotographs provide a more accurate record. NFL assessment with OCT has become an indispensable part of glaucoma assessment and should be performed early in the course of treatment to establish a baseline for future comparisons. Perimetry should be performed to establish a baseline; because there is a steep learning curve, automated fields are performed at least twice to obtain an accurate baseline if the patient is inexperienced at perimetry.

INITIATION OF THERAPY IN THE GLAUCOMA PATIENT

Most patients who have moderate-to-severe glaucoma are started on therapy to lower IOP. These patients have developed optic disc damage at their baseline, have untreated IOP, and are very likely to have continued progressive damage over time if the condition is left untreated. In most of these patients, the benefit of treatment far outweighs the risk of complications.

POAG is a bilateral disease, although it is often strikingly asymmetrical. If damage is present in one eye only, it is important to first rule out secondary causes of unilateral open-angle glaucoma, which most commonly include pseudo-exfoliation, traumatic angle recession, and corticosteroid-induced glaucoma. If secondary causes of glaucoma are excluded, the damage in one eye is predictive of damage in the other eye, and treatment often is considered in both eyes.

It is also important to look for signs of pigmentary glaucoma in evaluation of a glaucoma suspect. In some cases, IOP may be easier to control or normalize over time in cases of pigmentary glaucoma. In addition, older patients who may appear to be normal-tension glaucoma suspects, may, in fact, be in the regression phase of pigmentary glaucoma. The presence of a “pigment reversal sign,” with denser pigmentation of the superior trabecular meshwork compared with the inferior trabecular meshwork, may be helpful in making this diagnosis.<sup>31</sup>

INITIATION OF THERAPY IN THE GLAUCOMA SUSPECT

The decision to initiate therapy is much more controversial in the patient who is suspected of having glaucoma. It is particularly important for glaucoma suspects to be involved in the decision process. A person may be classified as a glaucoma suspect for many reasons. The most common glaucoma suspect has elevated IOP—those with ocular hypertension. Glaucoma suspects may also have other risk factors, such as thin CCT, strong family history, or suspicious optic discs or visual fields.

It is difficult to determine if a suspicious-appearing optic nerve is truly glaucomatous. Great overlap exists between normal and diseased optic nerves. The average optic disc has a CDR of 0.3–0.4, but a wide variation of normal occurs. The significance of the size of the cup depends on the size of the disc.<sup>32</sup> It is difficult to determine whether the large disc with a high CDR is pathological or physiological. Progressive disc changes may develop while visual field tests remain normal, and substantial axonal loss may develop before defects occur on perimetry.<sup>33</sup> Therefore, a normal visual field test does not rule out glaucoma. Evaluation of the NFL may be particularly important in these cases. OCT can help distinguish pathological optic nerves from normal or identify diminished NFL. Computerized images need to be interpreted carefully because results can be misinterpreted if scan quality or operator input is suboptimal; in cases of large, small, or tilted optic nerves; and in patients with high refractive errors. The normative databases for some of the OCT instruments are limited with regard to racial diversity, and all exclude high refractive errors. Software and hardware upgrades in imaging techniques continue to improve the discriminatory accuracy.

Initiating treatment should be considered in patients with more suspicious nerves, if NFL loss is detected, or if other significant risk factors for glaucoma exist. As discussed, in patients who have early glaucoma, treatment may be deferred, especially in those with limited life expectancy. However, treatment may be initiated at an earlier stage in subjects in whom it is difficult to detect change in the optic nerve status over time. This includes patients who have anomalous discs, disc drusen, high myopia, and tilted discs, as well as patients in whom an adequate fundus examination cannot be performed. Similarly, treatment may be begun at a lower threshold in patients who are unable to perform visual field testing or in patients who suffer nonglaucomatous causes of visual field loss.

The initiation of therapy is most controversial in patients who have elevated IOP and normal optic nerves and visual fields. As noted above, although the OHTS showed a significant reduction in the development of glaucoma with treatment, approximately 90% of patients in the observation group did not develop glaucoma during the first 5 years of the study.<sup>16</sup> Although deferring treatment increases the risk of developing glaucoma in those with ocular hypertension, subsequent initiation of treatment immediately lowers future risk. Delaying treatment in low-risk individuals only minimally increased the risk of developing POAG, whereas delaying treatment in high-risk individuals resulted in a greater increased risk.<sup>19</sup>

Risk calculators have been developed to help estimate the 5-year risk of developing glaucoma. Using data from the OHTS and the EGPS the calculators incorporate age, IOP, CCT, pattern standard deviation (Humphrey automated perimetry), and vertical CDR ratio in determining the risk of developing glaucoma in patients with ocular hypertension.<sup>9</sup> The model is available online at <http://ohts.wustl.edu/risk> or as an app on mobile devices. In an analysis of 13-year follow-up in the OHTS, treatment was more beneficial in patients whose baseline 5-year risk of developing POAG was higher.<sup>19</sup> For the patients in the highest third of baseline risk, the cumulative proportion of patients developing glaucoma was 0.40 in the original observation group and 0.28 in the original medication group; among patients in the lowest third of baseline risk, the proportion of patients developing glaucoma was very low and almost identical, at 0.08 in the original observation group and 0.07 in the original medication group.

Cost-utility analysis of the OHTS data have been developed that support the early treatment of those individuals with IOP ≥24 mm Hg and a 2% or greater annual risk of developing glaucoma.<sup>34,35</sup>

CONCLUSIONS

The decision of when to treat a patient to prevent glaucomatous damage cannot be simplified into a straightforward algorithm, although risk calculators can aid clinicians in treatment decisions. Only the physician, in concert with the individual patient, can weigh the risk of early measurable glaucoma loss, quality of life impact, and other social aspects of treatment in determining the optimal time to initiate therapy. Fortunately, a great

deal of active investigation has facilitated our decision-making process over the last decade, permitting treatment decisions based on sound data from large-scale, prospective, randomized clinical trials.

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## Which Therapy to Use in Glaucoma

## 10.23

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**Definition:** Long-term therapeutic intervention to preserve visual function while minimizing the unintended effects of glaucoma treatment.

### Key Feature

- The choice of therapy (alone or in combination) for patients with open-angle glaucoma includes medical treatment, laser treatment, and incisional glaucoma surgery.

## INTRODUCTION

The goal of glaucoma therapy is to maintain quality of life by preserving visual function while avoiding complications.<sup>1</sup> This can be achieved by maintaining intraocular pressure (IOP) in the target range, achieving stable optic nerve/retinal nerve fiber layer (RNFL), and stable visual field results. The optimal therapeutic intervention is determined on the basis of tolerable side effects, the patient's quality of life, and the patient's life expectancy. Although evidence-based medicine provides population-derived probabilities for treatment success and adverse events in general, each patient must be assessed individually before a treatment decision is made.

Although IOP appears to be the main risk factor for damage in glaucoma (hence the need for a specific target pressure in an individual eye),<sup>2</sup> other factors may be involved.<sup>3</sup>

IOP remains the most rigorously proven treatable risk/disease factor. All current modalities of treatment are designed to lower IOP to the point where deterioration of the disc or field ceases, thus preserving the patient's health-related quality of life, with a minimum of complications or side effects. Secondary benefits may also be gained, but the primary intent is to lower IOP. In the future, IOP-independent treatments may be added to the clinician's armamentarium. Once therapy is indicated, the initial target IOP reduction should be at least 25% of pretreatment level. The suggestion that an IOP of 21 mm Hg, 17 mm Hg, and 14 mm Hg or less prevents further glaucomatous damage was based on population statistics; however, some patients continue to develop progressive glaucomatous disease at IOP below this level, requiring adjustment of target IOP throughout the course of care. Establishing in advance the degree to which IOP must be lowered to preserve vision is only an estimate and should be individualized such that lowering IOP is intended to arrest the progression of visual loss.<sup>4,5</sup>

The choice of therapy for patients who have open-angle glaucoma consists of medication, laser trabeculoplasty (LTP), and incisional glaucoma surgery (or a combination of these), traditionally in that order. As more information emerges on the comparative outcomes of various therapies and surgical devices and techniques become safer and less invasive, the traditional paradigm is being refined. The selection of the most appropriate therapy must take into account factors that pertain to the individual patient and to each individual eye, such as age, severity of glaucoma, and other risk factors.

## HISTORICAL REVIEW

Topical medications to treat glaucoma were first used in the 1870s, with the introduction of physostigmine and pilocarpine. Subsequently, other drug categories have been added to the treatment armamentarium, including nonselective sympathomimetics in the 1920s (e.g., epinephrine, dipivefrin [later, the alpha-agonist apraclonidine in the early 1990s]), oral carbonic anhydrase inhibitors (e.g., acetazolamide) in the 1950s, and

beta-blockers (e.g., timolol and levobunolol) in the 1970s. Up until the late 1990s, beta-blockers were the medical therapy of choice in the majority of newly diagnosed cases of open-angle glaucoma. In the mid- to late 1990s, selective alpha-2-agonists (brimonidine), topical carbonic anhydrase inhibitors (CAIs: dorzolamide and brinzolamide), and prostaglandin analogues (PGAs: latanoprost, travoprost, bimatoprost, unoprostone) were introduced. Combination products are also available (beta-blocker-PGA, beta-blocker-CAI, beta-blocker-alpha<sub>2</sub>-agonist) but availability significantly varies from country to country. Since the late 1990s, PGAs have been considered the first-line agent for the majority of open-angle glaucomas.

Argon laser trabeculoplasty (ALT) was first described by Wise and Witter<sup>6</sup> in 1979. Initial short-term success was followed by less than satisfactory long-term control in many cases, with the result that this technique is not used as much as it was initially.<sup>7</sup> Selective laser trabeculoplasty (SLT) was first described by Latina in 1995.<sup>8</sup> A long-term study that compared 180° of ALT with 180° of SLT found both techniques to be equally successful.<sup>9</sup>

The first use of full-thickness filtering surgery, in the form of trabeculectomy, to shunt fluid from the anterior chamber into the subconjunctival space is credited to Cairns<sup>10</sup> in 1968. This procedure has been modified over the years to give better results and fewer complications. Recent modifications include the use of antimetabolites (e.g., 5-fluorouracil or mitomycin C) and the ExPress device (Alcon; Ft. Worth, TX).<sup>11,12</sup> There is a growing number of microinvasive glaucoma surgery or minimally invasive glaucoma surgery (MIGS) for the treatment of mild to moderate glaucoma. These ab interno procedures are adjunctive and do not preclude the future use of trabeculectomy or glaucoma drainage devices. The current mechanisms of IOP reduction includes increasing trabecular outflow (Trabectome, iStent, Hydrus, gonioscopy-assisted transluminal trabeculectomy, suprachoroidal shunts [CyPass micro stent]; reduction of aqueous production [endocyclophotocoagulation] and subconjunctival filtration [XEN gel stent]). Other incisional surgeries include canaloplasty (iScience, Menlo Park, CA), deep sclerectomy, and viscocanalostomy, which are nonpenetrating but technically challenging procedures that can achieve a moderate drop in IOP.

## TREATMENT MODALITIES

### Medical Treatment

Medical treatment is the most common initial intervention to lower IOP. Medications lower IOP by either decreasing aqueous secretion or increasing drainage. A range of topical and systemic antiglaucoma medications is available. Topical medication classes include miotics, beta-blockers, epinephrine derivatives, carbonic anhydrase inhibitors, alpha-agonists, and prostaglandin analogues. Prostaglandin analogues are the most frequently used initial medication to lower IOP. Medication choices are made based on several factors, such as cost, dosing schedules, extent of IOP-lowering effect desired, and side effects. Both ocular and systemic side effects may occur with medications (see Chapter 10.24).

The most common side effects of antiglaucoma drugs are neither life- nor sight-threatening. However, rare serious complications can include pulmonary compromise from beta-blockers, acidosis syndrome and aplastic anemia from carbonic anhydrase inhibitors, and retinal detachment associated with miotic therapy. Most patients are able to tolerate one or more of these medications without experiencing any side effects.

Patient-related factors, such as compliance, coincident systemic diseases, drug interactions, and side effects, can affect the success or failure of medical treatment. Inadequate compliance may be the most serious limiting factor in the nonsurgical therapy of glaucoma. Factors that influence compliance include complexity of the medical regimen, side effects



**Fig. 10.23.1 Inflammatory Changes in the Conjunctival Tissue.** A comparison of conjunctival biopsies from patients who underwent primary surgery with those from patients who received at least two topical medications for a minimum of 1 year before surgery showed a significantly greater increase in the number of macrophages, lymphocytes, mast cells, and fibroblasts in the conjunctiva and Tenon's capsule and a significantly greater decrease in the number of goblet cells in the medically treated group. Representative photomicrograph from the group of patients who received long-term eyedrop therapy. The substantia propria shows a round cell infiltrate of mainly lymphocytes. (From Sherwood M, Grierson I, Millar L, et al. Long-term morphological effects of antiglaucoma drugs on the conjunctiva and Tenon's capsule in glaucomatous patients. *Ophthalmology* 1989;96:327–35.)

of the medications, and patient understanding of the disease and its treatment.<sup>13,14</sup>

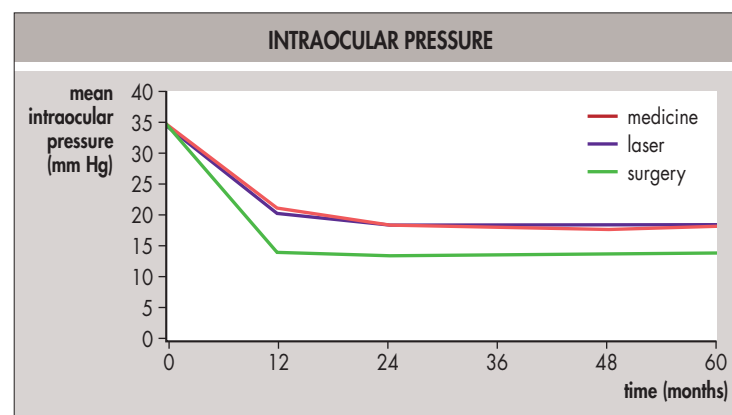
Polypharmacy is undesirable, and it is occasionally preferable to switch within class if the patient is near their target IOP rather than to add more drops. Although controversial, prior administration of topical antiglaucoma medications may influence the subsequent outcome of glaucoma filtering surgery, as a result of the active drug, the preservative, or both (Fig. 10.23.1).<sup>15</sup> Antiglaucoma medication use is associated with increased cataract formation.<sup>16–18</sup>

## Laser Trabeculoplasty

LTP induces biochemical changes in the trabecular meshwork to enhance aqueous outflow (see Chapter 10.25). LTP, especially SLT, is considered a first-line intervention to lower IOP in certain patients. The Glaucoma Laser Treatment (GLT) trial compared topical timolol with ALT as initial therapy and found that ALT has an advantage in terms of IOP (1.2 mm Hg lower) and preservation of visual field (0.6 dB higher) after 7 years.<sup>7</sup> The GLT trial had a confounding methodological issue in that eyes were randomized, rather than patients, so that the topical timolol administered in one eye could have had a contralateral effect.<sup>7</sup> Randomized controlled trials (RCTs) comparing SLT (360°) with a topical PGA as initial treatment showed no difference in IOP control at 1 year of follow-up.<sup>19,20</sup> LTP may also increase the risk of subsequent trabeculectomy failure,<sup>21–23</sup> but this is controversial.<sup>24,25</sup>

## Surgery

Surgical options in the management of glaucoma includes trabeculectomy, implantation of aqueous tube shunts, nonpenetrating glaucoma procedures, minimally invasive glaucoma surgery, and endocyclophotocoagulation, all of which can be done in conjunction with cataract extraction, when indicated. The most frequently performed filtering operation is the trabeculectomy (see Chapter 10.29), and it remains one of the most effective. However, complications, such as choroidal detachment or endophthalmitis, even years later, can occur. In nonpenetrating filtration



**Fig. 10.23.2 Mean Intraocular Pressures.** Medicine versus laser versus surgery. (Moorfields Primary Treatment Trial; Migdal C, Gregory W, Hitchings R. Long term functional outcome after early surgery compared with laser and medicine in open angle glaucoma. *Ophthalmology* 1994;101:1651–7.)

surgery (deep sclerectomy and canaloplasty), the advantages of not entering the anterior chamber must be balanced against a steep learning curve, the frequent need for adjunctive medications or laser goniopuncture, and the tendency to produce IOPs that are higher than those after trabeculectomy.<sup>26,27</sup> Additionally, procedures and devices designed to shunt fluid from the anterior chamber directly into Schlemm's canal (also called *canal procedures*)—ab interno trabeculectomy (e.g., Trabectome; Neomedix, Tustin, CA) and iStent (Glaukos, Laguna Hills, CA)—are available, but produce modest benefits.<sup>28,29</sup> After initial surgical intervention, nonvalved tube shunts had an advantage in maintaining IOP control compared with trabeculectomy for patients with uncontrolled IOP after previous incisional surgery after 3 years of follow-up.<sup>30</sup>

## Cyclodestructive Procedures

Destroying the ciliary body can lower IOP by decreasing aqueous production. Cyclocryopexy is no longer routinely performed because of the higher risk of complications compared with laser cyclodestructive procedures. External cyclophotocoagulation (CPC) using a diode laser is generally reserved for after all incisional procedures have failed. Endoscopically guided cyclophotocoagulation (ECP) offers the potential benefit of increased selectivity of ablation, allowing it to be performed earlier in the treatment algorithm and in conjunction with cataract extraction. However, the effectiveness of ECP is more limited.

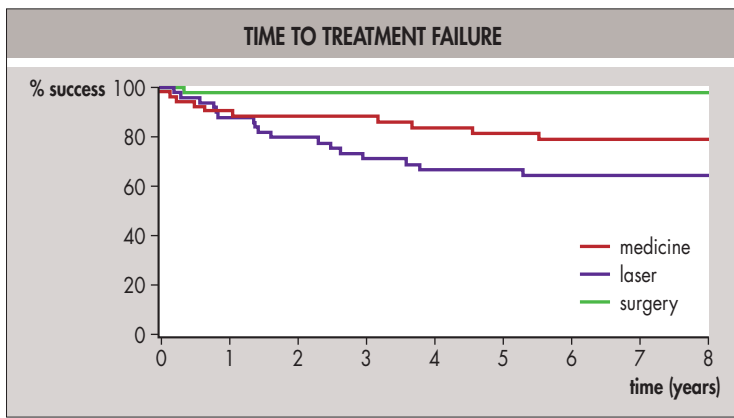
## TREATMENT ALGORITHMS

Traditionally, the initial standard therapy for primary open-angle glaucoma (POAG) is medical, with LTP and surgery reserved for patients who fail medical therapy. Generally, the progression is to LTP, followed by trabeculectomy, then tube shunt surgery, followed by CPC. (Note: Some practitioners will use multiple attempts at trabeculectomy or tube shunts.) New technologies, patient-specific factors, and disease-specific factors may alter this traditional stepping regimen. Furthermore, a number of clinical studies have challenged this traditional approach to therapy, and therefore reappraisal is necessary. The outcomes of these trials will continue to modify the criteria by which therapy is chosen.

To date, available evidence from prospective RCTs indicates that LTP is an excellent option compared with a topical PGA.<sup>19,20</sup> The Advanced Glaucoma Intervention Study compared ALT versus trabeculectomy in patients who had failed initial medical treatment, and it was found that persons of African descent had less visual field decline with ALT followed by trabeculectomy, whereas persons of European descent did better with trabeculectomy followed by ALT.<sup>31</sup> Although several prospective, multicenter studies outside the United States have found trabeculectomy more advantageous compared with medical therapy<sup>15,21,32–34</sup> (Figs. 10.23.2 and 10.23.3), the U.S.-based Collaborative Initial Glaucoma Treatment Study found no statistical difference in the rates of glaucoma progression despite a lower IOP in the surgically treated group, except with eyes whose baseline mean deviation was >less than –10 dB, where the advantage was with trabeculectomy.<sup>35,36</sup>

In general, canal-based procedures have excellent safety profiles, but modest effectiveness at IOP lowering.<sup>28,29</sup> Nonpenetrating surgeries also have excellent safety profiles and IOP results more comparable with those of trabeculectomy.<sup>37,38</sup>





**Fig. 10.23.3 Time to Treatment Failure by Treatment Group.** Medicine versus laser versus surgery. (Moorfields Primary Treatment Trial; Migdal C, Gregory W, Hitchings R. Long term functional outcome after early surgery compared with laser and medicine in open angle glaucoma. *Ophthalmology* 1994;101:1651–7.)

### BOX 10.23.1 Guidelines for Therapy in the Individual Patient

- Assess risk factors
  - Stage of disease
  - Family history
  - Myopia
  - Microvascular disease
  - Other risk factors
- Estimate a target pressure
- Medical therapy
  - Achieves satisfactory intraocular pressure (IOP) control in many cases
  - If problems with inadequate IOP, side effects, or compliance, consider alternative therapy
- Laser trabeculoplasty
  - Can be considered for primary therapy as well as after failed trabeculectomy
  - Adult patients who cannot tolerate medical therapy
  - Patients who are controlled inadequately and cannot or will not undergo surgery
- Surgery
  - If low IOP required or target IOP not reached with other treatments
  - Borderline control with medicine or laser
  - Poor compliance
  - Failed therapy with medicine or laser
  - Consider earlier surgery where appropriate, not only as a last resort!

## CONCLUSIONS

Several conclusions can be drawn from the completed studies with regard to the current role of medicine, laser, and surgery in the management of POAG. The goal of treatment of glaucoma is to maintain the IOP in a

target range such that there will no longer be progressive loss of visual field function. This permits the patient to maintain their health-related quality of life throughout their lifetime.

Medical therapy still has a definite place in the management of POAG and results in satisfactory IOP control in a good percentage of cases. The wider choice of eyedrops makes it even more important to select the most appropriate therapy for the individual patient.

LTP appears to be effective for the short-term control of IOP, but there is concern about the long-term efficacy of this treatment and it requires further study.<sup>39</sup> LTP, SLT in particular, can be considered as a primary treatment, and especially so in patients with compliance problems. These patients require continual monitoring because IOP control may be lost suddenly, with a resultant acute rise in pressure.

Filtering surgery can give excellent IOP control, but consideration should be given to the risk of complications. Early surgery can be a useful option if the IOP is not controlled by medical therapy, if a low target pressure is required and cannot be achieved with medical therapy, or if compliance is a problem.<sup>40</sup> Guidelines for therapy in individual patients are given in [Box 10.23.1](#).

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# Current Medical Management of Glaucoma

10.24

Ronald L. Gross, Brian D. McMillan

**Definition:** Medical management of glaucoma is performed using eyedrops, or less often systemic (oral or intravenous) medication for reduction of intraocular pressure.

## Key Features

Medications for treatment of glaucoma (currently approved by the U.S. Food and Drug Administration):

- Chronic treatment:
  - Prostaglandin analogues (increase outflow):
    - Latanoprost:
    - Latanoprostene bunod.
    - Bimatoprost.
    - Travoprost.
    - Tafluprost.
  - Beta-blockers (decrease inflow):
    - Nonselective:
      - Timolol.
      - Levobunolol.
      - Optipranolol.
      - Carteolol.
    - Selective:
      - Betaxolol.
  - Alpha-adrenergic agonists (decrease inflow):
    - Brimonidine.
    - Apraclonidine.
  - Carbonic anhydrase inhibitors (topical or oral) (decrease inflow):
    - Dorzolamide.
    - Brinzolamide.
    - Acetazolamide.
    - Methazolamide.
  - Miotics (increase outflow):
    - Pilocarpine.
    - Phospholine iodide.
  - Rho kinase inhibitors (increase outflow):
    - Netarsudil.
- Acute treatment:
  - Osmotics (oral or intravenous) (vitreous dehydration):
    - Glycerin.
    - Isosorbide.
    - Mannitol.
  - Carbonic anhydrase inhibitors (intravenous) (decrease inflow):
    - Acetazolamide.

## INTRODUCTION

The number of available agents for the medical treatment of glaucoma has expanded greatly. Years ago, the choice was limited to miotics, epinephrine, and oral carbonic anhydrase inhibitors. The introduction of topical beta-blockers in the 1970s represented a significant advance. Topical carbonic anhydrase inhibitors, alpha-adrenergic agonists, and prostaglandin (PG) analogues have also become available, which effectively lower intraocular pressure (IOP) and have side-effect profiles that appear to be advantageous in the majority of patients. Because of their superior efficacy and systemic safety, PG analogues have become the preferred choice for initial medical therapy.

Another aspect of efficacy is the use of generic agents. Unlike for oral agents, it is not necessary to prove bioequivalence or equal effectiveness when topical ophthalmic generics are introduced. Although these generic agents may be less expensive, the physician, patient, and policymakers must determine whether these savings are sufficient to justify their use. Unfortunately, few data are available to help in these decisions.

It is important to recognize that no single medication can be used in all patients in all circumstances. Each of the available drugs has unique advantages and disadvantages. It is necessary to individualize each patient's treatment regimen to maximize the benefits and limit the undesirable effects. It is vital to select the best agent for each particular patient's needs.

The first step in accomplishing this aim is to educate the patient about their glaucoma and their therapeutic choices. This allows the informed patient to participate in decision making about their care. Besides improving drug selection, better patient understanding of the disease and its treatment improves compliance with the medical regimen. Compliance in glaucoma patients is difficult to assess, but selection of an appropriate agent results in maximization of lowered IOP, ocular tolerability, and safety, which not only treats the glaucoma effectively but also minimizes the impact of treatment on the patient's quality of life.

Currently, the effectiveness of a medication in the treatment of glaucoma is measured by its ability to lower IOP. However, the impact of other factors (e.g., blood supply of the optic nerve, local mechanical factors that affect the optic nerve, neuroprotection of the optic nerve) on glaucomatous optic neuropathy has been recognized. Although the clinical importance of these factors is not yet understood, it is anticipated that improvement in the efficacy of glaucoma treatment may include these parameters.

Once the decision to begin medical treatment has been made, specific techniques may enhance the therapeutic index of any topical ophthalmic agent. First, patients are encouraged to perform nasolacrimal occlusion or gentle eyelid closure after the instillation of all topical ophthalmic drops. Such maneuvers decrease the systemic absorption of drugs and increase their intraocular levels, thus improving the therapeutic index.<sup>1</sup> In patients on multiple topical agents, these maneuvers also reinforce the need to allow sufficient time between the instillation of different agents to allow absorption of the first one before any dilution by instillation of a subsequent one.

Second, with the increased number of choices, it is important to determine that the drug is effective and well tolerated by utilizing appropriate follow-up to determine adequacy in reaching target IOP, percent IOP reduction, and possible side effects. Finally, it is important to instruct the patient on how and when to instill medications. Discussion of the preferred technique of instilling drops in the inferior cul-de-sac is vital. To confirm correct use, it is helpful to have the patient demonstrate the technique of drop instillation on a subsequent visit. Studies suggest that compliance is reduced when the frequency of administration is more than twice daily, which may be an important factor in the design of the patient's regimen. It is critical that the regimen be one that the patient can reasonably be expected to perform.

## DRUGS THAT DECREASE AQUEOUS PRODUCTION

### Beta-Blockers

Soon after their introduction, beta-blockers became the mainstay of medical glaucoma therapy. Over time, the importance of patient selection has become clear.



## Mechanism

Beta-blockers decrease aqueous humor production by the ciliary body and hence reduce IOP.<sup>2</sup> Evidence suggests that this occurs only during the day and not during sleep.<sup>3,4</sup> This may be important in patients who experience some of the systemic side effects (e.g., lower blood pressure and pulse rate) at night, with the potential for disease progression without other therapy to lower IOP.

## Efficacy

Beta-blockers are effective topical agents, with the mean peak IOP lowered by 25% and the mean trough lowered by 20% using nonselective agents.<sup>4,5</sup> In general, nonselective agents lower IOP equally effectively.<sup>5,6</sup> With betaxolol, a beta-1-selective agent, IOP reduction is slightly less.<sup>7</sup> None of the beta-blockers should be used more than twice daily. Certain nonselective agents, including timolol, may be used once daily (QD). QD instillation may be more convenient for the patient, which enhances compliance and reduces the amount of drug used. Furthermore, many agents are available in more than one concentration. Lower concentrations are preferred and are as effective in the majority of patients. Unfortunately, no studies have proven that lower concentrations have a lower incidence of side effects or produce less severe side effects.

## Side Effects

Contraindications to beta-blocker use include asthma, severe chronic obstructive pulmonary disease, bradycardia, second- or third-degree heart block, and congestive heart failure. Clinically, it is prudent not to use this class of drugs in any patient who has reactive airway disease (asthma), has a heart rate of less than 55 beats per minute, has or has had heart failure, has a history of present or past use of antidepressant medications, or has impotence. A positive history of cardiac problems or symptoms is usually present in patients who have greater than first-degree heart block.

Although cardiac and pulmonary side effects are the most obvious, in a large review, central nervous system problems were the most frequent,<sup>8</sup> ranging from hallucinations to depression to a general feeling of malaise. These side effects may be much more difficult to identify. In the majority of patients, if the drug used may be causing or exacerbating such problems, it is stopped to establish whether the symptoms improve. Older adults appear to be at the greatest risk for beta-blocker side effects. A conscious effort is required to identify susceptible patients (in line with the overall philosophy of individualization of therapy and specific assessment of drug effects). Other systemic side effects of topical beta-blockers, including alopecia, a dermatological problem, are rare.<sup>9</sup>

Locally, beta-blockers are well tolerated, although corneal hypesthesia and epithelial changes have been reported.<sup>10</sup> Additionally, some investigators believe that their use should be avoided in patients with diabetes because the symptoms of hypoglycemia may be masked and those of myasthenia gravis may be exacerbated.<sup>11,12</sup> Furthermore, it has been suggested that patients who are undergoing allergy tests or desensitization should not use beta-blockers of any kind, even topical agents because beta-blockade may make resuscitation more difficult should anaphylaxis occur. The use of beta-blockers in neonates is avoided because apnea may develop.<sup>13</sup> The implication that beta-blockers may have an undesirable effect on plasma lipids is less well understood. Systemic beta-blockers are known to result in undesirable changes in plasma lipid profiles. However, systemically, they are actually protective when the clinical outcomes of elevated plasma lipids (i.e., heart attack and stroke) are considered because of their positive effect on cardiovascular function. Topical timolol and, to a lesser extent, carteolol reduce high-density lipoproteins by 9% and 3%, respectively; however, no data indicate that this results in a higher risk of cardiovascular disease.<sup>14-16</sup> Although it is true that topical beta-blockers are effective and well tolerated by the majority of patients,<sup>17,18</sup> it is the clinician's obligation to identify patients who may benefit most from their use and those in whom their use should be avoided and other classes of agents should, instead, be used.

## Alpha-Adrenergic Agonists

The first specific alpha-agonist introduced was apraclonidine, a relatively selective alpha-adrenergic agonist derived from clonidine.<sup>19</sup> Brimonidine is the alpha-adrenergic agonist that is more commonly used in chronic therapy.

## Mechanism

Apraclonidine decreases aqueous production<sup>20</sup> but is also associated with an increase in outflow facility and a decrease in episcleral venous

pressure.<sup>21</sup> Brimonidine is 23 times more alpha-2 selective than apraclonidine and 12 times more selective than clonidine.<sup>22</sup> Its mechanism of action includes a reduction in aqueous formation as well as an increase in uveoscleral outflow.<sup>23</sup>

## Efficacy

The first clinical use of apraclonidine was to decrease IOP in the prevention of pressure spikes after anterior segment laser surgery. It was shown to be very effective for this purpose after argon laser trabeculoplasty,<sup>24,25</sup> argon laser iridectomy,<sup>25</sup> neodymium-doped:yttrium-aluminum-garnet (Nd:YAG) laser iridotomy,<sup>21</sup> Nd:YAG laser capsulectomy,<sup>24</sup> and even cataract surgery and trabeculectomy.<sup>26</sup> Additionally, it was used successfully in cases of acute angle-closure glaucoma<sup>27</sup> and as prophylaxis against high IOP spikes after cycloplegia.<sup>28</sup> Apraclonidine is rarely used in the chronic treatment of glaucoma.

Brimonidine 0.5% prevents the rise in postoperative IOP after laser trabeculoplasty. Spikes greater than 10 mm Hg occurred in 1%–2% of cases using brimonidine versus 23% using vehicle.<sup>29</sup> In a 12-month comparison of twice-daily brimonidine 0.2% versus timolol 0.5%, both were found to be equally effective at the 2-hour peak. No tachyphylaxis was seen with either drug over the 12 months of the study. At trough (12 hours), IOP reduction was 3.7–5.0 mm Hg with brimonidine, compared with 5.8–6.6 mm Hg with timolol. There was no difference between the groups in terms of optic disc and visual field, which were unchanged in 94% of patients.<sup>30,31</sup> Brimonidine is approved for use three times a day (TID) but is commonly used twice daily (BID) because at the morning trough, there is no difference in IOP between the two regimens.<sup>32</sup> Adherence rates are better in the BID group (72+/- 19%) compared with TID (62+/- 16%). However, dose frequency is higher in the TID group, 1.9 +/- 0.5 vs. 1.4 +/- 0.4 per day.<sup>33</sup> Lower concentrations of brimonidine (0.15% and 0.1%) have been introduced with Purite as the preservative (Alphagan P), demonstrating similar IOP-lowering efficacy to brimonidine 0.2%.<sup>34</sup>

## Side Effects

Chronic use of apraclonidine is limited by the risk for allergic reaction (Fig. 10.24.1), which may be severe. Previous studies using apraclonidine 1% reported a variable incidence of allergic reaction of up to 48%.<sup>35</sup> Systemically, this drug is well tolerated, with the primary systemic side effect being dry mouth. Brimonidine shows no effect on mean heart rate, mean blood pressure, or pulmonary function.<sup>30</sup> In the longer term (6- and 12-month studies of brimonidine compared with timolol), adverse effects included dry mouth in 30% of patients and fatigue/drowsiness in 15.8% (as a result of which 2.5% of patients left the study), compared with 13.6% with fatigue ( $P = 0.342$ ) in the timolol groups.<sup>30</sup>

Ocular effects included conjunctival blanching in 11%–17% (vehicle, 9%) of cases and burning/stinging in 24% (timolol, 41%). Within this class of agents, the allergy often limits the drug's clinical usefulness. The allergic response caused by brimonidine 0.2% is approximately 5% at 3 months and 12% at 12 months.<sup>30,31</sup> A different formulation of brimonidine has been introduced that reduces the concentration to 0.15% or 0.1% and replaces benzalkonium chloride with a proprietary Purite preservative. The most significant clinical improvement with the new formulation is a reduced incidence of allergic reactions by more than 50% (7.1% versus 17.1%).<sup>34</sup>

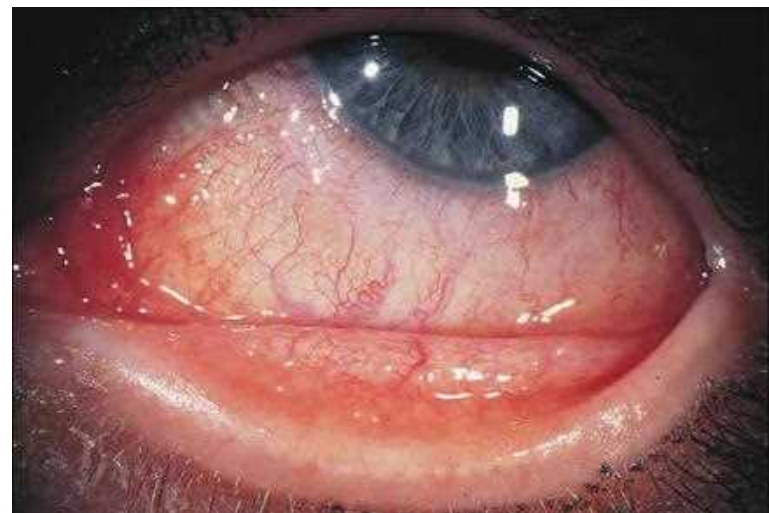


Fig. 10.24.1 Follicular conjunctival reaction to apraclonidine.

Use of the Purite preservative could be a great advantage to patients in whom benzalkonium chloride causes ocular surface disruption. This includes patients who are particularly sensitive to the preservative, as well as patients taking multiple drops in whom toxicity may be cumulative.

Brimonidine has been suggested to have potential neuroprotective effects on the optic nerve and retinal ganglion cells. Animal data supporting this claim are extensive. The results of a single trial in humans (Low-Pressure Glaucoma Treatment Study [LoGTS]) demonstrated significantly greater preservation of visual field after 4 years in patients with low-pressure glaucoma successfully treated with brimonidine 0.2% compared with timolol 0.5% despite similar and minimal IOP reduction in both groups.<sup>36,37</sup>

Brimonidine is generally contraindicated in children under 2 years old because of the risk of side effects, such as bradycardia, hypotension, hypothermia, hypotonia, lethargy, and apnea.<sup>38-40</sup>

## Carbonic Anhydrase Inhibitors

### Mechanism

Carbonic anhydrase is an enzyme that catalyzes the reaction of water (H<sub>2</sub>O) and carbon dioxide (CO<sub>2</sub>) in equilibrium with H<sup>+</sup> and HCO<sub>3</sub><sup>-</sup>. The net effect of the enzyme on aqueous production is to generate bicarbonate ions, which are transported actively across the ciliary epithelial membrane into the posterior chamber (sodium is the primary cation); an osmotic gradient is established.<sup>41</sup> Water passively follows because of the presence of the gradient, which results in aqueous production. Inhibition of this enzyme results in lower IOP because aqueous production is decreased approximately 50% or more<sup>42</sup>; aqueous outflow and episcleral venous pressure are affected little or not at all.

An important property of carbonic anhydrase is that it is necessary to inhibit nearly 100% of the enzyme. This requirement resulted in the extended time of development of a topical preparation that results in lower IOP because of decreased aqueous production, but systemic effects are minimized.

Dorzolamide 2%, a topical carbonic anhydrase inhibitor, is different in structure from the oral agents. It has increased aqueous solubility and has suitable lipid-water solubility for corneal penetration, which allows for effective topical application. Brinzolamide 1% was introduced as a suspension with a more physiological pH than dorzolamide solution. This resulted in a reduced occurrence of stinging with brinzolamide, but this medication is associated with transient blurring of vision after administration as a suspension.<sup>43</sup>

### Efficacy

Oral acetazolamide, 500 mg BID, as single agent produced an IOP reduction of 33.8 ± 7.1 % reduction.<sup>44</sup> In a 2% dorzolamide TID regimen, the peak effect was a 22% reduction of IOP, with a trough reduction of 18%, an effect that was statistically significant ( $P \leq 0.01$ ) compared with placebo.<sup>45</sup> The efficacy of brinzolamide 1% was shown to be essentially equivalent to that of dorzolamide 2% when used either two or three times daily as a single agent.<sup>46</sup> Topical carbonic anhydrase inhibitors are a reasonable choice for concomitant therapy or as monotherapy when other more effective agents cannot be used.

### Side Effects

#### Oral

Carbonic anhydrase inhibitors lower IOP very effectively; however, their use in the chronic treatment of glaucoma is limited by the frequency and severity of side effects. The most common is a constellation of symptoms that include malaise, fatigue, anorexia, and depression.<sup>47</sup> Gastrointestinal discomfort, which includes nausea, a metallic taste, and diarrhea, is also common. The more severe complications that limit the use of these agents are less common. Metabolic acidosis may occur in patients who have severe hepatic or renal disease. Sick cell crisis may be exacerbated by the acidosis as well, so patients at risk for sickle cell disease must be tested before the use of oral carbonic anhydrase inhibitors. Some investigators suggest that the acidosis lowers IOP further which may explain the general observation that acetazolamide lowers IOP more effectively than methazolamide. Morbidity is associated with the 11–15-fold increase in the incidence of renal calculi,<sup>48</sup> which most commonly occur within the first 6 months of treatment. Once renal stones occur in patients on these agents, the likelihood is high that they will occur again.

The greatest concern surrounding the use of oral carbonic anhydrase inhibitors is the potential mortality from blood dyscrasias. All blood components—red blood cells, white blood cells, and platelets—may be affected.

In 1989, 139 cases of adverse hematological effects possibly related to carbonic anhydrase inhibitors were reported, with some fatalities attributed to their use.<sup>49</sup> This usually occurs within the first 6 months and appears to be an idiosyncratic reaction that is neither dose dependent nor time dependent.<sup>50</sup> As a result, few investigators believe that periodic screening blood tests are justified. In fact, a strong case could be made that with the availability of topical carbonic anhydrase inhibitors, the use of oral agents should be limited to acute situations. In acute situations, when IOP must be lowered maximally, 500 mg of acetazolamide given orally as tablets (250 mg tablet × 2, not sustained release) has the most rapid onset of action. Often, oral administration is not possible because of nausea and vomiting, in which case the intravenous route is preferred; the peak effect by this route occurs in 10–15 minutes.<sup>51</sup>

### Topical

In controlled clinical trials, only 5% of patients discontinued the drug because of drug-related adverse events, the majority of which were ocular.<sup>52</sup> As part of the controlled clinical trials, plasma and urine were tested, but no evidence of any hematological or urinary disturbances, which included acid-base or electrolyte changes, was found.<sup>52</sup> The effects on blood pressure or heart rate were minimal. The only frequent systemic side effect was a bitter taste, reported in approximately 25% of patients.<sup>53</sup> Clinically, this effect can often be reduced if the importance of nasolacrimal occlusion or gentle eyelid closure for a few minutes after the instillation of all ophthalmic drops is emphasized.

With regard to adverse ocular events, approximately one third of patients treated with dorzolamide 2% experienced some level of ocular burn, sting, or discomfort. Superficial punctate keratitis was found in 12% of patients. This burning was less frequent with brinzolamide 1%.<sup>43,46</sup>

As with the oral agents, inhibition of carbonic anhydrase within corneal endothelial cells, which could result in a negative effect on the corneal endothelium, has not been found clinically thus far. The overall allergic rate was approximately 10%. In general, dorzolamide and brinzolamide are well tolerated.<sup>46</sup>

As to the potential for sulfonamide allergy, the portion of the sulfonamide molecule that is most responsible for the allergic response is not present in dorzolamide. A recent study suggests that patients with a self-reported sulfa allergy had similar rates of adverse reactions compared with patients with other non-sulfa allergies and had similar rates of adverse reactions to PG analogues.<sup>54</sup> However, caution must be used when sulfonamide allergy is a possible problem.

The use of dorzolamide in children was reviewed retrospectively in one study; no significant health problems were identified with acute or chronic use of this drug.<sup>55</sup>

## DRUGS THAT INCREASE AQUEOUS OUTFLOW

### Miotics

Miotic agents have long been an important class of drugs in the treatment of glaucoma. Their use has declined because of the availability of alternative agents with more desirable side-effect profiles.

### Mechanism

Miotics are parasympathomimetic agents whose action increases the contractile force of the longitudinal muscle of the ciliary body on its insertion into the scleral spur. This results in an increased facility of outflow of aqueous through the effects on the trabecular meshwork.<sup>56</sup> The miotics either mimic the effect of acetylcholine (e.g., pilocarpine) or prevent the breakdown of endogenous acetylcholine by inhibition of the pseudo-cholinesterase enzyme (e.g., physostigmine).

### Efficacy

Miotics were the earliest drugs used for glaucoma, and they lower IOP by 20%–30%. They are additive to beta-blockers, adrenergic agents, and carbonic anhydrase inhibitors.

### Side Effects

Although miotics lower IOP effectively, the clinical use of these drugs is often limited by their local ocular tolerance. From a systemic standpoint, they are quite safe. Cholinergic effects, such as increased gastrointestinal motility and increased salivation, are quite rare.<sup>57</sup>

The local undesirable effects associated with these drugs include pupillary miosis as a result of stimulation of the iris sphincter, burning on instillation of the drops, brow ache and headache after the initial use of

the drops, myopic shift of refractive error because of contraction of the circular muscle of the ciliary body with the resultant increase in power of the crystalline lens, and exacerbation of symptoms of crystalline lens opacity from the pupillary constriction. Such effects are often dose related. Pseudo-cholinesterase inhibitors are cataractogenic in adults and cause iris pigment epithelial cysts in children, although the latter effect may be prevented with concomitant use of topical phenylephrine. The use of miotics has rarely been associated with the development of retinal detachments and cicatricial pemphigoid.<sup>58</sup>

Pilocarpine gel was introduced to provide convenient daily dosing at bedtime, with the expectation that the majority of the undesirable effects would wear off by morning but the therapeutic effect would be maintained throughout the day.<sup>59</sup>

Patients whose eyes have undergone cataract surgery tend to better tolerate miotics because the miosis is less severe, no induced myopia occurs, and the patients tend to be older and suffer less brow ache and headache with use.

## Prostaglandin Analogues

PG analogues are the most recent class of drugs added to the armamentarium of glaucoma medications. Latanoprost initially and then bimatoprost, travoprost, and tafluprost have been approved for use in glaucoma or ocular hypertension. PGs are derived from arachidonic acid and display a wide range of biological functions. Recent changes in this class have included the availability of generic latanoprost, travoprost, and bimatoprost 0.03% with its potential issues and the introduction of new formulations, including a BAK-free travoprost (Travatan Z),<sup>60</sup> a reduced concentration of bimatoprost (Lumigan 0.01%) to decrease moderate to severe hyperemia,<sup>61</sup> and preservative-free tafluprost (Zioptan).<sup>62</sup>

### Mechanism

Animal studies have suggested that PGs reduce IOP by increasing uveoscleral outflow because no effect was found on fluorophotometrically measured aqueous flow or on tonographical outflow.<sup>63,64</sup> Further studies suggested that uveoscleral outflow increases because of relaxation of the ciliary body muscle and dilated spaces between ciliary muscle bundles, in addition to the altered metabolism of the extracellular matrix that surrounds the ciliary muscle cells.<sup>65</sup> Because uveoscleral outflow does not end in the episcleral venous circulation, it is possible to obtain an IOP that approaches episcleral venous pressure (9–11 mm Hg [1.2–1.5 kPa]), which may be very desirable, particularly in normal-tension glaucomas<sup>66</sup> (see Chapter 10.11). It appears that the effect on the ciliary body is mediated through modulation of tissue matrix metalloproteinases.<sup>67</sup>

### Efficacy

In multicenter trials that compared latanoprost 0.005% QD with timolol 0.5% BID for 6 months, latanoprost reduced IOP by 25%–34% and was statistically more effective than timolol.<sup>68</sup> The peak effect occurs approximately 12 hours after instillation. In addition, latanoprost reduced IOP in patients, day or night, and there was no suggestion of loss of effect during the 12 months of treatment. Travoprost 0.004% is a synthetic analogue of PGF<sub>2α</sub>, as is latanoprost. In many respects, travoprost and latanoprost are similar. Mechanistically, both bind the PGF receptor, travoprost appears to bind with higher affinity than latanoprost, and both lower IOP by increasing uveoscleral outflow. Both are administered QD. Their efficacy appears to be similar as well. In phase III studies involving 605 patients, travoprost 0.004% QD demonstrated about a 1.0–1.3 mm Hg greater reduction in IOP compared with timolol 0.5% BID.<sup>69</sup>

A 12-month study directly comparing travoprost 0.004% and latanoprost 0.005% showed little difference in mean IOP reduction (6.6–8.1 versus 6.2–8.1 mm Hg, respectively) and showed a statistical advantage favoring travoprost at the 16:00 hours' time point of the diurnal curve.<sup>70</sup> In comparisons of bimatoprost QD and timolol 0.5% BID, bimatoprost demonstrated statistical superiority in all measures of effectiveness in lowering IOP.<sup>71</sup> Various studies have compared the efficacy of these three agents. In the only trial comparing all three agents for 12 weeks, there was no statistically significant difference in IOP reduction among the three agents, although there were consistent differences in the magnitude of IOP reduction.<sup>72</sup> In a 6-month trial comparing latanoprost and bimatoprost, there was a statistically significant greater IOP reduction with bimatoprost than latanoprost at all time points.<sup>73</sup> Additionally, the rationale of switching among different agents in the class has been supported by a study that showed patients that are nonresponders to latanoprost have a high likelihood (13 of 15) of obtaining at least a 20% reduction in IOP when using bimatoprost.<sup>74</sup> Managed

care and limitation or changing of access to specific agents is common. Guidance of expectations when switches occur among these medications has shown very reasonable continuation rates. In a large-scale switch from latanoprost to bimatoprost involving over 43 000 patients, approximately 90% of the patients switched were still on bimatoprost 20 months later. Interestingly, over 90% of the patients started on bimatoprost continued with that therapy.<sup>75</sup>

Given the increasing recognition of the importance of angle-closure glaucoma worldwide, there are data showing that latanoprost was effective in lowering IOP in these patients and that the efficacy was not associated with the mean angle width or the amount of angle closure resulting from synechial closure.<sup>76</sup>

### Side Effects

Reported side effects in controlled trials of latanoprost 0.005% QD included conjunctival hyperemia (generally mild, 36%), burning and stinging (25%), blurred vision (17%), itching (15%), foreign body sensation (33%), tearing (6%), and eye pain (13%).

Latanoprost resulted in increased iris pigmentation in 11%–23% of patients<sup>68</sup> (Fig. 10.24.2). In most cases, the eyes in which the iris color changed had a characteristic concentric heterochromia before treatment, with greater pigmentation around the pupil than in the periphery. In patients who have pure blue, gray, green, or brown eyes, the risk of increased iris pigmentation is estimated to be 4%. In patients who have mixed blue and gray-brown irides, the estimated risk is 20% at 2 years, and for patients who have green-brown or yellow-brown irides, the estimated risk is 50% at 1 year. This increased pigmentation occurs slowly but may be noticeable at 3 months, with a 6.8%–11.6% increase in pigmentation seen at 6 months and a 15.5%–22.9% increase at 12 months; rarely, 18 months is required for the increased pigmentation to become manifest. Iris nevi do not appear to be affected. This change in pigmentation does not increase or decrease after cessation of latanoprost.<sup>77</sup> Animal data suggest that increased pigmentation may result from increased production of melanin within the iris melanocytes, rather than from cellular proliferation.<sup>78</sup>

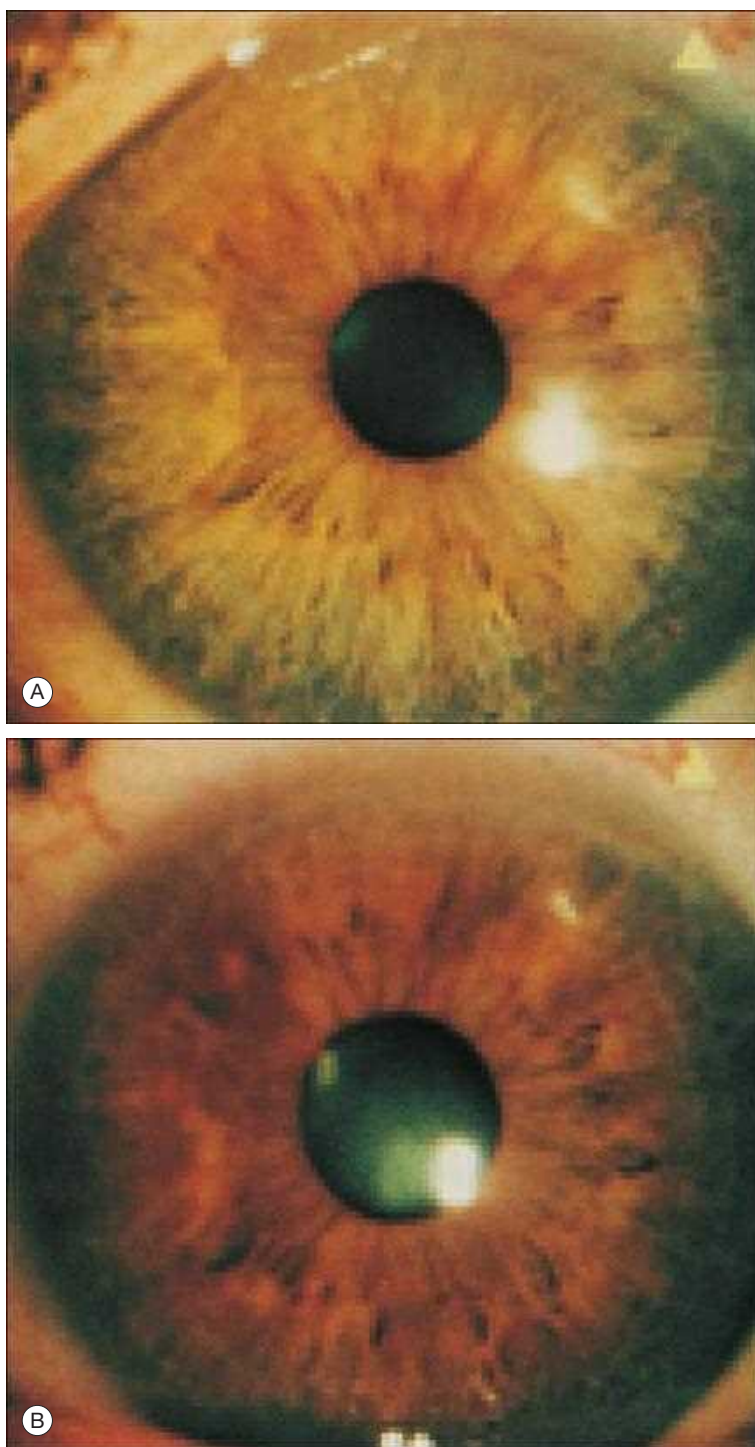
PG analogue-related orbitopathy, which often includes posterior migration of the lash line, horizontal eyelid shortening, deepening of the superior sulci, periocular erythema, meibomian gland dysfunction, and canthal deformities, has been described.<sup>79</sup> Periocular pigmentation occurs in 1% of patients treated with latanoprost and 6% of those treated with bimatoprost.<sup>80</sup>

There is a theoretical risk that PG analogues may break down the blood–aqueous barrier potentially worsening or reactivating uveitis, cystoid macular edema (CME) and herpes infections.<sup>81</sup> Findings from small studies utilizing flair meters support a breakdown in the barrier and associated CME seen in some patients with pseudo-phakia or aphakia<sup>82</sup> but has not been found to affect the incidence, progression, or response to treatment of diabetic macular edema.<sup>83</sup> There was also no worsening of anterior uveitis or development of CME in patients with uveitis treated with PG analogues compared with untreated fellow eyes.<sup>84</sup> Case reports have described the reactivation of herpes simplex keratitis when PG analogues were prescribed<sup>85</sup>; however, there are no high level data to suggest that PG use is strictly contraindicated.<sup>81</sup> Caution is, therefore, advised when prescribing PG analogues to patients with prior uveitis, CME, or herpes keratitis but may be indicated in patients whose condition is not controlled with alternatives.

The side effects among PG analogues are similar, but with a greater occurrence of hyperemia with travoprost than latanoprost (49.5% versus 27.6%) and a slightly lower chance of increased iris pigmentation (2.8% versus 5.2%).<sup>70</sup>

Hyperemia was found to be significantly more common with bimatoprost 0.03% than with latanoprost. The hyperemia appears to be conjunctival injection that is unrelated to either an allergic follicular conjunctival response or actual tissue inflammation. Overall, hyperemia occurred in about 45% of patients using bimatoprost 0.03%; the severity of the hyperemia was trace to mild, with less than 4% of patients discontinuing bimatoprost because of tolerability issues in this clinical trial. The incidence of moderate to severe hyperemia was substantially less with the reduced concentration 0.01% compared with 0.03% bimatoprost. Clinically, in some patients, the hyperemia is slightly greater and may be associated with mild burning. This appears to be most severe when beginning the medication and usually improves. Ocular evaluation showed no increase in aqueous flare. Ocular effects identified included eyelash growth, rare increase in iris color, and conjunctival hyperemia. At 12 months increased iris pigmentation with bimatoprost, evaluated by the treating physicians using photographs of patients' eyes, was only 1.5%.<sup>71</sup>





**Fig. 10.24.2 Iris Color Changes After Latanoprost Treatment.** (A) Before treatment in a patient with a green-brown iris. (B) After 6 months of latanoprost treatment, the iris shows increased pigmentation.

The experience with PG analogues has reassured us that this change in iris color is primarily a cosmetic concern and is often not recognized by the patient. Although the change is irreversible, it is common to treat patients until iris pigmentation changes occur and to make a decision later whether to continue the drug, based on the efficacy and the patient's input.

### Systemic Safety

Latanoprost 0.005% has a plasma half-life of only 17 minutes. Therefore, with the very low concentration delivered, minimal systemic side effects would be anticipated. No effect was found on resting heart rate, blood pressure, or blood and urine laboratory values. The use of latanoprost in young patients has not been evaluated. Bimatoprost demonstrated no effect on

blood pressure, pulse, hematology, urinalysis, or any other parameter of systemic safety.

## FIXED COMBINATION MEDICATIONS

Many different fixed combinations of these medications are available worldwide. In general, fixed combinations provide additional convenience to the patient with a decreased preservative load. Common formulations include timolol/dorzolamide (Cosopt, preservative-free Cosopt), timolol/brimonidine (Combigan), and brinzolamide/brimonidine (Simbrinza). Data show that the fixed combinations are more effective than either component alone.<sup>86</sup> Unfortunately, because of the minimal further IOP reduction provided by the addition of timolol to the prostaglandin analogs, the fixed combination of any of these medications has not been approved by the U.S. Food and Drug Administration (FDA) for use in the United States.<sup>87,88</sup> However, they are available in many other areas of the world.

## DRUG DEVELOPMENT PIPELINE

There are several new classes of medications currently being tested in phase III clinical trials. These medications would be the first new class of medication, if approved, since the FDA approval of latanoprost in 1996.

There are seven clinical trials on Rho kinase inhibitors, including ripasudil, which relaxes contractile tone of cells within the trabecular meshwork. Netarsudil, a Rho kinase/norepinephrine transporter inhibitor, has been found to reduce IOP by increasing outflow facility through the expansion of the juxtacanalicular connective tissue and dilating the episcleral veins<sup>89</sup> and may promote retinal ganglion survival.<sup>90</sup>

Latanoprostene bunod, a nitric oxide donating PGF<sub>2α</sub> analogue, may have improved efficacy over latanoprost alone via nitric oxide mediated relaxation of the trabecular meshwork and Schlemm's canal.<sup>91</sup>

Trabodenasol, a selective adenosine A1 receptor agonist that is thought to increase trabecular meshwork outflow facility, is also in early clinical trials.<sup>92</sup>

These medications represent possible new first-line treatments or, more likely, second-line treatments in addition to or in combination with currently available PG analogues.

## THE MEDICAL ARMAMENTARIUM FOR GLAUCOMA TREATMENT

As more experience with any drug is gained, its place in the decision-making process becomes clearer. Historically, beta-blockers were the most common first-line agents used in the medical treatment of glaucoma. However, with increasing experience with newer agents, specifically the PG analogues that facilitate outflow, they have been recognized as being more efficacious in lowering IOP and systemically safer than beta-blockers. As a result, they are generally the first-line agents in glaucoma treatment. When these agents are not appropriate, we still have other excellent choices, including the beta-blockers, alpha-agonists, and topical carbonic anhydrase inhibitors. In general, these agents are well tolerated by most patients, with a low rate of discontinuation attributable to the drugs. We must maintain vigilance to identify patients who should not receive these drugs because of the potential for ocular, pulmonary, cardiovascular, or central nervous system side effects. The current spectrum of glaucoma drugs is summarized in Table 10.24.1.

Because about 50% of patients with glaucoma take more than one class of agent, the availability of fixed combinations and an understanding of the characteristics of these agents are necessary to make the best choices for our patients. Data have also shown that utilizing a fourth topical medication may not have a clinically significant impact on IOP control.<sup>93</sup> Therefore, when using medications to treat glaucoma, it is imperative that the individual needs of the particular patient be considered. It is important to include the patient in the decision-making process, through education about the disease as well as discussion of the specific positives and negatives of the treatment options. The best regimen for an individual patient can be selected and tried using correct instillation techniques. In this way, maximal compliance, which is often difficult to achieve and a limiting factor in effective medical therapy for glaucoma, may be obtained.

TABLE 10.24.1 Drugs Used to Manage Glaucoma

Drug	Example	Mechanism of Action	Efficacy	Side Effects
Beta-blockers nonselective	Timolol Levobunolol Carteolol Metipranolol	Decreased aqueous production (waking hours only)	+ + +	Pulmonary: bronchoconstriction Cardiovascular: bradycardia/heart block Exacerbation of CCF Depression Impotence Death
Adrenergic agents nonselective	Epinephrine Dipivefrin	Outflow enhancement	+ (+)	External eye: toxic reaction
Alpha-adrenergic agents	Apraclonidine	Decreased aqueous production	+ + (+)	External eye: allergic reaction
	Brimonidine	Also, uveoscleral outflow increase with brimonidine		Lethargy Dry mouth Allergic reaction
Miotics	Carbachol Pilocarpine Echothiophate	Increased conventional aqueous outflow	+ + +	Eye ache Headache Dim vision
Carbonic anhydrase inhibitors				
Systemic	Acetazolamide	Decreased aqueous production	+ + + +	Malaise Blood dyscrasia Kidney stones
	Methazolamide			Depression Weight loss
Topical	Dorzolamide Brimonidine		+ +	Metallic taste
				Eye irritation
Lipids (Prostaglandin analogues, prostamides, decosanoids)	Latanoprost Travoprost Bimatoprost Tafluprost	Enhanced aqueous outflow (conventional and unconventional)	+ + + +	Iris color change Hyperemia Periocular skin pigmentation Orbitopathy

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# Laser Trabeculoplasty and Laser Peripheral Iridectomy

10.25

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**Definition:** Laser trabeculoplasty involves treatment to the trabecular meshwork to enhance outflow of aqueous humor from the eye, and laser peripheral iridectomy involves treatment to create a full thickness hole within the peripheral iris to alleviate pupillary block.

Key Features

- Laser trabeculoplasty: laser treatment to the trabecular meshwork to enhance outflow of aqueous humor from the eye.
- Laser peripheral iridectomy: laser treatment to create a full thickness hole within the peripheral iris to alleviate pupillary block.

Associated Features: Laser Trabeculoplasty

- Typically performed with argon or a frequency-doubled neodymium:yttrium–aluminum–garnet (Nd:YAG) laser.
- Indicated for ocular hypertension, primary open-angle glaucoma, pseudo-exfoliation, and a few select open-angle glaucomas.
- Immediate pressure spike can occur.
- May lose its effect over the long term.

Associated Features: Laser Peripheral Iridectomy

- Typically done with Nd:YAG and/or argon laser.
- Alleviates pupillary block angle-closure mechanism.
- Hemorrhage, uveitis, lens damage can occur.

LASER TRABECULOPLASTY

Introduction and Historical Review

The notion of anterior chamber angle photocoagulation, using a xenon-arc light source, was introduced by Zweng and Flocks in 1961.<sup>1</sup> Laser treatment of the human trabecular meshwork by puncturing Schlemm’s canal was performed initially by Krasnov in 1973, but the lowering of intraocular pressure (IOP) that he described was short-lived.<sup>2</sup> Ticho and Zuberaman noted that argon laser treatment of the angle was successful in lowering IOP despite lack of permanent trabecular openings.<sup>3</sup> Contemporary use of argon laser trabeculoplasty (ALT) is based on a report demonstrating safety and efficacy in a group of patients with open-angle glaucoma in 1979 by Wise and Witter.<sup>4</sup> In 1998, Latina et al. utilized a frequency-doubled neodymium:yttrium–aluminum–garnet (Nd:YAG) nonthermal laser to lower IOP successfully in patients with open-angle glaucoma.<sup>5</sup> This laser appears to selectively target pigmented cells with little or no damage to the surrounding structures, and hence is referred to as selective laser trabeculoplasty (SLT).<sup>6</sup> ALT and SLT are equally safe and effective in lowering IOP in open-angle glaucoma.<sup>7</sup> The mechanisms of action of ALT and SLT remain to be completely elucidated. With ALT, there appears to be a mechanical effect (one or more of tightening of the trabecular meshwork, opening intervening spaces, or opening a collapsed Schlemm’s canal) and/or a biological response (cytokines are released which open the meshwork spaces and wall of Schlemm’s canal and signal trabecular cells and/or macrophages to clear material that has accumulated within the meshwork). With SLT, a cellular or biological mechanism is more likely because the laser does not appear to cause shrinkage of tissue in animal models.<sup>8</sup>

Preoperative Evaluation and Diagnostic Approach

The main indications for laser trabeculoplasty include the following:

- First-line option in early to moderate stage OAG with IOP less than 35 mm Hg.
- Glaucoma suspects or those with open-angle glaucoma who are intolerant to medications, have difficulty with cost of medications, or are poorly compliant.
- Primary open-angle glaucoma (POAG) (including exfoliation, pigmentary, normal-tension, corticosteroid-induced glaucomas) uncontrolled with one or more medications.<sup>9–12</sup>
- Patients who may benefit from reduction in medication.

Relative contraindications include:

- Uveitic and neovascular glaucomas.
- Congenital or juvenile glaucoma.
- Aphakic or traumatic glaucomas.
- Inadequate visualization of trabecular meshwork.

Predictors for ALT success are presented in Table 10.25.1. With optimal patient selection, after ALT, IOP typically drops to 25%–30% below the initial IOP at 1 year (the effect fades with time at an attrition rate of about 10% per year). SLT offers a safe and effective IOP-lowering alternative to ALT in patients with open-angle glaucoma.<sup>7,13</sup> (Table 10.25.2).

IOP-lowering with SLT depends on baseline IOP but seems independent of trabecular meshwork pigmentation. Caution needs to be exercised,

TABLE 10.25.1 Positive and Negative Predictors of Argon Laser Trabeculoplasty Success

	Negative Predictors	Positive Predictors
Age (years)	<40	>65
Trabecular meshwork pigmentation	Little or none	Moderate to marked
Corneal clarity	Poor	Clear
Disease entities	Uveitic glaucoma	Pigmentary glaucoma
	Angle closure	Pseudo-exfoliative glaucoma
	Juvenile glaucoma	Primary open-angle glaucoma
	Angle recession	Low-tension glaucoma
Lens status	Aphakic or anterior chamber intraocular pseudo-phakia	Phakic or posterior chamber intraocular pseudo-phakia
Contralateral eye	Little effect	Strong effect

TABLE 10.25.2 Selective Laser Trabeculoplasty (SLT) Versus Argon Laser Trabeculoplasty (ALT): A Prospective, Randomized Clinical Trial

	Mean Intraocular Pressure at Various Time Points to 1 Year		
	ALT (SD)	SLT (SD)	P Value
Baseline	23.48 (4.21) (n = 87)	23.84 (4.88) (n = 89)	0.60
3 months	19.75 (4.79) (n = 73)	18.89 (4.71) (n = 76)	0.31
6 months	18.42 (4.20) (n = 79)	17.83 (4.33) (n = 79)	0.40
12 months	17.88 (3.92) (n = 74)	17.97 (4.74) (n = 73)	0.90
Reproduced from Damji KF, Bovell AM, Hodge WG, et al. Selective laser trabeculoplasty vs. argon laser trabeculoplasty: results from a one-year randomized clinical trial. Br J Ophthalmol 2006;90:1490–4.			

however, in patients with heavy degrees of meshwork pigmentation, as these patients are at higher risk for a sustained (irreversible) IOP spike.<sup>14</sup>

Treatment with ALT or SLT at 360° appears to be more effective than at 180° or 90°, but there is a higher risk of postoperative IOP spike. Studies suggest that both ALT and SLT can be utilized as first-line therapy in patients with open-angle glaucoma. In the Glaucoma Laser Trial the authors concluded that initial ALT is at least as effective as initial treatment with topical medication.<sup>15</sup> For SLT, two studies suggested that the laser can be utilized as first-line therapy, although follow-up in both these studies was limited to 12 months.<sup>12,16</sup>

One study by Hong et al.<sup>17</sup> suggested that repeating SLT once may be effective, but not as effective as initial treatment; however, much more work needs to be done in this area.

## General Techniques

### Patient Preparation

If the angle is closed or narrow, a laser iridoplasty or a peripheral iridectomy is performed beforehand to deepen and allow better visualization of the angle; a laser iridoplasty can be performed simultaneously with ALT, but when a peripheral iridectomy is performed, ALT is best deferred for a few weeks because of possible anterior chamber debris. A drop of apraclonidine (0.5%) or brimonidine (0.15% or 0.2%) is instilled in the eye 30–60 minutes preoperatively to minimize IOP elevation after treatment.

### Lens Choice

A Ritch or, more commonly, a three-mirror Goldmann lens with antireflective coating is used. The lens does not invert the image but reverses the position, such that the 12 o'clock position of the mirror represents the 6 o'clock position at the angle, the 1 o'clock position of the mirror represents the 5 o'clock position at the angle, and so forth.

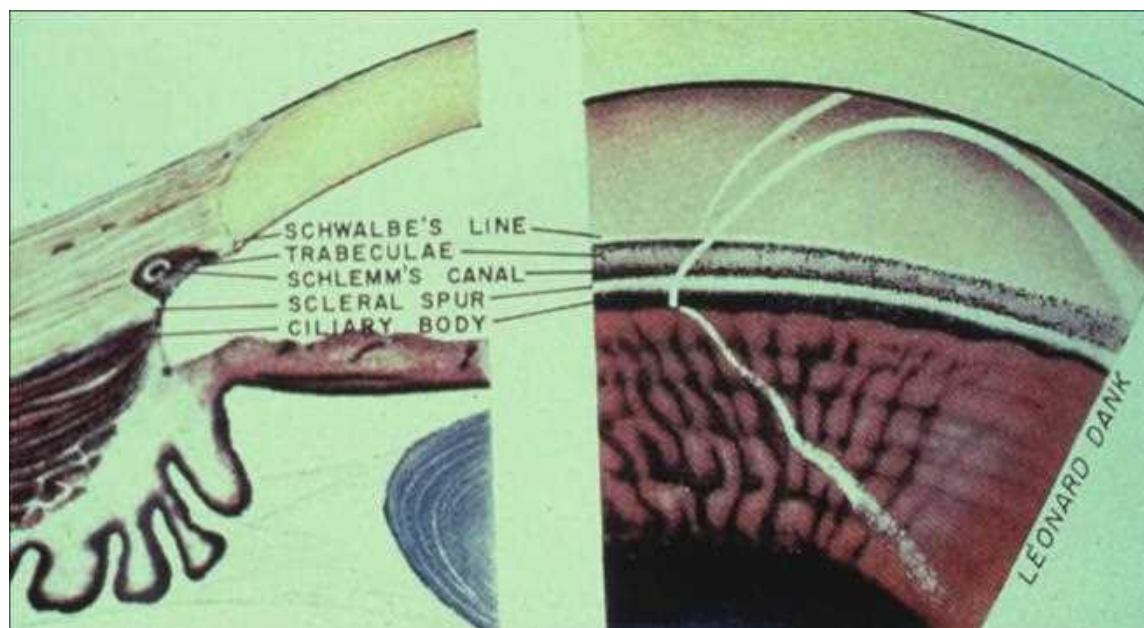
### Equipment Preparation

The trabecular meshwork may occasionally be variably pigmented, and a pigmented Schwalbe's line or a ciliary body band may be confused with the trabecular meshwork. In this case, the corneal wedge reflex can help to locate Schwalbe's line (Fig. 10.25.1).

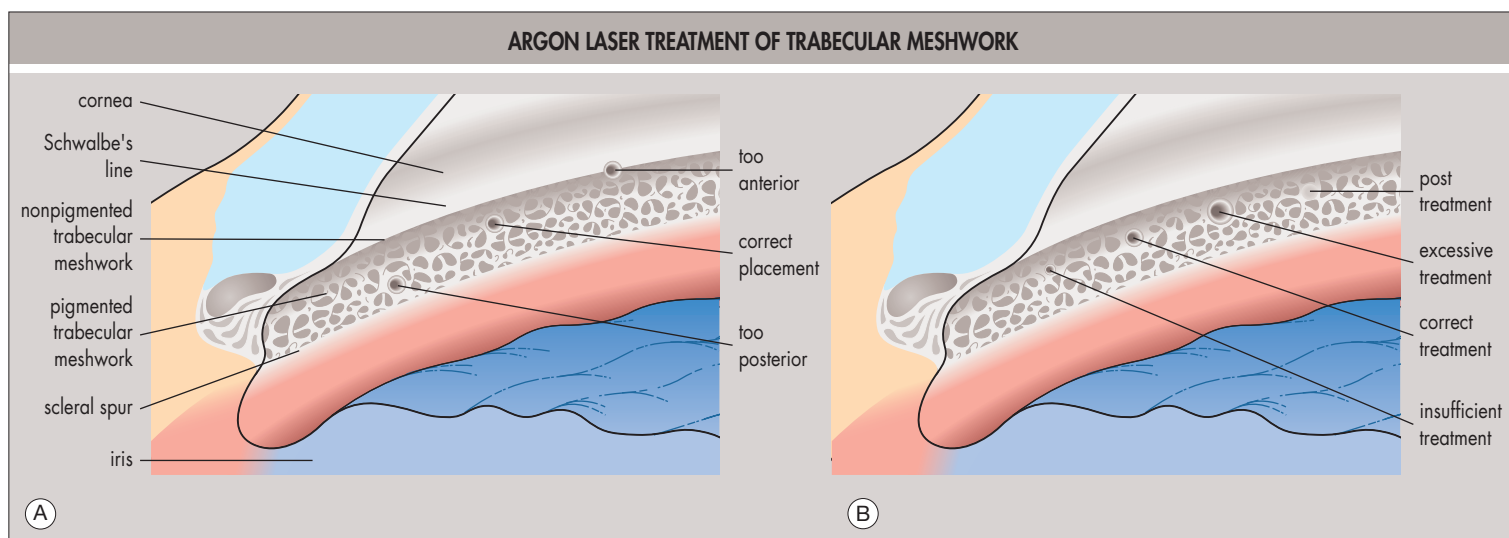
A topical anesthetic is instilled immediately before the procedure. The gonioscope is applied by using methylcellulose as the coupling agent. The procedure begins with the gonioscope at the 12 o'clock position (to visualize the inferior angle which is the deepest part of the angle), and the lens is typically rotated clockwise. To ensure delivery of laser energy with maximal efficiency, the aiming beam is always kept in the center of the mirror, round and sharp, keeping the gonioscope perpendicular to the laser beam. The lens is rotated after several applications.

### Treatment Guidelines

The laser spots for ALT are placed at the junction of the pigmented and nonpigmented trabecular meshwork, with a gap of about the diameter of one to two laser spots between spots (Fig. 10.25.2A). The author currently



**Fig. 10.25.1 Corneal Wedge Reflex.** A thin slit beam that is about 30–40° off center will demonstrate the anterior and posterior corneal beams that converge on Schwalbe's line. This is demonstrated on the right-hand panel of the schematic.

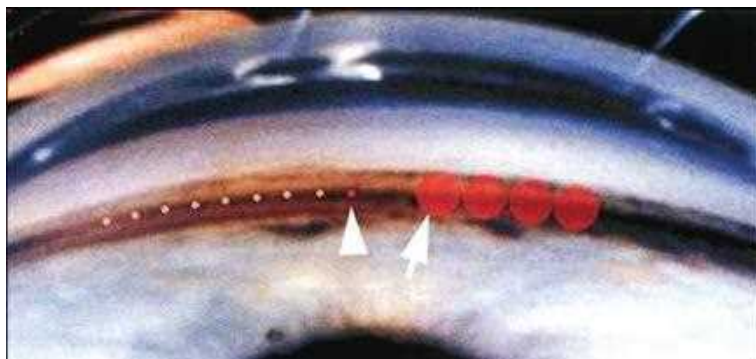


**Fig. 10.25.2 Argon Laser Treatment of Trabecular Meshwork.** (A) Optimal laser beam placement on the trabecular meshwork. (B) Trabecular meshwork tissue endpoint reaction to different intensities of argon laser treatment. (A, Reproduced with permission from Schwartz AL. Argon laser trabeculoplasty in glaucoma: what's happening (survey results of American Glaucoma Society members). *J Glaucoma* 1993;2:329. B, Reproduced with permission from Schwartz AL, Whitten M, Bleiman B, et al. Argon laser trabecular surgery in uncontrolled phakic open-angle glaucoma. *Ophthalmology* 1981;88:203–12.)



TABLE 10.25.3 Protocols for Laser Treatments

	ALT	SLT	MLT	Peripheral Iridectomy			Argon Laser Iridoplasty
				Argon		Yttrium–Aluminum–Garnet (YAG)	
				Light Irides	Dark Irides		
Spot size (μm)	50	400	300	50	50	Fixed	200–500
Spot duration (seconds)	0.1	0.3 nanoseconds	0.3	0.2	0.02–0.05	Fixed (nanoseconds)	0.2–0.5
Power (mW)	200–800	0.4–1.2mJ	1000	1000	1000	3–8 mJ	200–400
Number of spots	50 per 180°	50 per 180°	50–60 per 180°	15–25	25–100	1–5 shots (each burst consists of 1–3 pluses)	4–6 per quadrant. Typically treat 360°



**Fig. 10.25.3** Selective laser trabeculoplasty (arrow) versus argon laser trabeculoplasty treatment (arrowhead). (Courtesy M. Berlin, MD.)

treats 180° of the inferior angle in one session (it is generally best to treat the same portion of the angle first to avoid future confusion on completion of the remaining 180°). See Table 10.25.3 for recommended treatment guidelines.

Settings should be adjusted according to the tissue reaction endpoint, which is minimal blanching (see Fig. 10.25.2B). If the burn is too anterior, the treatment is more likely to be ineffective; if it is too posterior, it is more likely to create inflammation and peripheral anterior synechiae.

The selective laser has a relatively large 400 μm fixed spot size, which ideally should be centered on the trabecular meshwork. The energy is adjusted from 0.8 mJ downward or upward, depending on tissue response.

For SLT occasional bubble creation is the endpoint. The number of shots applied is about 50 over 180°, with 180–360° treated initially (if treating 360° then 90–100 spots are applied). The spots are almost confluent and span the entire angle width because of the large spot size (Fig. 10.25.3). Pre- and postoperative care is similar to that of ALT.

### Follow-Up

The IOP is measured 1 hour after LTP. If it is elevated, additional IOP-lowering medication is administered and the IOP is rechecked 30–60 minutes later. Topical prednisolone acetate 1% four times daily is prescribed for 4–7 days, and as long as the one hour IOP was similar to or lower than baseline, the patient can be seen 4–6 weeks later. If there is concern about IOP or inflammation, the patient can be reviewed after 1 week. If anterior uveitis is present at 1 week, topical corticosteroids are continued. With SLT, it is possible to use a topical nonsteroidal anti-inflammatory agent four times a day for 4–7 days instead of prednisolone acetate.

### Re-treatment

If 180° of treatment worked reasonably well, then completing treatment of the angle (i.e., treating the remaining 180°) is worth considering if IOP rises with time. However, the chance of success with a re-treatment (i.e., energy applied when the same area was previously treated) of the angle using ALT is considerably less than with an initial procedure, and the overall effect seems to wane considerably with time. With SLT, retreatment may be effective, but further data are needed in this area.<sup>17</sup>

### Complications

The most common risk is an IOP spike in about 3%–5% of patients, but this may be limited effectively using apraclonidine or brimonidine.<sup>18</sup> Corneal burns, which occur rarely, typically heal within a few days. There

have been reports of some cases that developed corneal edema within 1–7 days after SLT. It is not yet understood what may predispose a patient to corneal changes as a result of this procedure, although routine use of topical anti-inflammatory drops may help avoid this complication.<sup>19,20</sup>

### Outcome

A period of at least 4–6 weeks after ALT is required before the final result can be evaluated. In two long-term studies, ALT maintained IOP control in 67%–80% of eyes for 1 year, in 35%–50% for 5 years, and in 5%–30% for 10 years (i.e., an attrition rate of 6%–10% per year).<sup>21,22</sup> With SLT, IOP-lowering occurs within 1–2 weeks but can continue for up to 4–6 months after treatment; attrition of effect also continues for 3–5 years with a similar rate as ALT.<sup>8,23,24</sup>

## LASER PERIPHERAL IRIDECTOMY

### Introduction and Historical Review

Von Graefe<sup>25</sup> introduced surgical iridectomy for glaucoma in 1857. In 1920, Curran recognized that iridectomy was effective for angle-closure but not for open-angle glaucoma.<sup>26</sup> In 1956, Meyer-Schwickerath<sup>27</sup> demonstrated that an iridectomy could be created without the need for an incision, using xenon arc photocoagulation. This method failed to gain popularity, however, because of frequent occurrence of lens and corneal opacities.

Argon laser iridectomy (via photocoagulation) and, more recently, Nd:YAG laser (via photodisruption) iridectomy have essentially replaced surgical iridectomy in the vast majority of cases.

### Preoperative Evaluation and Diagnostic Approach

Laser iridectomy is the established procedure of choice for angle-closure glaucoma associated with pupillary block, whether primary or secondary, or acute, intermittent, or chronic.

### Indications

Laser iridectomy is indicated for therapeutic, prophylactic, and diagnostic indications:

- Therapeutic:
  - Acute angle closure.
  - Chronic (creeping) angle closure as long as the entire angle is not closed with peripheral anterior synechiae.
  - Mixed mechanism glaucoma.
  - Phacomorphic with an element of pupillary block.
  - Iris bombé.
- Prophylactic:
  - Patients with 180° or more of iridotrabecular apposition (i.e., occludable angle).
  - Patients who have had silicone oil placed in the eye; an inferior iridectomy is necessary to prevent pupillary block (silicone oil is lighter than water and would float up and block a superior iridectomy).
- Diagnostic:
  - Laser iridectomy also aids in the diagnosis of aqueous misdirection (see Chapter 10.19) and plateau iris syndrome (in a nonpupillary block narrow angle).

### Contraindications

Laser iridectomy is contraindicated in patients who are unable to sit and cooperate at the slit lamp, who have a cloudy cornea precluding adequate

visualization of the iris, or who have a flat anterior chamber with complete iridocorneal touch.

In such cases, surgical iridectomy may be preferred. Iridectomy is also contraindicated in situations where 360° of peripheral anterior synechiae exist (including neovascular glaucoma).

## General Techniques

### Argon versus Nd:YAG Laser

Both lasers are effective for the creation of iridectomies. The argon laser requires uptake of light energy by melanin pigment, but the Nd:YAG laser does not, and works well on all iris colors. The author prefers the Nd:YAG in light- and medium-colored irides because it is quicker and is associated with fewer late closures than argon laser.<sup>28</sup> In dark irides, however, some prefer pretreatment with the argon laser.

The Nd:YAG laser does not coagulate tissue, and small hemorrhages occur more frequently with this modality. Therefore, in eyes that have prominent unavoidable vessels or in patients affected by a bleeding diathesis, combined treatment may be preferred, first with the argon laser (to ablate vessels in the area) and then with the Nd:YAG laser (to establish a patent peripheral iridectomy).

### Patient Preparation

A drop of pilocarpine 1% is instilled twice, 5 minutes apart; miosis helps to stretch and thin the iris. A drop of apraclonidine 0.5% or brimonidine 0.2% is used a few minutes preoperatively to prevent a postoperative IOP elevation.

### Lens Choice

Two special therapeutic contact lenses limit eye movements and blinking, concentrate the energy delivered, magnify the target site, and act as a heat sink to minimize the risk of superficial corneal epithelial burns. The Abraham lens has a 66D planoconvex button. The Wise lens has a 103D planoconvex button, which concentrates the laser energy more compared with the Abraham lens because it minimizes the spot and magnifies the target even more; however, because of the higher power of the Wise lens, it is more difficult to focus. The other advantage of the Abraham lens is that energy delivered to both cornea and retina is four times less than that delivered to these tissues by the Wise lens.

## Specific Techniques

The iridectomy is typically placed in the peripheral iris under the upper eyelid to avoid ghost images that may arise through the iris hole when the iridectomy is bisected by the eyelid margin and/or the tear meniscus.<sup>29</sup> However, another study suggested that cortical cataract, rather than location of the iridectomy, correlates with ghost images.<sup>30</sup> Some practitioners choose a superior location for the iridectomy (typically 11 o'clock or 1 o'clock), whereas others choose a horizontal location (typically temporally or slightly inferotemporally). If iris crypts are present, these represent thinner iris segments and, as such, are penetrated more easily.<sup>31</sup>

### Argon Laser

Long pulses (0.2 seconds) are used for light-colored irides (blue, hazel, light brown), and short pulses (0.02–0.05 seconds) are used for dark brown irides. See Table 10.25.3 for recommended treatment guidelines.

A single area is treated with superimposed applications until perforation is obtained—that is, when a pigment within aqueous moves forward (“smoke sign” or “waterfall sign”) or, preferably, when the lens capsule is visualized through the patent iridectomy. Transillumination of the iridectomy is not an adequate indication of patency.

### Nd:YAG Laser

The Q-switched mode is used, which allows treatment independent of pigmentation. Iris blood vessels are avoided. The iridectomy spot may be placed anywhere between the 11 o'clock and 1 o'clock positions because bubble formation is minimal, or it may be placed temporally at the 3 o'clock or 9 o'clock positions. In a thick iris, the red aiming beams may be separated slightly if the focus is advanced toward the iris stroma. This retrofocusing of the beam delivers the full energy from the optical breakdown, facilitating breakdown of the thick iris. On some lasers, a posterior focus can be set (typically 75–100  $\mu\text{m}$ ) so that it is not necessary to manually focus more posteriorly. The energy used is 3–8 mJ with 1–2 pulses per shot, and one or more applications as required for penetration (see Table 10.25.3).

## Combined Argon–Nd:YAG Technique

Both argon and Nd:YAG lasers can be used in sequential combination for dark brown irides or for patients who are on chronic anticoagulant therapy. First, the argon laser (short-pulse mode; e.g., 0.05 s, with 900–1000 mW and 50  $\mu\text{m}$  spot) is used to thin the iris to 75%–80% of its original thickness and to coagulate vessels in the area. Then, the Nd:YAG laser is used, with the beam focused at the center of the crater with one or more pulses at 3–6 mJ to complete the iridectomy.

### Second Iridectomy

One patent iridectomy is almost always sufficient to relieve pupillary block. In rare instances where the long-term patency of the opening is uncertain or in the presence of inflammatory (uveitic) pupillary block, a second iridectomy may be made at the same sitting.

## Complications

### Intraocular Pressure Spikes

Elevated IOP occurs in approximately one third of eyes after treatment with laser,<sup>31</sup> but the use of apraclonidine 0.5% or brimonidine 0.2% significantly decreases this risk, except in individuals who are already on chronic apraclonidine treatment.

### Laser-Induced Inflammation

Laser-treated eyes may suffer transient iritis because of breakdown of the aqueous–blood barrier. Occasionally, inflammation may be quite severe, and posterior synechiae may develop. Prednisolone drops four times daily for 4–7 days should be used postoperatively.

### Iridectomy Failure

An iridectomy may fail because the opening created is too small or because perforation is not achieved, with a residual iris pigmented layer present. Theoretically, functional failure can be avoided with a peripheral iridectomy diameter of at least 50  $\mu\text{m}$ ; an iridectomy with a diameter of 100–200  $\mu\text{m}$  is ideal.<sup>32</sup>

### Diplopia

Diplopia, or a “ghost image,” is an occasional complaint, especially when the peripheral iridectomy is placed in a location where the upper lid bisects the iridectomy or there is a cortical cataract present in the region. In the former situation, this may be related to a prism effect created by the tear meniscus or the upper eyelid. Tinted glasses or sunglasses often improve symptoms. Intolerable monocular diplopia may be resolved by placing a cosmetic contact lens, or corneal tattoo, which blocks the light from the peripheral iridectomy but not from the pupil.

### Bleeding

Post-laser hyphema is not uncommon after use of the Nd:YAG laser and is generally minimal and self-limiting. Brisk bleeding during treatment may be stopped by applying direct pressure to the cornea using the contact lens to tamponade the bleeding site temporarily.

### Lens Opacities

The lens rarely may be damaged directly from laser irradiation or indirectly because of deficient nourishment of the lens (aqueous takes a short cut through the iridectomy and therefore has reduced contact with the central lens capsule). Opacities that are directly laser-induced tend to remain focal in the area of the peripheral iridectomy, away from the visual axis.

### Corneal Injury

Focal laser damage to the epithelium, Descemet's membrane, or endothelium occurs frequently but is usually transient. A shallow anterior chamber, pre-existing corneal edema, or pathological conditions of the cornea (e.g., guttae) make corneal injury more likely.

### Other Complications

Post-laser malignant glaucoma, retinal burns, and lens-induced uveitis are extremely rare but reported complications.

## Outcome

The patient can resume full activity without restrictions as long as no hyphema is evident. Patients are seen at 1 hour and then at 4 weeks after the procedure. Corneal status, IOP, anterior chamber reaction, and patency of the iridectomy with direct visualization are assessed

at each visit. Gonioscopy is critical to determine whether the angle has deepened.

If the peripheral iridectomy remains patent after 4–6 weeks and is of reasonable size, the opening usually remains open unless an active inflammatory response (e.g., uveitis, neovascularization) is present.

## LASER IRIDOPLASTY

Laser iridoplasty consists of the placement of a circumferential ring of nonpenetrating contraction burns at the far iris periphery, just inside the limbus, to contract the stroma and widen the angle. Laser iridoplasty is performed by the application of evenly spaced (4–10 burns per quadrant), large (200–500  $\mu\text{m}$ ), long (0.2–0.5 seconds), and low-powered (200–400 mW) burns at the far iris periphery through a goniolens or the Abraham iridectomy lens (see [Table 10.25.3](#)).

Laser iridoplasty does not require a clear cornea for the placement of the spots because the energy is relatively defocused. Laser iridoplasty is indicated in cases of plateau iris syndrome, plateau iris configuration when the height of the plateau is deemed sufficient to cause angle closure with pupillary dilation, pre-laser trabeculoplasty narrow angle (to increase visibility of the angle anatomy), and angle closure that is unresponsive to medical treatment and for which peripheral iridectomy cannot be performed because of corneal clouding.

## MICROPULSE LASER TRABECULOPLASTY

Micropulse later trabeculoplasty uses repetitive microsecond pulses with frequent periodic pauses, thereby decreasing coagulative damage by allowing intermittent cooling periods from consistent thermal energy.<sup>31,33</sup> The biochemical theory proposes cytokine release, resulting in increased outflow.<sup>32</sup> Studies have revealed a significant IOP reduction in patients with uncontrolled open-angle glaucoma with minimal complications.<sup>34,35</sup> Newer laser treatment modalities, such as titanium sapphire laser trabeculoplasty, have also shown early promising IOP reductions with minimal complications.<sup>36</sup> However, more studies are needed to determine treatment safety and efficacy. See [Table 10.25.3](#) for recommended treatment guidelines.

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# Cyclodestructive Procedures in Glaucoma

10.26

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**Definition:** Surgical and laser procedures that ablate the ciliary body to lower intraocular pressure for treatment of glaucoma.

## Key Features

- Use of a diode laser to destroy ciliary body tissue.
- Transscleral cyclophotocoagulation.
- Endoscopic cyclophotocoagulation.
- Transscleral micropulse diode laser.

## Associated Features

- Neovascular glaucoma.
- Endstage glaucoma.
- Combined cataract surgery and endoscopic cyclophotocoagulation.
- Hypotony.
- Chronic inflammation.
- Phthisis.

## INTRODUCTION

Cyclodestructive procedures reduce intraocular pressure (IOP) by decreasing aqueous production through destruction of the nonpigmented ciliary epithelium responsible for producing aqueous. Historically, destruction of the ciliary body has been difficult to titrate and can cause significant damage to adjacent structures and permanent alteration of the blood-aqueous barrier. Therefore, these procedures were reserved for eyes that had glaucoma refractory to medical, laser, and surgical treatment. Newer technologies have resulted in improved selective targeting of the ciliary epithelium with a reduction in the associated side effects of phthisis bulbi, visual loss, and unpredictable IOP reduction. Micropulse application of the diode laser has recently emerged as an additional treatment option that may further mitigate these risks.

## HISTORICAL REVIEW

Selective destruction of the ciliary body with nonpenetrating diathermy was described by Weve in 1933, and penetrating diathermy was described by Vogt in 1936. Destruction of the ciliary body by freezing or cryotherapy was introduced in 1950 by Biette and found to be less destructive and more predictable compared with cyclodiathermy.<sup>1</sup> However, the IOP reduction was still inconsistent, and the complication rate was relatively high.

Cyclophotocoagulation was made possible with the introduction of the xenon arc photocoagulation in 1961 and the ruby laser in 1971. The transpupillary route of laser delivery was hampered by limited visualization of the ciliary processes. Despite the absence of visualization, the transscleral route became the preferred method of cycloablation in cases of refractory glaucoma. In 1981, Fankhauser described a longer pulse duration thermal ablation using a neodymium:yttrium-aluminum-garnet (Nd:YAG 1064 nm) laser system to perform transscleral cyclophotocoagulation (TCP). The availability of the instrument facilitated wide clinical use,<sup>2</sup> but the introduction of a solid-state diode (810 nm) laser equipped with a disposable probe increased economy and accessibility.<sup>3-9</sup> More recently, endoscopic cyclophotocoagulation (ECP) with the use of a diode laser equipped with an endoscope has allowed direct visualization and targeting of the ciliary epithelium.

## PREOPERATIVE EVALUATION AND DIAGNOSTIC APPROACH

Cyclodestructive procedures are usually reserved for eyes with poor visual potential (<20/400), eyes in which incisional procedures have failed, eyes in which filtering surgery has a high failure rate (e.g., extensive conjunctival scarring, neovascular glaucoma, aphakic and pseudo-phakic glaucoma, and glaucoma associated with silicone oil), and eyes of patients who have a medical contraindication to filtration surgery.<sup>10</sup>

The risks of cyclodestructive surgery include inflammation, pain, chronic hypotony, macular edema, vitreous hemorrhage, and phthisis. Because of these risks, proper technique and patient selection are critical to achieving the desired therapeutic result. Improved treatment parameters in TCP has led to a reduction in side effects and a willingness to use the procedure in eyes with better vision. In ECP, cyclophotocoagulation is guided by visual endpoints that limit overtreatment and damage to non-targeted tissue. Indeed, the role of ECP has expanded and is now used in nonrefractory glaucoma, in pediatric glaucomas, in combination with cataract extraction, and in cases where glaucoma filtering surgery carries higher risks of complications and failure.

## MECHANISM OF ACTION

Cyclocryotherapy nonselectively damages the epithelial, vascular, and stromal components of the ciliary body. TCP lowers IOP by destroying ciliary epithelium and the associated vasculature, leading to decreased aqueous humor production. The semiconductor diode laser with a wavelength of 810 nm has lower scleral transmission compared with the previously used Nd:YAG laser (1064 nm) but greater absorption by melanin. This allows the use of 50% less energy compared to the continuous wave Nd:YAG laser to achieve the same therapeutic effect.

TCP laser energy is more effectively absorbed by pigmented tissue in the ciliary body compared with cryotherapy, which is diffusely absorbed by all structures. Contact methods of TCP produce less scatter and thus require less energy than the noncontact methods.<sup>2</sup> As a result, the contact method of treatment is preferred and has been traditionally indicated in advanced glaucoma, in which the IOP is inadequately controlled despite maximal treatment.

Histologically, both diode and Nd:YAG lasers used for TCP produce fragmentation and detachment of the epithelium of the ciliary processes with simultaneous destruction of the ciliary body vasculature.<sup>11</sup> At least three mechanisms are thought to be important in lowering IOP: (1) inflammation, which is prominent in the first week or so after treatment; (2) decreased aqueous production through ablation of the pars plicata, through either a direct or indirect effect on the vasculature; and (3) increased uveoscleral outflow resulting from laser delivery to the region of the pars plana.<sup>9</sup>

ECP diode laser treatment appears to limit coagulative necrosis to the ciliary epithelium and stroma of the ciliary processes, thus acting largely to decrease aqueous production at the level of the ciliary body epithelium.

## ALTERNATIVES TO A CYCLODESTRUCTIVE PROCEDURE

The alternatives to a cyclodestructive procedure include fistulizing surgery by trabeculectomy or drainage implantation. The TCP procedure is advantageous because it is quick, is external, and can be performed in the office.

It is generally reserved for eyes with poor visual potential because of the risk of chronic inflammation and decreased visual acuity. ECP must be performed in the operating room and does not effect a rapid drop in IOP but is less likely to result in pain, inflammation, and overtreatment compared with TCP.

## ANESTHESIA

The ciliary processes are highly innervated and painful to treat without adequate anesthesia. Transscleral procedures require local (retrobulbar or peribulbar) anesthesia and can often be performed in an office setting. ECP requires local (topical with intracameral lidocaine, retrobulbar/peribulbar block) or general anesthesia and is performed in an outpatient surgical or hospital setting.<sup>4</sup> Most glaucoma medications are continued before and after cyclodestructive procedures and are discontinued only if an adequate IOP lowering is achieved. Epinephrine drugs, miotics, and prostaglandin analogues should be used with caution postoperatively because of the risk of increased inflammation and its associated complications.

## SPECIFIC TECHNIQUES

### Cyclocryotherapy

Cyclocryotherapy has fallen out of favor because of its poor risk/benefit profile and inadequately controlled application. (The interested reader is referred to the third edition of this text.)

### Transscleral Cyclophotocoagulation

#### Noncontact and Contact Nd:YAG Laser

#### Cyclophotocoagulation

Nd:YAG laser cyclophotocoagulation has been largely supplanted by contact diode laser cyclophotocoagulation and has also fallen out of mainstream use. (The interested reader is referred to the third edition of this text.)

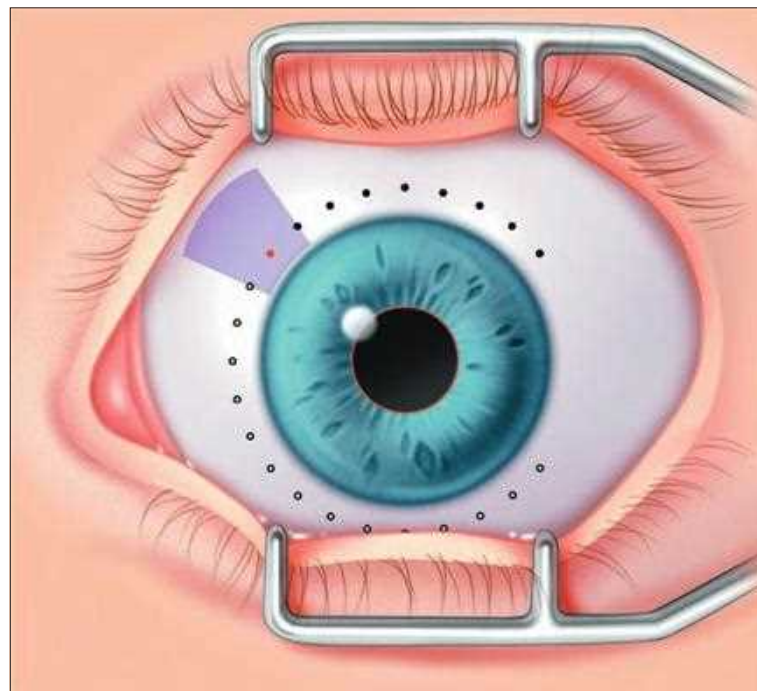
#### Semiconductor Diode Laser Transscleral Cyclophotocoagulation

Diode laser TCP is the most widely used method of ciliary ablation with reported success rates ranging from 40%–80%. The technique used for the semiconductor diode laser (wavelength 810 nm) is similar to that used for the contact Nd:YAG laser (Table 10.26.1). The anterior edge of the probe approximates the surgical limbus so that the laser beam is directed 1.2 mm posteriorly toward the ciliary processes (Figs. 10.26.1 and 10.26.2). Starting settings are 1500–2500 mW for 1.5–3 seconds and a total of 18–24 spots (Fig. 10.26.3). The 3 o'clock and 9 o'clock positions are spared. The results are similar to those achieved using Nd:YAG TCP<sup>3,4,10</sup> despite using lower energy (55% of that used with the Nd:YAG laser). In addition, because semiconductor diode lasers have a solid-state construction, they have the advantages of portability, durability, and smaller size compared with the Nd:YAG laser<sup>3,4</sup> (see Fig. 10.26.3).

#### Micropulse Diode Cyclophotocoagulation

The micropulse diode is a newer mode of delivering laser energy to the ciliary body. TCP delivers continuous energy to the ciliary body, whereas the micropulse delivers short bursts alternating with rest intervals, with

a typical on–off duty cycle of 31.3%. The micropulse probe is held with firm pressure at the edge of the limbus. The probe is swept in a continuous motion, treating the inferior and superior ciliary processes with 1500–2000 mW for 50–90 seconds each (Fig. 10.26.4). As with TCP, care is taken to avoid the long ciliary nerves at the 3 o'clock and 9 o'clock positions.



**Fig. 10.26.1 Diode Cyclophotocoagulation Application.** The unit is portable and equipped with a semidisposable probe. (IRIDEX Corporation, Mountain View, CA.)



**Fig. 10.26.2 Tip of G-Probe.** The laser probe tip is located 1.2 mm posterior to the limbus. (IRIDEX Corporation, Mountain View, CA.)

**TABLE 10.26.1 Comparison of Treatment Parameters for Laser Cyclophotocoagulation**

	Transscleral	Micropulse	Endoscopic
Anesthesia	Peribulbar, retrobulbar	Peribulbar, retrobulbar	Peribulbar, topical, intracameral
Setting	Office, OR	Office, OR	OR
Laser	810 nm	810 nm	810 nm
Power	1.5–3.0 W	1.5–2.0 W	0.25 W
Duration	1.5–3.0 seconds	100–180 seconds total	Continuous—based on whitening
Incision	None	None	Clear cornea, pars plana
Probe	G-probe or sapphire tip	Micropulse probe	Curved endoscope
Postoperative medications	Prednisolone, atropine	Prednisolone, atropine	Prednisolone, gatifloxacin, ketorolac



**Fig. 10.26.3 Diode laser unit.** (IRIDEX OcuLight SLx, IRIDEX Corporation, Mountain View, CA.)





**Fig. 10.26.4** Dual-function micropulse diode laser. (IRIDEX Cyclo G6, IRIDEX Corporation, Mountain View, CA.)

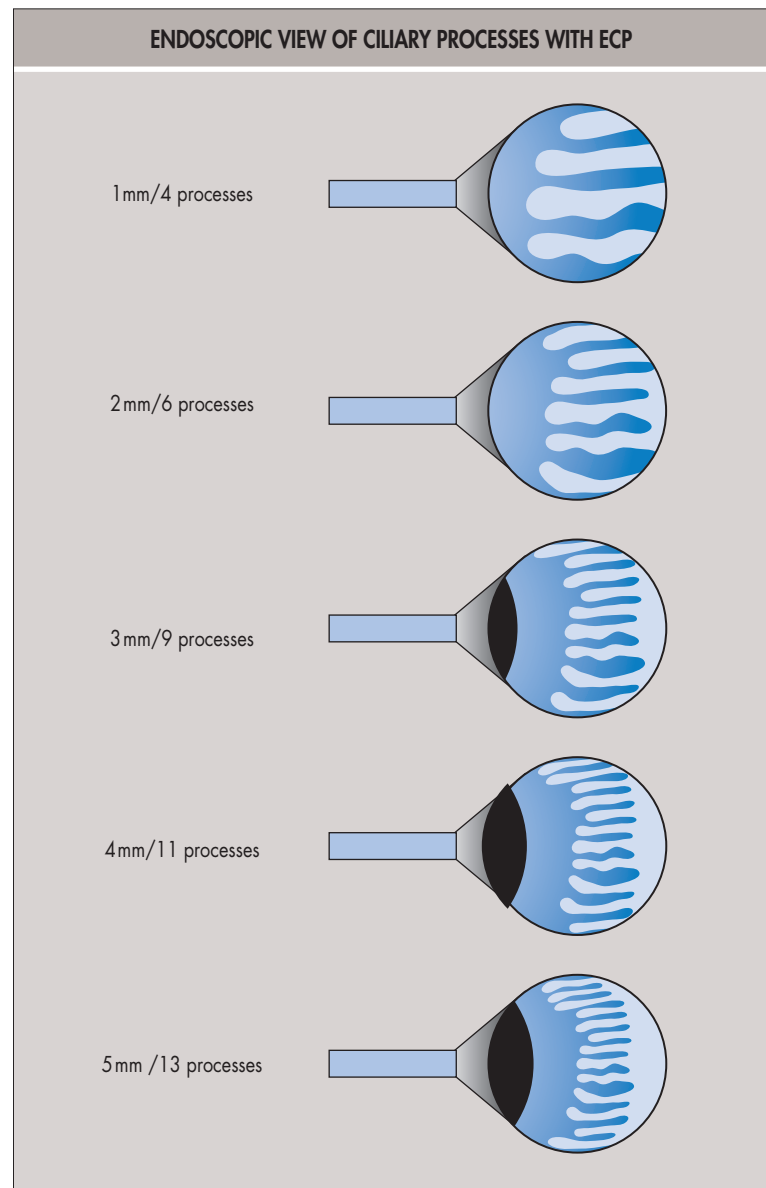
## ENDOSCOPIC LASER CYCLOPHOTOCOAGULATION

ECP is performed with an 810 nm diode laser, just as in TCP. The endoscopic unit is also equipped with a 175 W xenon light source that provides illumination and a helium–neon laser aiming beam (Endo Optiks, Little Silver, NJ). This fiberoptic imaging system allows for direct visualization of ciliary processes during treatment (Fig. 10.26.5). Maximum power is limited to 1.2 W, and exposure time is adjustable up to a continuous duration. Typically, starting settings are 0.25 W with continuous exposure time. The actual time of exposure is based on visual feedback of ciliary process shrinkage and whitening.<sup>12–17</sup> The procedure can be performed through a clear corneal incision, a scleral tunnel, or a pars plana incision (Fig. 10.26.6). Visibility of the ciliary processes is best in aphakia and pseudo-phakia but is limited in patients with phakia. Typically, the ciliary process is treated as completely as possible, as there is a significant portion posteriorly that cannot be treated, unless approached with the endoscope through the pars plana after a satisfactory vitrectomy has been performed. After the procedure, cycloplegics are not required, and corticosteroids are used in a similar manner to other anterior segment surgery. Follow-up is the same as for any other intraocular surgery.

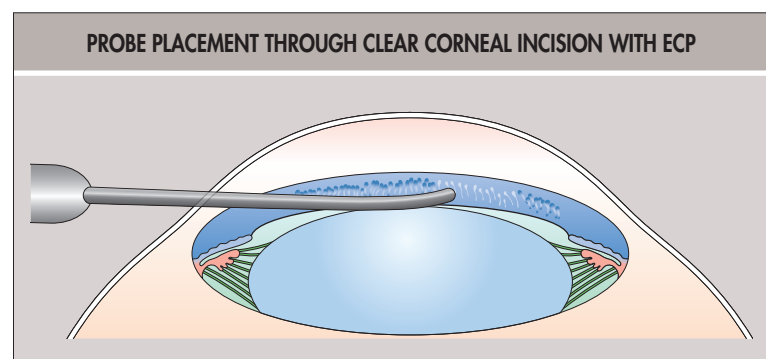
## COMPLICATIONS

All forms of cyclodestructive procedures may damage ciliary muscle, ciliary epithelium, iris, and retina (Table 10.26.2). Complications include reduced visual acuity, uveitis, pain, hemorrhage, and phthisis bulbi. All complications, especially pain and inflammation, seem less severe after laser TCP than after cyclocryotherapy, and complications with ECP seem to be less severe than those of TCP. Reports suggest that micropulse diode has lower rates of serious complications, which include hypotony, phthisis, and vision loss, compared with TCP.<sup>18–20</sup> As with TCP, repeat treatments may be required, but there is no evidence that retreatment rates are higher than with TCP.<sup>18</sup>

For transscleral procedures, the occurrence of audible tissue disruptions does not correlate with success rate. Audible pops correlate with intraocular tissue disruption but not necessarily at the target tissue of the ciliary body. These are considered unwanted side effects, as is intraocular hemorrhage.<sup>21</sup> Possible causes of decreased vision include IOP spikes in the perioperative period,<sup>5,6</sup> postoperative cystoid macula edema, and progression of glaucomatous optic neuropathy in spite of the cyclodestructive treatment. The occasional gain in vision presumably results from decrease in corneal edema.<sup>5</sup> Potential complications of diode TCP include conjunctival surface burns that occur when tissue debris becomes coagulated on the tip, and with increased perilimbal pigmentation, but these heal quickly.<sup>4</sup> A higher incidence of persistent hypotony and vision loss has been reported in neovascular glaucoma.<sup>22,23</sup> Corneal graft failure is a significant problem after cycloablation for refractory glaucoma. It has been reported to occur in 11%–44% of patients.<sup>4,24</sup> Hyphema and vitreous hemorrhage are rare. Phthisis, hypotony, and loss of visual acuity may become chronic complaints.



**Fig. 10.26.5** Endoscopic view of ciliary processes with endoscopic cyclophotocoagulation (ECP).



**Fig. 10.26.6** Probe placement through the clear corneal incision with endoscopic cyclophotocoagulation (ECP).

The potential complications of ECP include all risks listed except for conjunctival surface burns; however, these complications appear to occur at a much lower rate compared with TCP. In addition, ECP carries the risk of damage to the crystalline lens, zonular rupture, and the inherent risks of an intraocular procedure, which include retinal detachment and endophthalmitis.

## OUTCOME

Diode TCP has been reported to produce results equivalent to prior technologies (i.e., cyclocryocoagulation and Nd:YAG cyclophotocoagulation—IOP

TABLE 10.26.2 Complications of Cycloablative Techniques

	Transscleral Cyclophotocoagulation	Micropulse Diode Cyclophotocoagulation	Endoscopic Cyclophotocoagulation
Conjunctival burn	++	+	0
Hyphema	+	+	+
Inflammation	+++	++	++
Pain	++	++	+
IOP spike	++	++	++
Cataract	++	+	+
Pupil abnormality	+	+	++
Hypotony	+	0	0
Need for retreatment	+	++	++
Loss of visual acuity	++	+	+
Vitreous hemorrhage	+	+	+
Choroidal detachment	+	+	+
Phthisis	++	0	+
0, never; +, rare; ++, sometimes; +++, frequent. IOP, Intraocular pressure.			

less than 22 mm Hg in 60%–84% and re-treatment rate of 28%–45%)<sup>25,26</sup> while offering certain technological advantages. Postoperative complications, including pain, inflammation, hyphema, and phthisis, have been reported to be less common than in other cyclodestructive procedures. Three different kinds of lasers (diode laser, free-running Nd:YAG laser, and continuous wave mode Nd:YAG laser) were compared in patients with neovascular glaucoma. Diode TCP had the best success in lowering IOP in 55.9% of patients after 3 years with the fewest complications.<sup>26</sup>

The literature on micropulse diode is more limited because this is a newer technology. A prospective study of 48 patients were randomized to receive either TCP or micropulse, and those in the micropulse group demonstrated a significantly higher success rate (75%) compared with the TCP group (29%) at 1 year, although this difference was not maintained through 18 months of follow-up. However, the micropulse group had significantly lower complication rates, including hypotony and vision loss, compared with the TCP group.<sup>18</sup> Although further studies are needed, micropulse is a promising new modality with an improved side-effect profile compared with TCP.

Studies evaluating ECP for treatment of refractory glaucoma used 500–900 mW for 0.5–2.0 seconds over a mean 245° of the ciliary body.<sup>14</sup> Mean decreases in IOP of 34% were reported. The studies showed that visual acuity improved or remained stable in 94% of eyes, whereas 6% lost two or more lines of acuity. Postoperative complications included anterior chamber fibrin, hyphema, cystoid macular edema, and choroidal effusion. No hypotony or phthisis was observed.

ECP has been compared favorably with the Ahmed valve, with IOP decreasing to 14.7 ± 6.4 mm Hg compared with 14.0 ± 7.2 mm Hg, with the ECP group less likely to have serious postoperative complications, including choroidal effusions and shallow anterior chambers.<sup>27</sup> In studies of pediatric patients with glaucoma, Neely and Plager reported on 51 ECP

procedures involving 260 ± 58° of treatment.<sup>28</sup> Posttreatment IOP was reduced to 23.6 ± 11.1 mm Hg from a baseline of 35.1 ± 8.6 mm Hg at mean follow-up of 19 months. Complications included two retinal detachments, one case of hypotony, and one case of decreasing vision from hand motion to no light perception vision. Gayton et al. compared the combined procedures of cataract extraction (CE) and trabeculectomy with CE and ECP.<sup>27</sup> They found that 30% of combined CE–ECP patients achieved an IOP below 19 mm Hg at 2 years of follow-up.<sup>29</sup>

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Goniotomy and Trabeculotomy

Sarwat Salim, David S. Walton

10.27

**Definition:** Anterior segment surgical techniques for the treatment of childhood glaucoma.

Key Features

- Angle surgery uses an ab interno or ab externo surgical approach to create a direct communication between the anterior chamber and Schlemm’s canal by incising the trabecular meshwork to lower intraocular pressure.
- Trabeculotomy is performed when the cornea is too cloudy to allow visualization of the angle or when the operating surgeon is unfamiliar with the goniotomy technique.
- Specialized operating instruments: goniotomy uses operating gonioscopy lens and cutting needle or knife; trabeculotomy uses trabeculotomes, Prolene suture, or illuminated microcatheter.
- Success of goniosurgery for primary congenital glaucoma relies on adequate development of the filtration angles based on gonioscopic assessment.

Associated Feature

- Postoperative hyphema is a complication of both procedures.

INTRODUCTION

Goniosurgery represents a unique approach to glaucoma surgery because its goal is to improve outflow facility. By incising the tissue obstructing the trabecular meshwork (Fig. 10.27.1), a direct conduit between the anterior chamber and Schlemm’s canal is created. This is in contradistinction to the creation of an aqueous bypass through a surgical fistula, as seen in filtration surgery. The modern era of goniosurgery began with goniotomy, first performed by Barkan, and has been shown to be effective in the treatment of many types of childhood glaucomas.<sup>1</sup> The growing popularity of trabeculotomy to achieve similar results to goniotomy occurred in parallel

with the introduction and use of the operating room microscope for anterior segment ophthalmic surgery.<sup>2</sup>

INDICATIONS

The indications for goniotomy and trabeculotomy are similar, with trabeculotomy often reserved for cases where adequate visualization of the angle is compromised by corneal opacification. Goniosurgery can be performed in both primary and secondary glaucomas, with variable expected outcomes (Table 10.27.1). The glaucoma type and the severity of the angle defects are the most important prognostic factors when entertaining these interventions, whereas the age of the patient is of less importance.

INSTRUMENTS

Specialized instruments are necessary and must be available for both trabeculotomy and goniotomy procedures. A goniotomy may be performed with use of an independent head-mounted light source and magnification loupe or with a tilting microscope, but a trabeculotomy always requires the surgical microscope. Suggested necessary supplies and instruments are listed in Table 10.27.2.

TABLE 10.27.1 Diagnostic Indications for Goniosurgery

Favorable Prognosis	Unfavorable Prognosis
Infantile primary congenital glaucoma (PCG)	Nevus flammeus–associated glaucoma
Iridotrabeculodysgenesis (iris hypoplasia)	Newborn PCG
Juvenile open-angle glaucoma	Axenfeld–Rieger anomaly/syndrome
Recurrent infantile PCG	Neurofibromatosis (NF-1)
Congenital aniridic glaucoma	Acquired aniridic glaucoma
Congenital infantile rubella glaucoma	Infantile aphakic glaucoma
Corticosteroid-induced glaucoma	Congenital iris ectropion syndrome
Glaucoma secondary to uveitis	Lowe syndrome–related glaucoma

TABLE 10.27.2 Instruments and Supplies: Goniotomy and Trabeculotomy Procedures

Goniotomy	Trabeculotomy
Supplies	
Balanced saline solution (BSS)	BSS
Apraclonidine 0.5%	Apraclonidine 0.5%
Pilocarpine hydrochloride (HCl) 1%	6-0 nylon suture
Intracameral acetylcholine chloride 1:100	9-0 or 10-0 absorbable suture
Viscoelastic material	10-0 nylon suture
9-0 or 10-0 absorbable suture	
70% isopropyl alcohol	
Instruments	
Loupe or tilting operating microscope	Operating microscope
Operating gonioscopy lenses—small and large	Paracentesis knife
Barkan lens; Swan–Jacob lens	Trabeculotomy probes (Harms)—right and left
Goniotomy knives: No. 69 Beaver blade	
Storz SP62233; Swan knife	Vannas scissors
No. 15 Bard–Parker blade	
25-gauge needle	
Locking fixation forceps	
Paracentesis knife	



Fig. 10.27.1 Goniotomy procedure showing incision of the trabecular meshwork.

## PREOPERATIVE CARE

Attention to the preoperative preparation of a patient for a goniotomy or trabeculotomy procedure is helpful. Glaucoma medications used prior to a planned goniotomy can successfully clear a glaucoma-related corneal opacity and improve view of the angle during surgery. Oral acetazolamide, at a dose of 10–15 mg/day, can produce significant lowering of intraocular pressure (IOP) and clearing of the cornea within 1 week. However, this medication should be discontinued after surgery to allow restoration of aqueous production to decrease the risk of postoperative hypotony and a secondary reflux hyphema.

Congenital nasolacrimal duct obstructions and acute respiratory infections are common in infants and young children. If a patient presents with dacryocystitis and purulent discharge, successful lacrimal probing should be performed prior to the planned glaucoma procedure. Upper respiratory infections also must be recognized and may postpone general anesthesia.

## EXAMINATION UNDER ANESTHESIA

Following the induction of anesthesia, the ocular examination is repeated to confirm and obtain additional clinical patient information. Because of the IOP-lowering effect of inhalational anesthetic agents, tonometry is best done soon after the initiation of anesthesia. Corneal diameter measurements and appearance of the optic nerves should be recorded for comparison with future observations. Specialized assessments, including anterior segment slit-lamp examination, gonioscopy, corneal pachymetry, photography, and ultrasonography, can be reserved for this time.

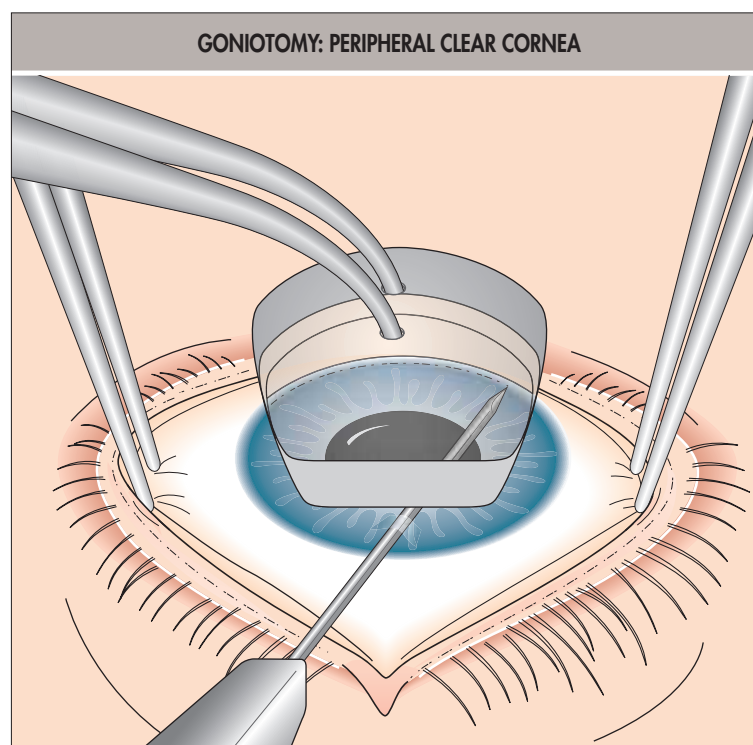
Gonioscopy is essential preparation for goniotomy and trabeculotomy procedures. This is best performed during the examination under anesthesia (EUA) by using Koeppel lenses, which provide a direct view of the filtration angle, or alternatively with mirrored lenses by using the operating microscope. The angle anomaly or acquired defects must be assessed to determine their severity, to establish the diagnosis of the glaucoma type, and to prepare for appropriate surgical procedure. The surgeon's intimate familiarity with the architecture of the angle structures is vital for a successful procedure. When a goniotomy is planned, corneal clarity sufficient to allow visibility of the angle structures must be confirmed at the time of the EUA.

## PROCEDURES

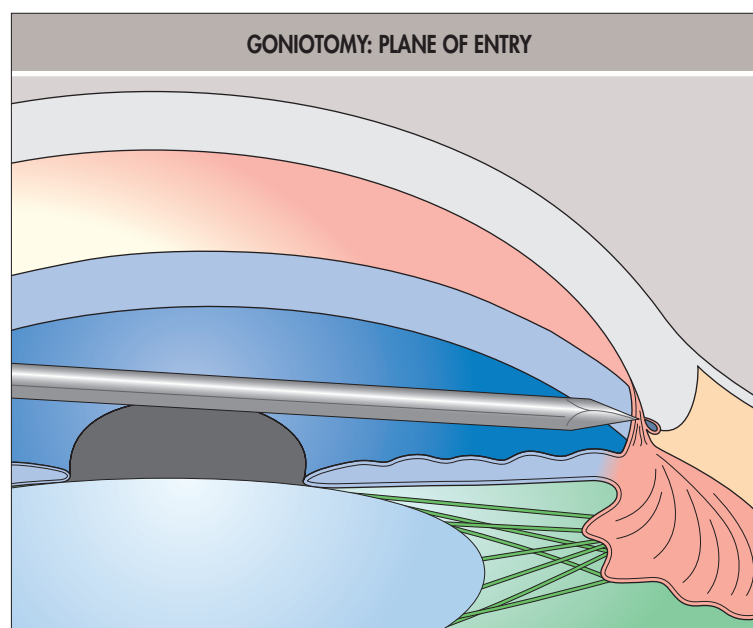
### Goniotomy

The surgical technique for goniotomy has not changed significantly since Barkan's original description, which persists as the best reference for this procedure.<sup>3</sup> If the gonioscopic view is impeded by epithelial edema despite medical management, the epithelium can be removed intraoperatively to provide a clearer window to view the angle adequately. This is usually accomplished by applying a small drop of 70% isopropyl alcohol to the cornea, followed by gentle removal of the epithelium by using a rounded scalpel blade. Before preparation of the surgical field, apraclonidine 0.5% is applied to the limbal region in proximity to the angle quadrant to be treated to reduce the amount of postoperative reflux hyphema. After the eye is prepped and draped in the usual manner, the lashes are taped to prevent contact with the goniotomy instruments. The eye is positioned with the plane of the iris tilted away from the surgeon after placement of locking-fixation forceps on the vertical rectus muscles, if nasal or temporal goniotomy is to be performed (Fig. 10.27.2). Conversely, for an inferior goniotomy, the horizontal rectus muscles can be fixed with forceps. The operating microscope should be tilted toward the surgeon to enable a comfortable view of the angle through an operating goniolens placed on the cornea. The lens must be small enough to allow entry of the operating knife or needle through the peripheral cornea. Rotation of the eye prior to entry will change the position of the incision in the trabecular meshwork, whereas rotation after entry can enable a longer trabecular meshwork incision above and below the starting point. Viscoelastic material may be introduced into the anterior chamber prior to the goniotomy procedure to reduce the risk of losing the anterior chamber. Some surgeons also prefer to use low-strength pilocarpine or miocchol preoperatively to constrict the pupil to lessen the risk of injury to the crystalline lens. However, one needs to be mindful that these agents may lead to narrowing of the angle from forward shift of the lens-iris diaphragm, making the procedure technically more difficult.

The goniotomy needle or knife is inserted into the anterior chamber and its path viewed attentively as it passes across the anterior chamber. The

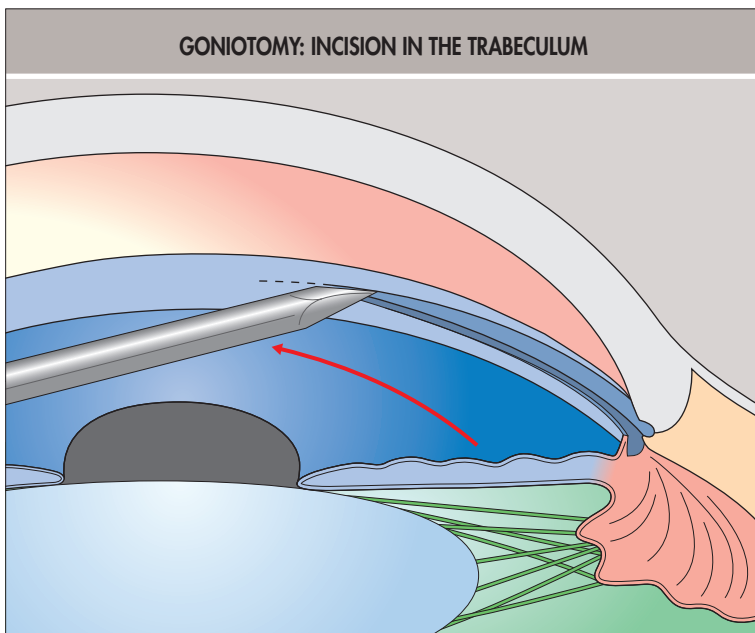


**Fig. 10.27.2 Goniotomy.** The eye is fixated with forceps and rotated away from the surgeon to facilitate entry of the knife or needle through the peripheral clear cornea.



**Fig. 10.27.3 Goniotomy.** The plane of entry of the cutting instrument is carefully monitored.

cutting instrument should be visually guided across the anterior chamber anterior to the iris (Fig. 10.27.3). The mid-trabecular meshwork is engaged diametrically opposite the point of entry (Fig. 10.27.4), and the incision is then extended to the right maximally. The knife may be returned to the starting point followed by continuation of the trabecular incision to the opposite side. The incision should be created smoothly with minimal resistance and effort while keeping the knife at the same depth into the trabeculum. The progress of the incision in the trabecular meshwork can be followed by visualization of a white line or cleft. Usually 4–6 clock hours of trabecular meshwork is incised. Following careful removal of the knife or needle, the anterior chamber is deepened and the entry site secured, if necessary. Any remaining viscoelastic material must be removed by irrigation. A small reflux hyphema commonly occurs and ceases after restoration of the anterior chamber.



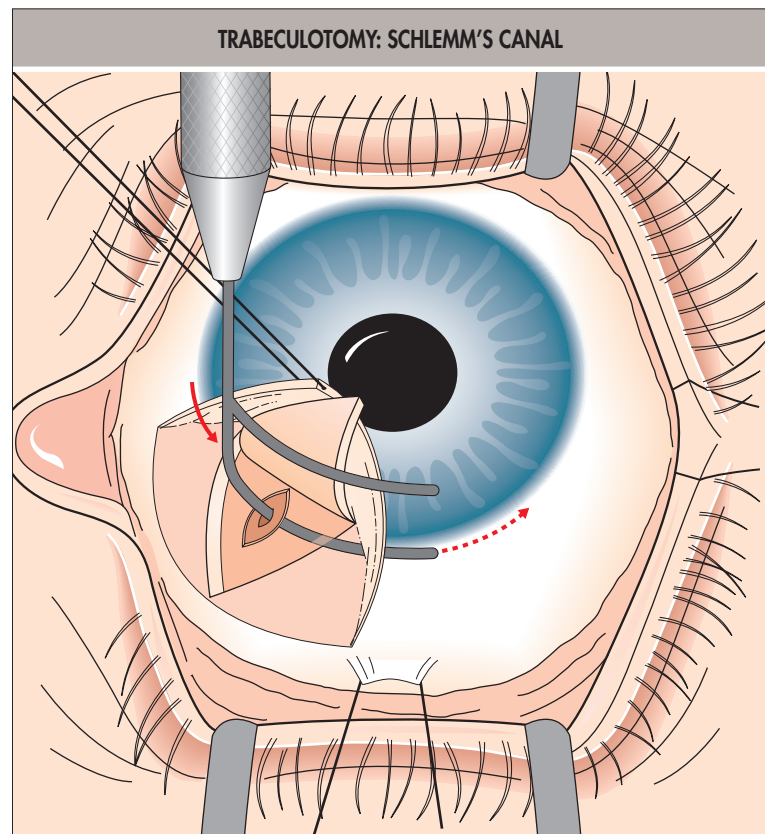
**Fig. 10.27.4 Goniotomy.** The incision in the trabeculum is visualized behind the cutting instrument.

## Trabeculotomy

For trabeculotomy, the eye is prepared and positioned in a manner similar to that for adult eye surgery. A temporal approach may be considered to preserve the superior conjunctiva for future filtration surgery, if ever indicated. A fornix or limbal-based peritomy is performed to expose sclera above Schlemm's canal. An anterior chamber paracentesis is placed for future access to the anterior chamber. A 3-mm triangular partial-thickness scleral flap is created and extended anteriorly to allow visualization of the more anterior darker-blue limbal tissue adjacent to the sclera. A radial scleral incision 2 mm in length is then made over the sclerolimbic junction and continued more deeply until the circumferential fibers of Schlemm's canal are seen and entry occurs, often evident by leakage of clear fluid or blood. The presence and patency of Schlemm's canal may be confirmed by introducing a short segment of 6-0 Prolene or nylon suture material. In some cases, if the view permits, a gonioscope may be used to establish the proper location of the suture in the angle. In cases with cloudy corneas, attention should be directed to the resistance encountered during the passage of the suture, which should enter with minimal difficulty when correctly placed.

Trabeculotomes, right and left, are used to incise the inner wall of Schlemm's canal and the trabecular meshwork. The distal arm of the instrument is entered into Schlemm's canal and advanced for approximately 2 clock hours circumferentially (Fig. 10.27.5). The instrument is then rotated into the anterior chamber without encountering resistance and above the iris to expose approximately two thirds of its length (Fig. 10.27.6). The proximal arm serves as a guide during the procedure. The trabeculotome is then withdrawn and a similar maneuver performed on the opposite side of the scleral incision. It may be helpful to introduce a small amount of viscoelastic before the pass of the trabeculotome to make the eye firm and to move the iris more posteriorly, away from the plane of the trabeculotome, to minimize complications. A small hyphema may occur. The scleral flap is closed with interrupted 10-0 nylon or 8-0 polyglactin sutures. The conjunctiva is repaired with a 9-0 or 10-0 polyglactin suture.

An alternative trabeculotomy technique that allows the trabecular meshwork to be opened 360° employs a 6-0 polypropylene suture that is fed into Schlemm's canal circumferentially before being pulled into the anterior chamber through the trabeculum.<sup>4</sup> This procedure, which has worked well, has no indication different from goniotomy and standard trabeculotomy. Recently, illuminated microcatheter (iTrack 250A; iScience Interventional, Menlo Park, CA), has been employed to perform circumferential trabeculotomy.<sup>5,6</sup> After identification of Schlemm's canal, as in traditional trabeculotomy, the microcatheter is introduced into the canal and threaded circumferentially around the canal. After successful cannulation, both ends of the catheter are grasped, pulled in opposite directions, and removed from the eye, breaking through the trabecular meshwork. The illuminated microcatheter offers the advantages of verification of the catheter tip inside the Schlemm's canal and prevents inadvertent misdirection into the suprachoroidal space that could potentially occur with suture



**Fig. 10.27.5 Trabeculotomy.** Minimal resistance is encountered when the distal arm of the trabeculotome is placed in Schlemm's canal.

trabeculotomy. In addition, unlike traditional trabeculotomy performed with trabeculotomes, this technique may allow treatment of the entire angle in one setting, minimizing surgical and anesthetic risks.

Viscotrabeculotomy is another technique that involves injection of high-viscosity sodium hyaluronate (Healon GV, Pfizer, NY) into Schlemm's canal prior to the passage of trabeculotome.<sup>7</sup> The viscoelastic agent prevents collapse of Schlemm's canal, adhesions of incision lips, and shallow anterior chamber.

Grover et al.<sup>8</sup> recently described a new technique for ab interno trabeculotomy. This procedure is termed *gonioscopy-assisted transluminal trabeculotomy* (GATT). Essentially, paracentesis are made in the superonasal or inferonasal quadrant and temporally using a 23-gauge needle. A viscoelastic agent is injected into the anterior chamber. Under gonioscopy visualization, a 1- to 2-mm nasal goniotomy is created. Microsurgical forceps are used to direct a suture or illuminated microcatheter into Schlemm's canal. The distal tip of the suture/catheter, once it has passed through the entire canal, is retrieved and externalized, thus creating a 360° trabeculotomy. The viscoelastic is removed from the anterior chamber with stromal hydration of the paracentesis sites.

## POSTOPERATIVE CARE

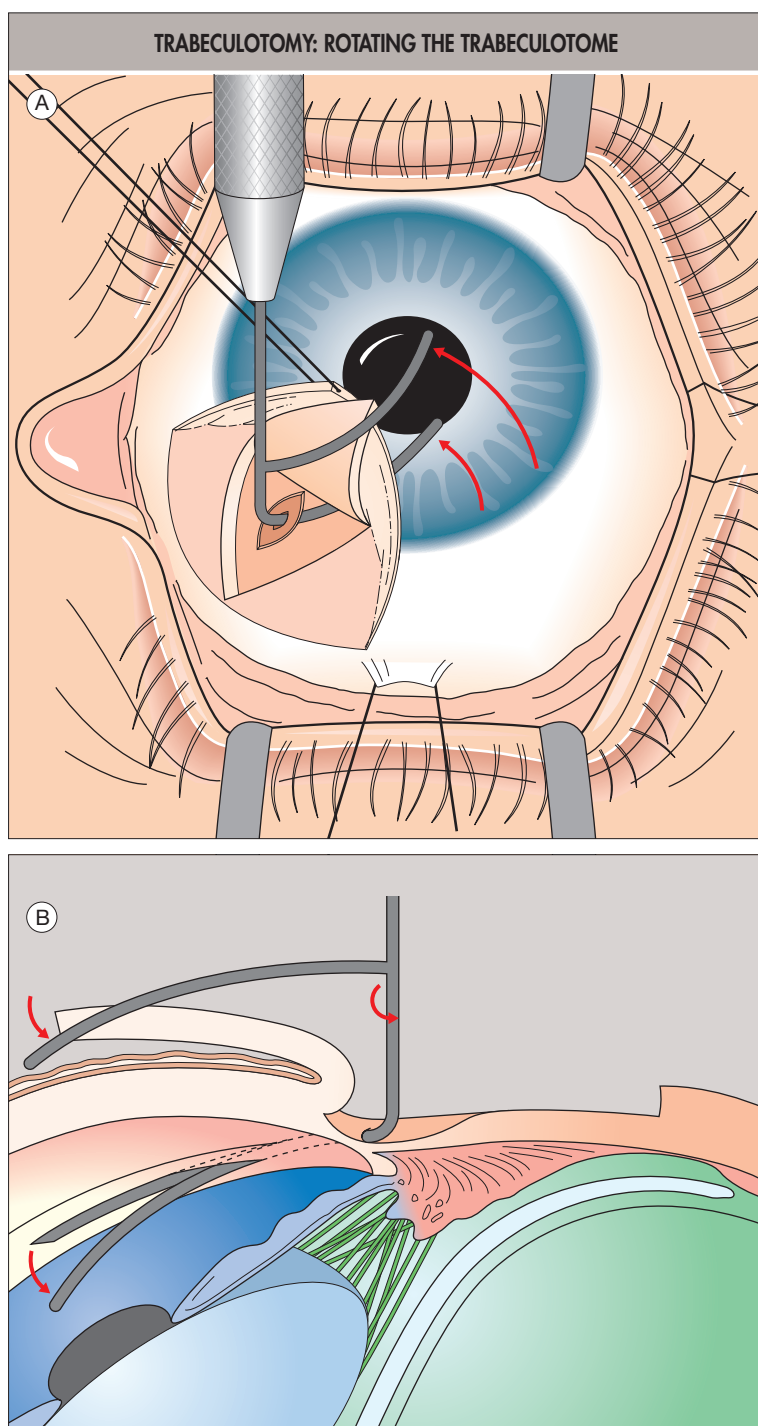
An eye patch and shield are applied after the surgery and removed at the first examination. A combination of corticosteroid and antibiotic drops is prescribed for a few days. The risk of an excessive postoperative hyphema may be reduced by administration of topical apraclonidine 0.5% and head elevation. Frequent follow-up examinations are necessary to determine the success or occurrence of complications.

## RESULTS

The results of goniotomy and trabeculotomy vary greatly with the type of glaucoma and severity of the filtration angle defects. The procedures are considered to have similar efficacy for childhood glaucomas, and unfortunately, there is no reason to consider either after failure of the other.

The outcome of goniotomy for primary congenital glaucoma is very favorable, with a reported success rate greater than 80%.<sup>9</sup> As should be expected, children with newborn primary congenital glaucoma respond poorly to goniosurgery related to their severe filtration angle anomaly.<sup>10</sup> The success of goniotomy for primary congenital glaucoma has been correlated inversely with the severity of the IOP and secondary abnormalities.<sup>11</sup> Relapse





**Fig. 10.27.6 Trabeculotomy.** (A,B) The trabeculotome is rotated inwardly and parallel to the iris to lessen the risk of injury to the cornea and the iris.

following successful goniotomy is not common, and more common after repeat procedures.<sup>12</sup> For children with primary infantile glaucoma, repeat goniotomy should be offered for relapse before other procedures are recommended on the basis of gonioscopic determination of the potential for additional incision of the trabeculum.

The results of goniotomy for other types of childhood glaucomas are quite variable (see Table 10.27.1). The results are disappointing often with glaucoma related to Sturge–Weber syndrome or aphakia. In contrast, select patients with uveitic glaucoma have obtained excellent results.<sup>13</sup>

Trabeculotomy is just as effective in cases of primary congenital glaucoma. A study of trabeculotomy for 99 eyes reported success rates of 92% and 82% at 5 and 10 years, respectively, after one or multiple procedures.<sup>14</sup> Yassin et al.<sup>15</sup> reported surgical outcomes of trabeculotomy, trabeculectomy, and combined trabeculotomy-trabeculectomy in 148 eyes with primary congenital glaucoma over a 20-year period. All procedures resulted in a progressive decline in surgical success (defined as IOP  $\leq$  21 mm Hg with

or without medications) from 97% at 5 months to less than 50% after 11 years, without statistically significant difference between procedures. Khalil et al.<sup>16</sup> compared the outcomes of primary trabeculotomy to combined trabeculotomy-trabeculectomy in eyes with congenital glaucoma and reported a success rate of 85.7% in both groups at 3 years. Given similar outcomes with both procedures, the authors suggested that trabeculotomy should be the initial surgery for congenital glaucoma. Ozawa et al.<sup>17</sup> reported higher success rates in primary childhood glaucoma than in secondary childhood glaucoma after conventional trabeculotomy.

Beck et al.<sup>18</sup> evaluated surgical outcomes of 360° suture trabeculotomy in primary congenital glaucoma with a poor prognosis (birth-onset presentation, presentation after 1 year of age, prior failed goniotomy, glaucoma after cataract surgery, and glaucoma associated with other ocular and systemic anomalies) and concluded that this technique has a role in children who have a wide range of ocular pathologies and historically have been thought to be poor candidates for traditional angle surgery. They reported success rates of 63% and 58% at 1 and 2 years, respectively.

El-Sheikha et al.<sup>7</sup> compared the efficacy of with that of conventional trabeculotomy in a prospective, randomized comparative study. Both techniques were reported to have similar IOP reduction with no additional benefit with viscotrabeculotomy. The major limitation of this study was a very short follow-up of 6 months.

Girkin et al.<sup>6</sup> found qualified success of 91.6% and unqualified success of 83.3%. Approximately 50% of the eyes had 360° of the angle treated successfully, with a mean IOP reduction of 57%. The most common complication reported was transient hyphema. In other work, at 2 years postoperatively, microcatheter trabeculotomy demonstrated lower IOP and less need for subsequent glaucoma procedures compared with conventional trabeculotomy.<sup>19</sup>

Grover et al.<sup>20</sup> reported outcomes of GATT in 14 eyes with primary congenital glaucoma and juvenile open-angle glaucoma at a mean follow-up of 20 months. The mean IOP decreased from 27.3 mm Hg to 14.8 mm Hg, and the mean number of medications required decreased from 2.6–0.86. The most common postoperative complication was hyphema, which cleared by 1 month in all cases. GATT may be superior to goniotomy because it opens 360° of the angle unlike goniotomy. The ab interno approach also spares the conjunctiva for future filtration or drainage implant surgery.

## COMPLICATIONS

Serious surgical complications after goniotomy and trabeculotomy are infrequent. Postoperative hyphemas are commonly seen after both procedures but usually are of no clinical significance. When a significant amount of blood does reflux into the anterior chamber and causes a secondary elevation of the IOP, anterior chamber washout must be considered. Infection has rarely been reported after goniosurgery. Injury to the iris or lens is potentially possible with both procedures. Iridodialysis and Descemet's membrane detachment of the cornea can occur with false entry of the trabeculotome during trabeculotomy. As mentioned before, one potential complication of suture trabeculotomy is misdirected suture into the suprachoroidal space. With circumferential trabeculotomy using illuminated microcatheter, 360° passage of the catheter may not be achievable, especially in eyes with previous angle surgery. Most complications of goniosurgery can be circumvented by careful selection of cases and appropriate preoperative preparation, familiarity with the anterior segment and angle structures, and meticulous surgical technique.<sup>21</sup>

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# Minimally Invasive and Microincisional Glaucoma Surgeries

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10.28



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**Definition:** Minimally invasive glaucoma surgery and microincisional glaucoma surgery offer the theoretical advantages of lowering intraocular pressure with incisional surgery but have lower risks compared with conventional operations. Approaches include the use of microdevices for removal or bypass of abnormally high-resistance tissues.

## Key Features

- Minimally invasive glaucoma surgery offers lower surgical and postoperative risk, but often less IOP reduction, compared with conventional glaucoma surgical techniques.
- Minimally invasive and microincisional glaucoma surgeries:
  - Trabeculectomy ab interno (trabectome).
  - Trabecular meshwork bypass stents.
  - iStent G1 and iStent G2 Inject.
  - Hydrus.
  - Subconjunctival shunt.
  - Suprachoroidal shunts.
  - Gold shunt.
  - CyPass.
  - iStent G3 Supra.
  - Canaloplasty.
  - Endocyclophotocoagulation.

## INTRODUCTION

Progress in biomedical engineering and the ability to image and understand delicate outflow structures in the living human eye using optical coherence tomography<sup>1</sup> have led to the development of new surgical options for glaucoma. Glaucoma is now a leading cause of irreversible blindness with increasing prevalence in an aging population.<sup>2,3</sup> Despite the many new arrivals (see list below), the concepts behind trabeculectomy are not entirely new:

- Ab interno (trabectome; Neomedix, Tustin, CA).<sup>4</sup>
- Trabecular meshwork (TM) bypass stents (iStent G1 and iStent G2 Inject; Glaukos, Laguna Hills, CA).<sup>5</sup>
- Hydrus (Ivantis, Irvine, CA).<sup>6</sup>
- Subconjunctival (XEN; AqueSys, Irvine, CA); or suprachoroidal shunts (Solx, Waltham, MA).<sup>7</sup>
- Cypass (Transcend Medical, Menlo Park, CA).<sup>8</sup>
- iStent G3 Supra, Glaukos, Laguna Hills, CA), canaloplasty (iScience Interventional, Menlo Park, CA).<sup>9</sup>
- Endocyclophotocoagulation (Endo Optiks, Little Silver, NJ).<sup>10</sup>

Open-angle glaucoma has been surgically treated for 150 years by either increasing external filtration (De Wecker, 1867),<sup>11,12</sup> internal filtration (angle surgery: Taylor, 1891<sup>13</sup>; suprachoroidal drainage: Heine, 1900<sup>13</sup>), or ciliodestruction (Hancock, 1861).<sup>13</sup>

The development of new devices and technologies was spurred by the realization that the standard surgeries performed today for

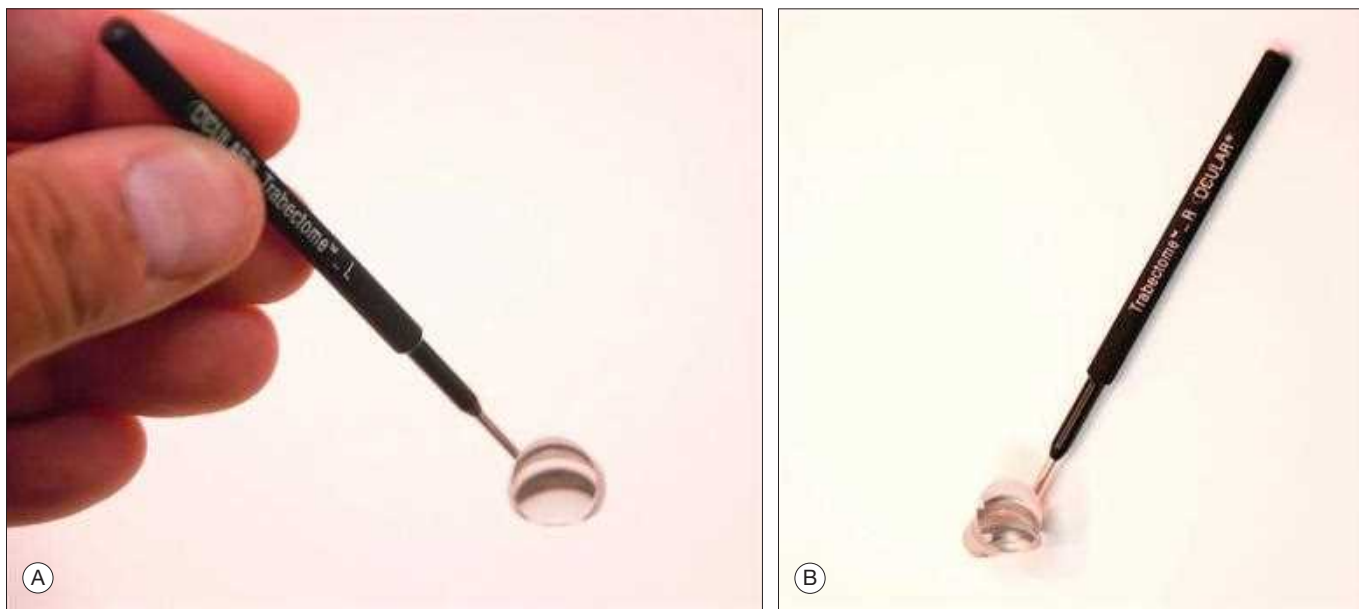
glaucoma—trabeculectomy and epibulbar glaucoma drainage device surgery—have relatively high failure and complication rates.<sup>14</sup> Although not as rudimentary and unsuccessful as at the time of their inception in the form of guarded external filtration by Sugar in 1962<sup>15</sup> or in the form of the gold wire shunt by De Wecker in 1876,<sup>11</sup> both present iterations, trabeculectomy and epibulbar glaucoma drainage device (“tube shunt”) implantation, seem suboptimal, given that postoperative interventions may have to be performed in 70% of trabeculectomies and 25% of tube shunts.<sup>16</sup> In the “tube versus trab” (TVT) study, early postoperative complications occurred in 37% of patients with trabeculectomy and 21% of patients with tube shunts, whereas additional complications during 5 years of follow-up occurred in 38% of trabeculectomies and 36% of tube shunts, and at least two lines of vision were lost in 43% of trabeculectomies and 46% of tubes.<sup>16</sup> For the past 30 years, trabeculectomy was the standard of care for surgical intervention for glaucoma and was made more successful by refinements, such as the use of antimetabolites, argon laser suture lysis, and releasable sutures, but this has also led to more complications, for example, hypotony with or without maculopathy, shallowing of the anterior chamber, choroidal effusions or hemorrhages, hyphema, and cataract formation. Long-term complications are associated with undesirable bleb morphology resulting in late bleb leak, blebitis, or endophthalmitis.<sup>17–22</sup>

As found in the TVT,<sup>23</sup> tube shunts and trabeculectomies can achieve low postoperative intraocular pressure (IOP)—tube shunts averaged 14.4 mm Hg and trabeculectomies achieved 12.6 mm Hg (but were not significantly different from each other) after 5 years.<sup>14</sup> Because these surgeries have not been compared in a randomized controlled fashion to microincisional glaucoma surgery (MIGS), it is not known whether pressure lowering is superior and worth the considerable risk. In fact, prospectively collected MIGS data indicate only slightly higher IOP of 15.2 mm Hg for phaco-trabectome procedures at 5 years<sup>24</sup> and 16.1 mm Hg for the iStent with same session phacoemulsification (“phaco”) at 5 years.<sup>25</sup> The most serious complication of MIGS is a temporary, greater than 10 mm Hg IOP increase during the early postoperative phase that can occur in 3%–10% of trabectome patients<sup>26</sup> and nearly 10% of iStent patients.<sup>27</sup> Early postoperative, transient hyphema is characteristic for all canal surgeries and more common in procedures that generate access to many outflow segments by bypassing the TM over a large arc of the naturally discontinuous and septated Schlemm’s canal (SC). Two reasons why the ab interno procedures are done on the nasal TM are the ease of surgical access directly opposite the surgeon and Schlemm’s canal being shown to be 33% wider nasally than temporally,<sup>28</sup> potentially offering greater outflow.

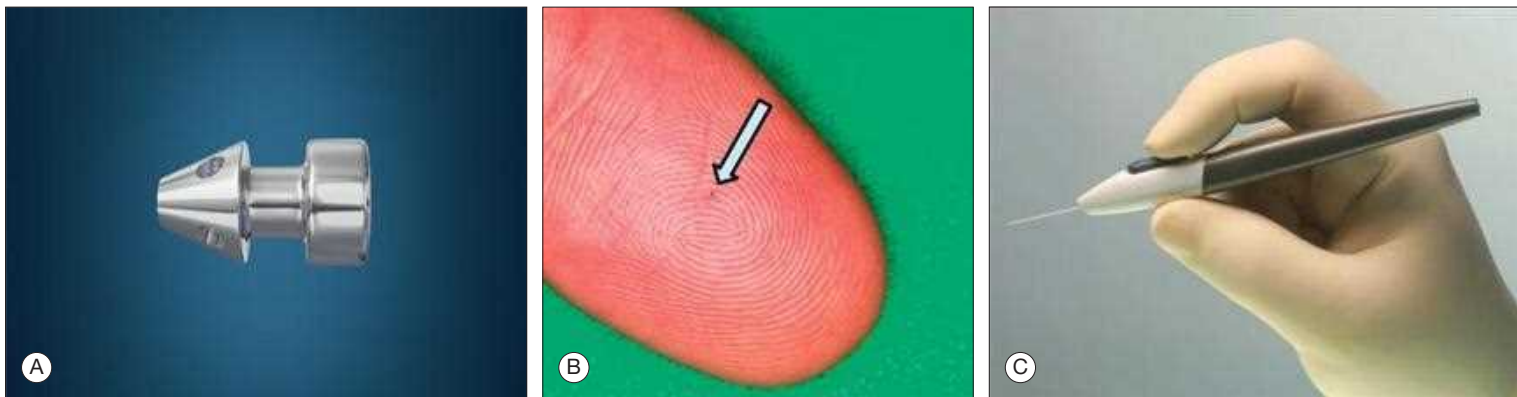
This chapter reviews presently available minimally invasive glaucoma surgery and MIGS ordered by their extent of outflow tract alteration, mechanism, and degree of invasiveness. MIGS bypasses the primary outflow resistance in glaucoma that resides in the TM (reviewed in<sup>29</sup> and<sup>30</sup>), whereas suprachoroidal shunts enhance uveoscleral flow, and others (e.g., XEN) involve alternative drainage pathways entirely.

## CONSIDERATIONS FOR PATIENT SELECTION

Generally, minimally invasive glaucoma surgery and MIGS can be considered in any patient who is a candidate for trabeculectomy or tube shunt implantation. With their improved safety profile, these procedures may also be performed before someone qualifies for conventional filtering surgery. Another argument for earlier surgical intervention are results



**Fig. 10.28.1** Modified Swan–Jacob gonioscope for right-hand dominant (A) and left-hand dominant surgeons (B) that is commonly used in microincisional glaucoma surgery (MIGS). (Courtesy Neomedix Corp.)



**Fig. 10.28.2** iStent Inject. (A) Magnified view of the stent. (B) Size comparison (shunt barely visible at the tip of the arrow). (C) Injector preloaded with two stents. (Courtesy Glaukos Corp.)

from the Collaborative Initial Glaucoma Treatment Study, which suggested that mild to moderate glaucomatous optic neuropathy may be controlled with IOPs in the high teens, whereas advanced changes required IOPs in the low teens.<sup>31</sup> Compliance even with modern once-a-day prostanoids may be as low as 30% at 1 year,<sup>32</sup> and only 10% of patients have their medication available continuously.<sup>33</sup> The cost of surgical reduction of IOP decreases with time because the cost of surgery is divided by the number of years of life from the time of surgery. This is in contrast to medical therapy, which escalates with time paralleling the increased cost and number of medications required to control IOP.<sup>34</sup> When nonmedical therapy is chosen as the first line of glaucoma treatment, the costs of glaucoma, up to \$150 000 per quality-adjusted life-year can be greatly reduced and even provide returns for the healthcare spending.<sup>35</sup> Furthermore, increased diurnal variations of IOP in glaucoma are an independent risk factor for progression,<sup>36,37</sup> and IOP may be better controlled surgically than medically.<sup>34,38,39</sup>

Further considerations for MIGS are patients with poor conjunctiva, patients at risk for postoperative hypotony (i.e., younger age, male gender, moderate to high myopia)<sup>40</sup> or for the development of a serous or hemorrhagic choroidal effusion (myopia, older age, hypertension, atherosclerosis, history of a choroidal effusion or hemorrhage, short axial length—especially nanophthalmos and previous vitrectomy<sup>41–43</sup>). Expedited visual recovery compared with that in trabeculectomy is an additional benefit, especially for monocular patients. Ab interno procedures may produce transient visual obscuration from hyphema, which varies, depending on the extent of access to the angle and the subsequent potential for pressure gradient and flow reversal.<sup>44</sup> As most MIGS procedures are performed under gonioscopic visualization, patients must have clear corneas and a sufficiently wide lid fissure (Fig. 10.28.1). Surgeons have to master gonioscopy and learn to control movements in a highly confined and vulnerable space as

well as instrument rotation using only one hand, as when the direction of ablation is changed in trabectome surgery.

## ANGLE SURGERIES

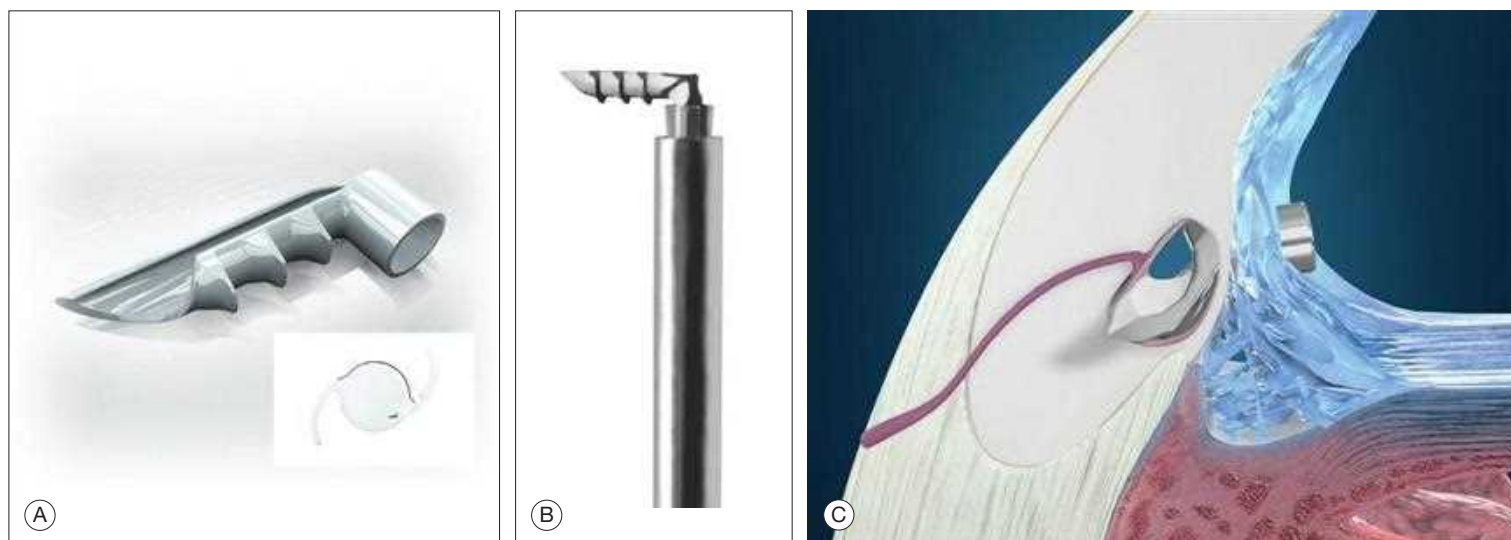
### Trabecular Microbypass Stents

#### Concept

These stenting devices (Fig. 10.28.2) are inserted internally to offer a wider pore into Schlemm's canal because 50% of the pores on the inner wall of Schlemm's canal had a diameter 1  $\mu$ m or less in one histological study.<sup>45</sup> Trabecular microbypass stents directly connect the anterior chamber to SC and the collector channels after implantation. The advantages of having a trabeculotomy-maintaining device currently seem to exceed the disadvantages of a permanent foreign body in the eye that could migrate or damage adjacent structures. The recently introduced iStent G2 Inject will be discussed before the original trabecular microbypass stent, the iStent G1, because we have ordered the discussion of angle surgeries according to their degrees of invasiveness and size.

#### iStent G2 Inject (GTS-400)

The preoperative and anesthetic regimens are identical to those of standard phaco.<sup>46</sup> After cataract extraction, intracameral acetylcholine is used to induce miosis. The chamber is deepened with viscoelastic. The insertion device is moved across the chamber under gonioscopic view by using a Swan–Jacob gonioscope. The second-generation iStent, iStent Inject (Glaukos Corporation, Laguna Hills, CA), is 0.4 mm long and 0.3 mm wide and is made of titanium with a heparin coating. Compared with the larger iStent G1 discussed below, it contains two preloaded stents to avoid



**Fig. 10.28.3** Trabecular microbypass stent iStent G1. (A) Magnified view of 1 mm titanium stent (*insert: size comparison with intraocular lens*). (B) Preloaded in inserter. (C) Implanted in Schlemm's canal. (Courtesy Glaukos Corp.)

having to withdraw and reload the inserter, thereby avoiding hypotony and reflux of blood from the collector channels and SC.<sup>47</sup>

### Technique

The bullet-shaped stents are placed by direct forward penetration into the canal rather than the sideward, sweeping implantation of the first-generation device.<sup>5</sup> Because it is not angled, there is a single stent design for either the right or the left eye. Stents can be placed approximately 2 clock hours apart.<sup>48</sup>

### Results

Bahler et al. found that the outflow facility doubled after inserting one stent and doubled again after the second stent in an anterior chamber perfusion model.<sup>47</sup> Although insertion was done under ideal viewing conditions with direct visualization through a microscope and not gonioscopically through a cornea, the inevitable stent tilt caused apposition of some of the drainage holes against SC or the TM as demonstrated with electron microscopy. The reported data, to date, suggest that from a mean baseline IOP of 22 mm Hg, two iStent G2s lowered IOP by 30% to 15 mm Hg, on average.<sup>27,49–51</sup> The only identified risk factor for failure is lower baseline IOP.<sup>49</sup> The most common complications are hyphema/reflux from deroofing a vein in up to 90%<sup>50</sup> and transient elevations in IOP in 10–15%.<sup>27,52</sup> In the largest study (n = 99), 7% of stents were obstructed, although only half of those needed to be treated (laser synechiolysis).<sup>27</sup>

### iStent G1

The original iStent G1 (Glaukos Corporation, Laguna Hills, CA, USA) (Fig. 10.28.3) is nearly three times as large as the iStent G2 Inject. It has a 1-mm-long body with an angled intake and is also coated with heparin. The body of this titanium device is inserted through the nasal TM into SC by using a dedicated injector. Because SC is discontinuous and septated,<sup>1,28</sup> outflow segments can likely be accessed over 30–60° with a single device.<sup>53</sup>

### Technique

Directing the tip of the implant toward the TM and SC, the stent is inserted midnasally (Video 10.28.1). Tilting the stent 15° toward the TM may ease insertion.<sup>54</sup> Intraoperative confirmation of placement into SC is achieved by noting blood reflux through the stent. The stent is then released from the applicator and the applicator withdrawn from the eye. Tapping the stent can help confirm that it is parallel to the iris and fully inserted. Multiple stents can be placed approximately 2 clock hours apart facing opposite directions.<sup>48</sup> The viscoelastic is aspirated and the wound hydrated. Postoperatively, a fourth-generation fluoroquinolone is given four times per day for 1 week, and prednisolone acetate 1% 4–6 times a day (tapered weekly). All oral or topical glaucoma medications are discontinued and added back, as needed. Proper placement can be confirmed by using ultrasound biomicroscopy (UBM).

### Results

Measurements on human donor eyes have shown that insertion of one stent can nearly double the outflow facility<sup>55</sup> and that the insertion of

two stents can more than quadruple it.<sup>47</sup> The strongest level of evidence comes from a randomized, parallel trial (n = 36) that compared patients who underwent stand-alone phaco with a combined group of patients who underwent phaco with stent placement.<sup>56</sup> After 15 months, there was a 17% decrease in IOP in the combined group compared with only a 9% decrease in the stand alone phaco group despite being on one more medication, on average. The only study-related complications were two cases of stent malposition. Another, larger randomized, parallel trial (n = 240) required an entry IOP at 22 mm Hg or greater following medication washout.<sup>5</sup> By protocol, postoperative IOP was maintained below 21 mm Hg with topical medications in both groups, so mean reduction of IOP versus baseline was only 1.5 mm Hg in the treatment group versus 1 mm Hg in the control group. In the combined group, 66% achieved a 20% reduction in IOP without medications, but it was only 48% in the phaco group. After 24 months, the IOP decrease from baseline was 8% in the combined group versus 1% in the phaco group.<sup>57</sup>

On average, from a mean baseline IOP of 19–21 mm Hg, one first-generation iStent lowers IOP by 21%, two by 23%, and three by 31%.<sup>50</sup> A meta-analysis found that standalone iStent (without phaco) with one iStent lowered IOP by an average of 22% after 18 months, two iStents by 30% at 6 months, and three iStents by 41% after 6 months.<sup>58</sup> Medication load was reduced by one medication in all three groups. For combined iStent with phaco, a meta-analysis found that one iStent lowered IOP by an average of 26% after 18 months, two iStents by 18% after 6 months, and three iStents by 20% after 6 months, again on one less medication compared with baseline.<sup>59</sup> Averaging of present data suggests that the insertion of either two first-generation iStents, three first-generation iStents, or two second-generation iStents can help achieve an IOP 15 mm Hg or less off medications in approximately 84 ± 6% of cases for the first 1–1.5 years, with results of single first-generation stents being more variable.<sup>49,60,61</sup>

The complication profile is similar for first- and second-generation iStents. Complications in first-generation studies similarly include obstruction by fibrin or peripheral anterior synechiae (PAS) (as occurred in 4% of 111 patients<sup>5</sup>) and stent malposition (14%). Stent obstruction has been managed with observation, argon laser, and injection of tissue plasminogen inhibitor (this last intervention was not successful). Four of 111 patients were taken back to the operating room to reposition or replace the stent. Although increased IOP following stent placement can be relatively common (IOP spike >5 mm Hg in 20% of 96 cases),<sup>62</sup> it occurred more frequently in the control group (stand-alone phaco) in the largest trial.<sup>57</sup> Loss of two lines of Snellen visual acuity has not been attributed to the stent in any case. There are no reports of choroidal effusion, persistent hypotony, bleb formation, or endophthalmitis after stent placement. Experimental outflow studies in animal models suggest that outflow is restricted to the area of implantation.<sup>63</sup>

## Hydrus: Ab Interno Schlemm's Canal Scaffold

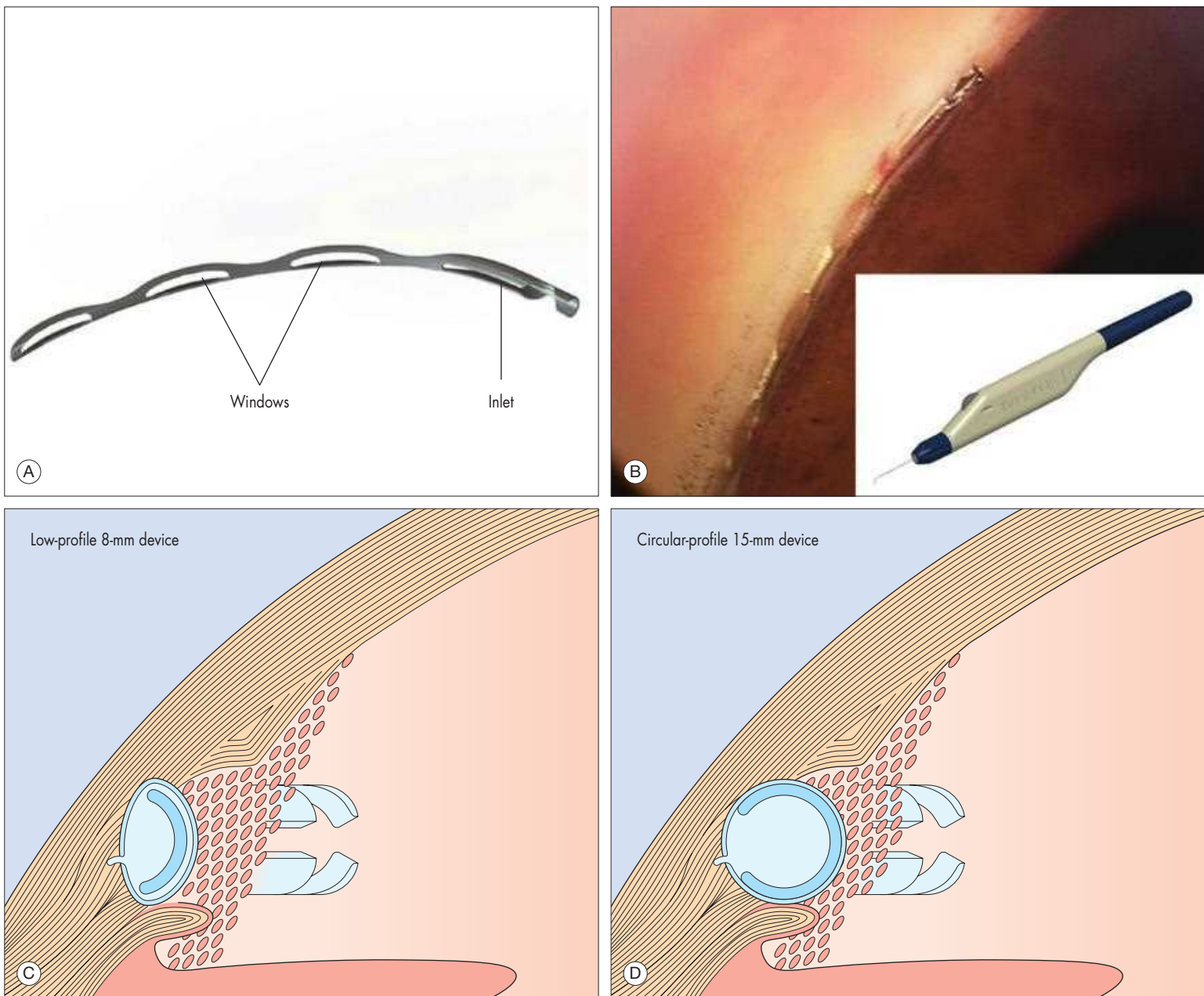
### Concept

This scaffold device is composed of nitinol, a nickel–titanium alloy that forms a flexible, open stent. There is a 1-mm terminal lumen that is left in



See clip:  
10.28.1





**Fig. 10.28.4** Ab interno Schlemm's canal scaffold Hydrus. (A) Magnified view showing the inlet which is left in the anterior chamber. (B) Gonioscopic view of the implant (insert: device inserter). Comparison of low-profile 8-mm device (C) and 15-mm device (D). (Courtesy Ivantis Inc.)

the anterior chamber as a snorkel. After placement of the initial, 15-mm-long<sup>6</sup> Hydrus microstent scaffold (Ivantis Inc., Irvine, CA), a shorter, flatter, 8-mm-long<sup>64</sup> scaffold was introduced (Fig. 10.28.4), and most reports focused on the second model. The stent functions by dilating SC to a diameter of 241 microns, or approximately four times the physiological cross-section.<sup>6</sup> Besides improving aqueous access to the collector channels by dilating the canal and preventing the TM from prolapsing into SC, the 1-mm snorkel in the anterior chamber allows the TM to be bypassed. Finally, it may also extend the range of circumferential flow by disrupting SC septations, which could otherwise limit flow to only a few clock hours.<sup>65</sup> The 15-mm stent dilates about 5 clock hours of SC and doubles the outflow facility, but the shorter and less curved 8-mm stent was also found to produce similar increases in outflow facility.<sup>6,64</sup>

### Technique

Similar to the iStent, this device is preloaded in an injector to allow insertion into SC under gonioscopic view. After topical and intracameral anesthesia, miosis is induced, and the injector tip is directed along the nasal TM. The hydrus is advanced and engages the TM. After careful insertion, the device is advanced along SC. Following retraction, blood can be seen refluxing from the tip. Viscoelastic is evacuated and the corneal incision closed.

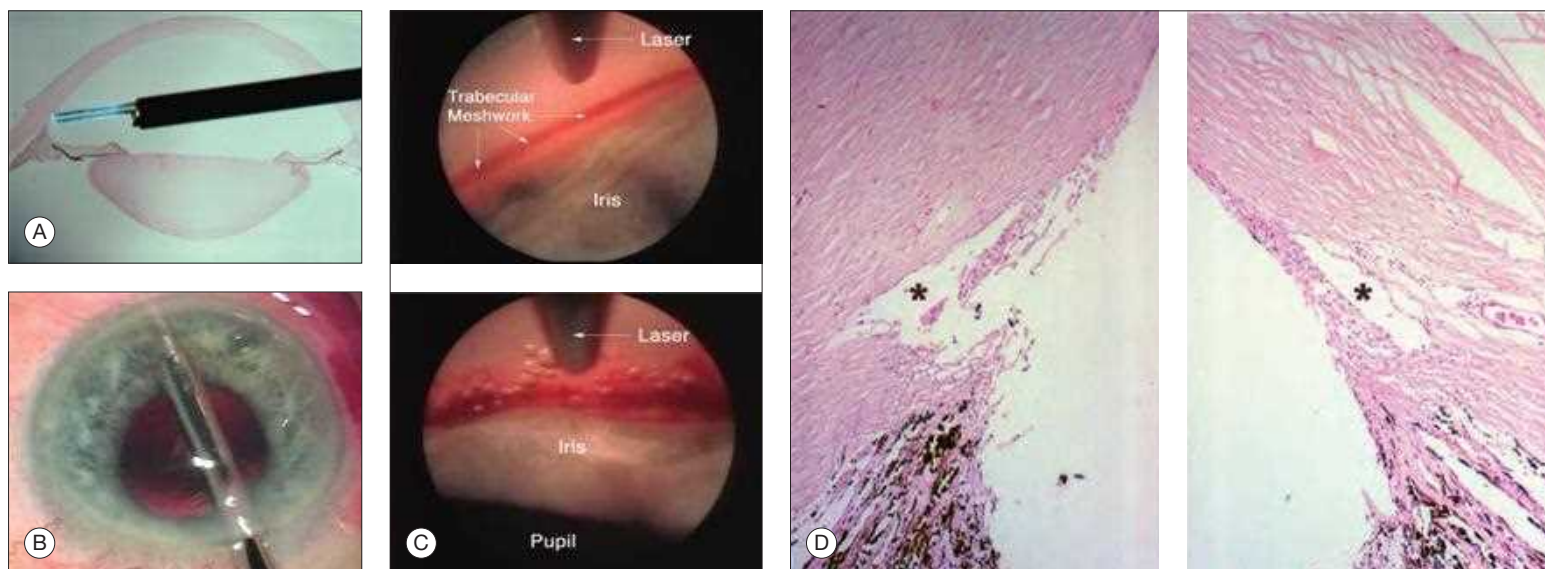
### Results

The single clinical peer-reviewed study performed so far was a randomized, parallel trial comparing IOP reduction with combined phaco with scaffold insertion ( $n = 50$ ) to stand-alone phaco ( $n = 50$ ) for cases of primary open-angle glaucoma (POAG), pseudo-exfoliation, or pigmentary glaucoma.<sup>66</sup> From a mean baseline IOP of 19 mm Hg in both groups on two medications, at 24 months, IOP had decreased to around 16.4 mm Hg (13% decrease) on 1.5 fewer medications with the scaffold versus 17.1 mm Hg (8% decrease) with one less medication after phaco. Although 73% of combined patients were off medications at the end of the study, only 38% of patients who underwent phaco were medication-free. As with most devices, there can be an early but transient IOP spike (defined in this study as an IOP  $>35$  mm Hg) in 26% of combined cases versus 10% of phaco. Focal PAS developed in 19% after 2 years, but as with microbypass stents, the clinical significance is unknown because the cases with or without PAS had a statistically similar IOP and medication load. No patient lost vision.

### Laser-Assisted Endoscopic Trabeculotomy

#### Concept

Laser-assisted endoscopic trabeculotomy (Fig. 10.28.5) can create an immediate bypass of the TM by directing flow into an alternative drainage



**Fig. 10.28.5** Endoscopic laser trabeculotomy. (A) Demonstration of position and size of the probe on an anterior segment slide. (B) View through a microscope. (C) Endoscopic view of chamber angle (top). Hypotony is induced to induce reflux of blood into Schlemm's canal to visualize the ablation target in the setting of poor pigmentation. The probe is held directly against the trabecular meshwork (TM) to apply laser and then moved away to confirm penetration as evidenced by reflux of blood into the anterior chamber. (D) Left: Histology section of circular ablation site. Lips do not roll up against the outer wall as in goniotomy because the surrounding TM is intact and away from the outer wall. Right: Nontreated control. (Courtesy Jens Funk.)

pathway and does not leave behind any stents or devices that may erode, incite a foreign body reaction, or contribute to fibrosis. However, TM ablation has to be large enough and with minimal collateral tissue damage as to not cause a wound-healing response that would cause the ablation sites to close. Krasnow first attempted laser ablation and perforation of trabecular tissue in 1972 with a ruby laser system,<sup>67-71</sup> erbium:yttrium-aluminum-garnet (Er:YAG)<sup>72-74</sup> and excimer laser.<sup>75</sup> Focal Er:YAG trabeculotomy limited to a few microns diameter had been performed soon after the introduction of this laser for capsulotomy and iridectomy, but the effect only lasted several weeks before the trabeculotomies closed.<sup>68,76,77</sup> Dietlein et al. recognized that sufficiently large ablation could only be achieved with end-firing endo-probes that have a 200–320-micron diameter to create large circular craters using 4–6 mJ energy.<sup>78</sup> Despite such extensive ablation, a closure can still occur either via migration of immediately adjacent cell types<sup>79</sup> but also that of remote cell types.<sup>80</sup> The results indicate considerable differences in repair and cell migration mechanisms when the TM is ablated with laser and possibly with other techniques (e.g., trabectome, as discussed below) that occur depending on age and species.

As with endoscopic excimer laser trabeculotomy described above, endoscopic Er:YAG laser (Sklerotom 2.9, Endognost system; Schwind) at a wavelength of 2.94 microns has also been used to increase conventional outflow through 300-micron perforations in the TM.<sup>81</sup> Also in common with an endoscopic excimer laser, because the technique relies on water vaporization, the laser tip must be brought to the TM to avoid excess energy loss to the aqueous humor. A standard treatment of 18 pulses at 16 mJ is typically applied to the nasal TM.

Another challenge common to all ab interno canal procedures is the difficulty in identifying the TM and SC and applying the ablation energy, whether laser or plasma ablation (trabectome) to the correct structure. The laser endoscope probe does not directly enter SC as do ab interno stents (e.g., iStent and Hydrus) and ablation devices (trabectome) so determining the proper placement of subsequent applications are less definite resulting either in incomplete ablation or damage of adjacent tissue. For instance, once SC is entered with the trabectome, ablation continues along the same structure that is easily recognizable by the pale appearance of the outer wall and reflux when pressure is lowered. Because of this, some investigators have developed an ab intracanalicular ablation of TM that guarantees proper anatomical location, the closest approximation to the TM and complete and powerful penetration without damaging other canal structures as the beam is directed inward, toward the center of the anterior chamber.<sup>82</sup>

### Endoscopic Excimer Laser Trabeculotomy Technique

Endoscopic excimer laser trabeculotomy (ELT)<sup>83,84</sup> (AIDA; TUI-Laser, Munich, Germany) increases conventional outflow. The 308-nm wavelength ELT creates 500-micron penetrations through the TM opening into SC.<sup>85</sup> The collateral thermal damage is less than with Er:YAG laser, but

variable energy transmission presents a challenge. Similar to the other procedures described in this chapter, the instrument tip must be inserted across the anterior chamber and guided gonioscopically to the TM. The mechanism of photoablation with this laser is water vaporization with tissue disruption. During the application, the TM blanches, and a few bubbles are seen. Successful penetration into SC produces blood reflux when IOP is less than episcleral venous pressure.

### Results

After a standard application of eight laser shots, 21 patients demonstrated a 32% IOP decrease from a baseline of 25 mm Hg after an average of 2 years while decreasing the mean number of medications from 2.2–0.7. Only 38% of patients sustained a 20% decrease in IOP. A larger group of 75 patients showed a 30% decrease from a baseline of 24 mm Hg after 1 year.<sup>84</sup> However, the number of medications did not change. Only 46% of patients successfully maintained a 20% IOP decrease and had a final IOP less than 21 mm Hg. When combined with cataract surgery, the success rate using the same definition increased to 66%, although the number of medications did not decrease. ELT was compared with 180° selective laser trabeculoplasty (SLT) treatment in a randomized, parallel trial.<sup>83</sup> ELT lowered the IOP by 30% versus 21% in the SLT group. The SLT group had a longer survival time, although the difference was not statistically significant. There was an IOP spike on postoperative day 1 in 20% of the ELT group versus 13% in the SLT group. No vision-threatening complications were reported.

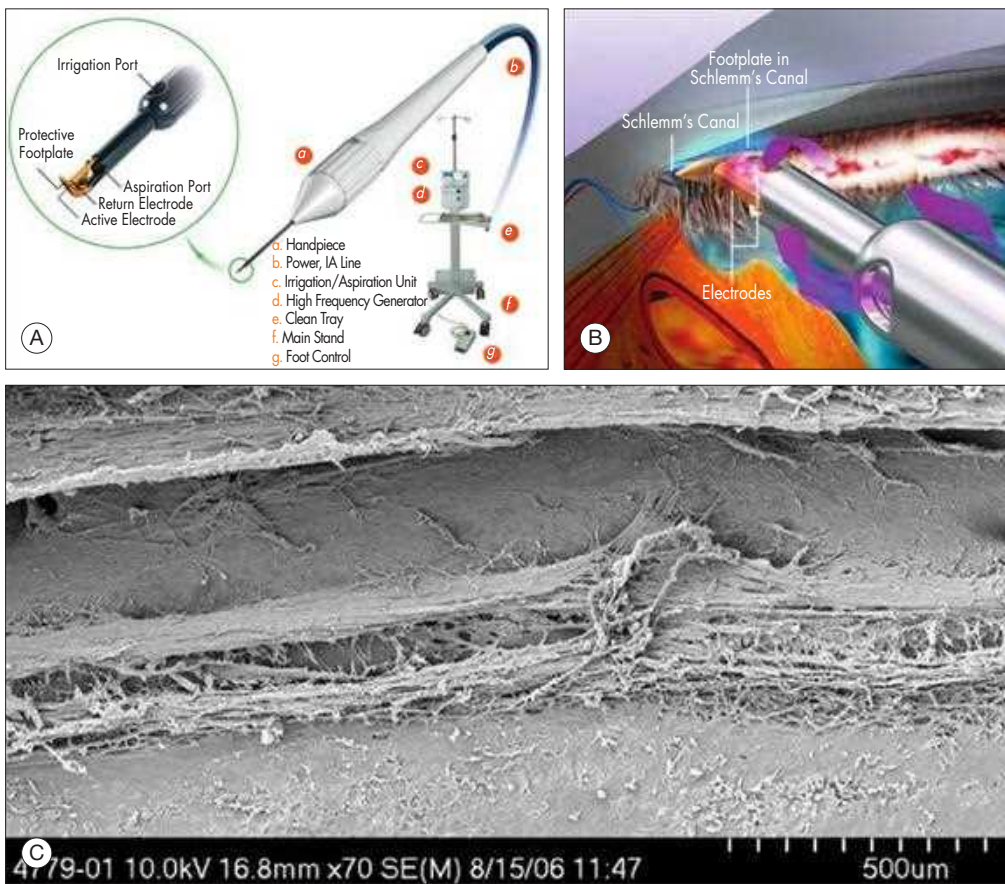
## Trabeculectomy Ab Interno: Trabectome

### Concept

Ab interno trabeculectomy (Fig. 10.28.6) with the trabectome (Neomedix Corp., Tustin, CA) is a plasma surgery technique that uses a bipolar 550-kHz electrode tip to ablate the TM. The device is the result of research funded by the National Institutes of Health (R44-EY015037; Small Business Innovation Research [SBIR]). This device was described 15 years ago by Baerveldt and Chuck,<sup>86</sup> and approved by the US Food and Drug Administration on February 9, 2004, for the treatment of adult and pediatric glaucoma.<sup>87</sup> It represents the refinement of a mechanical goniotomy instrument.<sup>86</sup> In contrast to the TM-bypass surgeries discussed above, this technique removes the substrate of the primary outflow resistance, the juxtacanalicular TM,<sup>88,89</sup> and allows additional access to the outflow system distal to the left and right end of the ablation arc.

As in earlier studies,<sup>26,90</sup> novice surgeons can often only ablate 30–60° of the TM, but because the aqueous flow is not circumferential and SC discontinuous or septated,<sup>65,91,92</sup> aiming for extensive ablation of TM over 180° provides access to more outflow sectors than can be achieved with microstents or scaffolds. This may increase surgical success and broaden indication criteria, including glaucoma types and disease stages previously





**Fig. 10.28.6** Trabectome. (A) Trabectome handpiece with cautery unit. (B) Schematic of trabectome ablating trabecular meshwork (TM), opening a view to the white inner wall of Schlemm's canal. (C) Scanning electron microscopy image of Schlemm's canal after successful TM ablation, with a collector channel seen clearly at the far right.

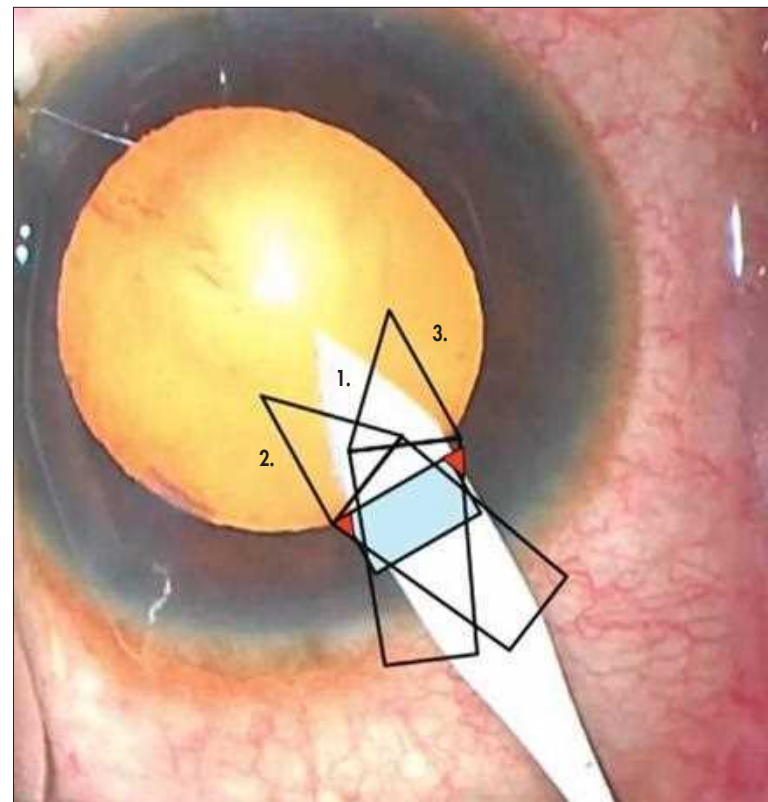
thought to be contraindicated (e.g., end-stage glaucoma, acute and chronic angle closure, inactive neovascular glaucoma). No foreign body remains in the eye to incite a potential foreign body reaction or device migration. Stents have a considerable risk to be occluded by peripheral anterior synechiae because they provide only a single point of access to SC with relatively high flow speeds. In contrast, 5–6 collector orifices are opened per millimeter of SC following trabectome surgery and at different levels (hidden collector intakes in Fig. 10.28.6), each of which has lower flow speeds and aspiration risk than a single intake. This broad-based access to the outflow system may also explain the slightly higher rate of small hyphemas at the conclusion of the surgery compared with microstents when the IOP may temporarily be lower than the episcleral venous pressure.

Trabectome ablation of TM is fundamentally different from goniotomy in that only minimal TM stumps are left that are unable to occlude the collector channel intakes. Goniotomy is effective in children<sup>93</sup> because the scleral spur is elastic enough to drop posteriorly after the incision, but in adults, the spur is more rigid and allows the TM lips to reapproximate and occlude. It is possible that a short stump of viable TM after trabectome surgery may be advantageous by serving as a viable cell barrier to endothelial cell down growth and descemetization of the angle<sup>70</sup> by maintaining contact inhibition of cell division.<sup>94</sup>

### Technique

Trabectome surgery can achieve high rates of surgical success even in complex glaucomas when the following key steps are followed: (1) Visualization is maximized using an iris-planar, flared incision and avoiding viscoelastics during ablation; (2) outward push during ablation is avoided to prevent damage to collector channel intakes; (3) ablation arc is maximized to access more outflow segments; (4) and hyphema is minimized by pressurizing the anterior chamber with viscoelastic during and at conclusion of surgery (Fig. 10.28.7).

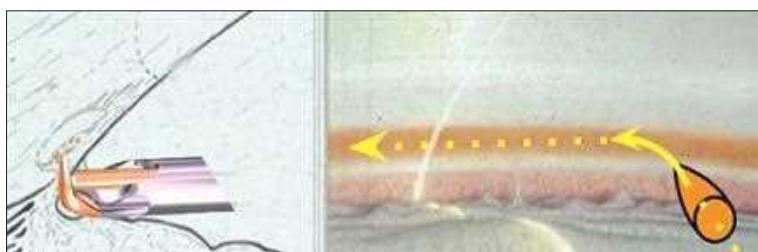
Before combined phaco-trabectome procedures, dilation as for routine phaco is performed with 2.5% phenylephrine and 1% tropicamide. After intracameral preservative-free lidocaine is injected through a paracentesis, a 1.6-mm iris-parallel, uniplanar main incision is fashioned 2 mm anterior to the limbus to improve handpiece mobility (Fig. 10.28.7). The internal, lateral aspects of the incision should be flared to further improve range and eliminate striae from torque. The eye should now be slightly hypotonous to allow reflux of blood into SC, marking the intended ablation site. Wrong site ablation is a common mistake in eyes with lightly pigmented TM because either the ciliary body band or Sampaolesi's line can



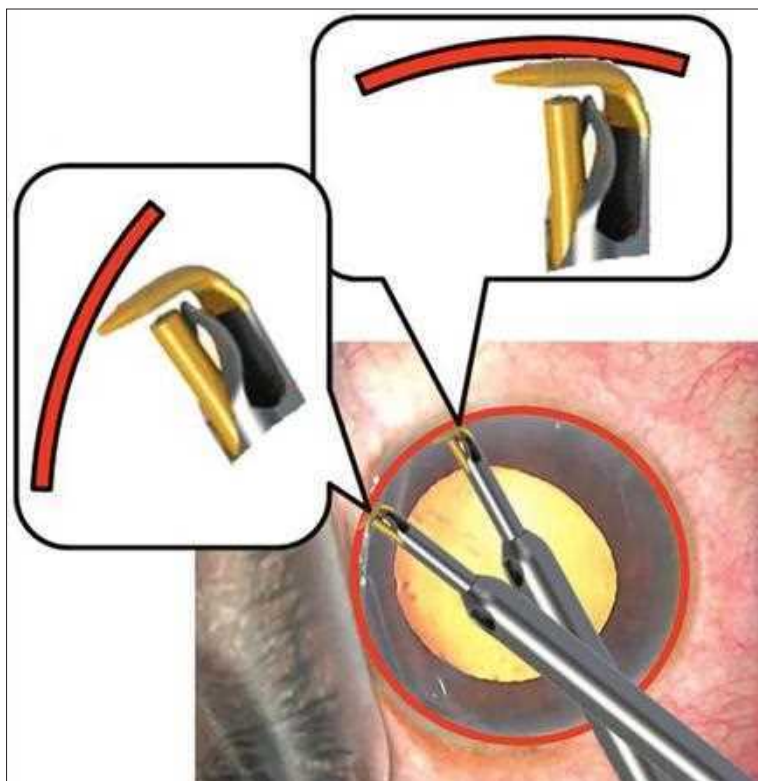
**Fig. 10.28.7** Main incision for trabectome surgery into the anterior chamber. Entry is made 2 mm anterior to limbus and parallel to the iris at (1). The left (2) and right (3) internal aspects of the wound are then enlarged, allowing for more torque without striae.

be confused with it. The patient's head is turned approximately 30° away from the surgeon to maximize view of the angle, while the microscope's viewing axis is tilted about 45° toward the surgeon. For patients who may have significant difficulty rotating the neck, the microscope tilt can be increased.





**Fig. 10.28.8** The trabectome tip should be angled 45° and inserted directly anterior to the scleral spur to avoid collapse of the canal. (Adapted from Alward WLM. Color atlas of gonioscopy. Mosby-Verlag, Iowa; 1994. p. 52–7.)



**Fig. 10.28.9** It is more efficient to engage the trabecular meshwork (TM) at a more pointed angle, as in the left inset compared with that in the right inset, where the tip is shown parallel to the TM.

A modified Swan–Jacobs direct gonioscopy lens (Ocular Instruments, Bellingham, WA) is placed lightly on the cornea to confirm angle visualization. The irrigation bottle should be raised to the maximum height and left on continuous irrigation to deepen the angle. By not using any viscoelastic prior or during ablation, optical interfaces and trapping of ablation bubbles can be avoided. Under gonioscopic view, the TM should be approached with the tip at a 45° upward left angle at the level of the scleral spur for right handed surgeons (Fig. 10.28.8). The scleral spur maintains the space and makes it easier for the footplate to glide into SC. Once engaged, exerting slight inward pull helps counteract the natural tendency to push outward, which would force the trabectome handpiece against the outer wall of SC and potentially damage the 50-μm collector channel intakes. It is easier to enter SC slightly toward the left of the opposite side of the anterior chamber because of a more pointed contact (Fig. 10.28.9).

The footplate of the trabectome tip will appear obscured by the transparent, lacy TM when properly inserted. The ablation can be carried out starting at 0.8 mW and titrated up. Blackening along the ablation lips indicates coagulative heat damage that may incite undesirable wound healing and progressive failure. Adequate ablation is confirmed visually by the appearance of the white outer wall SC. Ablation should continue for 90°, the tip is disengaged from SC, rotated 180°, and then inserted where the original ablation was started. The handpiece is rotated and the wrist is pronated such that the ablation can proceed for the remaining

90°. The ablation arc can be maximized with proper goniolens placement, rotation, finger position, and wrist supination and pronation (Fig. 10.28.10). The handpiece is disengaged from the TM and then withdrawn from the eye. A small amount of viscoelastic can be retained to prevent postoperative hypotony and protect against hyphema. Hypotony is very common after standard cataract surgery and can contribute to wound gape (Video 10.28.2).<sup>95–97</sup>

Postoperative drops consist of discontinuation of all oral or topical glaucoma medications to be added back as needed, a fourth-generation fluoroquinolone four times per day for 1 week, prednisolone acetate 1% four times a day (tapered weekly), and pilocarpine 1% or 2% four times a day for 1 month, then three times per day for 1 month, and reduced to twice per day before being discontinued. The reason for extended pilocarpine use is to flatten the iris and draw the scleral spur posterior to reduce the chance of peripheral anterior synechiae or to break adhesions.<sup>98</sup> Because most flow occurs where the TM was removed,<sup>99</sup> a significant pressure-lowering effect from pilocarpine-mediated tension on the scleral spur and meshwork cannot be expected after trabectome surgery.<sup>100</sup>

## Results

Trabectectomy ab interno with the trabectome has established itself as a safe and effective MIGS procedure for adult and infant glaucomas with over a decade of experience since its invention. To date, more than 50 000 cases have been documented, more than 5000 of which were recorded in detail and followed up long term via a repository that is made available to researchers.

The largest study came from the manufacturer's database with 4659 cases (stand-alone and combined) and detailed a mean IOP decrease of 26% from a baseline of  $23.1 \pm 8$  on 1.5 fewer medications at 75 years.<sup>101</sup> Only 7% of cases required reoperation. IOP less than 21 mm Hg with a 20% decrease occurred in 56% for stand-alone trabectome cases at 75 years and in 85% of combined cases at 5 years. A meta-analysis found that stand-alone trabectome lowered the mean IOP by 10 mm Hg and combined cases by 6 mm Hg, while decreasing the number of medications by one.<sup>102</sup> The only identified risk factors for failure are a lower baseline IOP<sup>103</sup> and younger age.<sup>104</sup> Previous laser trabeculoplasty was shown not to reduce the efficacy of trabectome,<sup>103</sup> and a failed trabectome did not increase the failure rate of a subsequent trabectectomy ab externo.<sup>105</sup> Our experience with 200 consecutive trabectome surgeries for patients who would normally have received a tube or trab (open or closed angle glaucoma, including failed trabectomies and tube shunts), suggest that a final IOP of less than 18 mm Hg can be achieved in 81%, less than 15 mm Hg in 52%, and less than 12 mm Hg in 27%.<sup>163</sup>

## Phaco Combined With Trabectome

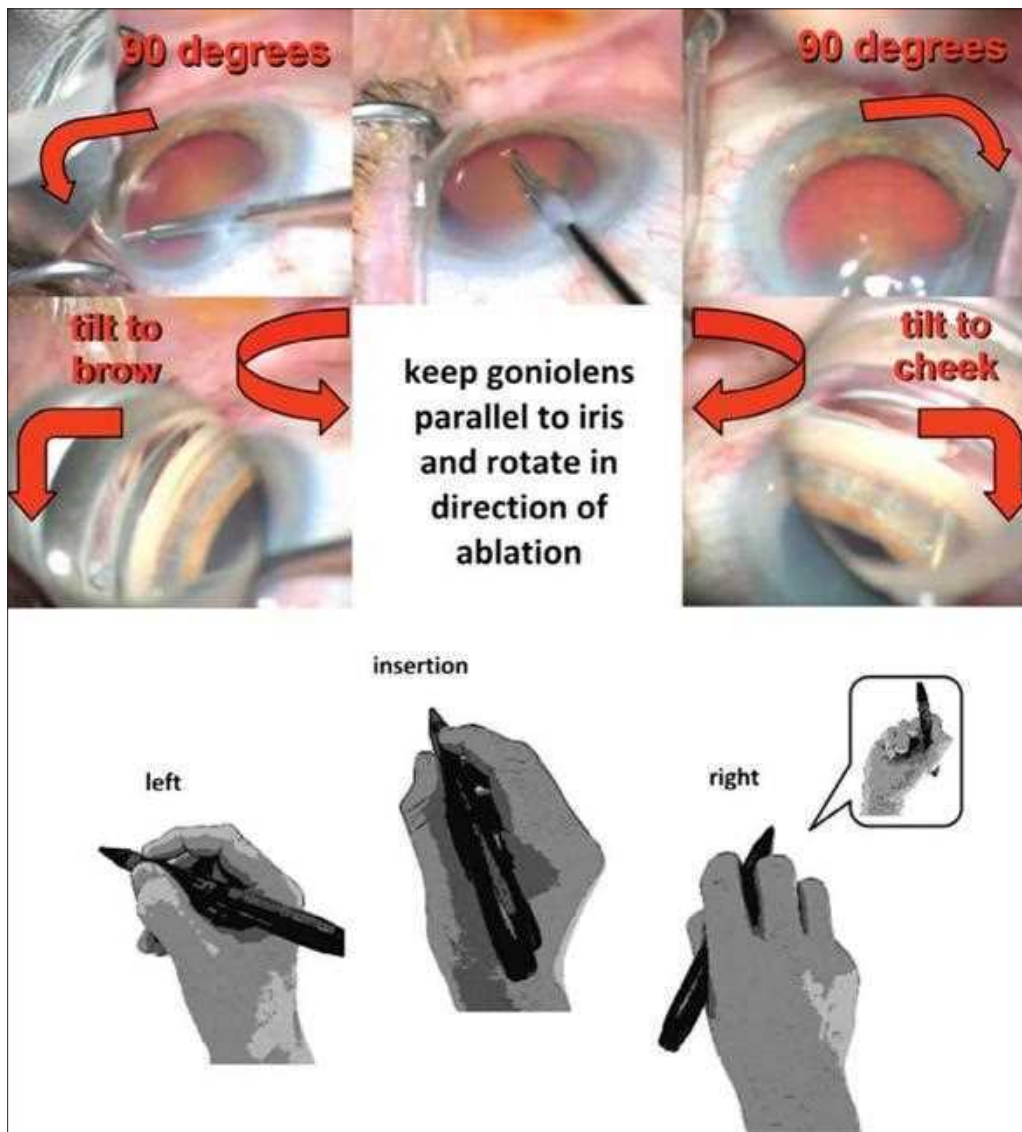
In contrast to trabecular microbypass stents,<sup>5</sup> adding cataract surgery to trabectome surgery does not provide any significant additional IOP reduction.<sup>106,107</sup> As a bypass leaves most of the TM untouched, there may be a trabeculoplasty-like effect from cataract surgery (ultrasound, trabecular meshwork stretch) that occurs to a much smaller degree when up to half of the TM is removed by trabectome surgery.<sup>63,108</sup> A recent review of 498 patients undergoing phaco–trabectome surgery demonstrated a greater reduction in IOP in more severe glaucoma, as well as corticosteroid-induced glaucoma<sup>109,110</sup> and pseudo-exfoliative glaucoma.<sup>111,112</sup> The focus on a percentage reduction is misleading because of the increase of outflow facility that is only limited by posttrabectome outflow resistance. Cases with a high preoperative IOP can be expected to drop close to a similar postoperative IOP of almost 16 mm Hg as cases with a lower preoperative IOP.<sup>109,113</sup>

## Trabectome Alone in Pseudo-Phakic and Phakic Eyes

The lens status seems to have no significant impact on IOP reduction. In a review of 235 patients with pseudo-phakia undergoing trabectome surgery compared with 352 patients undergoing phaco–trabectome, individuals who had undergone phaco–trabectome had only slightly lower IOPs ( $0.73 \pm 0.32$  mm Hg) compared with patients who underwent trabectome alone.<sup>106</sup> In a prospective study of 261 patients undergoing trabectome or phaco–trabectome, there was a trend toward a greater benefit in phaco–trabectome compared with trabectome alone in phakic or pseudo-phakic eyes.<sup>114</sup> However, in a review of 255 patients with phakia undergoing trabectome compared with 498 patients undergoing phaco–trabectome, patients with phakia had a 21% reduction in IOP compared with an 18% reduction in patients undergoing stand-alone phacoemulsification with a statistically similar IOP and medication load, suggesting that phaco itself may not contribute significantly to IOP reduction.<sup>107</sup>



See clip:  
10.28.2



**Fig. 10.28.10** The goniolens should be rotated into the direction of ablation to ablate nearly 180°. Gonioscopic prism power and angle view at the terminal ends is increased by lifting the lens off the cornea to float in the pool of saline. The lower part of the diagram illustrates proper grasp of the instrument as well as increasing pronation during the second half of the ablation.

### Trabectome and Goniosynechialysis in Narrow Angles and Angle Closure

Previously, it was hypothesized that angle-based glaucoma surgery in patients with narrow angles would lead to synechiae and fibrosis, so this has been considered a relative contraindication to trabectome surgery. However, a retrospective review of 671 patients undergoing either trabectome or phaco-trabectome offered evidence that trabectome surgery can be successful even in these patients after 1 year. Patients with a narrow angle (Shaffer grade  $\leq 2$ ) had a 42% IOP reduction after trabectome and a 24% reduction in IOP after phaco-trabectome. Similarly, patients with an open angle (Shaffer grade  $\geq 3$ ) had a 37% reduction in IOP after trabectome and a 25% reduction in IOP after phaco-trabectome. There was no statistically significant difference between the groups in IOP, the number of medications, or success rates, suggesting that trabectome surgery is a viable option for patients with narrow angles.<sup>115</sup>

### Trabectome After Failed Trabeculectomy or Tube Shunt Surgery

Reoperations after failed trabeculectomy or tube shunt are some of the most challenging surgeries for a glaucoma specialist. Trabectome may be a suitable alternative to a revision or repeat filter or shunt. In a retrospective review of 20 patients undergoing trabectome surgery after prior failed tube shunt, there was a statistically significant reduction in IOP from 23.7  $\pm$  6.4 mm Hg to 15.5  $\pm$  3.2 mm Hg at 12 months. The authors report an 84% success rate at 12 months, with only three patients requiring further surgery.<sup>116</sup> In a retrospective review of 73 patients undergoing trabectome surgery after failed trabeculectomy, there was a 28% reduction in IOP following trabectome and a 19% reduction following phaco-trabectome, with a 1-year success rates of 81% and 87%, respectively.<sup>117</sup> Another review of 60 patients undergoing trabectome after failed trabeculectomy demonstrated a 36% reduction in IOP and a 14% decrease in medications, with 25% of patients requiring further surgery in the course of follow-up.<sup>118</sup> Although

these studies were limited by their retrospective nature and the relatively small number of patients included, the results suggested that the distal outflow tract is patent and functioning contradicting the assumption that an unused outflow system atrophies. Presumably, this assumption was the product of a misinterpretation of the high IOP that often follows closure of the drainage cleft of a cyclodialysis, a historical surgery now rarely performed.<sup>119–121</sup>

### Adjuvant Trabectome Surgery at the Time of Tube Shunt Surgery

Finally, with its favorable safety profile, trabectome surgery may be used as an adjuvant during tube implantation. In a matched comparison of 117 patients undergoing Baerveldt tube implantation alone versus 60 patients undergoing Baerveldt combined with trabectome surgery, both groups showed similar IOPs and visual acuities at each postoperative time point.<sup>122</sup> However, the combined group required fewer IOP-lowering drops at each time point. Adjuvant trabectome surgery may improve the quality of life by reducing medication burden. Results from Ahmed tube implantations were similar<sup>123</sup>; trabectome surgery plus two medications reduced the IOP by 12 mm Hg, whereas Ahmed implantation plus four medications lowered IOP by 15 mm Hg.

### Trabectome Surgery in Severe Glaucoma

When trabectome surgery outcomes are stratified by glaucoma severity, patients with more medications, a higher baseline IOP and worse visual field experience a larger IOP reduction than subjects with less aggressive glaucoma.<sup>109,113</sup> A glaucoma index was created that captures the clinical treatment resistance and the risk by combining baseline IOP, the number of medications, and visual field status. The analysis of 843 patients indicated that patients in the most advanced glaucoma group and higher baseline IOP had a threefold larger IOP reduction than the ones in the mild glaucoma group. Individuals with advanced glaucoma had a lower success



rate of 71% compared to ones with mild glaucoma who had a success rate of 90%. Age, pseudo-exfoliation, and corticosteroid-induced glaucoma were found to be significantly associated with a greater IOP reduction, with Hispanic ethnicity and cup-disc ratio showing a weaker association.<sup>109,113</sup> Traditional filtering surgeries remain a good option after failed trabectome surgery,<sup>124</sup> whereas SLT is less successful in this situation.<sup>125</sup>

One of the main benefits of trabectome surgery is the greatly reduced risk of vision-threatening complications typical to traditional glaucoma surgeries while being effective in achieving average pressures of about 16 mm Hg. The most common complication is reflux of blood from the collector channels, which occurs in nearly all cases, indicating a free and unobstructed communication with the drainage system.<sup>104</sup> There are three published cases detailing surgical intervention for hyphema because of an associated IOP spike.<sup>126,127</sup> The vast majority of microhyphemas and layered hyphemas are cleared by 1 week. Spontaneous hyphema has been reported in a small case series up to 31 months after trabectome,<sup>126</sup> but in our experience with over 900 cases, only two patients had symptomatic late-onset hyphema. In one study, the second-most common complication was PAS, which was found, to some degree, in 24% of patients.<sup>128</sup> Transient postoperative IOP spikes of at least 10 mm Hg have been seen in 4%–10%<sup>26,129</sup> of patients consistent with other MIGS procedures. Other complications reported in less than 1% of reported cases include cyclodialysis cleft,<sup>104</sup> transient hypotony, lens injury, aqueous misdirection,<sup>130</sup> and choroidal hemorrhage.<sup>130</sup>

Two studies that did not use matching to balance groups compared the results of two second-generation iStents to trabectome. The first combined all cases with phaco ( $n = 54$ ) and found that from a mean baseline close to 22 mm Hg in both groups, the IOP decreased by 30% after trabectome and by 34% after two iStents with a similar and small ( $<1$ ) medication decrease after 1 year, and the difference between groups was not statistically different.<sup>131</sup> Another retrospective study found that from a similar baseline IOP close to 20 mm Hg, after 12 months the IOP decrease was 27% with phaco combined with two second-generations versus only a 16% decrease with phaco combined with trabectome surgery.<sup>132</sup> The IOP was 18 mm Hg or less off medications in 14% with trabectome versus 39% for stents ( $P = 0.006$ ). Unfortunately, neither of these studies used case matching to account for the number-one risk factor for failure, lower baseline IOP.<sup>50</sup>

## Other Ab Interno Trabeculectomy and Trabeculotomy Techniques

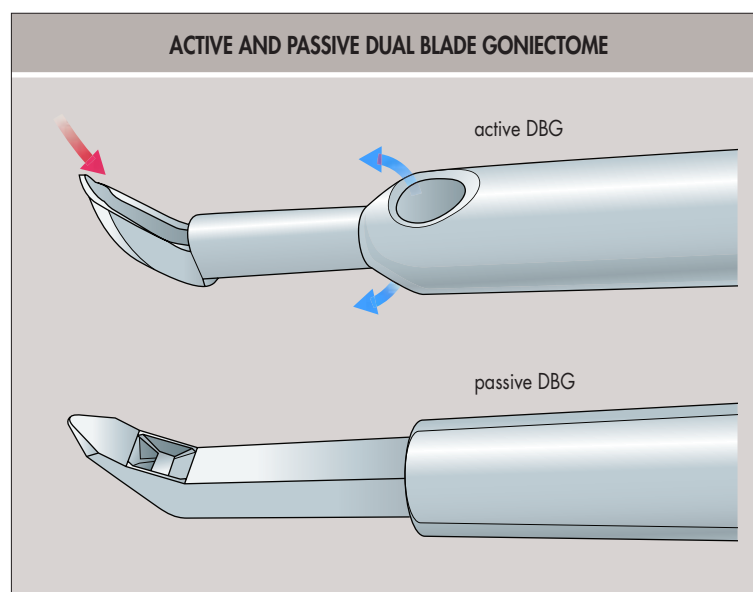
There are several other surgical options that are similar (Fig. 10.28.11). A key feature of the trabectome is a ramping “footplate” that provides the key function of lifting the TM and putting it on a slight stretch, positioning the tissue for maximal discharge effect from above while protecting underlying tissue.<sup>133</sup> It represents the refinement of a mechanical goniectomy instrument.<sup>86</sup> While the plasma created at the tip of the electro-surgical trabectome molecularizes the TM and is the more atraumatic and drag-free TM removal technique, it does require a high-frequency generator that is not necessary with the goniectome<sup>86</sup> or the dual blade introduced a few years later.<sup>134</sup> This device has recently been reintroduced for use in operating rooms where a high-frequency generator is not available<sup>135,136</sup> in the form of the Kahook dual blade and a goniotome with active irrigation and aspiration.<sup>137</sup> Preclinical investigations on ab interno trabeculectomy with the trabectome and a passive dual-blade device demonstrated a similar decrease in IOP in an eye perfusion model.<sup>135</sup> A key differentiator among these instruments, however, is the active irrigation and aspiration system that facilitates visualization,<sup>137</sup> a challenge that is well described in the pediatric goniosurgery literature.<sup>138–140</sup> A comparison in a pig eye model

indicated higher average outflow after the active dual-blade goniectome compared to the Kahook dual blade, but the results were limited by eye number and did not reach statistical significance.<sup>137</sup> Gonioscopy-assisted transluminal trabeculotomy (GATT) requires a gonioscope and a suture or illuminated catheter. A 1–2 mm goniotomy is created to thread either a microcatheter or suture (i.e., 4-0 nylon)<sup>141</sup> for 360° through SC. The suture is then externalized, creating a 360° trabeculotomy. In 41 patients with POAG, the IOP fell by 39% from a baseline 26 mm Hg on one less medication.<sup>142</sup> IOP less than 21 mm Hg with a 20% decrease from baseline was achieved in 70% of cases, whereas 12% of patients required reoperation within 1 year. All complications (i.e., hyphema in 25%) spontaneously resolved by the 3-month visit.

## SUBCONJUNCTIVAL MICROSHUNTS

### Concept

A subconjunctival microshunt can be seen as a consequential improvement on a stent that is meant to make the sclerectomy step in trabeculectomy easier, the Ex-Press (Alcon, Fort Worth, TX) (Fig. 10.28.12). The Ex-Press was found to confer only small advantages in surgery and postoperative management compared with trabeculectomy while introducing new challenges as a result of introducing a foreign body into the eye.<sup>143</sup> Nevertheless, these devices take advantage of the more than half a century of experience with subconjunctival filtration as an alternative to the natural outflow pathway, which includes diffusion through the conjunctiva, diffusion into the venous system of the sclera and conjunctiva, and potential lymphatic pathways.



**Fig. 10.28.11** Active and passive dual-blade goniectomes (DBGs). The active dual-blade goniectome (active DBG, top<sup>86,134</sup>) has two irrigation ports that maintain the chamber (blue arrows). The trabecular meshwork (TM) is put under stretch by an angle-shaped ramp and excised by a left blade and a right blade. The cut trabecular meshwork strip, blood, and debris are aspirated into the tip (red arrow). The passive dual-blade goniectome (passive DBG, bottom<sup>136,137</sup>) requires viscoelastic to maintain the anterior chamber. It also puts the TM under stretch by an angle-shaped ramp and cuts the TM with a left blade and a right blade. The TM strip can be left attached in the eye or amputated and extracted with microforceps.



**Fig. 10.28.12** Subconjunctival microshunt XEN. (A) Size comparison—the XEN shunt is approximately twice as thick as a human hair. (B) Insertion into the subconjunctival space. (C) Anterior-segment optical coherence tomography of a shunt showing subconjunctival insertion. (Courtesy AqueSys, Inc., Irvine, CA.)



There are two subconjunctival microshunts with published results. The XEN (AqueSys, Irvine, CA) consists of a 6-mm long, permanent, hydrophilic porcine gelatin tube that is cross-linked with glutaraldehyde. This material is pliable and considerably smaller than traditional aqueous shunts, which may prevent problems associated with larger drainage devices, most importantly erosion and corneal endothelial damage.<sup>144</sup> Three different versions offer increasing bore size for increased outflow in more advanced cases from the Nano to the Mini to the standard (largest bore). The XEN is inserted gonioscopically, preserving the integrity of the patient's conjunctiva with less inflammation and subsequent fibrosis. The InnFocus microshunt (InnFocus Inc., Miami, FL) shares a similar concept, has a 70-mm diameter, 8.5-mm long lumen made of poly(styrene-bloc k-isobutylene-block-styrene) but is inserted externally.<sup>145</sup>

## Technique

The XEN device is inserted under gonioscopic view in a manner similar to the bypass shunts explained above. The XEN is a 25- or 27-gauge needle and designed to exit into the subconjunctival space approximately 2.5–3.5 mm posterior to the limbus. Future studies may incorporate mitomycin C.<sup>146</sup> The external approach for the microshunt requires a limbal 6–8 mm wide sub-Tenon's dissection, followed by topical mitomycin C on sponges (0.4 mg/mL mitomycin C for 3 minutes).<sup>145</sup> Next, the entry site is chosen 3 mm posterior to the limbus for a 1 × 1 mm partial thickness scleral incision. Either a 25- or 27-gauge needle is used to enter this incision and advanced into the angle. The microshunt is advanced through the needle tract by using forceps until 2–3 mm of the tube is in the anterior chamber. The tubes are not sutured in place. The limbal peritomy is closed with 10-0 nylon sutures.

## Results

The XEN was combined with phaco in 32 patients and showed a mean 29% IOP decrease on three fewer medications from a baseline of 21 mm Hg on three medications after 12 months.<sup>147,148</sup> An IOP 18 mm Hg or greater off medications was achieved in 90% of cases. The only complications reported were bleeding in anterior chamber (87%) or at the scleral incision (90%), and in two cases (6%), the stent could not be inserted.

Another study on the microshunt (n = 23) showed a mean 55% IOP decrease on two fewer medications from a higher baseline of 24 mm Hg on two medications after 36 months.<sup>145</sup> IOP 14 mm Hg or less (on an unspecified number of medications) was achieved in 82% at 3 years. Transient hypotony (13%), shallow anterior chamber (13%), and choroidal detachment (9%) all resolved without intervention. There were two cases (9%) of elevated IOP, one of which was treated by irrigating the tube through the anterior chamber to clear fibrin. More serious complications included one case each of vitreous hemorrhage and bleb leak, with no necessary interventions reported. Reoperation (a second microshunt) was performed in one case, for an encapsulated bleb. Interestingly, 22% of the blebs appeared to be flat yet retained good IOP control without intervention. No patient lost more than one line of vision.

## SUPRACHOROIDAL DRAINAGE DEVICES

### Concept

Aqueous humor is produced by the ciliary body and exits the eye through either the TM or the uveoscleral route. Although traditional glaucoma surgical techniques have targeted the conventional trabecular outflow route, some newly developed ones use space-retaining devices to increase the uveoscleral outflow route.

Because in classic glaucoma surgery aqueous humor is shunted to a pocket covered only by thin conjunctiva and Tenon's capsule, fibrosis and infection remain a lifelong concern.<sup>149</sup> In an attempt to avoid these problems, suprachoroidal devices have been developed to drain aqueous humor into a potential space—the suprachoroidal space. This approach takes advantage of the hydrostatic pressure gradient between the anterior chamber and the suprachoroidal space.<sup>150</sup> Once the aqueous reaches the suprachoroidal space, the fluid is thought to leave mainly through one of three routes: (1) Hypoechoic pockets<sup>7</sup> at the tail end of shunts may represent fluid leaving through the choroidal vasculature.<sup>151</sup> (2) Successful shunts may have larger and denser conjunctival microscopic tracks within a spongy sclera that could be the result of a spongy sclera from surgical manipulation,<sup>152</sup> suggesting that intrascleral egress routes lead to subconjunctival drainage. (3) Finally, vasculature sharing features with lymphatic

vessels have been seen on histology within and around suprachoroidal shunts.<sup>151</sup>

The idea of reducing IOP by diverting fluid into the suprachoroidal space was first realized at the beginning of the twentieth century when Ernst Fuchs identified the cyclodialysis cleft.<sup>153</sup> This approach was complicated by an unpredictable closure of the cleft responsible for aqueous humor drainage, resulting in drastic and painful pressure spikes. Extended function seemed possible with a cleft maintainer. However, the materials and size were not tolerated well enough and led to poor long-term outcomes.<sup>154</sup> Advances in engineering and material science have now allowed for the reduction of bioreactivity and drainage device size. These devices can be implanted via the ab externo or ab interno approach and preserve the TM and can spare the conjunctiva.

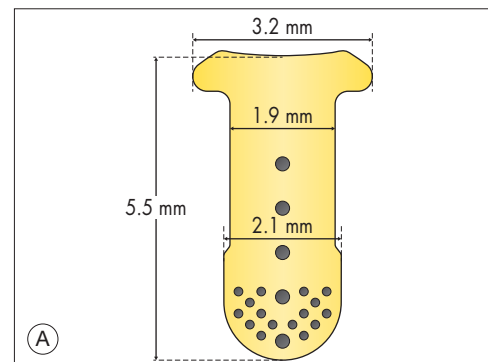
## Ab Externo Suprachoroidal Shunts

### SOLX Gold Micro-Shunt

The current generation SOLX Gold Micro-Shunt (GMS Plus; SOLX Ltd., Waltham, MA) is a nonvalved, 24-karat gold implant, which weighs 9.2 mg and is 0.06 mm thick, 5.5 mm long, and 3.2 mm wide posteriorly with interior channels (Fig. 10.28.13).

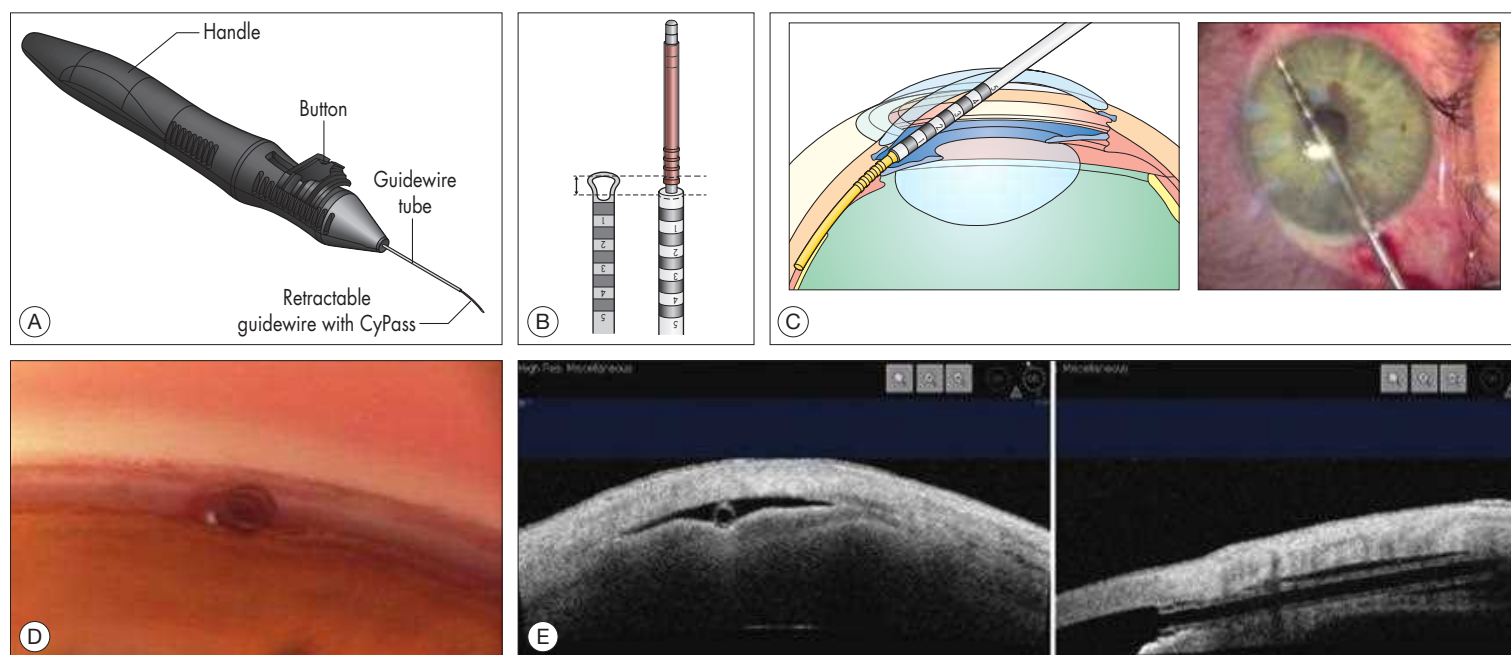
### Technique

GMS implantation surgery is performed under cover of local anesthesia with the use of sub-Tenon's or peribulbar injections. The GMS can be implanted in any quadrant as long as the scleral tissue in the area of surgery is healthy. After a 4-mm fornix-based conjunctival peritomy, a scleral incision of about 3.5 mm is created 2 mm posterior from the limbus. A 95% thickness scleral pocket is then created posterior and anterior to the incision to accommodate the GMS without entering the anterior chamber. The remaining thin layer of sclera overlying the choroid at



**Fig. 10.28.13** SOLX GMS suprachoroidal gold shunt that is implanted via an ab externo approach. (A) The head and shoulder have flow channels that open toward the anterior chamber, whereas aqueous egresses posteriorly. (B) The shunt in its final position in the chamber angle. (C) Implantation is possible at any clock hour as in this patient who had previous surgery superiorly (note previous superior iridectomy). (Courtesy Solx Inc.)





**Fig. 10.28.14** Suprachoroidal shunt CyPass. (A) CyPass preloaded in an injector. (B) Goniometer for implantation without goniolens. (C) Demonstration of implantation without goniolens. (D) CyPass in the chamber angle after implantation and (E) surrounded by aqueous humor in the suprachoroidal space as visualized by high-resolution ultrasound biomicroscopy. (Courtesy Transcend Medical, Inc.)

the base of the initial incision is cut to expose the choroid. The GMS is inserted through the scleral tunnel into the anterior chamber. The anterior drainage openings should be visible and clear of angle structures and the incisions are closed in a watertight fashion.

### Results

The first report was a prospective 12-month study of 38 patients who had glaucoma as well as uncontrolled IOP (half had already failed previous incisional surgery).<sup>7</sup> The study demonstrated a 33% decrease in mean IOP from a baseline of 28 mm Hg on 0.5 fewer medications. Complications included shunt exposure, synechiae, or exudative retinal detachment in three patients. Hyphema occurred in 21% and resolved spontaneously within 2 days in all cases. Choroidal detachment occurred in 11%, and all resolved spontaneously; corneal edema occurred in 4%.<sup>155</sup> There have been two cases of serous retinal detachments that lead to device explantation.<sup>7,155</sup>

## Ab Interno Suprachoroidal Shunts

### CyPass Micro-Stent

The CyPass Micro-Stent (CMS; Transcend Medical, Menlo Park, CA) is a polyamide fenestrated microstent that is implanted under gonioscopic view just posterior to the scleral spur to directly connect the anterior chamber to the suprachoroidal space to increase uveoscleral outflow (Fig. 10.28.14).<sup>156</sup>

### Technique

CMS implantation is done via an ab interno approach through a clear corneal incision. Initially, the anterior chamber is filled with viscoelastic to maintain the chamber and expand the angle. The CMS device is loaded onto a retractable, curved guide wire. This device can be inserted by using a goniometer (markings are on the inserter) to estimate insertion position and depth under gonioscopic view. After fashioning a clear corneal incision, the guide wire is designed to bluntly dissect the ciliary body from the sclera and to create a micro-cyclodialysis cleft which will serve as a passage into the supraciliary space. Once the stent is correctly positioned, the guide wire is retracted and withdrawn from the eye. Upon retraction of the guide wire from the implant, the implant re-forms to its original, straighter configuration. Correct placement can be evaluated by using UBM or anterior-segment optical coherence tomography.

### Results

Two large studies on the CMS have been performed. One only provided washed-out IOP values ( $n = 374$ ) and compared phaco to combined phaco-CMS. The combined group had a 30% IOP decrease on one less medication from a baseline of 24 mm Hg on 1.4 medications.<sup>157</sup> After 24 months, an IOP 18 mm Hg or less off medications was achieved in 67%

of combined cases versus 41% of phaco cases. There were no statistically significant differences in complications between the two groups. There was transient hypotony in 3% of combined cases, obstruction in 2%, and device migration in 0.5%. Another study ( $n = 167$ ) divided results based on whether baseline IOP was less than 21 mm Hg.<sup>158</sup> Cases with baseline IOP 21 mm Hg or greater (mean 26 mm Hg) had a 37% IOP decrease on an average of one less medication, whereas the other group (mean IOP 17 mm Hg) had a 5% decrease on 1.5 fewer medications. This suggests that as with other MIGS, cases with higher baseline IOP have better results when measured by IOP and medication reduction.<sup>50</sup> Possible reasons for this are differing surgical indications (i.e., the surgeon and the patient may consider stopping a medication with no change in IOP as a success) leading to different patient populations. Another possibility (that may, in the future, be proven with aqueous angiography) comes from theoretical modeling suggesting that at higher baseline IOPs, a greater proportion of aqueous outflow will exit through a TM bypass.<sup>159</sup>

### iStent G3 Supra

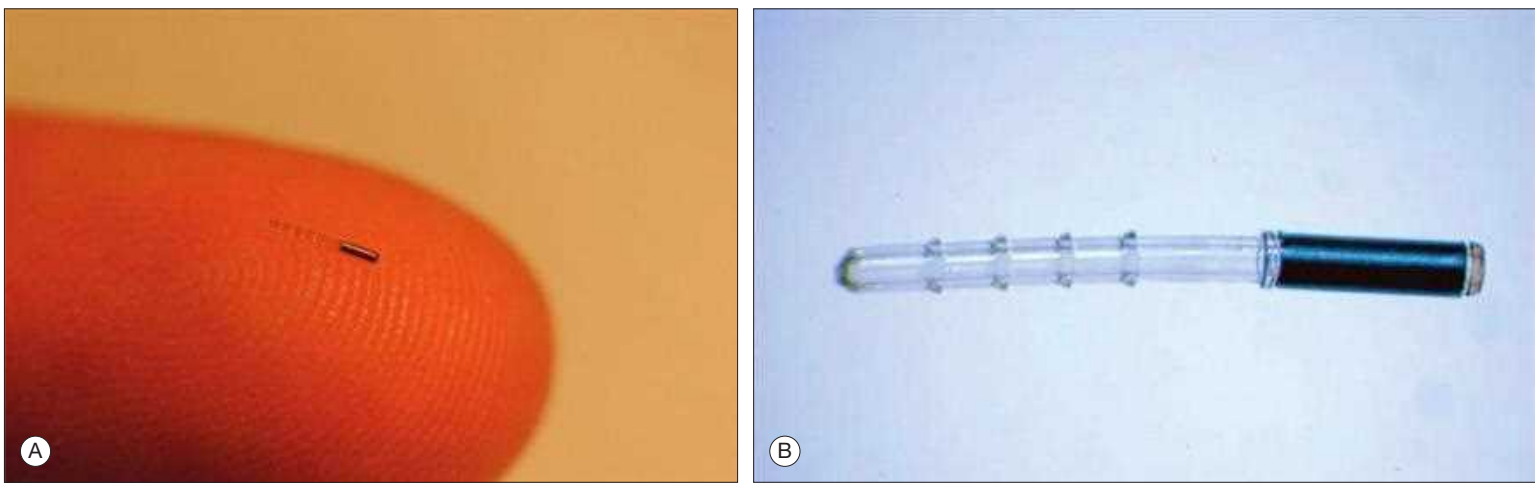
The iStent G3 Supra (Glaukos, Laguna Hills, CA) is the latest third-generation iStent device and is very similar in design to the CMS (Fig. 10.28.15). The device is 4 mm long and is made of heparin-coated polyethersulfone and a medical-grade titanium sleeve.<sup>156</sup> It is designed to be implanted via an ab interno approach into the suprachoroidal space. Clinical studies have not yet been reported.

## CONCLUSIONS

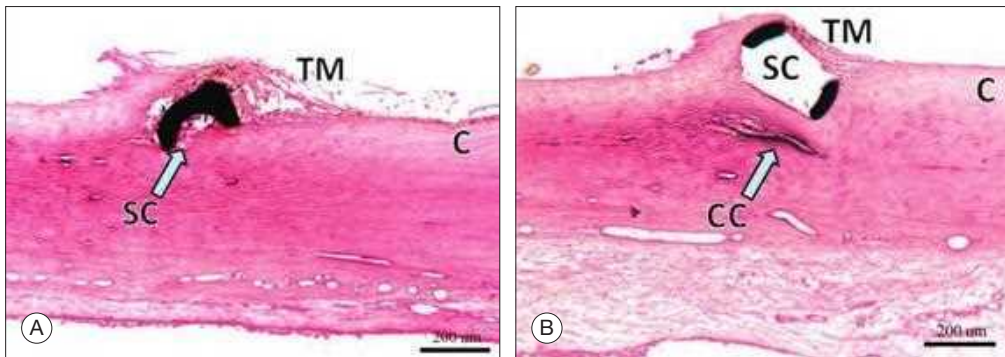
Trabeculectomy has been the gold standard in the first-line surgical management of glaucoma for the last 30 years, and more recently, glaucoma drainage devices have gained popularity partly because of a decreased need for postoperative management and greater predictability.<sup>160</sup> Despite refinements in technique and the introduction of adjunctive measures, the complication rates remain relatively high and long-term success moderate. Because MIGS provides safer surgical profiles, it offers the ability to intervene earlier, mitigating the perennial issue of noncompliance and associated costs. MIGS is highly standardized and considerably faster compared with standard incisional surgery and can be easily combined with cataract surgery, with or without toric lens implantation to correct astigmatism. The incision used is often the same as that used for cataract surgery and allows for accurate calculations of surgically induced astigmatism.

The decrease in risks, including that of hypotony and related complications (e.g., suprachoroidal hemorrhages or effusions), is one of the main benefits of these newer glaucoma procedures, but it comes at the cost of a reduced ability to reliably achieve IOPs below 15 mm Hg without additional medications. However, it is notoriously difficult to achieve very low





**Fig. 10.28.15** iStent G3 Supra. (A) Size comparison on the fingertip. (B) High-power view. The device has an intake composed of a different material and a tail with retention rings. (Courtesy Glaukos Corp.)



**Fig. 10.28.16** Cross-section showing iStent in Schlemm's canal and Hydrus implant. (A) iStent in Schlemm's canal (white arrow) and Hydrus implant on the right (B). In (B), note that because of septations in the canal, the Hydrus is stenting open a portion while compressing another portion inferior to it (white arrow). C, cornea; CC, collector channel; SC, Schlemm's canal; TM, trabecular meshwork (Courtesy Glaukos Corp.)

target pressures even with classic glaucoma surgical procedures. Even if the probability of achieving an IOP of 12 mm Hg or less after MIGS is only 37% (or 50% for pseudo-exfoliative glaucoma), it may still benefit the patient to first try MIGS combined with phaco and then proceed to more risky trabeculectomy or aqueous shunt surgery if target pressures cannot be achieved even with eyedrops. As internal MIGS does not violate the conjunctiva, the success rate of subsequent trabeculectomy likely remains unchanged.<sup>105</sup>

The advantages of MIGS are compelling, but to date, no randomized controlled trials have compared them with classic procedures. This observation is similar to the more technology-dependent phaco, which revolutionized cataract surgery and drastically reduced the number of extracapsular cataract extractions performed.

The IOP differences between the different MIGS modalities may be directly related to how many individual collector outflow segments are accessed. For instance, iStent G2 is a space maintainer for a pointed trabeculotomy, whereas iStent G1 is a longer device, which is followed by the 8-mm Hydrus (spanning 45°), the 15-mm Hydrus (150°), the trabectome (120–180°), and GATT (360°). Increasing efficacy with increasing segment access may be reflected in the growing likelihood of postoperative hyphema, which indicates a flow reversal in the collector channels as a result of an inverted pressure gradient (lower in the anterior chamber than in the episcleral venous system).

There are distinct disadvantages to drainage devices and stents in the eye, whether they are placed subconjunctivally (tube shunts) or into SC (MIGS stents discussed in this chapter). As well known from interventional radiology, stenting devices can block the branching vessels, compress the adjacent lumina, and obstruct the lumen they are intended to maintain (Fig. 10.28.16). Hardware may also serve as a nidus for infection.

Over time, even precious metals or other inert materials, such as silicone, can stimulate a foreign body reaction and fibrosis. The TM does have the ability to present antigens but has been invoked in induced tolerance (anterior chamber-associated immune deviation).<sup>161</sup>

Similar to larger vessels treated in interventional radiology and cardiology, outflow tract anatomy can vary widely, and it will likely become standard to image each patient's specific outflow tract before stent or scaffold implantation, as can be done with readily available spectral-domain optical coherence tomography.<sup>1,28,92,162</sup> Advances in microengineering and imaging

technology and a better understanding of glaucoma pathogenesis have enabled the use of new surgical modalities that allow for tapping into the natural drainage system directly.

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# Trabeculectomy

Cynthia Mattox

# 10.29



**Definition:** A surgical procedure featuring a partial-thickness scleral flap that creates a fistula between the anterior chamber and the subconjunctival space for filtration of aqueous fluid and the creation of a conjunctival bleb in an effort to lower intraocular pressure.

## Key Features

- Bleb formation.
- When successful, lowers intraocular pressure significantly from preoperative levels.
- Wound healing influences success.
- Meticulous intraoperative technique is required.
- Intense postoperative observation and management is necessary.

## Associated Features

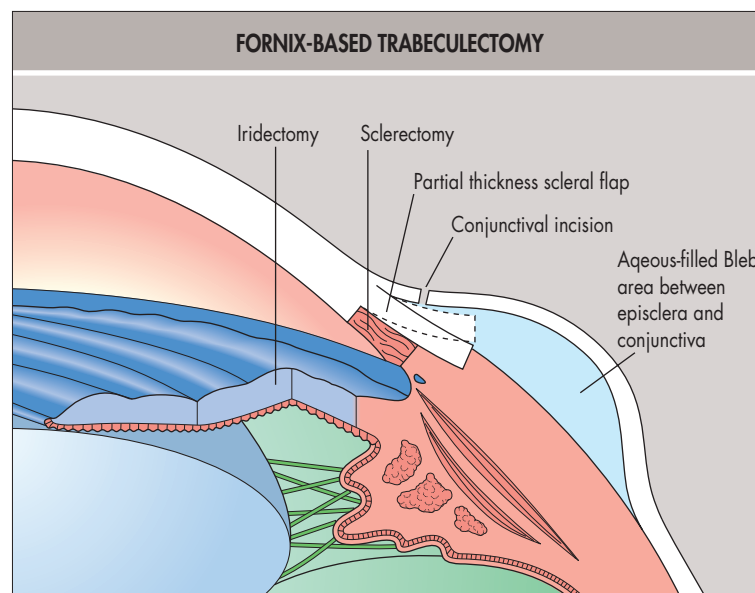
- Antimetabolites (mitomycin C or 5-fluorouracil).
- Hypotony.
- Choroidal detachment.
- Bleb leak.
- Bleb-associated endophthalmitis.

## INTRODUCTION

Trabeculectomy is the most common form of modern filtration surgery used to lower intraocular pressure (IOP) in a patient with glaucoma. In trabeculectomy, a fistula for aqueous fluid is created between the anterior chamber and the subconjunctival space, beneath a partial-thickness scleral flap, to create an area of “filtration” called the *bleb*. Trabeculectomy techniques have evolved from full-thickness sclerectomy forms of filtration surgery to minimize postoperative complications while achieving the goal of successful lowering of IOP. With all forms of filtration surgery, the most sight-threatening complications, such as suprachoroidal hemorrhage, occur in the setting of hypotony. Surgeons embraced trabeculectomy as a way to avoid hypotony, yet historically, the move to trabeculectomy from full-thickness filtration surgery was gradual, as techniques were developed to achieve ultimate success and adequate IOP lowering for the long term.

Trabeculectomy was originally described by Cairns<sup>1</sup> in 1968 and has continued to be modified as surgical instrumentation and suture have improved in recent decades. Modalities to alter wound-healing fibrosis in the subconjunctival space, such as use of antimetabolites (5-fluorouracil and mitomycin C)<sup>2-8</sup> and laser suture lysis,<sup>9</sup> have continued to offer improvements in postoperative success. Trabeculectomy is still considered the “gold standard” surgery for primary glaucoma filtration because it is effective, relatively low risk, and technically within the skills of the well-trained ophthalmic surgeon. Variations of technique among surgeons and variability in wound-healing among patients are the norm, and it is said that astute and careful postoperative management by the surgeon is key to the successful outcome of trabeculectomy for a patient.

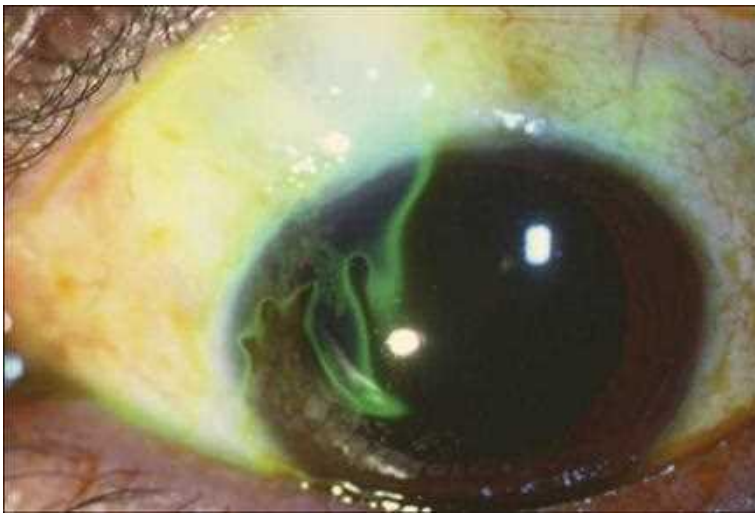
It is helpful to understand the anatomy of a trabeculectomy to recognize the optimal conditions for successful surgery. In many ways, the trabeculectomy is a complicated series of “incisions,” most of which must remain free from healing or scarring to establish a functional filtration



**Fig. 10.29.1** Fornix-based trabeculectomy.

bleb.<sup>10</sup> In fact, the only incision that requires complete healing is the conjunctival incision, either at the limbus in a fornix-based flap or at the fornix in a limbal-based flap. Otherwise, the iridectomy, sclerectomy, underside of the partial-thickness scleral flap, the sides of the scleral flap, and the extremely important surface area between the episclera and conjunctiva must remain free of obstruction to allow aqueous fluid to migrate through the fistula (Fig. 10.29.1).

Although the goal in trabeculectomy is to establish a subconjunctival filtration bleb that lowers the IOP sufficiently, the bleb itself is the cause of many of the late-onset complications that may occur. Blebs can leak, become infected and induce endophthalmitis, or cause chronic discomfort (Fig. 10.29.2). Antimetabolite use increases the risk of leaking and infection because of the permanent changes in the conjunctiva that promote a thin-walled bleb<sup>11,12</sup> (Fig. 10.29.3). Yet antimetabolites offer a more successful long-term lowering of IOP in patients who are at high risk for filtration failure and in primary trabeculectomies.<sup>7,8</sup> It is the risks of the established bleb that have led to the development of non-bleb-forming filtration surgeries. The main disadvantage of non-bleb-forming procedures, where aqueous is shunted to alternative outflow pathways, such as the episcleral venous system or suprachoroidal space, is lowering of IOP<sup>13,14</sup> to a less significant level that may not be adequate in some patients and may still allow glaucoma progression to occur (Table 10.29.1). Newer devices that allow access to the subconjunctival space with minimal or no (via ab interno insertion through the angle) incisions in the conjunctiva have also been instituted in an attempt to improve the morphology of the bleb and minimize complications. In recent years, after publication of the findings of the randomized Tube Versus Trabeculectomy Study for eyes with previous surgery, as well as the ongoing Primary Tube Versus Trabeculectomy Study, surgeons are recognizing that glaucoma drainage implant surgery may rival or improve on the long-term results of trabeculectomy, although controversy remains about the complication profile for each procedure, and the ideal surgical procedure for advanced glaucoma.<sup>15</sup>



**Fig. 10.29.2** Leaking Bleb With Positive Seidel Sign After Fluorescein Dye Is Applied. See Video 10.29.1.



**Fig. 10.29.3** Example of localized, cystic, thin-walled bleb.

## INDICATIONS

The goal of glaucoma management is to preserve visual function while maintaining or improving the patient's quality of life. When surgery is necessary, trabeculectomy is the procedure of choice for most cases of severe primary glaucomas. Success in glaucoma surgical studies is usually reported as a final IOP <21 mm Hg and/or 30% decrease in IOP, with or without additional medications, even though for many eyes that undergo trabeculectomy the goal is for postoperative IOP control in the low teens. Success with the typical definition in forms of open-angle glaucoma and primary angle-closure glaucomas has been reported in approximately 80% of eyes over 1–2 years, with lower IOP achieved with antimetabolite use.<sup>8,12,16–26</sup> Relatively few studies have evaluated the long-term preservation of visual field and optic nerve function as an outcome measure, yet it seems that glaucoma surgery is successful in this regard for the majority of eyes that have resulted in successful control of IOP.<sup>27</sup>

The decision to offer trabeculectomy is based on the patient's current stage of their glaucoma and the risks for ongoing progression of the disease without further intervention. The rate of progression differs among patients as does the goal for IOP control. Each individual must be carefully evaluated as to the best treatment modality. There are some patients who are likely to need trabeculectomy soon after diagnosis of their glaucoma, yet there are many patients who will never need trabeculectomy even after many years of the disease (Box 10.29.1).

## SURGICAL PLANNING

Surgical planning begins in the office with a careful history, ocular examination, and review of the patient's risk factors for failure (Table 10.29.2).

**TABLE 10.29.1** Trabeculectomy Versus Non-Bleb Filtration Surgery

Advantages	Disadvantages
<b>Trabeculectomy</b>	
Proven long-term success	Wound healing reaction important
Technical skills moderate	Creates a bleb—risk for infection
Gold standard	Creates a bleb—risk for discomfort
Relatively low risk of hypotony	Duration of effect—limited
Instrumentation readily available	More postoperative interventions: laser suturelysis, 5-fluorouracil injections
<b>Non-Bleb Filtration Surgery</b>	
Low risk of hypotony	Less intraocular pressure lowering long term Fewer published reports on long-term success
No bleb or bleb complications	Some techniques more technically difficult, time-consuming in operating room
	Need postoperative interventions: iridotomy, Descemet's puncture
	Additional instrumentation and/or devices

**TABLE 10.29.2** Risk for Failure

Average Risk	Moderate Risk	High Risk
POAG	JOAG	Childhood onset
Pseudo-exfoliation glaucoma	Pigmentary glaucoma, mainly due to younger age of patient	Neovascular glaucoma— inflamed eye
Mixed mechanism	Blunt trauma, angle recession	Uveitis, inflammatory
Prior clear cornea phacoemulsification	Conjunctival scarring after phacoemulsification	Conjunctival scarring after ECCE, ICCE
	Neovascular glaucoma— quiet eye	Conjunctival scarring after vitrectomy
	Fellow eye with encapsulated bleb	Fellow eye failed filter
	Combined with phacoemulsification	Prior filter failed
	After acute angle closure	Perforating/penetrating traumas
	Corticosteroid-induced glaucoma	ICE syndrome
	Chronic angle-closure glaucoma	Epithelial downgrowth
Elderly	Middle age	Youth
White, Asian		Hispanic, African descent

ECCE, Extracapsular cataract extraction; ICE, iridocorneal endothelial syndrome; ICCE, intracapsular cataract extraction; JOAG, juvenile-onset open-angle glaucoma; POAG, primary open-angle glaucoma.  
(Sources: Skuta et al.<sup>7</sup>; Mietz et al.<sup>28</sup>; AGIS Investigators<sup>29</sup>)

### BOX 10.29.1 Indications for Trabeculectomy

- Intraocular pressure (IOP) too high to prevent future glaucoma damage and functional visual loss
- Documented progression of glaucoma damage at current level of IOP with treatment
- Presumed rapid rate of progression of glaucoma damage without intervention
- Poor compliance with medical therapy: cost, inconvenience, understanding of disease, refusal
- Intolerance to medical therapy because of side effects

On the basis of this assessment, the surgeon will plan the approach to surgery, including fornix-based or limbal-based conjunctival flap dissection, placement of the scleral flap and sclerostomy, need for and type of antimetabolite, tightness of the scleral flap sutures to titrate the amount of aqueous fluid egress in the early postoperative period, need for releasable scleral flap sutures, and any preoperative treatments.

## PREOPERATIVE FACTORS TO CONSIDER

Preoperative factors that need to be considered are given in Table 10.29.3.

TABLE 10.29.3 Preoperative Factors

Location	Finding	Considerations
External/adnexa	Abnormal lid position or lagophthalmos	Increases risk for exposure, thinning, discomfort, and infection of bleb If prior blepharoplasty/ptosis repair, conjunctival fornix may be under tension
	Blepharitis	Increases risk for infection in the early and late postoperative periods
Conjunctiva	Allergy, toxicity	Discontinue any drops causing topical toxicity for several weeks prior to surgery. Consider preoperative topical corticosteroids to quiet eye
	Dry eye, keratoconjunctivitis sicca	Should be treated. Punctual plugs, omega-3s, and cyclosporin are considered. May be more at risk of infection in the early or late postoperative period
Conjunctival scarring <sup>a</sup>	Prior pterygium or tumor removal	Less mobile conjunctiva overall, and scarring nasally
	Prior ECCE surgery	Entire limbal area, conjunctiva and sclera, may be scarred
	Prior scleral tunnel phacoemulsification	Localized area of limbal scarring, may be able to position trabeculectomy flap to one side of tunnel
	Prior pars plana vitrectomy	Localized areas of conjunctiva scarring posterior to limbus, and/or entire limbal area may be scarred
	Prior scleral buckle	Entire limbal and posterior conjunctiva is scarred
	Trauma	Careful inspection for wound, scarring
Cornea	History of herpes simplex virus infection	Consider antiviral coverage during the postoperative period
	Prior penetrating or endothelial keratoplasty	Position trabeculectomy to avoid encountering host-graft interface or peripheral anterior synechiae
Anterior chamber	Uveitis	Treat aggressively prior to and after surgery. Eye often at risk for hypotony because of low aqueous production
Iris, angle	Peripheral anterior synechiae	Gonioscopy to locate and avoid
	Trauma	Avoid sclerostomy near iris dehiscence—may encounter vitreous if zonules absent. Vitrectomy should be considered, if necessary
	Neovascularization	Aggressive treatment before surgery with panretinal photocoagulation, anti-VEGF agents, topical corticosteroids and atropine preoperatively, waiting several weeks for trabeculectomy, if possible. Early hypotony should be avoided to minimize hyphema and fibrin postoperatively
Lens	Aphakic	Vitrectomy should be planned; hypotony should be avoided. There is increased risk of suprachoroidal hemorrhage. Sclera is thin, and conjunctival scarring may occur at the limbus
	Pseudophakic	Sclera is thin at the superior cataract surgery incision Usually less likely to develop postoperative anterior chamber shallowing
	Phakic	Slightly more likely to develop shallow anterior chamber postoperatively Cataract may develop or progress postoperatively
Refractive errors	Myopia	Sclera may be thin. Patients with moderate to high myopia are at risk for hypotony maculopathy when antimetabolites used
	Hyperopia	More likely to develop shallow anterior chamber postoperatively More likely to develop “aqueous misdirection syndrome”
	Prior refractive surgery	Patient may have been had high myopia (see above)
Retina	Comorbid disease	May affect long-term vision; unrelated to glaucoma
Patient issues	Uncooperative, poor understanding of directions	Type of anesthesia, block versus general, should be determined Determination of laser suture lysis or releasable sutures <sup>30</sup> Family, friends, and caregivers enlisted to help with postoperative regimen and follow-up
	Noncompliant	Noncompliance may extend to the postoperative follow-up and medication regimens
	Unrealistic expectations	Extensive counseling preoperatively and postoperatively

ECCE, Extracapsular cataract extraction.

<sup>a</sup>Almost all patients who have conjunctival scarring near the limbus should undergo a fornix-based trabeculectomy. Patients with extensive scarring, neovascular glaucoma, or iridocorneal endothelial syndrome may have better success with glaucoma drainage implantation.

## PATIENT COUNSELING

Long before surgery becomes necessary, it is hoped that the surgeon and the patient have begun a dialogue about the goals for glaucoma treatment. Because glaucoma is usually asymptomatic until far advanced, patients deserve a detailed explanation of the disease in general and the findings in their case in particular. It is likely that the patient realizes that glaucoma is progressing or is at risk for progression, as there has often been an escalation of medical therapy or possibly laser treatment prior to the proposal that trabeculectomy is the next step. At that point, it is appropriate to thoroughly review and discuss the patient's past course and interventions, and the surgeon's rationale for recommending a trabeculectomy. Once the surgical plan is formed, the surgeon and patient should have a thorough discussion about the goals of surgery, the risks, and the usual course of the surgical and postoperative experience. Any individual characteristics of the patient's ocular condition that may influence the surgical outcome should be explained, and the patient should feel well informed and comfortable with the decision to proceed with surgery (Box 10.29.2).

## SURGICAL TECHNIQUES

Perioperative preparation of the patient includes the following:

- Intravenous sedation.
- Adequate anesthesia—topical and subconjunctival, posterior Tenon's, peribulbar, or retrobulbar.<sup>31</sup>
- Positioning to maximize exposure of superior globe.

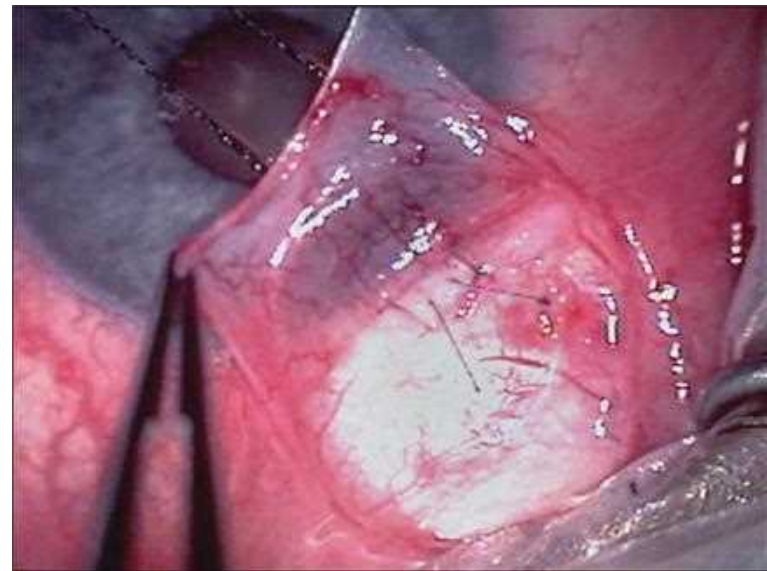
### BOX 10.29.2 Preoperative Counseling and Informed Consent

- Goals for surgery
  - Expectations for intraocular pressure control
  - Expectations for maintaining, not improving, vision
- Description of surgery
- Experience of surgery
  - Operative—type of anesthesia, expectations for pain, intravenous access, recovery
  - Requirements in postoperative period for drops, activity restrictions, frequent visits
  - Visual difficulties, visual fluctuations during postoperative period
  - Intraocular pressure fluctuations in the early postoperative period
  - Need for postoperative interventions, laser suture lysis, 5-fluorouracil, cycloplegics
  - Duration of postoperative period
- Risks
  - Intraoperative and early postoperative—suprachoroidal hemorrhage, infection, hypotony, shallow chamber, choroidal effusions, bleb leaks, aqueous misdirection, discomfort, cystoid macular edema, astigmatism, hypotony maculopathy, vision loss, failure, need for additional surgery
  - Late postoperative—discomfort, leaks, infection, failure, cataract development or progression, ptosis, permanent vision decrease or loss, need for additional surgery



## Intraoperative Technique: Limbal-Based Conjunctival Flap

The limbal-based conjunctival flap technique is shown in [Fig. 10.29.4](#). The scleral flap has been reapproximated with 2–4 interrupted 10-0 nylon sutures and tightness has been adjusted to allow for a small amount of aqueous oozing at the edges of the scleral flap. Limbal-based conjunctival flap technique, with the conjunctival incision being placed far posteriorly in the fornix, usually 9–10 mm from the limbus, and completed with a running conjunctival suture closure, is less commonly used now due to concerns that this technique creates more restricted blebs prone to late leaks.



**Fig. 10.29.4** Appearance of the Scleral Flap and Conjunctival Dissection Prior to Conjunctival Closure in a Limbal-Based Conjunctival Flap Trabeculectomy. Note the corneal traction suture.



## Surgical Technique: Fornix-Based Conjunctival Flap

See clip:  
10.29.2

The fornix-based conjunctival flap technique is given in [Table 10.29.4](#).

### Avoiding Intraoperative Complications

Careful surgical technique is required to avoid buttonholes of the conjunctiva and to allow minimal manipulations of the conjunctival flap edge. Excessive bleeding into Tenon's capsule is to be avoided because it can absorb blood like a sponge. However, excessive cautery is likely to promote fibrosis and/or scleral thinning. The scleral flap needs to be of sufficient thickness to allow for suture placement without cheesewiring of the suture. Despite its name, trabeculectomy is no longer performed as an excision of the trabecular meshwork. The fistula is less prone to obstruction if the

**TABLE 10.29.4** Surgical Technique: Fornix-Based Conjunctival Flap

Procedure	Instruments
1. Partial-thickness corneal traction suture 7-0 silk <sup>a</sup>	Needle holder, cotton swab for counter traction near limbus
2. Rotate globe inferiorly to maximize superior conjunctival exposure, attach to drape	Hemostat
3. If using injected antimetabolite: Inject desired volume and concentration of mitomycin C (MMC) far superiorly and massage toward limbus, wait minimum of 2 minutes before opening conjunctiva	Syringe with 30-gauge needle and prepared MMC
4. Incise conjunctiva and Tenon's capsule at the limbus, approximately 4–6 mm length. If using modified-Wise conjunctival closure, incision is placed 1 mm posterior to limbus to allow for small “bolster” of conjunctiva at the limbus	Sharp-tip Westcott scissors, toothed forceps Colibri type, nontoothed Max Fine forceps
5. Perform subconjunctival dissection spreading tangentially and radially away from limbus, as broad an area as possible, lifting edge of conjunctiva and dissecting alongside the superior rectus	Rounded Westcott scissors, nontoothed Max Fine forceps holding broad area of conjunctival edge
6. Perform wet field cautery to area of episclera in preparation for creating scleral flap	23-gauge Mentor rounded tip
7. Outline desired width of scleral flap with half-thickness depth	Diamond blade or crescent blade, Colibri
8. Use crescent blade to create a scleral tunnel of the desired width and half thickness, extending into clear cornea, just past end of limbal vessels <sup>b</sup>	Crescent blade, Colibri
9. If using sponge applied antimetabolites: Apply MMC or 5-fluorouracil (5-FU) on 2–6 pieces of sponge, covering a broad area of superior episclera, drape conjunctival flap back toward the incision and hold the edges away from contacting the sponges. Apply MMC for 1–3 minutes based on risk factors and conjunctival condition. Alternatively, apply 5-FU for 5 minutes. Remove sponges, flush with 20–30 mL of balanced salt solution (BSS), dry	
10. If not already released, release corneal traction suture. Perform paracentesis through temporal clear cornea aiming toward 6 o'clock angle <sup>c</sup>	15° super-sharp blade or diamond knife
11. Convert scleral tunnel to a scleral flap by placing two radial incisions, not extending all the way to the limbus	Vannas scissors
12. Lift scleral flap and insert super-sharp blade at farthest anterior part of the tunnel into anterior chamber, angling more vertically than horizontally, move blade steadily across the extent of the base of the bed, taking care not to retract the blade when aqueous gushes forward	Colibri holding scleral flap, super-sharp blade
13. Use Kelly scleral punch to fashion a small central sclerectomy <sup>d</sup>	Kelly punch, Colibri to hold scleral flap
14. Create peripheral iridectomy using jeweler's forceps inserted radially into sclerostomy to grasp iris, and cutting with angled Vannas scissors held circumferentially <sup>e</sup>	
15. Reapproximate the scleral flap with 2–4 interrupted 10-0 nylon sutures. Consider tying first 1–2 sutures temporarily, reinflating anterior chamber with BSS, and adjusting tightness to allow for a small amount of aqueous oozing at edges of scleral flap	Needleholder, Colibri, BSS on 27-gauge cannula and 3-mL syringe
16. Attach corneal traction suture to drape for exposure, if needed	Hemostat
17. Close conjunctival-Tenon's flap at the limbus with any variety of closures, such as a modified-Wise Condon running mattress suture, <sup>f</sup> purse-string wing sutures, and/or interrupted mattress sutures, ensuring watertightness ( <a href="#">Fig. 10.29.5</a> )	Needleholder, curved tying forceps, 10-0 nylon or 9-0 Vicryl
18. Reinflate anterior chamber with BSS and elevate bleb. Check for leaks with 2% fluorescein solution over entire bleb surface	

Two-site combined phacoemulsification and trabeculectomy usually begins with a temporal clear cornea approach to the phacoemulsification (phaco). After the cataract surgery is completed and the corneal incision secured with a 10-0 nylon suture, the surgeon repositions to perform a fornix-based (easier, less time-consuming) or limbal-based conjunctival flap trabeculectomy superiorly.

<sup>a</sup>Most surgeons use this to avoid bleeding from the blind pass of a bridle suture under the superior rectus.

<sup>b</sup>Most surgeons take advantage of the improved exposure of the fornix-based flap to use a familiar technique used with scleral tunnel phaco. Creating a scleral tunnel is also useful in the setting of limbal thinning from a previous ECCE incision, to avoid transecting the scleral flap at the juncture of the previous incision that can occur with traditional dissection.

<sup>c</sup>If performing a combined phaco and trabeculectomy with a single site incision, begin phaco procedure here. Leave viscoelastic in the eye until sclerectomy is performed. Then aspirate viscoelastic, instill intracameral acetylcholine or carbachol, then perform iridectomy and proceed with trabeculectomy closure.

<sup>d</sup>A peripheral iridectomy may not be necessary in pseudo-phakic eyes or when combining trabeculectomy with phaco.

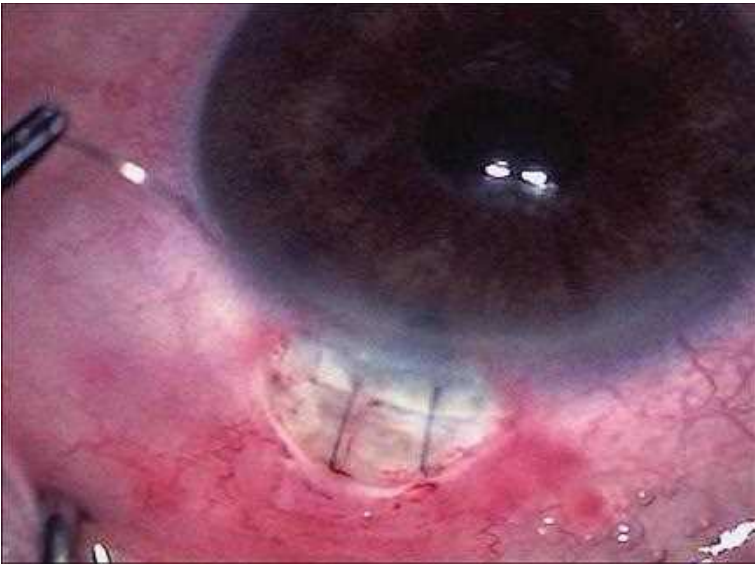
<sup>e</sup>Most surgeons use a punch, whereas others excise a block of tissue. The larger the sclerostomy, the greater is the likelihood of inducing irregular astigmatism. Usually, a 1–2-mm opening suffices.

<sup>f</sup>Again, variation in techniques is common.<sup>32–34</sup> The goal is to achieve watertight closure that will resist deformation of the cornea and a pressure-head of aqueous in the postoperative period. For modified Wise conjunctival closure, see Video 10.29.2 and reference 34.

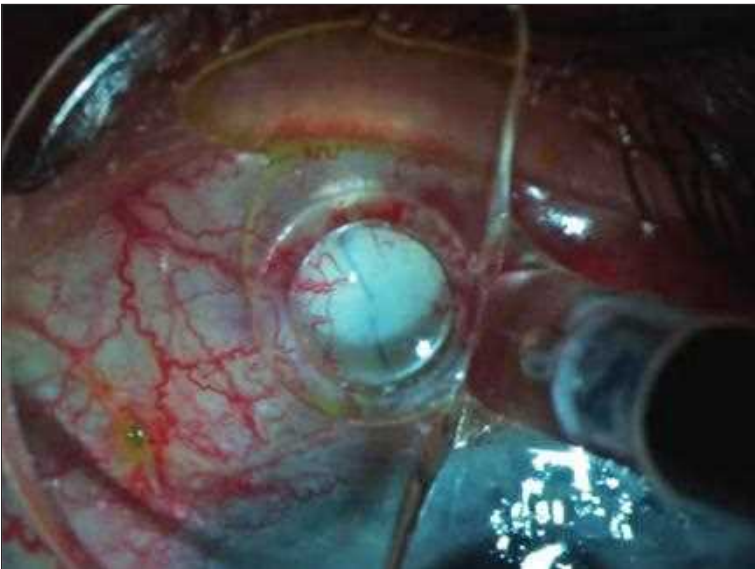
entry into the anterior chamber occurs well into the peripheral cornea. Meticulous conjunctival closure to avoid wound leaks is imperative.

POSTOPERATIVE CARE

Surgical technique, although extremely important, is just the prelude to the subsequent management that is necessary to achieve a long-term successful filtration surgery (Table 10.29.5). The most critical factor for success is to establish an elevated bleb within the first few days after surgery. Creating a physical separation with aqueous between the conjunctiva and episclera prevents subsequent fibrosis that will limit the surface area available for filtration and ultimately result in inadequate IOP lowering. In fact, in the early postoperative period, the appearance of a bleb is a more important factor to consider than the IOP. An elevated bleb with IOP that is slightly higher than desired in the early days after surgery is more acceptable than a flat bleb with a low IOP. An inflamed bleb with engorged conjunctival vessels<sup>36</sup> or extensive subconjunctival hemorrhage bodes warnings of subconjunctival fibrosis that may progress rapidly if no intervention is made in the first days after surgery (Fig. 10.29.7). Frequent examinations of the patient are required for observation of the bleb so that the appropriate modality can be employed to encourage success of the surgery. The desired appearance of a bleb is diffuse and elevated, with relatively avascular but not ischemic conjunctiva<sup>37</sup> (Fig. 10.29.8). The ultimate goal is the desired appearance plus lowered IOP to the level that will prevent further glaucoma damage. Individual healing characteristics



**Fig. 10.29.5 Fornix-Based Conjunctival Flap Trabeculectomy.** Needle will pass half-depth through peripheral cornea to begin wing suture to attach conjunctiva. For conjunctival closure, see Video 10.29.2.



**Fig. 10.29.6** View through Hoskins lens after scleral flap suture has been lysed with a laser.

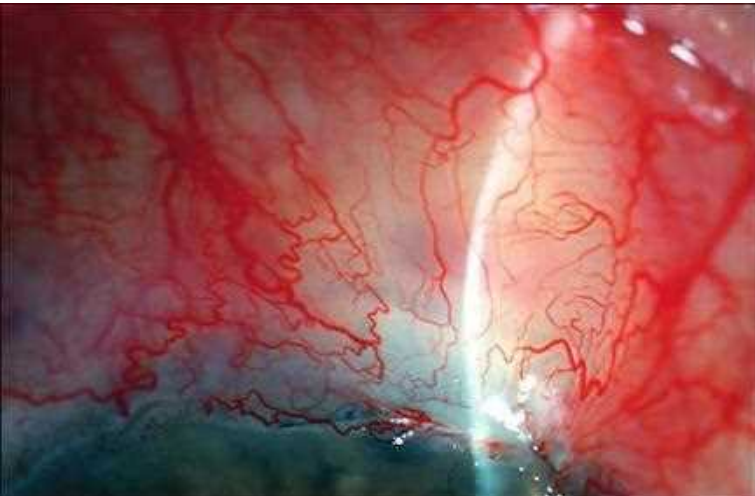
vary tremendously and the surgery is at risk if features that portend failure develop and yet go unrecognized or untreated.

For all patients, the following medications are suggested:

- Topical corticosteroids 6–8 times a day, with gradual taper over 3 months
- Topical cycloplegic drugs for patients with phakia, angle-closure, hypotony
- Topical antibiotics for 1–2 weeks

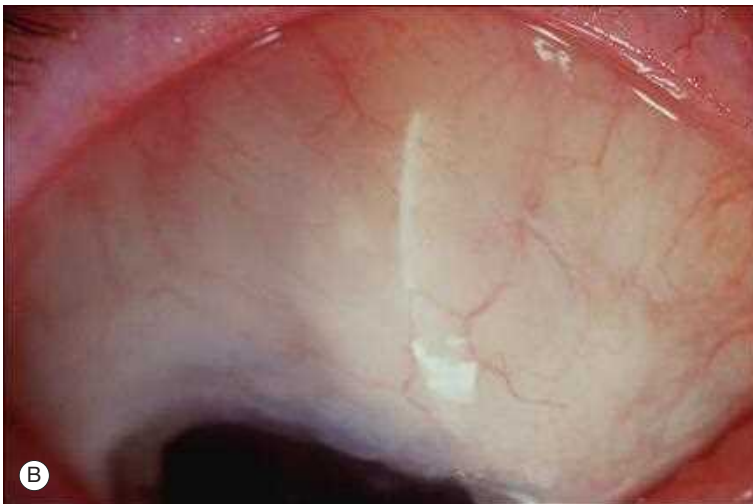
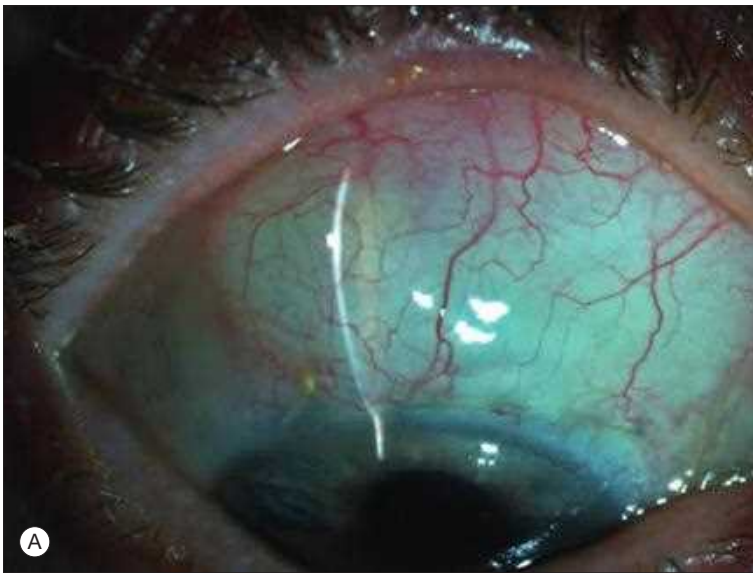
TABLE 10.29.5 Early Postoperative Manipulations	
Observation	Intervention
Low Bleb, High or Moderate IOP	
Determine level of obstruction	
Most common:	
Tight scleral flap	Release scleral flap suture—laser or releasable (Fig. 10.29.6)
Subconjunctival fibrosis	5-FU injections <sup>a</sup>
Episcleral fibrosis just around scleral flap	Needling with 5-FU, at 4–6 weeks postoperatively
Uncommon:	
Internal sclerostomy obstruction: iris	Laser to release
Internal sclerostomy obstruction: blood	Time, massage, or tissue plasminogen activator intracamerally
Low Bleb, Low IOP	
Leak at incision or in bleb substance	Bandage contact lens or suture in office or operating room
Hypotony caused by uveitis, low aqueous production	Time, topical corticosteroids
Choroidal effusions	Time, cycloplegia, topical corticosteroids, anterior chamber reformation with viscoelastic, drainage, if necessary
Rare:	
Cyclodialysis cleft	Cycloplegia, time, consider repair
Retinal detachment	Repair
High Bleb, Low IOP	
Overfiltration	Time. Watch for increasing choroidal effusions or hypotony maculopathy. May need revision if decreased vision persists
High Bleb, High IOP	
Encapsulation or “Tenon’s cyst”	Time, glaucoma meds, needling with 5-FU, if necessary
Engorged conjunctival vessels	Consider 5-FU injection <sup>a</sup>
HypHEMA	Time, 5-FU injection <sup>a</sup> if bleb is low or inflamed
Fibrin	Increase topical corticosteroids, subconjunctival corticosteroid, 5-FU injection <sup>a</sup>
Early encapsulation before increased IOP	Digital massage
5-FU, 5-fluorouracil; IOP, intraocular pressure. <sup>a</sup> For subconjunctival injection of 5FU, see Video 10.29.3. (Sources: Van Buskirk <sup>10</sup> ; Shingleton <sup>35</sup> )	

See clip: 10.29.3



**Fig. 10.29.7** Early postoperative trabeculectomy with marked vascularity and tortuous vessels.





**Fig. 10.29.8** Two examples of a diffuse, elevated, noninflamed, nonischemic bleb.

Follow-up visits should be made on day 1 following surgery, then weekly for the first 3 weeks, and then typically every other week for an additional 2 months.

## CONCLUSIONS

Trabeculectomy is an effective surgical procedure for managing glaucoma. Attention to detail preoperatively, intraoperatively, and postoperatively provides the best opportunity to tailor the procedure for individual cases and provide the appropriate care.

Changes in surgical technique that could make the surgery safer in the future include the use of glues to seal the conjunctival incision or bleb leaks, as well as the development of agents that provide effective long-term inhibition of subconjunctival fibrosis or are able to reverse hypotony.

Although trabeculectomy techniques have evolved over the last half century, it remains a variation on filtration surgery performed for over 100 years. Trabeculectomy surgical techniques and nuances of postoperative interventions will continue to be refined until such time that we are able to protect the retinal ganglion cells with other measures or procedures that make a bleb-associated fistulizing surgery obsolete.

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# Antifibrotic Agents in Glaucoma Surgery

10.30

*Peng Tee Khaw, Richard M.H. Lee, Cynthia Yu-Wai-Man, Jonathan C.K. Clarke, Alastair J. Lockwood*

**Definition:** Medical adjunctive agents and associated surgical techniques used intraoperatively and/or postoperatively to modulate the wound healing associated with glaucoma surgery in an effort to increase its success.

## Key Features

- Mitomycin C.
- 5-fluorouracil.
- Topical intraoperative use.
- Subconjunctival postoperative use.

## Associated Features

- Most commonly indicated for patients with elevated risk of failure, including previous surgery, neovascular glaucoma, black African descent.
- May increase the incidence of hypotony.
- May increase the rate of bleb-associated complications, including endophthalmitis.
- Simple changes in application and surgical technique markedly reduce bleb-related and other complications.

## INTRODUCTION

The use of antimetabolites with safe application of improved surgical techniques represents one of the major advances in the surgical management of glaucoma over the past 20 years. Antimetabolites help prevent scarring after glaucoma filtration surgery. They were used in only the highest-risk patients in the 1980s, but a more recent survey revealed that mitomycin C (MMC) is used in 84% of all patients undergoing primary trabeculectomy by university-based glaucoma physicians in the United States.<sup>1</sup> Studies have shown that a target intraocular pressure (IOP) at the lower end of the normal range (around 12 mm Hg) is required to arrest glaucomatous progression over a decade.<sup>2,3</sup> The concept that the healing response should be modulated to achieve such a target IOP after all surgery has become the new paradigm. The healing response is the major determinant of long-term IOP levels after glaucoma surgery, and prospective studies have demonstrated that the use of antimetabolites improves trabeculectomy survival outcomes.<sup>4,5</sup> Studies of more recent microincisional glaucoma surgery (MIGS) devices that drain into the subconjunctival space have also demonstrated the need to apply antimetabolites to prevent fibrosis and sustain the presence of the postoperative bleb.<sup>6</sup> Modulation of this healing response, together with meticulous surgical techniques, may enable the surgeon to set IOP at the lowest level while avoiding the complications that can be associated with antimetabolites.

## TYPES OF ANTIFIBROTIC AGENTS

The majority of attention has been focused on antimetabolites, such as 5-fluorouracil (5-FU) and MMC. However, other strategies exist to prevent fibrosis and scarring after glaucoma filtration surgery (summarized in Table 10.30.1). Many of the agents listed in Table 10.30.1 have multiple actions on the healing cascade. Other agents, such as corticosteroids, are

used as adjuncts to antimetabolites and are typically used over a longer period.<sup>7</sup> Intraoperative beta irradiation (1000 cGy) by a strontium-90 probe may be similar to a single-dose intraoperative 5-FU application<sup>8,9</sup> or lower dose MMC or at times even stronger.<sup>10</sup> A randomized trial of 320 patients with open-angle glaucoma, who were of black African descent, found the estimated risk of failure of trabeculectomy at 1 year to be 5% in the irradiated arm compared with 30% in the placebo group. The incidence of cataract at 2 years in the irradiated arm, however, was significantly greater.<sup>11</sup> More recently, several antagonists to growth factors are being tested in clinical practice. The antifibrotic agents used most commonly at present are discussed in this chapter.

## INDICATIONS FOR ANTIMETABOLITE USE

Certain patient characteristics increase the risk of scarring and failure after glaucoma surgery, as summarized in Table 10.30.2. However, the risk may still vary within subgroups. More than one risk factor, although each may be categorized as low risk individually, overall may result in placing the patient in a higher risk category. Furthermore, there may be hidden risk factors for failure in what were previously regarded as low-risk “first time surgery” groups. There are recognized changes after chronic topical treatment.<sup>12</sup> Fibroblasts appear to be activated in Tenon’s capsule in patients with open-angle glaucoma. It is not conclusive, however, that this is caused by the drops and not the disease.<sup>13</sup> The extent to which topical treatment might affect patient outcomes after surgery is not fully understood, but there appears to be a clearer correlation with inflammation and fibrotic failure.<sup>14,15</sup> The use of antifibrotic agents after tube drainage surgery has not been conclusively proven, and studies on the use of antifibrotics with newer surgical devices are still ongoing.

## Patient Groups With a High Risk of Scarring

Patient characteristics associated with a high risk of surgical failure include previous failed trabeculectomies, previous cataract surgery through a conjunctival incision, neovascular glaucoma, inflammatory eye disease, aphakia, neovascular glaucoma, black African ancestry, recent intraocular surgery, young age, and chronic topical medication.<sup>16</sup> Most glaucoma specialists agree that patients with any of these should have some form of antimetabolite treatment.

The most definitive study of 5-FU injections in high-risk patients was the randomized, prospective National Eye Institute 5-Fluorouracil Filtration Surgery Study, which showed a 51% failure rate after filtration surgery in patients who had failed trabeculectomy previously or in those who had undergone cataract surgery with a conjunctival incision. In the group that received 5-FU 5 mg injections (twice a day for days 1–7, once a day for days 8–14, total 21 injections), the failure rate was 51% compared with 74% in the placebo group after 5 years.<sup>4</sup> Since then, randomized studies undertaken to compare intraoperative MMC application (0.4–0.5 mg/mL) with 5-FU injections<sup>17–19</sup> have suggested that in high-risk patients, a single application of MMC provides superior long-term pressure control compared with injections of 5-FU without the risk of keratopathy. Corneal epithelial complications are much more common with injectable 5-FU, but both groups had thin avascular blebs, these being more prominent in the MMC-treated groups. A comparative 3-year study of West African patients found fewer postoperative hypotensive medications were required for the MMC-treated group (0.5 mg/mL for 3 minutes) compared with those who received 5-FU application (50 mg/mL for 5 minutes), although with a total of 68 patients, a statistical difference in success was not reached.<sup>20</sup>

TABLE 10.30.1 Wound Healing and Possible Modification After Glaucoma Surgery

Event	Potential Modulation
Previously damaged conjunctiva	Stop medical therapy especially those causing very red eye, if possible
"Preactivated" cells	Preoperative corticosteroids for 1–2 weeks (may not be possible if pressure responder)
Conjunctival/episcleral/scleral incisions	Minimal trauma
Damage to connective tissue	Less invasive surgical techniques
Release of plasma proteins and blood cells	Hemostasis (vital: blood can reverse mitomycin effects) Use of adrenaline or iopidine drops
Activation of clotting and complement Fibrin/fibronectin/blood cell clot	Agents preventing/removing fibrin—e.g., heparin, tissue plasminogen activator (although breakdown products may be fibrogenic)
Aqueous released from eye Some breakdown of blood–aqueous barrier	Blood–aqueous barrier stabilizing agents (e.g., corticosteroids)
Release of growth factors into aqueous	Nonsteroidal anti-inflammatory agents Growth factor antagonists e.g., bevacizumab
Aqueous begins to flow through wound	
Migration and proliferation of polymorphonuclear neutrophil cells, macrophages, and lymphocytes	Anti-inflammatory agents (e.g., corticosteroids/cyclosporine) TNF- $\alpha$ inhibitors (e.g. infliximab) Including systemic immunosuppression. Analogues to serum amyloid P (e.g., PRM-151) inhibit conversion of circulating monocytes into fibroblasts and profibrotic macrophages
	Antimetabolites (e.g., 5-FU/MMC)
Activation, migration, and proliferation of fibroblasts	Preoperative corticosteroids to reduce activation Antimetabolites MMC, 5-FU (MRTF/SRF pathway inhibitors) Rho kinase (ROCK) inhibitors (Possibly local anesthetics which inhibit fibroblasts)
Wound contraction	Anticontraction agents (e.g., colchicine, taxol) MMP inhibitors
Fibroblast synthesis of tropocollagen	MMC, 5-FU, IFN- $\alpha$
Glycosaminoglycans and fibronectin	MMC, 5-FU, MMP inhibitors
Collagen cross-linking and modification	Anti-cross-linking agents (e.g., beta-aminopropionitrile/penicillamine)
Blood vessel endothelial migration and proliferation and blood vessel leakage	Inhibitors of angiogenesis and blood vessel leakage (e.g., bevacizumab and ranibizumab, angiostatin)
Resolution of healing	MMC, 5-FU
Apoptosis	Death receptor ligands
Disappearance of fibroblasts	Stimulants of apoptosis pathways
Fibrous subconjunctival scar	
Anti-inflammatory Inhibits production and activity of TGF- $\beta$	Pirfenidone in idiopathic pulmonary fibrosis
Events and agents have overlapping time duration and action. 5-FU, 5-fluorouracil; IFN, interferon; MMC, mitomycin C; MMP, matrix metalloproteinase; MRTF/SRF, myocardin-related transcription factor/serum response factor; TNF- $\alpha$ , tumor necrosis factor-alpha.	

Using a single intraoperative 5-FU application, Egbert et al.<sup>21</sup> carried out a randomized prospective study in a group of West African patients who had a high risk of failure. They showed success rates of 83% in the 5-FU-treated group versus 39% in the control group, with a mean follow-up of 282 days.

The intraoperative MMC regimen, rather than postoperative subconjunctival 5-FU injections, has become the treatment of choice for high-risk patients. There is increased efficacy, ease of application, and virtual absence of corneal side effects. However, longer periods of follow-up are needed to monitor the development of bleb leaks, hypotony, and endophthalmitis, in view of the thinner and highly avascular blebs seen with MMC. The incidence of these so-called high-risk blebs has been dramatically reduced, however, because of the introduction of a theory of cystic bleb formation, that changed the method of antimetabolite application during glaucoma surgery.<sup>22–25</sup> Systemic corticosteroids and immunosuppressants are used in particular high-risk groups but are not routine and can have severe side effects if used by an inexperienced physician.<sup>26</sup>

Patient Groups With an Intermediate or Low Risk of Scarring

In patients with no previous ocular surgery and no significant comorbidity apart from glaucoma, the use of antimetabolites is more controversial. Intraoperative MMC application not only increases the success rate of surgery but also increases the incidence of hypotony.<sup>27</sup> Bindlish et al. reported an incidence of late hypotony (IOP <6 mm Hg) in 42% of eyes at some point between 6 months and final follow-up at 5 years, in a series of 123 primary trabeculectomies with MMC.<sup>28</sup> Hypotony occurs more in younger patients, particularly those who have myopia with thin sclera.<sup>27,29</sup>

5-FU injections have been used in lower-risk groups, which include those who have undergone first-time filtration surgery,<sup>30</sup> young patients,<sup>27</sup> and those with normal-tension glaucoma,<sup>31</sup> to achieve lower IOPs and

superior success rates. Complications, such as corneal epithelial changes, are more common but generally only in the short term.<sup>30</sup> Cell culture experiments suggest that a single 5-minute application of 5-FU is able to inhibit fibroblasts for several weeks without severe long-term damage and be equivalent to low-dose 5-FU injections.<sup>32,33</sup> Several studies using single applications of intraoperative 5-FU with short-term follow-up have reported promising results in low-risk patients. Lanigan et al.<sup>34</sup> reported a success rate of 77% in high-risk patients (those with neovascularization, previous failed filtration surgery, aphakia, uveitis, or multiple risk factors), with a 100% success rate in the low-risk groups. Feldman et al.<sup>35</sup> reported an overall success rate of 85% in high-risk patients and a success rate of 92.9% in low-risk patients; no hypotony was seen in the Feldman study. However, both studies were of short duration and had no controls. Therefore, failure occurs in higher-risk patients who have a prolonged or aggressive healing response, but in lower-risk patients the success rate is very good (>90%) with no clinically significant hypotony. An improvement in survival was also found for patients in East Africa with a single 5-minute application of low dose 5-FU (25 mg/mL), interestingly with a much lower failure rate in the control group<sup>36</sup> compared with patients in West Africa.<sup>21</sup> There is evidence that 5-FU trabeculectomy maintains IOP in the low teens compared with nonaugmented surgery.<sup>37,38</sup>

Comparative studies for primary trabeculectomy have not found one antimetabolite to be clearly superior to another. A trial of 5-FU 50 mg/mL versus MMC 0.2 mg/mL in first-time trabeculectomy (low risk) in the United States did not show any statistically significant differences, to date, in efficacy or side effects of 115 eyes randomized to receive either treatment.<sup>39</sup> These findings were similar to those of WuDunn et al.,<sup>40</sup> who used the same doses of 5-FU and MMC.

A single antimetabolite regimen may not be adequate for all patients. The type and dose of drugs needs to be titrated depending on the individual patient's risk factors and healing response. The authors use a "titratable" regimen that is based on laboratory<sup>33</sup> and clinical data gained from experience using the different single-application agents and concentrations



TABLE 10.30.2 Risk Factors for Scarring After Glaucoma Filtration Surgery

Risk Factors	Risk (+ to + + +)	Comments
<b>Ocular</b>		
Neovascular glaucoma (active)	+ + +	May require panretinal photocoagulation ± anti-VEGF
Previous failed filtration surgery	+ + (+)	Consider tube surgery
Previous conjunctival surgery	+ +	Uncertain
Chronic conjunctival inflammation	+ + (+)	
Previous cataract extraction (conjunctival incision)	+ + (+)	
Aphakia (intracapsular extraction)	+ + +	
Previous intraocular surgery	+ +	Depends on type of surgery
Uveitis (active, persistent)	+ +	
A red, injected eye	+ +	
Previous topical medications (Beta-blockers + pilocarpine)	+ (+)	Particularly if they cause a red eye
(Beta-blockers + pilocarpine + adrenaline)	+ + +	
New topical medications	+ (+)	
High preoperative intraocular pressure (higher with each 10 mm Hg rise)	+ (+)	
Time since last surgery	+	
(especially if within last 30 days)	+ + (+)	
Inferiorly located trabeculectomy	+	Increased risk of endophthalmitis
<b>Patient</b>		
African-Caribbean descent	+ +	
West African descent	+ + (+)	
East African descent	+	
Indian subcontinent descent	+	
Hispanic descent	(+)	
Japanese descent	(+)	
Older adult (over 60 years)	(+)	
Adolescent/younger adult (16–40 years)	+ (+)	
Children (under 16 years)	+ +	

VEGF, Vascular endothelial growth factor.

(the authors call this the *Moorfields/Florida regimen* [“More Flow regimen”]). This regimen evolves constantly, but the present one is summarized in [Box 10.30.1](#). Postoperative, subconjunctival injections of 5-FU may be used in addition to the application of intraoperative antimetabolites.

APPLICATION TECHNIQUES

There are great variations in technique used to deliver intraoperative antimetabolites, which may account for some of the published variations in efficacy and complications. It is important for individual surgeons to maintain a consistent technique and to periodically re-evaluate their experience in the use of this technique. Intraoperative MMC applications are commonly used, but preoperative MMC injections are also now used prior to glaucoma filtration surgery.<sup>41</sup> It is now better understood how antimetabolites, particularly MMC, work in vivo causing long-term tissue cell death and growth arrest.<sup>33</sup> There is remnant functional activity in peripheral fibroblasts, which form a ring of scar tissue around the bleb (“ring of steel”).<sup>42</sup> This has allowed the development of strategies in antimetabolite delivery and associated surgical techniques, which increase safety and improve bleb appearance dramatically ([Fig. 10.30.1](#)). Optimization of the application technique is important for refinement and long-term IOP control of MIGS devices that drain into the subconjunctival space (the “R1R2” principle, where R1 is the outflow resistance due to the device and R2 is the outflow resistance caused by the bleb).

This change has led to a reduction in the number of cystic blebs from 90% to 29% and has reduced bleb-related complications, particularly endophthalmitis, from 15% to 0% over a 3-year follow-up period ([Fig. 10.30.2](#)).<sup>25</sup> More recent reports of this safer trabeculectomy technique have recorded a success rate of 96.7% (IOP <21 mm Hg) at 3 years in a complex case mix,<sup>43</sup> and Stalmans et al. reported a success rate of 100% (IOP <21 mm Hg) in lower-risk patients at 15.7 months mean follow-up with few complications (flat anterior chamber 1.8%; hypotony beyond 3 weeks 1.5%).<sup>44</sup> Simple

STRATEGIES IN ANTIMETABOLITE DELIVERY AND ASSOCIATED SURGICAL TECHNIQUES

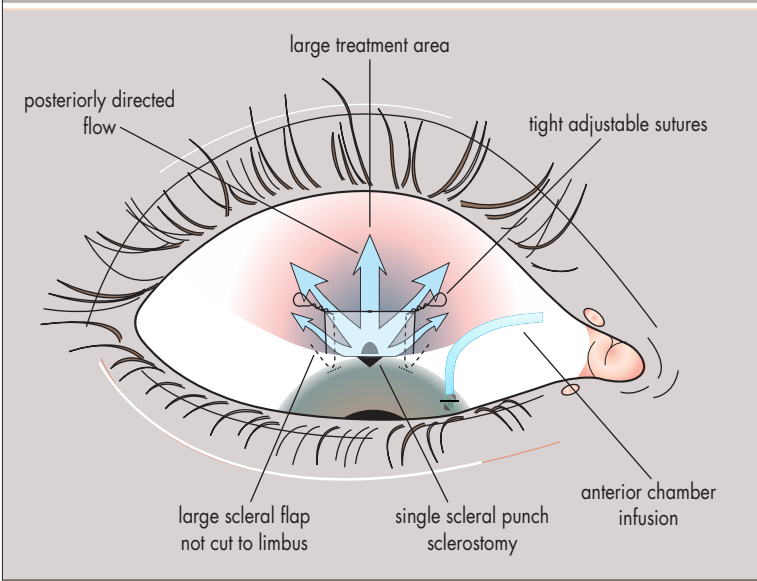


Fig. 10.30.1 Strategies in antimetabolite delivery and associated surgical techniques that increase safety and improve bleb appearance dramatically.

BOX 10.30.1 Moorfields Eye Hospital/University of Florida (More Flow) Regimen

Low-Risk Patients (Nothing or 5-FU 50 mg/mL 5 min)<sup>a</sup>

- No risk factors
- Short-term topical medication
- Older adults

Intermediate-Risk Patients (5-FU 50 mg/mL 5 min or MMC 0.2 mg/mL 3 min)<sup>a</sup>

- Chronic topical medications or others that cause a red eye
- Previous cataract surgery without conjunctival incision (capsule intact)
- Several low-risk factors
- Combined glaucoma filtration surgery/cataract extraction
- Previous conjunctival surgery (e.g., squint/detachment surgery)
- East African ancestry

High-Risk Patients (MMC 0.5 mg/mL 3 min) (Consider Tube Implantation)

- Neovascular glaucoma (combine with bevacizumab)
- Chronic persistent uveitis (anti-inflammatory/immunosuppression)
- Previous failed trabeculectomy/tubes with or without antimetabolites
- Chronic conjunctival inflammation
- Cicatricial conjunctival disease
- Multiple risk factors
- Aphakic glaucoma (a tube with antimetabolites may be more appropriate in many of these cases)
- West African ancestry

An intraoperative, single-dose regimen for scarring after glaucoma filtration surgery. (This regimen is still evolving.) Other factors may also determine the choice of agent, such as the need for a low target pressure resulting from advanced disease (require a stronger antimetabolite treatment). Beta-radiation 10Gy can also be used.

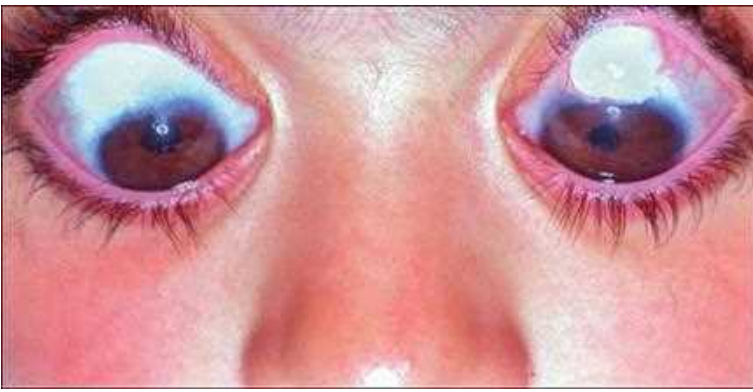
Postoperative 5-FU injections can be given in addition to the intraoperative applications of antimetabolite.

5-FU, 5-fluorouracil; MMC, mitomycin C.

adjustments of technique should result in much lower complication rates for many thousands of patients (summarized in [Box 10.30.2](#)).

Type and Concentration of Intraoperative Agent and Time of Exposure

The optimal concentration of intraoperative MMC has not been established.<sup>45</sup> Chen et al.<sup>46</sup> reported results in high-risk patients since 1981



**Fig. 10.30.2** Focal cystic bleb prone to leakage, infection, and dysesthesia in the left eye (limbus-based conjunctival flap, small scleral flap, and smaller area of mitomycin C [MMC] 0.4 mg/mL treatment). Diffuse noncystic bleb appearance in right eye of the same patient (fornix-based flap, larger scleral flap, and larger area of MMC 0.5 mg/mL treatment).

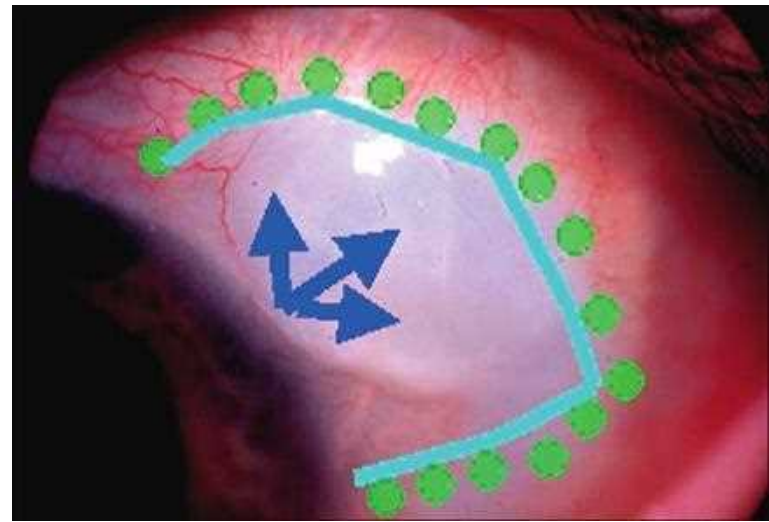
### BOX 10.30.2 Improvements in the Use of Intraoperative Antimetabolites

- Use of weaker agents (intraoperative 5-FU), lower concentrations of MMC for lower-risk individuals or individual at high risk of hypotony or other complications of antimetabolites
- Nonfragmenting sponges (polyvinyl alcohol rather than methylcellulose)
- Protection of cut edge with special clamp (John Weiss or Duckworth and Kent, UK) to prevent dehiscence
- Treatment under both scleral flap and conjunctival flap. The use of the sponge both under the scleral flap and the conjunctiva does seem to enhance the success rate
- Measures to secure scleral flap—smaller sclerostomy, larger scleral flaps, multiple tight sutures that are both adjustable (adjustable suture control [ASC]) and releasable
- Intraoperative flow control—continuous positive pressure infusion giving accurate indication of flow, maintaining blood–aqueous barrier and washing out cytokines
- Measures to produce diffuse noncystic blebs—large scleral flaps, fornix-based conjunctival flap, or extremely posterior limbus-based incision and large surface area of antimetabolite treatment; **big** (treatment area, scleral flap) and **backward** (aqueous flow direction) is better for blebs

without failures but a 66% rate of hypotony with MMC 0.4 mg/mL, a 22% failure rate with no hypotony with MMC 0.2 mg/mL, and a 37% failure rate with no hypotony with MMC 0.1 mg/mL. In a randomized, prospective study of Japanese patients given primary surgery, Kitazawa et al.<sup>47</sup> had a 100% success rate with MMC 0.2 mg/mL (but transient hypotony maculopathy and cataract progression in 18%) and a 64% success rate with MMC 0.02 mg/mL with no hypotony or cataract progression. For intraoperative 5-FU, both 50 mg/mL and the weaker 25 mg/mL have been used, but no direct comparison has been made between the two.

The optimal time of exposure has also not been determined. Megevan et al. retrospectively compared eyes treated with MMC 0.2 mg/mL for 2 minutes or 5 minutes.<sup>48</sup> There was no statistically significant difference in success rate or complications, but hypotony and endophthalmitis still occurred. In another study MMC was administered intraoperatively at 0.5 mg/mL for 5 minutes or 0.4 mg/mL for 3 minutes in Indian patients.<sup>49</sup> No significant difference occurred in postoperative IOP, hypotony, or postoperative filtration failure rate. However, the group treated with the higher concentration for 5 minutes had a higher incidence of serous choroidal detachment. One patient from each group developed postoperative endophthalmitis during the study period. Shorter applications of 2–3 minutes, compared with 5 minutes, appear to have the same efficacy, but if applications are shortened to less than 2 minutes, suboptimal cellular and tissue absorption may occur. In a study of 5-FU uptake in tissues, the concentrations reached a plateau at 3 minutes.<sup>50</sup> Even shorter application times may result in greater variations in drug delivery.

Changes in the concentration of the agent are more likely to give reproducibly titratable effects compared with variations in exposure time. Therefore, to achieve consistent and predictable results, it is probably



**Fig. 10.30.3** Diagrammatic illustration of the “cystic bleb” hypothesis requirements for cystic bleb formation with or without antimetabolites. Blue arrows indicate anterior aqueous flow; light blue line and green dots indicate a ring of scar tissue, the so-called ring of steel.

more important that the individual surgeon becomes accustomed to one or two concentrations and one exposure time. The authors use MMC 0.2 or 0.5 mg/mL and 3 minutes, on the basis of our previous studies.

### Type of Sponge

Small variations in technique may have profound effects on the clinical result and complications. The type of sponge may affect significantly the amount of drug delivered. Chen et al.<sup>46</sup> originally used a Gelfoam sponge, but most clinicians use commercially available sponges (e.g., Weck cell, Merocel), which have different retention and drug-releasing capabilities and which may be cut to different sizes. Attempts to standardize the dose of drug delivered have been made,<sup>51</sup> and the accurate application of MMC drops to a standard sponge will deliver a known dose. The authors currently use polyvinyl alcohol sponges (Merocel, Mystic, CT) as these do not disintegrate like methylcellulose and leave fragments in the wound that can cause significant foreign body granulomas.<sup>52</sup> A formulation and kit licensed by the U.S. Food and Drug Administration is now available (Mobius Therapeutics, St. Louis, MO).

### Larger Areas of Antimetabolite Treatment

On the basis of clinical observation, a hypothesis as to why cystic blebs occur has been put forward (Fig. 10.30.3). By treating larger areas, bleb-related complications can be reduced.<sup>25</sup> This clinical finding has been confirmed experimentally.<sup>53</sup> A specially designed clamp (2-686; Duckworth & Kent, Baldock, UK) for use during either limbal or fornix-based surgery helps protect the conjunctival edge from exposure (Fig. 10.30.4).

Treatment under both the scleral flap and conjunctival flap, particularly in high-risk cases, can be considered.<sup>54</sup> Finally, staining of the antimetabolites with trypan blue has been described permitting the delineation of the treatment area.<sup>55</sup> This principle has been adopted very successfully for current devices with good success rates and diffuse noncystic blebs.<sup>6</sup>

### POSITION OF DRAINAGE AREA UNDER EYELID

The positioning of the scleral flap and treated area is often neglected but is extremely important. Interpalpebral and inferiorly placed blebs have a high incidence of endophthalmitis, particularly in association with antimetabolites.<sup>56,57</sup> In addition, it is important to assess the lid position preoperatively and to try to place the bleb at the point of maximum coverage of the lid. If no space exists for a superior trabeculectomy with antimetabolite, better alternative methods may include tube drainage devices or cyclodestructive procedures.

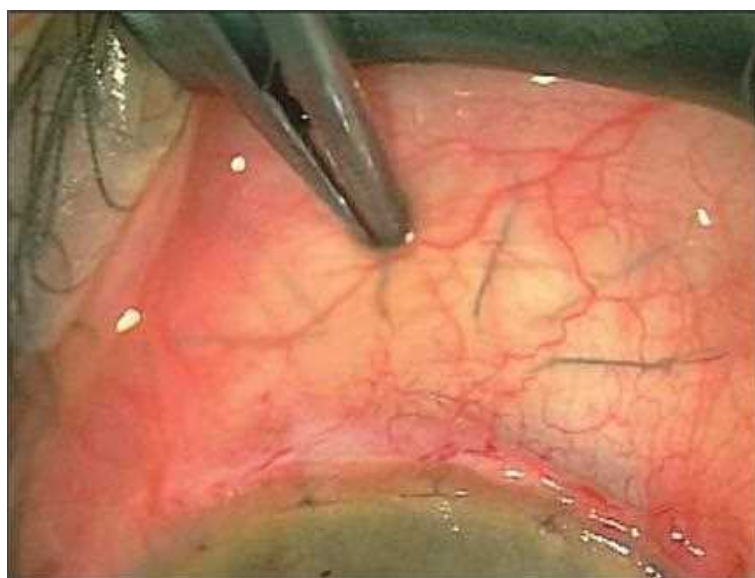
### CLOSURE OF SCLERAL FLAP AND ASSOCIATED SURGICAL TECHNIQUES

Healing at the cut edge of conjunctiva may be markedly inhibited by antimetabolites, and hypotony is prevented primarily by the resistance afforded





**Fig. 10.30.4 Intraoperative Antimetabolite Being Applied.** The cut edge of conjunctiva is protected by a special clamp (Duckworth and Kent) during surgery. As large an area as possible is treated to achieve a diffuse noncystic bleb.



**Fig. 10.30.5 Adjustable Suture Control.** Sutures being adjusted through the conjunctiva with duck-billed forceps to ensure gradual lowering of intraocular pressure after antimetabolite use.

by the scleral flap. Therefore, this flap has to be sufficiently thick and wide relative to the sclerostomy to provide this resistance, and it has to be sutured adequately enough to achieve this resistance and yet be adjustable gradually. This adjustability is achieved by laser suture lysis, or adjustable/releasable sutures, although too early a release of sutures may be associated with long-term hypotony.<sup>27</sup> When antimetabolites (particularly MMC) are used, suture lysis (even several months after surgery) may result in hypotony.<sup>58</sup> This also applies to occluding sutures left within or around the tube lumen after tube implant surgery.

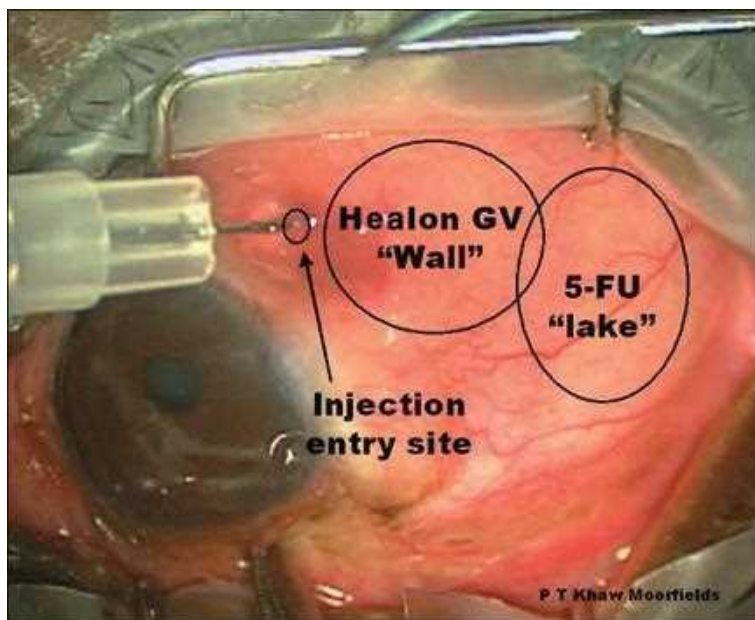
Late choroidal effusions and hemorrhage after suture removal have been reported, even many months after the surgery.<sup>59</sup> With MMC, sutures should be released late. In particular, the adjustable/releasable suture(s) should be tied tighter, but IOP should be checked in patients who have marked visual field loss in the first few hours after surgery. If the pressure is raised on the first postoperative day, then gentle pressure is applied to the back of the scleral flap, which very slightly loosens the flap, allowing outflow of aqueous, and lowers the opening pressure without the complete loss of tension that occurs when sutures are released. Alternatively, a technique of adjustable sutures can be used in which a special pair of highly polished forceps (Khaw forceps 2-502; Duckworth & Kent, Baldock, UK) can be used transconjunctivally to adjust the sutures and thus the IOP downward gradually until the target pressure is reached (Fig. 10.30.5).<sup>60</sup> Results of a subsequent study suggest that suture adjustment may be superior to both posterior lip massage and releasable sutures for managing IOP in the early phase following glaucoma surgery.<sup>61</sup> Manipulation of the scleral flap and associated sutures may only lower the IOP for minutes to hours but the effect persists if the suture tension is decreased. Ultimately, optimizing the success of the surgery with antimetabolites is dependent on a combination of simple technical modifications, which the authors have termed the *Moorfields Safer Surgery System*.<sup>60</sup>

## POSTOPERATIVE INJECTIONS

Subconjunctival injections of 5-FU may be used postoperatively on their own or in combination with intraoperative MMC or 5-FU, if the pressure rises and the healing response is still marked. A meta-analysis suggested that three injections or fewer may have no impact on long-term success and only five injections or more may be effective if no antimetabolite is used intraoperatively.<sup>62</sup>

The technique of injection has evolved. The 5-Fluorouracil Filtration Surgery Study regimen was 5-FU 5 mg in a volume of 0.5 mL given 180° from the filtration site (current practice is summarized in Box 10.30.3). On the basis of pharmacokinetic studies, the authors also sometimes use a subconjunctival viscoelastic injection (Healon GV, Pharmacia, NJ) and then inject the 5-FU on the far side of the viscoelastic, which prevents any 5-FU reflux into the tear film (Fig. 10.30.6). This also lengthens the duration of action. Corneal side effects are very rare with this regimen.

Subconjunctival injections of MMC have been advocated and described increasingly, particularly with procedures, such as needling,<sup>62-65</sup> and there



**Fig. 10.30.6** Viscoelastic wall to prolong duration and minimize side effects of subconjunctival 5-fluorouracil.

### BOX 10.30.3 Improvements in Injectable 5-Fluorouracil

- Reduction in number of injections given
- Injections given closer to bleb area—increased efficacy for same dose
- Long injection track—reduction in epitheliopathy
- Use of small-bore needle (e.g., 30-gauge)
- Injection of viscoelastic—prolonged release and no corneal side-effects
- Use in conjunction with intraoperative antimetabolites—reduced need for injections

is some evidence that it may be superior to subconjunctival 5-FU. Although successful needling revisions of blebs have been reported above using subconjunctival injections of smaller volumes (0.01 mL at 0.2–0.4 mg/mL), the potential risks of subconjunctival MMC are significant. Given the cytotoxicity of MMC, this should be used with great caution.

## COMPLICATIONS

Many complications of filtration surgery have been described, and the use of antimetabolites increases the incidence of some of these. In particular, short-term and long-term hypotony associated with maculopathy (which



**BOX 10.30.4 Potential Complications of Antimetabolites****Hypotony**

- Particularly if scleral flap not adequately closed or high-dose MMC used

**Prevention**

- Close scleral flap securely—releasable sutures are very useful. May require multiple sutures, particularly if MMC used
- Do not make scleral flap too small or thin, otherwise outflow cannot be adequately restricted
- Delayed suture release—if MMC used suture release even months after surgery may result in hypotony
- Adjustable suture control (ASC)—gradual loosening of sutures down to target pressures

**Complications of Hypotony**

- Including maculopathy, which may be irreversible even after pressure is restored, choroidal effusions and bleeding, cataract and phthisis

**Prevention**

- Caution when using strong antimetabolites in high-risk patients, for example, those with myopia who appear more prone to get hypotony-associated problems, such as maculopathy (soft sclera)
- Intraoperative infusion (Lewicky cannula) to gauge outflow; do not finish until flow secured
- Low threshold to resuture; use intraocular viscoelastic as a temporizing measure

**Wound Edge Leaks****Prevention**

- Identify patients at risk of poor wound healing (e.g., vitamin deficiencies or alcohol dependence)
- Small conjunctival incision and minimal tissue handling
- Ensure wound is securely closed, vascular needle prevents buttonholing
- Mattress sutures if fornix-based flap—test at end of surgery to ensure watertight
- Protect cut edge of conjunctiva from drug (e.g., special clamp)

**Epithelial Erosions**

- Mainly with injected 5-FU, which leaks into tear film

**Prevention**

- Use intraoperative sponge technique
- Use long injection track for injections to prevent tear film reflux and washout by tears after injection

5-FU, 5-fluorouracil; MMC, mitomycin C.

- Use viscoelastic to prevent tear film reflux in susceptible patient (e.g., surface problems)

**Intraocular Penetration and Damage**

- Intraocular damage can include endothelial damage and ciliary body destruction—possibly with high-concentration MMC (controversial)

**Prevention**

- Treat with antimetabolite sponge and washout before making scleral incision
- Great care when injecting 5-FU subconjunctivally close to the bleb, particularly in a soft eye
- High risk if MMC is injected

**Infection—Blebitis and Endophthalmitis, Bleb Breakdown and Leakage****Prevention**

- Identify patients at risk (e.g. meibomian disease)
- Avoid overtreating—use appropriate antimetabolite for patient
- Use large surface area treatment and large scleral flap—radically reduces incidence of cystic blebs prone to infection and leakage
- Avoid thin scleral flaps
- Avoid interpalpebral or inferiorly sited blebs—infection rate may be 5–10 times higher than bleb under upper lid

**Scleritis**

- Occurs particularly with interpalpebral/inferior blebs

**Prevention**

- Avoid interpalpebral and inferior blebs
- Minimize strength of antimetabolite

**Scleromalacia/Thinning/Necrosis****Prevention**

- Avoid areas of scleral thinning—theoretical possibility

**Malignancy/Teratogenicity/Long-Term Cumulative Effects****Prevention**

- Continued surveillance—on both patient and medical staff
- Careful handling and disposal of cytotoxics required
- Avoid using if any chance of pregnancy in patient
- Potentially more long-term complications with mitomycin C than with 5-fluorouracil

may be irreversible), choroidal effusions, or hemorrhage may occur with an increased incidence. The other major concern is the potentially high long-term incidence of endophthalmitis, especially with avascular cystic blebs, seen particularly with the use of higher concentrations of MMC. Using the appropriate surgical techniques can considerably reduce the risk of these complications. A list of major potential complications and possible ways to prevent some of these are presented in [Box 10.30.4](#).

**FUTURE STRATEGIES TO PREVENT FIBROSIS**

Although current agents (particularly MMC) are extremely effective in the prevention of fibrosis, considerable room still exists for improvement. Long-term complications may only become apparent many years later. A key area for the future lies in a better understanding of the cellular and molecular processes involved in the healing processes, and of the exact effects of the various agents used to modulate the process. Biological factors may have profound effects.

A number of novel antifibrotic agents are currently under development and at various stages of nonclinical and clinical trials. The necessity for long periods of follow-up and valid outcome endpoints is a significant challenge. Trabio (anti-transforming growth factor beta [TGF- $\beta$ ] antibody) was shown to be effective in reducing scarring in vivo<sup>66</sup> and in pilot human studies<sup>67</sup> with relatively diffuse noncystic blebs. However, the dose used in the later trial based on initial studies<sup>66</sup> may have been wrong, and long-term prolonged dosing as shown in the subsequent study by Mead et al. may be necessary.<sup>68</sup> Serum amyloid P (human pentraxin-2) is a serum protein that inhibits the transformation of circulating monocytes into fibrocytes and the activation of macrophages involved in fibrosis.<sup>69,70</sup> A recombinant form

(PRM-151) has been shown to inhibit myofibroblast generation in rabbit corneas,<sup>71</sup> and a phase II trial in the form of a series of conjunctival injections after trabeculectomy has been completed.

Vascular endothelial growth factor (VEGF) antibody therapy has recently exhibited considerable potential in the modulation of wound healing for glaucoma filtration surgery. VEGF is both stimulatory to endothelial cells in blood vessel development<sup>72</sup> and is upregulated in fibroblasts in tissue where scarring is active.<sup>73</sup> The inhibition of VEGF has been shown to reduce scar tissue deposition in cutaneous wounds in the mouse.<sup>74</sup> VEGF is upregulated in the aqueous after glaucoma filtration surgery and can stimulate Tenon's fibroblast proliferation. Furthermore, in the rabbit, an aggressive scarring animal model of glaucoma filtration surgery, bevacizumab injections can promote bleb survival.<sup>75</sup> When compared with 5-FU in this model, bevacizumab-injected blebs resulted in a better bleb morphology and prolonged survival.<sup>76</sup> Combining 5-FU and bevacizumab also appears to work in a synergistic way.<sup>77</sup> Evidence in humans that anti-VEGF antibodies could modulate conjunctival scarring after glaucoma filtration surgery came initially from a report of a successful bleb needling procedure using bevacizumab.<sup>78</sup> Grewal et al.<sup>79</sup> performed a prospective case series of trabeculectomies for open-angle glaucoma patients using bevacizumab as an adjunct. Although the numbers were small (12) and the follow-up 6 months, those authors found good control of IOP with no signs of ocular toxicity or adverse effects.<sup>79</sup> Vandewalle et al. also reported that perioperative administration of intracameral bevacizumab significantly reduced the need for needling interventions and led to a higher success rate after trabeculectomy.<sup>80</sup>

Anti-VEGF therapy may be particularly applicable in the treatment of patients undergoing trabeculectomy with neovascular glaucoma. As yet,

there are only reports of individual cases; however, intravitreal injection at the time of surgery has been reported to have resulted in both good control of proliferative disease and IOP and profound regression of iris neovascularization.<sup>81</sup>

Intracellular triggers of fibroblast activity may also be suppressed. Adenoviral *p53* gene transfer leads to a significant growth inhibition of human Tenon's capsule fibroblast *in vivo*.<sup>82</sup> The downstream suppressor protein of *p53* is *p21 WAF-1/Cip-1*. Adenoviral-mediated treatment of an animal glaucoma model demonstrated prevention of wound healing and has potential as a novel treatment option.<sup>83</sup> Human RAD50 (*hRAD50*) is involved in the repair of mammalian DNA, and overexpression has been demonstrated to have antiproliferative activity. *In vitro* studies have demonstrated that histological antiproliferative effects of local *hRAD50* on the conjunctival fibroblasts are similar to those of MMC in an animal model but that damage to the basal lamina and other structures was not seen.<sup>84</sup> Modulation of matrix metalloproteinase activity has also proved to be a very exciting modality of future treatment with results in an experimental model almost equal to MMC without the tissue destruction seen with MMC.<sup>85–87</sup> New modalities of scar reduction, including nanotechnology to produce agents that suppress inflammation, have also been shown to dramatically reduce scar formation after experimental glaucoma surgery.<sup>88</sup>

Ultimately, it is likely that antiscarring agents will be used in all patients, possibly in combination, analogous to the situation in cancer chemotherapy. These combination regimens together with new device and drug release technologies will evolve to give us the safe, prolonged, long-term, maximal lowering of IOP that is associated with minimal or no progression of glaucoma—the Holy Grail of glaucoma treatment.

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# Drainage Implants

Kateki Vinod, Steven J. Gedde

10.31

**Definition:** Glaucoma drainage implants are surgically placed to lower intraocular pressure. They may be used at any stage in the treatment of glaucoma.

**Key Feature**

- Glaucoma drainage implants bypass the natural aqueous outflow systems and typically shunt aqueous humor via a silicone tube from the anterior chamber to a plate in the sub-Tenon's or subconjunctival space, generally more than 8 mm posterior to the limbus.

**Associated Features**

- Glaucoma drainage implants may be either valved or open tubes.
- Tube exposure is a major risk factor for endophthalmitis.

**HISTORICAL PERSPECTIVE**

Modern glaucoma drainage implants (GDIs) have evolved from the eponymous device first described by Molteno in 1969.<sup>1</sup> Refinements in implant design and surgical technique have led to the routine use of GDIs in the surgical management of glaucoma. Analysis of Medicare claims data demonstrated a 77% decline in trabeculectomy use in the United States between 1994 and 2012, with a concurrent 410% increase in the number of GDI surgeries.<sup>2</sup> Surveys of the American Glaucoma Society membership have shown a similar shift in surgical practice patterns between 1996 and 2008, with a significant increase in the use of GDIs in various clinical settings.<sup>3-5</sup>

**BASIC CONCEPT**

Drainage implants share a common design consisting of a silicone tube, which is inserted into the eye through a scleral fistula and shunts aqueous humor to an episcleral endplate located in the equatorial region of the globe. Capsule formation around the endplate occurs over a period of 4–6 weeks and provides resistance to aqueous flow. Aqueous pools within the

reservoir created by the capsule diffuses across the bleb wall for eventual reabsorption into the systemic circulation, thereby lowering intraocular pressure (IOP). Thinner blebs with larger surface areas tend to produce lower IOP.

Commercially available GDIs include the Ahmed glaucoma valve (New World Medical, Inc., Rancho Cucamonga, CA), Baerveldt glaucoma implant (Abbott Medical Optics, Inc., Santa Ana, CA), and Molteno glaucoma drainage device (Molteno Ophthalmic, Ltd., Dunedin, New Zealand). These differ in surface area, endplate composition, implant profile, and presence or absence of a valve (Table 10.31.1). Valved devices (i.e., Ahmed implants) house a mechanism that allows aqueous egress above a minimum opening pressure and provide immediate IOP control, whereas nonvalved devices (i.e., Baerveldt and Molteno implants) require ligation to provide temporary restriction to flow while awaiting formation of an adequate capsule.

**INDICATIONS**

Drainage implants were traditionally reserved for eyes with complex, refractory glaucomas with one or more prior failed filtering surgeries or considered at high risk for trabeculectomy failure. Eyes with neovascular glaucoma, uveitic glaucoma, certain childhood glaucomas, iridocorneal endothelial syndrome, or extensive scarring from prior surgery, trauma, or conjunctival cicatrizing disease were among those chosen for primary GDI surgery. The role of GDIs has expanded in recent years, in part as a result of evidence from randomized clinical trials supporting their use in eyes at lower risk of filtration failure (see Evidence from Randomized Clinical Trials).

Glaucoma drainage implant surgery may be performed using a staged approach or in combination with cataract, corneal, and/or vitreoretinal surgery in patients with multiple ocular comorbidities. Drainage implants appear to be less prone to failure than trabeculectomy in eyes requiring subsequent cataract surgery because postoperative inflammation can compromise the longevity of a filtering bleb.<sup>6</sup> Patients who have suffered a bleb-related complication or trabeculectomy failure in one eye may be considered for a primary drainage implant if incisional glaucoma surgery is required in the fellow eye. Although all patients need careful postoperative follow-up after incisional glaucoma surgery, those who are unable or less likely to adhere to the more rigorous postoperative visit schedule required after trabeculectomy may be better candidates for GDI surgery.

TABLE 10.31.1 Features of Commercially Available Glaucoma Drainage Implants

Implant Type	Manufacturer	Model	Single or Double Plate	Surface Area (mm <sup>2</sup> )	Endplate Composition	Implant Profile (mm)	Valve
Ahmed®	New World Medical, Inc. (Rancho Cucamonga, CA)	FP7	Single	184	Silicone	2.1	Present
		FP8 <sup>a</sup>	Single	102	Silicone	2.1	
		S2	Single	184	Polypropylene	1.6	
		S3 <sup>a</sup>	Single	85	Polypropylene	1.6	
Baerveldt®	Abbott Medical Optics, Inc. (Santa Ana, CA)	BG103-250	Single	250	Silicone	0.84	Absent
		BG101-350	Single	350	Silicone	0.84	
		BG102-350 <sup>b</sup>	Single	350	Silicone	0.84	
Molteno®	Molteno Ophthalmic, Ltd. (Dunedin, New Zealand)	GL	Single	230	Polypropylene	1.5	Absent
		GS	Single	175	Polypropylene	1.5	
		SL	Single	245	Polypropylene	0.95	
		SS	Single	185	Polypropylene	0.95	
		R2/L2	Double	274	Polypropylene	1.5	
		DR2/DL2	Double	274	Polypropylene	1.5	
		S1	Single	137	Polypropylene	1.5	

<sup>a</sup>Designed for use in pediatric cases or small eyes.

<sup>b</sup>Includes a 90° Hoffman elbow for pars plana insertion.

Data from <http://www.newworldmedical.com>; <http://www.abbottmedicaloptics.com>; <http://www.molteno.com>.

## PREOPERATIVE CONSIDERATIONS

Assessment of conjunctival mobility at the slit lamp in eyes with previous surgery can help guide quadrant selection for placement of a GDI. Preoperative gonioscopy allows identification of high peripheral anterior synechiae that may impede anterior chamber tube entry through certain portions of the angle. Glaucoma drainage implants are most commonly inserted into the anterior chamber, but a shallow anterior chamber or endothelial cell dysfunction may necessitate sulcus or pars plana placement in patients with pseudo-phakia or aphakia. Sulcus or pars plana placement may also be preferable in pseudo-phakic or aphakic eyes with a corneal graft or those in which future corneal surgery is likely because drainage implants may contribute to graft failure.<sup>7</sup>

Patients in whom pars plana tube placement is planned should undergo thorough pars plana vitrectomy, with particular attention to shaving of the vitreous base in the quadrant of intended tube insertion. Repeat vitrectomy is usually necessary in patients who have been previously vitrectomized to ensure adequate vitreous removal. Combined pars plana vitrectomy and pars plana GDI insertion has been shown to lower IOP successfully in patients with aphakia and pseudo-phakia,<sup>8,9</sup> with an efficacy comparable with that of anterior chamber tube insertion.<sup>10,11</sup> If preoperative examination reveals vitreous in the anterior chamber as a result of prior posterior capsular rupture or zonular dehiscence, then a vitrectomy is indicated prior to or at the time of GDI surgery to minimize the risk of vitreous occlusion of the distal tube tip.<sup>12</sup>

Patients with neovascular glaucoma should be treated preoperatively with panretinal photocoagulation or anti-vascular endothelial growth factor, whenever possible, to minimize the risk of intraoperative bleeding. Use of preoperative intravitreal bevacizumab has been associated with a decreased risk of postoperative hyphema, but it has not demonstrated an effect on postoperative IOP or success rates following GDI surgery.<sup>13–15</sup>

## IMPLANT SELECTION

Valved devices are often selected in patients with severely elevated preoperative IOP who require immediate IOP lowering, such as those with neovascular glaucoma. Patients at high risk for hypotony, including those with uveitis or who have undergone prior cyclodestructive procedures, may also benefit from placement of a valved implant. Evidence from recent clinical trials may further guide the selection of a particular implant type, endplate size, or endplate composition (see [Evidence from Randomized Clinical Trials](#)). Ultimately, the choice of implant depends on the surgeon's comfort and preference, which is determined by his or her experience.

## SURGICAL TECHNIQUE

### Anesthesia

Glaucoma drainage implant surgery is typically performed under monitored anesthesia care with a retrobulbar or peribulbar block to provide local anesthesia. Alternatively, a sub-Tenon's block can be administered after an initial conjunctival peritomy and posterior dissection are performed and may be useful in patients who are monocular or under anticoagulation therapy. General anesthesia is rarely required.

### Quadrant Selection

The superotemporal quadrant is usually chosen for placement of a first GDI because of better surgical exposure and a reduced likelihood of postoperative strabismus. The inferonasal quadrant is generally selected in the presence of an existing superotemporal GDI or extensive conjunctival scarring from prior surgery, trauma, or inflammation. The superonasal quadrant is generally avoided because it is associated with a higher rate of postoperative strabismus and a risk of acquired Brown's syndrome,<sup>16–20</sup> as well as with a theoretical risk of optic nerve impingement with excessively posterior endplate placement in smaller eyes.<sup>21,22</sup> Use of the inferotemporal quadrant is less common because of the presence of the inferior oblique muscle<sup>22</sup> but may be required in eyes in which the superotemporal and inferonasal quadrants are not available because of conjunctival scarring or scleral thinning. Inferior GDI placement is generally preferred in eyes with silicone oil or that are likely to require retinal detachment repair with silicone oil in the future. Silicone oil is buoyant in aqueous, and an inferior tube minimizes the risk of oil migration through the tube lumen into the subconjunctival space where it can cause inflammation.<sup>23–25</sup>



**Fig. 10.31.1** A polyglactin corneal traction suture is placed to allow intraoperative movement of the globe and facilitate surgical exposure.



**Fig. 10.31.2** A fornix-based conjunctival flap is created.

### Conjunctival Flap and Dissection

A perilimbal 6-0 or 7-0 polyglactin corneal or scleral traction suture facilitates globe movement to optimize visualization during surgery ([Fig. 10.31.1](#)). Blunt scissors and nontoothed forceps are used to create a limbus- or fornix-based flap in the selected quadrant ([Fig. 10.31.2](#)). Hemostasis of the scleral bed is achieved with judicious use of wet-field cautery. Dissection between conjunctiva/Tenon's capsule and sclera is carried posteriorly to create a pocket between the superior and lateral rectus muscles for superotemporal quadrant endplate placement and between the inferior and medial rectus muscles for inferonasal quadrant endplate placement.

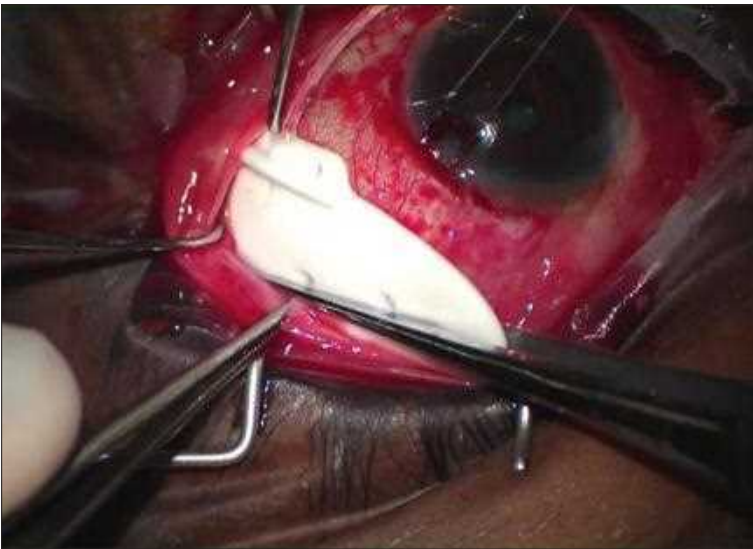
### Endplate Attachment

Posterior dissection is followed by identification and isolation of the adjacent rectus muscles. One muscle hook is used to isolate the first rectus muscle, and a second muscle hook is placed immediately behind the first and then slid further posteriorly to reveal a clean scleral pocket beneath the muscle ([Fig. 10.31.3](#)). Care must be taken to hook the entire muscle without splitting it. The endplate is then placed into position 8–10 mm posterior to the limbus between the two adjacent rectus muscles. Each wing of the Baerveldt 250 mm<sup>2</sup> or 350 mm<sup>2</sup> endplate is designed to be tucked beneath adjacent rectus muscle bellies ([Fig. 10.31.4](#)). The Ahmed and single-plate Molteno implants are narrower and may be centered between adjacent rectus muscles. Double-plate Molteno implants occupy two quadrants, and the bridging silicone tube between the two endplates can be tucked under or draped over the superior rectus muscle. The endplate is then





**Fig. 10.31.3** The rectus muscle is isolated and a pocket created for insertion of the endplate.



**Fig. 10.31.4** The endplate is inserted beneath the rectus muscle.



**Fig. 10.31.5** The endplate is secured to sclera 8–10 mm posterior to the limbus using nylon suture on a spatulated needle.

secured to sclera with interrupted nonabsorbable sutures (typically, 8-0 or 9-0 nylon on a spatulated needle), which are passed through each of two eyelets on the anterior edge of the plate (Fig. 10.31.5). The suture knots are buried within the eyelets to prevent future erosion through overlying conjunctiva.



**Fig. 10.31.6** A 7-0 polyglactin ligature is placed near the tube-plate junction to provide flow restriction of the nonvalved tube.

## Implant Preparation

Implants are prepared differently, depending on whether they are valved or nonvalved. The Ahmed implant contains a valve mechanism that requires priming prior to its insertion. Balanced salt solution is injected via a 30-gauge cannula into the tube tip to break the surface tension between the valve leaflets, and patency is confirmed when flow is observed within the device's trapezoidal chamber. This step is generally performed before attachment of the endplate. The endplate should be handled delicately to avoid damaging the valve mechanism.

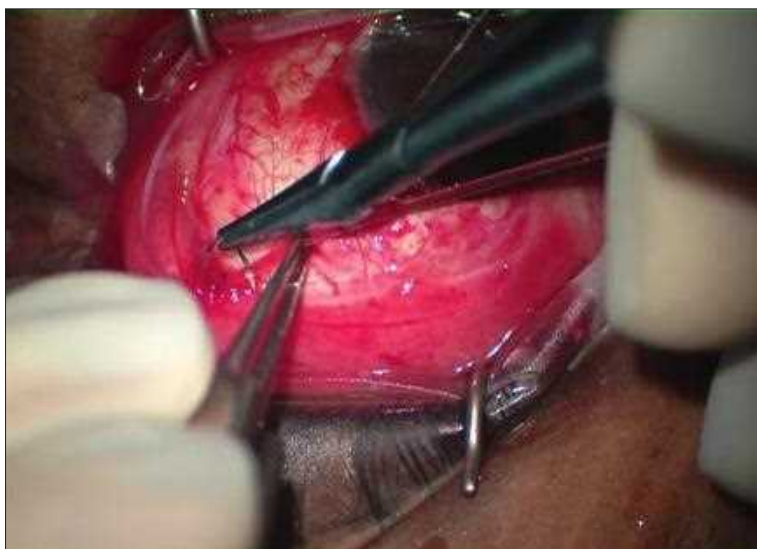
Nonvalved implants require ligation to provide temporary restriction to flow while capsular fibrosis occurs around the endplate. The tube may be ligated with absorbable (polyglactin) suture (Fig. 10.31.6), which will spontaneously lyse approximately 4–6 weeks after surgery, or nonabsorbable (polypropylene) suture. Polypropylene suture ligation is especially useful in patients at high risk for hypotony; in these patients, laser suture lysis to open the tube in a controlled setting is preferable. If laser suture lysis is planned, the ligature should be placed roughly 5 mm anterior to the tube-plate junction to facilitate later visualization at the slit lamp. After ligation, balanced salt solution is injected by using a 30-gauge cannula to confirm proper tube occlusion. Flow restriction can also be accomplished by using an intraluminal stent or ripcord (4-0 or 5-0 polypropylene or nylon suture) instead of, or in addition to, an external ligature. The end of the stent suture is positioned subconjunctivally in a separate quadrant from the endplate, allowing later removal at the slit lamp once an adequate capsule has formed. Alternatively, a 9-0 polypropylene suture can be used to ligate the distal (intracameral) portion of the tube, and argon laser can be used to later melt the ligature.

Patients who receive a nonvalved implant and have higher preoperative IOP may require interventions to allow aqueous egress and provide IOP reduction in the immediate postoperative period while awaiting tube opening. Venting slits, or fenestrations, may be placed anterior to the ligature using a suture needle or blade (Fig. 10.31.7). The number of fenestrations can be titrated on the basis of the preoperative IOP. Fenestrations have been shown to effectively reduce IOP immediately after GDI surgery but may be accompanied by a greater rate of early hypotony and hypotony-related complications, most of which are transient.<sup>26</sup> Another option is to create a fenestration using the needle of a 9-0 or 10-0 monofilament polyglactin suture and to leave a short segment of the same suture in place to serve as a wick.

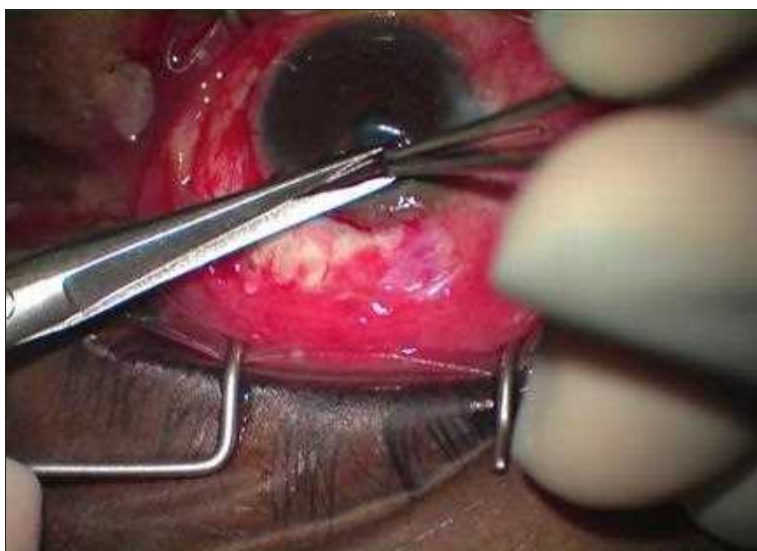
## Tube Insertion

Prior to creation of a sclerostomy, a clear corneal paracentesis may be created using a side port blade to allow access to the anterior chamber, if needed. The globe is returned to primary position, and the site of intended tube entry is determined. The tube is then draped across the corneal surface and trimmed with sharp scissors to the desired length, such that 2–3 mm will be visible within the anterior chamber (Fig. 10.31.8). A slightly longer intraocular tube length may be helpful for sulcus and pars plana tubes so that the tube tip can be more easily visualized at the slit





**Fig. 10.31.7** A fenestration is placed anterior to the ligature using a suture needle.



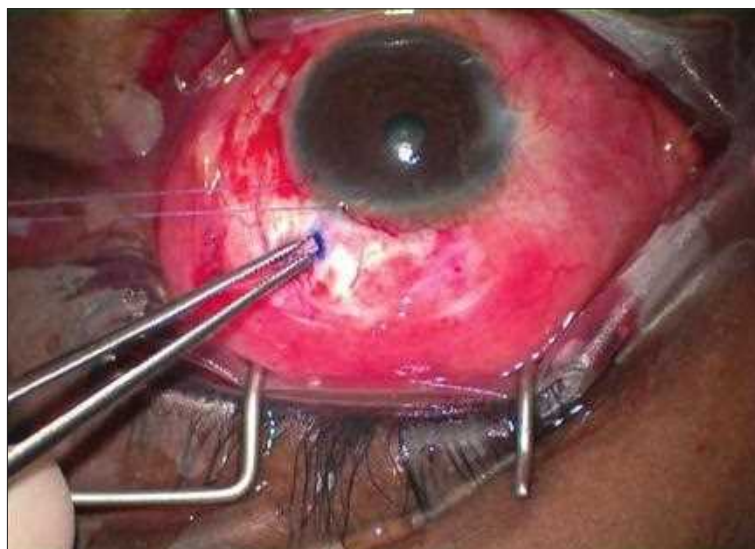
**Fig. 10.31.8** The tube is trimmed with an anterior bevel in preparation for anterior chamber insertion.



**Fig. 10.31.9** A scleral fistula is created by using a 23-gauge needle.

lamp postoperatively. Tubes are trimmed with an anterior bevel for anterior chamber and pars plana entry, and with a posterior bevel for sulcus entry, to avoid iris incarceration.

A 23-gauge needle is bent to a right angle or a slightly obtuse angle by using the jaws of a heavy needle holder, and a sclerostomy is made into the anterior chamber (or sulcus, or pars plana) (Fig. 10.31.9). A short scleral



**Fig. 10.31.10** The tube tip is inserted through the scleral fistula into the anterior chamber and noted to be in good position without proximity to the corneal endothelium or iris.



**Fig. 10.31.11** An interrupted polyglactin suture is placed through episclera to secure the tube just posterior to its site of entry.

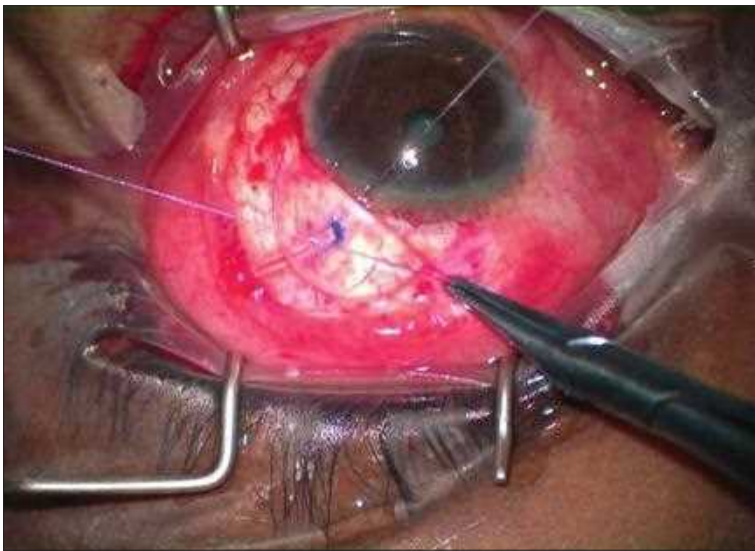
tunnel may be created with the 23-gauge needle prior to entry into the eye to help protect the tube from future erosion. The scleral fistula for anterior chamber placement should result in tube placement just above and parallel to the iris plane to avoid proximity to the corneal endothelium (which can cause endothelial dysfunction) or iris contact (which can incite inflammation, or bleeding if rubeosis is present). Nontoothed forceps or a tube inserter (Model TI; New World Medical, Inc., Rancho Cucamonga, CA) is then used to advance the tube tip into the eye through the needle track (Fig. 10.31.10). An 8-0 or 9-0 nylon or 7-0 or 8-0 polyglactin suture in interrupted or figure-of-eight fashion can be used to secure the tube to sclera posterior to its entry site (Fig. 10.31.11). This stabilizing suture should not be tightened excessively because this may impede aqueous flow.

Many surgeons leave cohesive viscoelastic in the anterior chamber when placing a valved implant to minimize the risk of postoperative hypotony. Cohesive viscoelastic is also helpful to tamponade intraoperative bleeding in neovascular eyes.

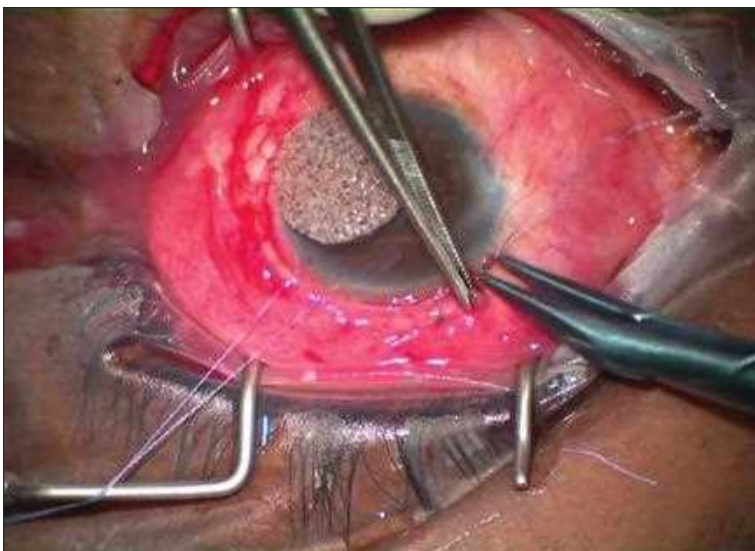
### Patch Graft Placement

The site of tube entry is covered with a patch graft to minimize the risk of conjunctival erosion and subsequent tube exposure. Several different materials exist for use as a patch graft, including the cornea, sclera, pericardium, dura, and fascia lata. The patch is secured to sclera in at least two points with polyglactin suture, with care taken to completely cover the site of tube entry (Fig. 10.31.12). A longer scleral tunnel may obviate the need for a patch graft and is useful in cases where patch graft material is unavailable.





**Fig. 10.31.12** A corneal patch graft is used to cover the site of tube entry and secured to episclera with polyglactin suture.



**Fig. 10.31.13** The conjunctiva is reapproximated to the limbus and closed using polyglactin suture.

## Conjunctival Closure

Reapproximation of the conjunctiva to the limbus is achieved by using nontoothed forceps. Rotating the eye toward the operated quadrant and loosening the eyelid speculum slightly can facilitate a difficult closure. The conjunctiva is closed using 7-0 or 8-0 polyglactin suture, either in running or interrupted fashion (Fig. 10.31.13). Additional mattress sutures at the limbus help prevent conjunctival retraction. Subconjunctival antibiotics and corticosteroids are administered at the conclusion of the case.

## POSTOPERATIVE MANAGEMENT

Patients are examined on the first postoperative day, and the subsequent frequency of follow-up is determined based on IOP and the general condition of the operated eye. Topical antibiotics and corticosteroids are initiated. Antibiotics can be discontinued at the first postoperative week visit, but corticosteroids are continued for 2–3 months postoperatively. Glaucoma medications may be resumed on the first postoperative day after insertion of a nonvalved GDI unless fenestrations or a wick were placed. Tube opening after nonvalved GDI surgery with an absorbable ligature occurs spontaneously between postoperative weeks 4 and 6 and may be accompanied by a significant and sometimes fibrinous anterior chamber reaction requiring an increase in topical corticosteroid frequency. Because of the risk of hypotony and shallowing of the anterior chamber, patients should be monitored closely during the time the tube is expected to open. Alternatively, laser suture lysis may be performed after adequate encapsulation around the endplate has occurred, which usually requires approximately 4 weeks. Cohesive viscoelastic may be injected intracamerally after laser suture lysis if the IOP is very low or in patients at high risk for hypotony

**TABLE 10.31.2** Potential Complications Associated With Glaucoma Drainage Implants

### Intraoperative Complications

Conjunctival buttonholes or tears  
Hyphema  
Scleral perforation  
Tube truncation

### Postoperative Complications

Anterior chamber shallowing  
Aqueous misdirection  
Bleb encapsulation  
Choroidal effusion  
Corneal decompensation  
Endophthalmitis  
Hypotony maculopathy  
Retinal detachment  
Strabismus and diplopia  
Suprachoroidal hemorrhage  
Tube occlusion  
Tube or endplate exposure  
Tube or endplate migration  
Wound leak

and hypotony-related complications. Argon laser suture lysis settings vary by surgeon preference but usually include a spot size of 50 microns, duration of 0.02–0.05 seconds, and power of 250–800 mW. A Hoskins lens aids in visualization of the ligature.

## COMPLICATIONS

Various complications, some of which are unique to GDI surgery, may arise intraoperatively or postoperatively. These are summarized in Table 10.31.2.

### Intraoperative

An excessively deep scleral pass during endplate or patch graft placement may result in scleral perforation, occasionally causing immediate hypotony and anterior chamber collapse. The needle should be withdrawn from its track and the anterior chamber filled with viscoelastic. An intraoperative or postoperative retinal consult to perform cryotherapy and examine the peripheral retina for breaks may be warranted.

The tube may be inadvertently severed because of an overly tight ligature or overzealous fenestration. Tube extension using a 22-gauge angiocatheter, Crawford tube, or the commercially available Tube Extender (New World Medical, Inc., Rancho Cucamonga, CA) may be needed. If truncation occurs close to the tube–plate junction, then the device may require replacement.

Significant adhesions from prior surgery may impede creation of the initial conjunctival flap. A super sharp blade may help achieve a clean dissection through scar tissue at the limbus. A larger peritomy and relaxing incisions at either extent of the peritomy may mitigate tearing, particularly when the conjunctiva is thin and/or friable.

### Postoperative

Hypotony and its sequelae may occur in the immediate postoperative period because of decreased aqueous production or overfiltration. Aggressive fenestration or excessive flow resulting from wick placement within a nonvalved tube can result in very low pressures. Most cases of hypotony can be managed successfully with conservative therapy (i.e., cycloplegia and topical corticosteroids) and frequent observation if the anterior chamber remains formed. Anterior chamber reformation with viscoelastic may be required in cases where hypotony is accompanied by significant anterior chamber shallowing with lens–endothelial touch and/or large choroidal effusions. Significant choroidal effusions or choroidal hemorrhage may require surgical drainage. Inadequate ligation of a nonvalved device or a valve that is suspected to be malfunctioning may require reoperation.

Hypotony may occur later in the postoperative course, especially when the ligature of a nonvalved tube is released either spontaneously or with laser suture lysis. Frequent follow-up during the time of expected spontaneous tube opening or after ligature release by laser is recommended so that hypotony and its sequelae can be recognized and treated promptly. Cohesive viscoelastic may be placed intracamerally after the tube opens to reform a shallow chamber or in patients at high risk of hypotony-related problems.



Drainage implants are subject to a number of unique complications related to their design. The tube tip may become occluded by fibrin, blood, iris, or vitreous. Obstruction of the tube lumen may be visible during slit-lamp examination, and B-mode echography is helpful to confirm reduced or absent flow around the endplate. Increasing the frequency of topical corticosteroids may melt a fibrinous or hemorrhagic net blocking the tube lumen. Intracameral injection of tissue plasminogen activator (0.1 mL of 5–20 µg/0.1 mL) may be needed in select cases, and carries a risk of hypotony and/or hyphema.<sup>27,28</sup> Iris–tube occlusion may respond to pupillary constriction with pilocarpine and/or application of argon laser to contract iris tissue near or occluding the tube lumen,<sup>29</sup> but surgical revision may be required in refractory cases. Vitreous occlusion of the tube lumen may occur after insertion of a tube into the pars plana after incomplete vitrectomy or delayed hyaloid separation and with anterior chamber or sulcus tubes in the presence of a disrupted posterior capsule or zonular dehiscence. Neodymium:yttrium–aluminum–garnet laser vitreolysis is variably successful, and many patients require repeat pars plana vitrectomy with manual extraction of the vitreous plug from within the tube lumen to completely reverse the occlusion. Obstruction of flow resulting from kinking of pars plana tubes at their entry sites has also been described and may require tube repositioning.<sup>30</sup> Use of an oblique angle, rather than a perpendicular angle, when creating a scleral fistula for pars plana tube insertion helps avoid this complication. Alternatively, the Baerveldt model with a 90° Hoffman elbow designed for pars plana insertion (BG102-350; Abbott Medical Optics, Inc., Santa Ana, CA) may be used.

Endplate migration occurs rarely and can be prevented with proper fixation to the equatorial sclera. Baerveldt glaucoma implants are less likely to migrate because their wings are tucked beneath the adjacent rectus muscles. Tube retraction and anteriorization of the tube tip are more common in children because of reduced scleral rigidity and growth of the eye and may necessitate tube extension and/or repositioning.

Erosion of the conjunctiva overlying a tube may result from eyelid rubbing, repetitive eye movements, poor ocular surface lubrication, immunological factors, and/or vector forces at the site of tube entry. Directing tube entry close to the 12 o'clock position for superotemporal implants and the 6 o'clock position for inferonasal implants minimizes this risk, as the site of tube entry is always covered by the eyelid in these locations.<sup>31</sup> Tube

exposure is a major risk factor for endophthalmitis,<sup>32,33</sup> and its recognition should prompt immediate initiation of topical antibiotics and timely surgical intervention. Replacement of the patch graft may suffice in select cases of limited tube exposure, but tube repositioning through a new scleral fistula is often needed. Glaucoma drainage implant removal may be required with large erosions over the tube, or if erosion has occurred over the endplate.

Bleb encapsulation, or hypertensive phase, occurs more commonly with valved than nonvalved devices.<sup>34,35</sup> Development of a thick-walled bleb contributes to decreased permeability of aqueous through the conjunctiva, resulting in at times severe IOP elevation. Exposure to inflammatory mediators within the aqueous may contribute to increased fibrosis.<sup>34</sup> Aqueous suppression usually lowers the IOP sufficiently for bleb remodeling to occur, but resolution may require weeks to months. Bleb needling or additional glaucoma surgery may be required in refractory cases.<sup>36</sup>

Corneal decompensation may occur as a result of improper tube positioning within the anterior chamber, prolonged hypotony resulting in contact between the native lens or intraocular lens implant and endothelium, or immunological factors. Meticulous intraoperative positioning of the tube far from the corneal endothelium usually avoids this complication, but some patients with pseudo-phakia or aphakia may require tube repositioning to the sulcus or pars plana and corneal transplantation surgery.

Strabismus and diplopia may occur after GDI placement as a result of scarring, mass effect of the endplate or a large resulting bleb, and fat fibrosis.<sup>16,37</sup> Sufficiently posterior endplate placement to avoid crowding of the rectus muscle insertions and avoidance of the superonasal quadrant help avoid this complication. Most cases of diplopia are transient, but some patients may require aqueous suppression to reduce an exuberant bleb, prisms, strabismus surgery, or, rarely, implant removal.

EVIDENCE FROM RANDOMIZED CLINICAL TRIALS

A number of randomized clinical trials have compared the outcomes of drainage implantation and trabeculectomy as well as different drainage implants. Their findings are summarized in Table 10.31.3.

TABLE 10.31.3 Randomized Clinical Trials Evaluating Glaucoma Drainage Implants			
Author (year)	N	Study Groups	Key Results
Drainage Implants Versus Trabeculectomy			
Wilson et al. (2003) <sup>38</sup>	123	Ahmed glaucoma valve (S2) Trabeculectomy with mitomycin C	Lower IOP in trabeculectomy group during postoperative year 1 Similar IOP in both groups after postoperative year 1 No difference in visual outcomes, number of medications, success rates, or complication rates at final follow-up
Gedde et al. (2012) <sup>39</sup>	212	Baerveldt glaucoma implant (350 mm <sup>2</sup> ) Trabeculectomy with mitomycin C	Higher rates of failure and reoperation for glaucoma in trabeculectomy group Similar IOP and number of medications in both groups More frequent early complications in trabeculectomy group Similar rates of late and serious complications in both groups Similar visual outcomes in both groups
Valved Versus Nonvalved Drainage Implants			
Nassiri et al. (2010) <sup>41</sup>	92	Ahmed glaucoma valve (FP7) Molteno implant (single-plate)	Similar success rates in both groups Similar IOP, number of medications, and visual acuity in both groups at 2 years No devastating complications in either group
Budenz et al. (2015) <sup>42</sup>	276	Ahmed glaucoma valve (FP7) Baerveldt glaucoma implant (350 mm <sup>2</sup> )	Similar failure rates in both groups at 5 years Lower IOP in Baerveldt group after month 1 Fewer medications required by Baerveldt group at 5 years Higher rate of serious complications in Baerveldt group at 5 years Similar visual outcomes in both groups
Christakis et al. (2016) <sup>35,44</sup>	238	Ahmed glaucoma valve (FP7) Baerveldt glaucoma implant (350 mm <sup>2</sup> )	Lower failure rates in Baerveldt group at 5 years Lower IOP in Baerveldt group after month 1 Less medications required by Baerveldt group at 5 years Higher rate of hypotony-related vision-threatening complications in Baerveldt group at 3 years Similar visual outcomes in both groups
Drainage Implants of Different Endplate Size			
Heuer et al. (1992) <sup>45</sup>	132	Molteno implant (single-plate) Molteno implant (double-plate)	Higher success rates in double-plate group More frequent choroidal hemorrhage in double-plate group Similar visual outcomes in both groups
Lloyd et al. (1994) <sup>46</sup>	73	Baerveldt glaucoma implant (350 mm <sup>2</sup> ) Baerveldt glaucoma implant (500 mm <sup>2</sup> )	Similar success rates in both groups at 18 months
Britt et al. (1999) <sup>47,a</sup>	107	Baerveldt glaucoma implant (350 mm <sup>2</sup> ) Baerveldt glaucoma implant (500 mm <sup>2</sup> )	Higher success in 350 mm <sup>2</sup> group at 5 years Similar IOP and number of medications in both groups at 5 years Similar rates of vision loss and complications in both groups
<sup>a</sup> Follow-up study to Lloyd et al. (1994) <sup>46</sup> enrolling an additional 34 patients and reporting outcomes for a total of 107 patients through 5 years. IOP, Intraocular pressure; N, number of enrolled patients.			

## Drainage Implants Versus Trabeculectomy

Surgical outcomes of drainage implantation and trabeculectomy were directly compared in a prospective trial by Wilson et al.,<sup>38</sup> who randomized 123 patients with glaucoma and without prior intraocular surgery to undergo trabeculectomy with mitomycin C (0.3–0.4 mg/mL for 3–4 minutes) or placement of an Ahmed glaucoma valve (S2). Although lower mean IOP was achieved by the trabeculectomy group during postoperative year 1, similar IOPs were observed in the trabeculectomy and Ahmed groups thereafter. Success rates, adjunctive medications, visual outcomes, and complication rates were comparable between the two groups at the final (41- to 52-month) follow-up interval.

The Tube Versus Trabeculectomy (TVT) Study<sup>39</sup> randomized 212 patients with previous cataract extraction and intraocular lens implantation and/or failed filtering surgery to undergo Baerveldt glaucoma implantation (350 mm<sup>2</sup>) surgery or trabeculectomy with mitomycin C (0.4 mg/mL for 4 minutes). At postoperative year 5, IOP and number of medications were similar between the two groups. Failure (i.e., IOP >21 mm Hg or <20% reduction, IOP ≤5 mm Hg, additional glaucoma surgery, or loss of light perception) occurred more frequently in the trabeculectomy group (46.9%) than in the tube group (29.8%) over 5 years of follow-up ( $P = 0.002$ ). The trabeculectomy group also had a higher rate of reoperation for glaucoma compared with the tube group (29% trabeculectomy group versus 9% tube group,  $P = 0.025$ ). Although early postoperative complications (i.e., those occurring within postoperative month 1) were more common in the trabeculectomy group (37% trabeculectomy group versus 21% tube group,  $P = 0.012$ ), rates of late postoperative complications (36% trabeculectomy group versus 34% tube group,  $P = 0.81$ ) and serious complications needing reoperation and/or producing loss of ≥2 Snellen lines (18% trabeculectomy group versus 22% tube group,  $P = 0.29$ ) were similar between the two groups.<sup>40</sup> Similar visual outcomes were reported for both groups at 5 years. Results from the TVT Study support an expanded role for GDIs beyond the refractory glaucomas, to which they have traditionally been relegated.

## Valved Versus Nonvalved Drainage Implants

Outcomes of implantation of the Ahmed glaucoma valve (FP7) and single-plate Molteno drainage device were compared in a prospective, randomized study of 92 patients with refractory glaucoma (i.e., IOP >21 mm Hg using maximal medical therapy and/or failed non-GDI glaucoma surgery).<sup>41</sup> Rates of success (i.e., IOP <21 mm Hg and >6 mm Hg without phthisis bulbi, loss of light perception, GDI removal, additional glaucoma surgery, or devastating complications) over 2 years of follow-up were similar between groups (82% Ahmed group versus 84% Molteno group,  $P = 0.65$ ). Lower IOP was achieved in the Ahmed group at day 1 and week 1 ( $P < 0.001$ ) as would be expected after implanting a valved device, but the Molteno group achieved lower IOP thereafter ( $P < 0.01$ ) through the 2-year study endpoint. The number of glaucoma medications and visual acuity were similar in both groups at all time points. No devastating complications occurred in either group.

The Ahmed Baerveldt Comparison (ABC) Study<sup>42,43</sup> and Ahmed Versus Baerveldt (AVB) Study<sup>35,44</sup> both compared the outcomes of placement of the Ahmed glaucoma valve (FP7) and the Baerveldt glaucoma implant (350 mm<sup>2</sup>) in patients with refractory glaucoma. The ABC Study and AVB Study randomized a total of 276 and 238 patients, respectively. Failure was defined somewhat differently in the two trials (i.e., IOP >21 mm Hg or <20% reduction, IOP ≤5 mm Hg, reoperation for glaucoma, implant removal, or loss of light perception in the ABC Study and IOP >18 mm Hg or <20% reduction, IOP <5 mm Hg, reoperation for glaucoma, vision-threatening complication, or loss of light perception in the AVB Study), although they shared a similar study design. Although mean IOP was significantly lower in the Ahmed group during the first few postoperative weeks in both studies, the Baerveldt group demonstrated greater sustained reductions in IOP after postoperative month 1. The Baerveldt group also required fewer medications at 5 years than the Ahmed group in both studies. Failure rates were lower in the Baerveldt group at 5 years in the AVB Study (40% Baerveldt group versus 53% Ahmed group,  $P = 0.04$ ), but similar between groups at 5 years in the ABC Study (39.4% Baerveldt group versus 44.7% Ahmed group,  $P = 0.65$ ). Serious complications requiring reoperation or associated with loss of 2 or more Snellen lines were more common in the Baerveldt group over 5 years in the ABC Study (24.7% Baerveldt group versus 15.9% Ahmed group,  $P = 0.034$ ).<sup>43</sup> The Baerveldt group had a higher rate of hypotony-related vision-threatening complications at 3 years in the

AVB Study (6% Baerveldt group versus 0% Ahmed group,  $P = 0.005$ ).<sup>44</sup> Visual outcomes were comparable in both groups in both studies.

## Drainage Implants of Different Endplate Sizes

A randomized trial comparing outcomes of single-plate implants versus double-plate Molteno implants in 132 aphakic and pseudo-phakic eyes with nonneovascular glaucoma found a higher rate of success (i.e., IOP ≥6 mm Hg and ≤21 mm Hg without additional glaucoma surgery or devastating complication) in the double-plate group at 2 years (71% double-plate group versus 46% single-plate group,  $P = 0.0035$ ).<sup>45</sup> Visual outcomes were similar between the two groups. Choroidal hemorrhage was significantly more common in the double-plate group than in the single-plate group (8% double-plate group versus 0% single-plate group,  $P = 0.043$ ). Other complications, including serous choroidal effusions, flat anterior chamber, and corneal decompensation, also occurred more frequently in the double-plate group, but these differences were found to be not statistically significant.

Lloyd et al.<sup>46</sup> randomized 73 patients with nonneovascular glaucoma and aphakia, pseudo-phakia, or failed filtering surgery to undergo placement of a 350 mm<sup>2</sup> or 500 mm<sup>2</sup> Baerveldt implant. Success rates (i.e., IOP ≥6 mm Hg and ≤21 mm Hg without additional glaucoma surgery, devastating complications, or loss of light perception) were similar between the two groups at 18 months (93% in 350 mm<sup>2</sup> versus 88% in 500 mm<sup>2</sup>,  $P = 0.93$ ). Britt et al.<sup>47</sup> recruited 34 additional patients and reported longer-term results for a total of 107 patients. Over 5 years of follow-up, a higher success rate was observed among patients receiving a 350 mm<sup>2</sup> implant compared with those receiving a 500 mm<sup>2</sup> implant (79% in 350 mm<sup>2</sup> group versus 66% in 500 mm<sup>2</sup> group,  $P = 0.05$ ), suggesting that additional surface area beyond a certain threshold does not contribute to greater surgical success. IOP and number of medications were similar between the two groups at 5 years. Rates of vision loss and complications were also comparable between the 350 mm<sup>2</sup> group and the 500 mm<sup>2</sup> group.

## CONCLUSIONS

Drainage implants are routinely used in the surgical management of glaucoma, and their role has expanded in recent years to include use in eyes at lower risk for trabeculectomy failure. Randomized clinical trials have provided invaluable information supporting the relative efficacy of drainage implants in comparison with trabeculectomy and comparisons of different types of drainage implants. Glaucoma drainage implant surgery may be associated with certain unique complications, some of which can be avoided with careful preoperative planning and diligent intraoperative technique.

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# Complications of Glaucoma Surgery and Their Management

Leon W. Herndon, Jr.

10.32



IN THIS CHAPTER  
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**Definition:** Untoward events occurring with glaucoma surgery intraoperatively or postoperatively that can limit the success of the surgery.

## Key Features

- Can occur in the intraoperative, early postoperative, or late postoperative period.
- May or may not be technique dependent.
- May cause pain, decreased vision, double vision, irritation, or loss of vision.

## Associated Features

- Conjunctival buttonhole.
- Intraocular hemorrhage.
- Hypotony.
- Shallow anterior chamber.
- Infection.
- Cataract.
- Diplopia.

## INTRODUCTION

The primary goal of glaucoma surgery is to preserve the vision and ocular health of the patient by preventing disease progression. Improving the patient's function is crucial. This cannot be achieved by procedures that result in decreased visual acuity or increased discomfort. Therefore, steps should be taken to avoid lowering intraocular pressure (IOP) too much, thereby causing disability as a result of pain, photophobia, or double vision. The increased use of antimetabolite therapy during surgery has led to more postoperative complications. Techniques should be modified to avoid complications, and with proper selection, patients should be matched with appropriate surgical approaches.

## TRABECULECTOMY

Complications associated with trabeculectomy surgery can occur intraoperatively, early postoperatively, and late postoperatively.

### Intraoperative Complications

#### Conjunctival Buttonhole

Meticulous technique is the best way to avoid complications associated with glaucoma surgery. This axiom is certainly appropriate in the management of buttonholes of the conjunctiva. Toothed forceps should not be used when handling the conjunctiva. In addition, the conjunctiva should be touched only with the initial incision—whether the fornix or limbal approach is used. Tenon's layer should be manipulated to direct the conjunctival dissection. If a buttonhole does occur, proper management requires immediate attention, as further manipulation will likely enlarge the buttonhole. Complete closure of the buttonhole is necessary to achieve successful results. If complete closure cannot be ensured, then rotation of

the site of the trabeculectomy flap to a different area should be considered. Conjunctival buttonholes come in different locations, sizes, and shapes. They can occur near the limbus, in the midportion of the bleb, or posteriorly. An 8-0 or 9-0 polyglactin suture on a vascular needle in a horizontal mattress fashion can be used to close a small hole, or in a running fashion with single-layer or double-layer closure for larger holes. A “clothesline” suturing technique has been described for repair of buttonholes.<sup>1</sup>

#### Trabeculectomy Scleral Flap Tear/Disinsertion

The surgeon should create a scleral flap that is about two thirds depth of the total scleral thickness. Occasionally, a “ratty” or thin sclera leads to a flap that tears or disinserts. If the tear is small, the flap can be repaired with a 10-0 nylon suture. If the flap disinserts completely, an attempt can be made to reposition the flap by rotating the thicker part of the flap over the sclerectomy. There are reports of successful repositioning of a totally disinserted flap using two 10-0 nylon sutures through the flap base and out the peripheral cornea.<sup>2</sup> Often, however, the quality of the sclera is so poor that placement of sutures through the original flap is not possible because of a “cheesewire” effect, and placement of an additional cover over the flap becomes necessary. Choices of cover material include donor sclera,<sup>3</sup> dura, pericardium, or even fascia lata.<sup>4</sup> Cornea tissue and amniotic membrane have also been used for this repair.<sup>5,6</sup> A rectangular piece of the material of choice is prepared and fashioned to be approximately 2 mm larger and wider than the trabeculectomy flap. The cover is sutured into place with at least one 10-0 nylon suture to each corner of the material. Postoperatively, these sutures may be lysed using an argon laser to increase drainage, as desired.

#### Intraoperative Bleeding

Excessive bleeding from the iris vessel/root most commonly occurs at the time of iridectomy. Bleeding occurs from cut radial vessels or from a traumatized greater arterial circle within the ciliary body. Such bleeding can be observed, as most iris root/ciliary body bleeding will stop spontaneously within minutes. Applying pressure to the area with a cellulose sponge may speed clot formation. Excess cautery should be avoided because it may lead to vitreous presentation. Cautery should be applied liberally to the scleral flap bed prior to making the scleral flap incision, and the scleral flap should not be sutured until all of the bleeding has stopped. Premature suturing often leads to postoperative blockage of the internal ostium by the clotted blood.

A suprachoroidal hemorrhage (SCH) can occur during surgery, the hallmark being shallowing of the anterior chamber in the presence of an enlarging dark posterior segment mass visible through the pupil. If an intraoperative choroidal hemorrhage is suspected, the wound should be closed immediately. The anterior chamber should be reformed with air or a viscoelastic agent. Once the eye has been closed, intravenous acetazolamide and mannitol can be used to lower IOP. Drainage of the hemorrhage may be necessary later. Immediate recognition of SCH is paramount, because an expulsive choroidal hemorrhage is disastrous. The risk of SCH is reportedly higher in patients with high myopia, aphakia, or pseudo-phakia, in vitrectomized patients, in patients with bleeding disorders, and in the presence of elevated blood pressure. The results of the Fluorouracil Filtering Study<sup>7</sup> showed that only high preoperative IOP was associated with a statistically significantly increased risk of SCH. None of the 63 patients with a preoperative IOP less than 30 mm Hg developed SCH.

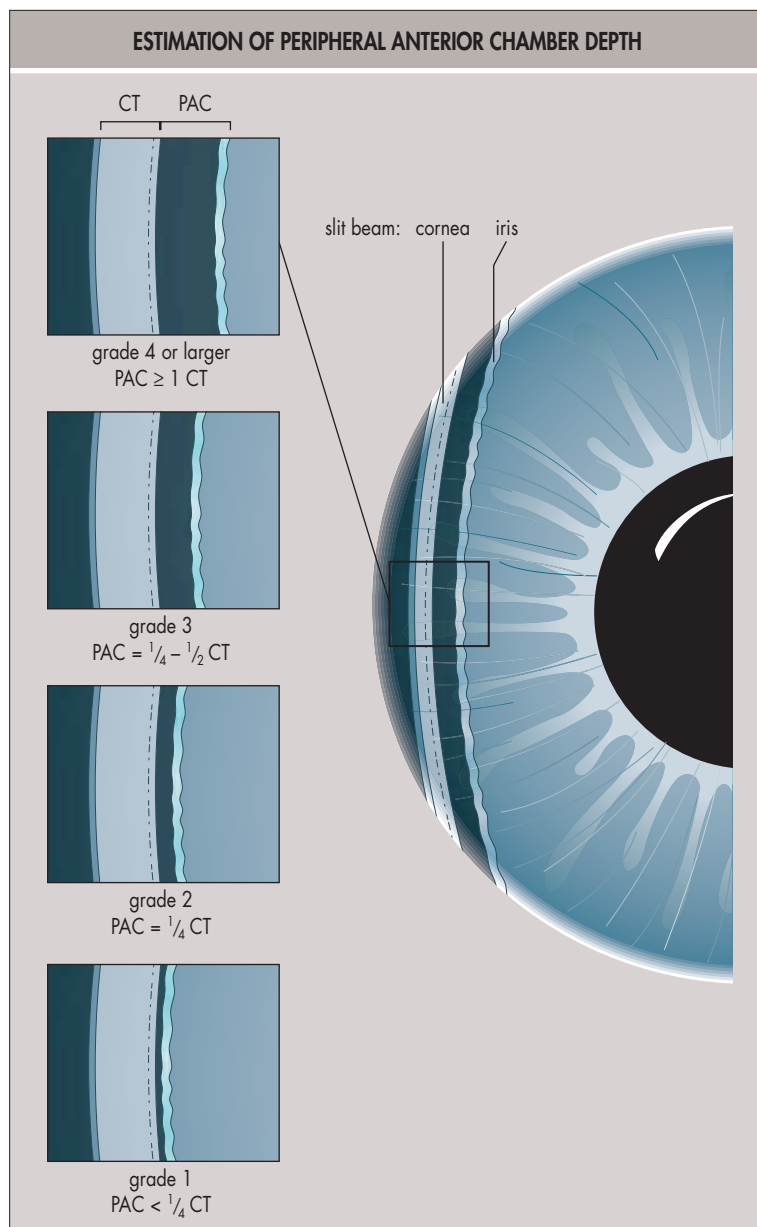
Preoperatively, it is important to check IOP when the patient is in the holding area. Intravenous mannitol (1–2 g/kg) is recommended if the IOP is greater than 30 mm Hg. Mannitol has an onset of action of less than an hour, so if it is given prior to the surgery, the IOP should be significantly lower before an intraocular incision is made. Furthermore, blood pressure should be monitored and treated if it is elevated.

Intraoperatively, the risk of SCH may be reduced by decompressing the eye slowly and carefully with the initial paracentesis. In addition, it is important to suture the scleral flap snugly and to achieve meticulous conjunctival wound closure. Leaving the eye partially filled with viscoelastic can be considered to minimize the likelihood of anterior chamber shallowing in the early postoperative period.

## Early Postoperative Complications

### Shallow Anterior Chamber

Shallow anterior chamber in the early postoperative period can be associated with low or high IOP. It is important to have a system of measuring the central anterior chamber depth to determine if anterior chamber shallowing is progressive. It is not adequate simply to note “shallow anterior chamber” in the record because a more objective measure is necessary to determine response to therapy. One system involves notating the central anterior chamber depth based on the modified van Herick technique (Fig. 10.32.1). This technique compares the central anterior chamber depth with the thickness of the central cornea.



**Fig. 10.32.1 Modified van Herick Technique to Assess Peripheral Anterior Chamber Depth.** The same technique can be applied to the central anterior chamber. (Modified with permission from Shields MB. Textbook of Glaucoma. 3rd ed. Baltimore, MD: Williams & Wilkins, 1992.)

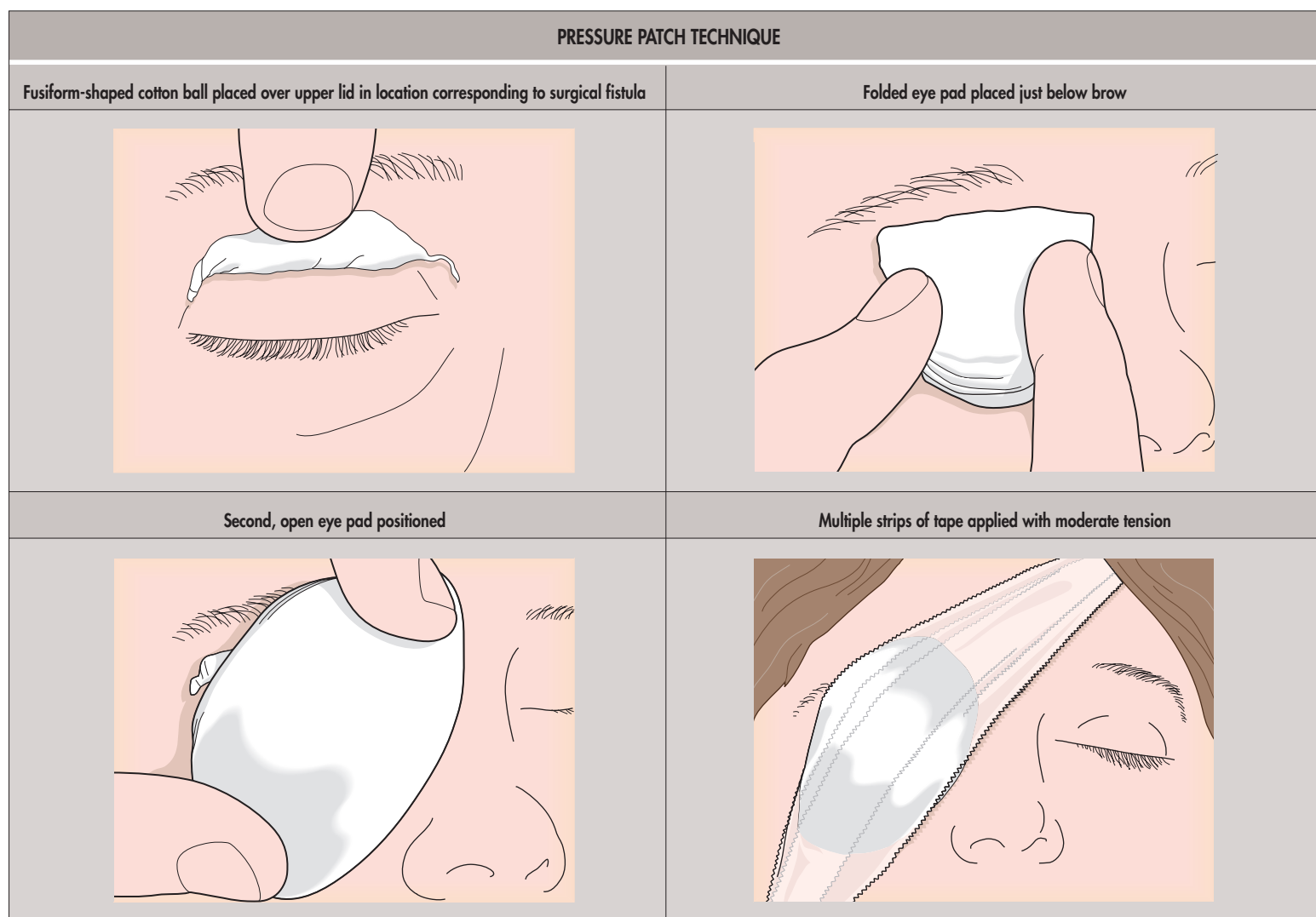
Shallow chamber associated with low IOP suggests either overfiltration and/or a bleb leak. Overfiltration results from inadequate scleral flap closure resulting in a high bleb. If the bleb is high and no corneal–lens touch or appositional choroidal effusion occurs, observation with a cycloplegic agent is appropriate. If anterior chamber shallowing is progressive, injection of viscoelastic material into the anterior chamber may lead to early “scarring” of the bleb and decreased aqueous outflow with subsequent deepening of the anterior chamber.<sup>8</sup> Viscoelastic material with greater viscosity is particularly helpful in such cases. It is useful to use the pre-existing paracentesis site created during surgery to facilitate postoperative access to the anterior chamber. Trying to create a new access port in soft eyes, especially phakic ones, can be challenging. Alternatively, some surgeons use a “torpedo” patch that is created by placing a fusiform-shaped cotton ball over the lid in the area of the trabeculectomy flap.<sup>9</sup> This cotton ball is held in place with gauze pads to act as a tamponade (Fig. 10.32.2). If this type of pressure dressing is used, the patient should be kept awake, with the fellow eye open and looking straight ahead, because Bell’s phenomenon of sleep may place the tamponade over the center of the cornea. If overfiltration continues with the development of choroidal effusions that touch, or of lens–corneal touch, a return to the operating room for further flap closure, anterior chamber reformation, and effusion drainage may be indicated.

Initial “overfiltration” with a bleb leak may frequently be the result of a buttonhole missed at the time of surgery. A buttonhole is far more difficult to manage postoperatively. On examination, these patients generally are found to have a low or flat bleb. It is important to use 2% fluorescein to stain the bleb because more dilute fluorescein agents may not discern a slow leak. Patching techniques or the placement of an oversized bandage contact lens may be used initially. Other options include autologous fibrin tissue glue,<sup>10</sup> autologous blood injection (Fig. 10.32.3),<sup>11–14</sup> and cyanoacrylate glue with contact lens application.<sup>15</sup> A large, early-postoperative bleb leak may require a return to the operating room to develop a new conjunctival flap from tissue posterior to the defect.<sup>16</sup>

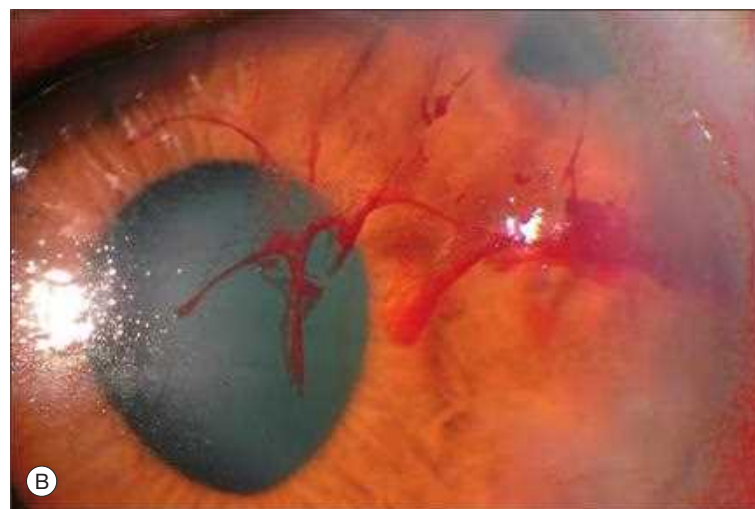
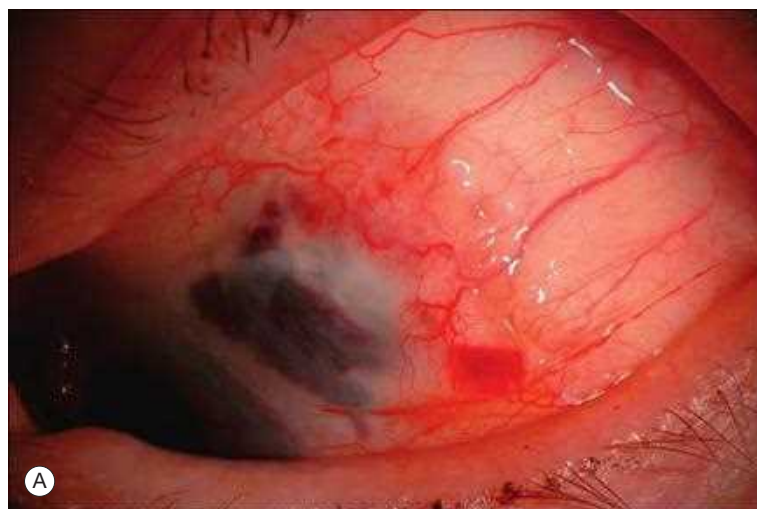
One other cause of a shallow anterior chamber associated with low IOP in the early postoperative period is ciliary body shutdown secondary to intense postoperative inflammation. Such eyes present with flat blebs, no bleb leaks, shallow anterior chambers, low IOP, and occasionally inflammatory choroidal effusions. Postoperative 5-fluorouracil injections should be considered to help prevent subconjunctival adhesions in the period before aqueous flow resumes. Occasionally, mitomycin will also lead to ciliary body shutdown early postoperatively because of cytotoxic effects on the ciliary epithelium.<sup>17</sup>

Shallow anterior chamber associated with high IOP in the early postoperative period can result from an incomplete iridectomy with pupillary block, delayed SCH, or aqueous misdirection (malignant) (see Chapter 10.19) glaucoma. If the presence of a full-thickness iridectomy can be confirmed postoperatively, pupillary block can be ruled out. However, if doubt exists with regard to the patency of the surgical iridectomy, a laser iridectomy or surgical iridectomy should be performed as soon as possible (Fig. 10.32.4). Once a pupillary block is excluded, the presence of SCH should be determined. Patients with SCH generally present during the first few postoperative days with severe pain, occasional nausea, and a marked reduction in vision. IOP is usually, but not always, elevated; the anterior chamber is shallow or flat; and large choroidal detachments, often with central apposition, are present. If ophthalmoscopy is not helpful, B-scan ultrasonography will be necessary (Fig. 10.32.5). Management of a patient with a delayed SCH involves observation and corticosteroid and cycloplegic therapy initially. If there is no clinical improvement, evacuation of the SCH in the operating room should be considered. Vitrectomy with the instillation of an intraocular expandable gas can be useful to facilitate return of the retina and choroid to their anatomical positions. There is some debate among the vitreoretinal community, however, regarding the optimal time to intervene. Some recommend waiting 7–10 days following the hemorrhage to allow for the clot to liquefy, but others favor intervening earlier to allow for quicker visual recovery.<sup>18</sup>

Another cause of shallow anterior chamber with high IOP is aqueous misdirection. Forward displacement of the vitreous into apposition with the iris and ciliary body, possibly associated with thickening of the anterior hyaloid, has traditionally been proposed as the mechanism.<sup>19</sup> Posterior pooling of aqueous humor, either within or behind the vitreous, causes forward movement of the lens–iris or hyaloid–iris diaphragm, resulting in a flat anterior chamber with elevated IOP. Medical treatment of aqueous misdirection with cycloplegic therapy and aqueous suppressants and/or osmotics is successful in about 50% of cases. Other useful medical adjuncts include phenylephrine 2.5% and frequent topical corticosteroids.



**Fig. 10.32.2** Pressure patch technique. (From Shields MB. Textbook of Glaucoma. 3rd ed. Baltimore, MD: Williams & Wilkins, 1992.)



**Fig. 10.32.3** (A) Bleb appearance immediately after autologous blood injection. (B) Suspended heme in viscoelastic-filled anterior chamber after autologous blood injection.

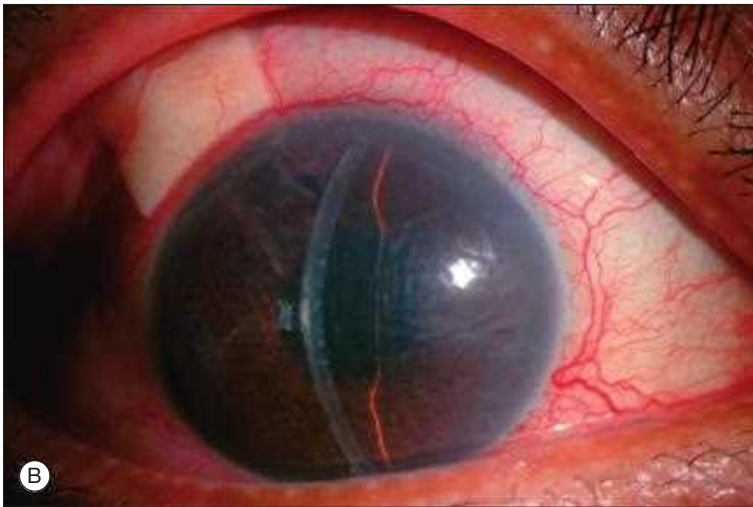
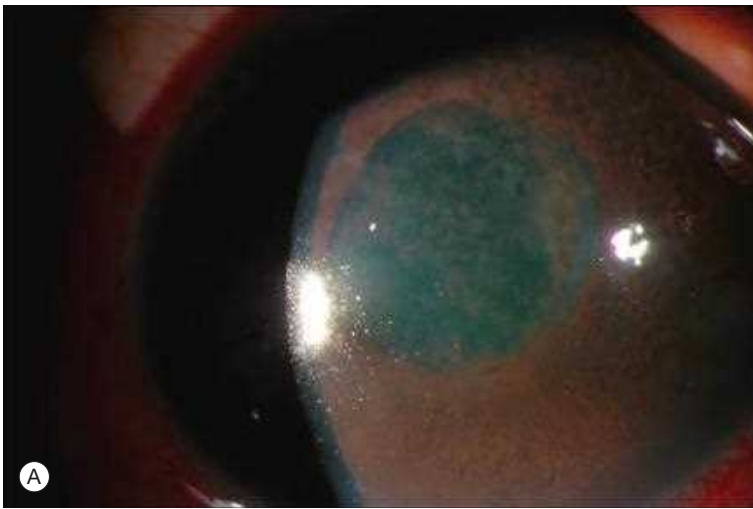
Therapy also may include argon laser treatment of visible ciliary processes, neodymium:yttrium–aluminum–garnet (Nd:YAG) anterior hyaloidectomy, or possible capsulectomy, in aphakic and pseudo-phakic eyes. Surgical therapy is necessary if these medical and laser techniques are ineffective. Pars plana vitrectomy with rupture of the vitreous face often produces definitive results.

### Low Filtration

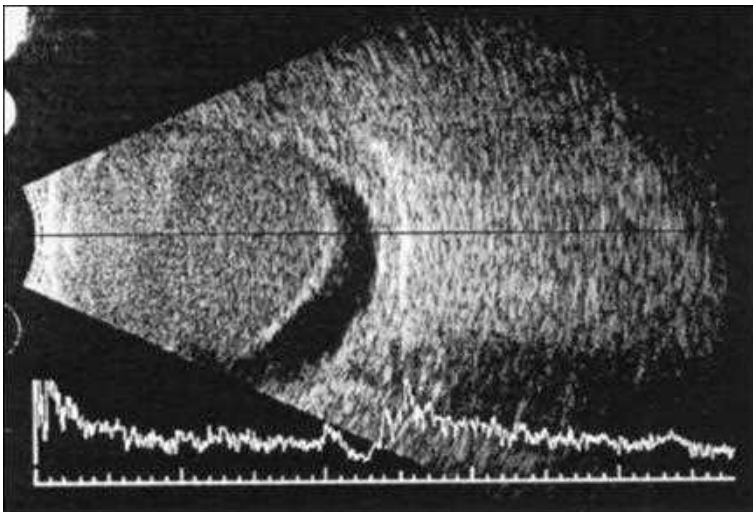
In the early postoperative period, low filtration is a consideration when the bleb is low and not associated with a bleb leak and the anterior chamber is deep. IOP may be high, normal, or low, depending on the level of aqueous production. It is important to confirm with gonioscopy that the sclerectomy

is not blocked by blood or fibrin. Low filtration is managed by sequential release of scleral flap sutures. The appearance of the bleb, not necessarily IOP, should guide the decision to perform laser suture lysis. If permanent sutures have been placed, the suture may be lysed with the argon laser and a Hoskins (or Ritch) lens.<sup>20</sup> Krypton red (or blue–green argon) 50  $\mu$ m spot size at 300 mW are usually effective settings. To improve the success of suture lysis postoperatively, it is helpful to intraoperatively place the nylon suture that is as long as possible and to note which suture was associated with the best flow at the time of surgery, so as to be selectively efficient in postoperative management. A partial tenonectomy can be useful to improve visualization of the scleral sutures. Alternatively, several releasable suture techniques are available if difficulty with suture visualization





**Fig. 10.32.4** (A) Shallow anterior chamber after glaucoma drainage tube placement. (B) Deeper anterior chamber after surgical peripheral iridectomy.

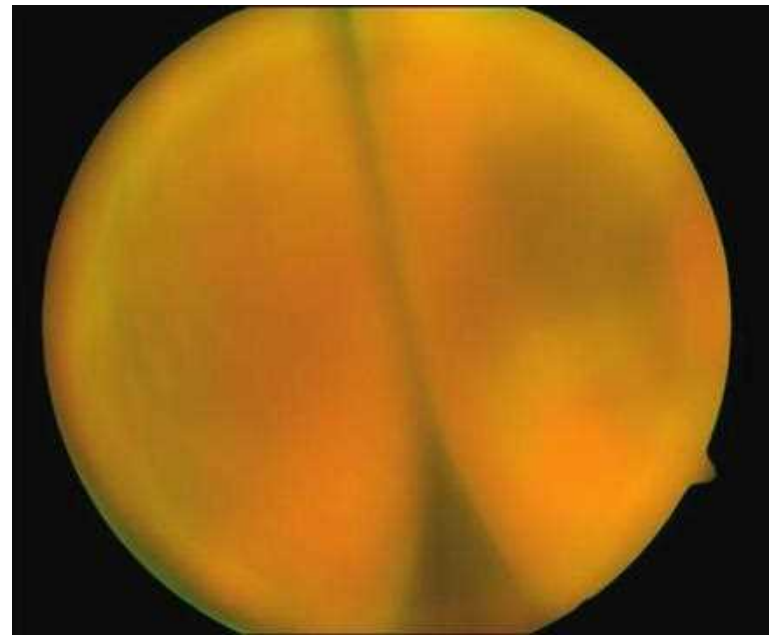


**Fig. 10.32.5** B-scan ultrasonography picture of a suprachoroidal hemorrhage.

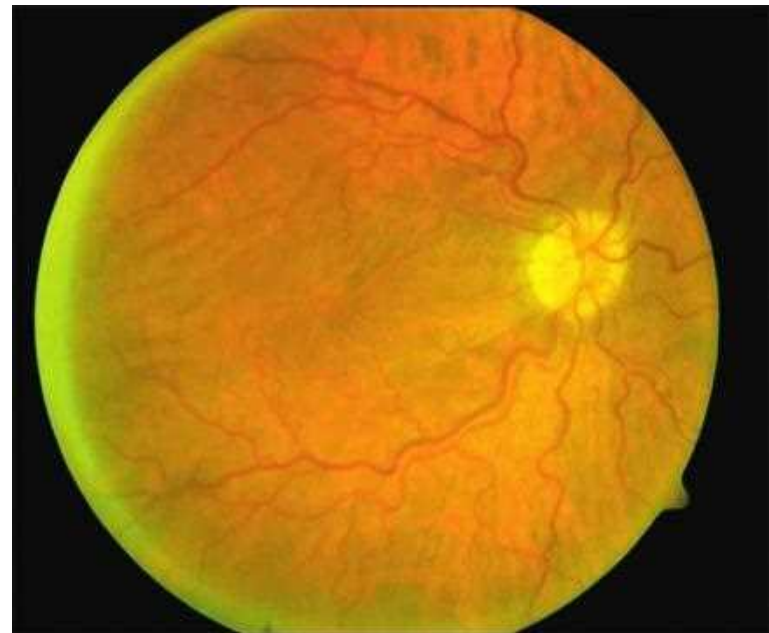
postoperatively is anticipated.<sup>21-23</sup> If the sclerectomy is blocked by fibrin or blood, tissue plasminogen activator may be helpful.<sup>24,25</sup>

### Choroidal Effusion

Although posterior choroidal effusions (Fig. 10.32.6) often occur in conjunction with shallow anterior chamber and low IOP. They may also occur in eyes that have full-depth chambers and low IOP. Management usually consists of cycloplegia, topical corticosteroids, and observation. As long as the effusions do not touch ("kiss"), drainage is usually not required. If touch does occur centrally, many surgeons choose to perform effusion drainage via posterior sclerotomies inferiorly because of the potential danger of retinal adhesion formation and the profound effect on visual function.



**Fig. 10.32.6** Photo of serous choroidal effusion ("kissing" choroidals).



**Fig. 10.32.7** Hypotonous maculopathy.

## Late Postoperative Complications

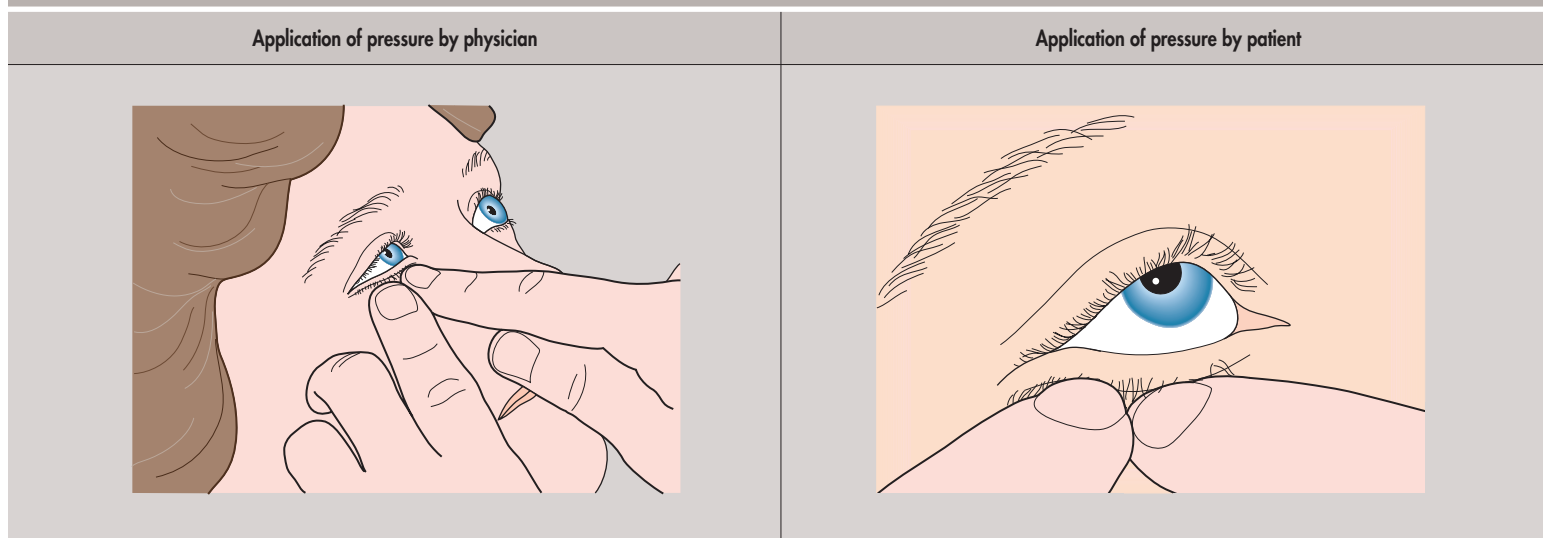
### Late Hypotony

Antimetabolites have introduced a new entity, late hypotony, to the list of postoperative trabeculectomy complications. Most commonly, the history is of mitomycin use, with loose scleral flap closure leading to IOP in the low single digits. Characteristically, vision is decreased, the eye is soft, and the bleb is large, thin, and avascular. Retinal and/or choroidal folds may be seen in the macula (Fig. 10.32.7), in association with tortuous retinal vessels and a swollen optic nerve head. Available treatments include autologous blood injection,<sup>11,26</sup> compression suture placement,<sup>27</sup> and Nd:YAG bleb treatment.<sup>28</sup> If these measures fail, a return to the operating room to revise the thin bleb and/or resuture the flap is indicated.<sup>14,29</sup> A donor patch graft over the scleral flap may be necessary to limit aqueous egress. Alternatively, if a symptomatic cataract is present, the cataract extraction-associated inflammation frequently slows filtration through bleb "scarring" and may resolve the hypotony.<sup>30</sup>

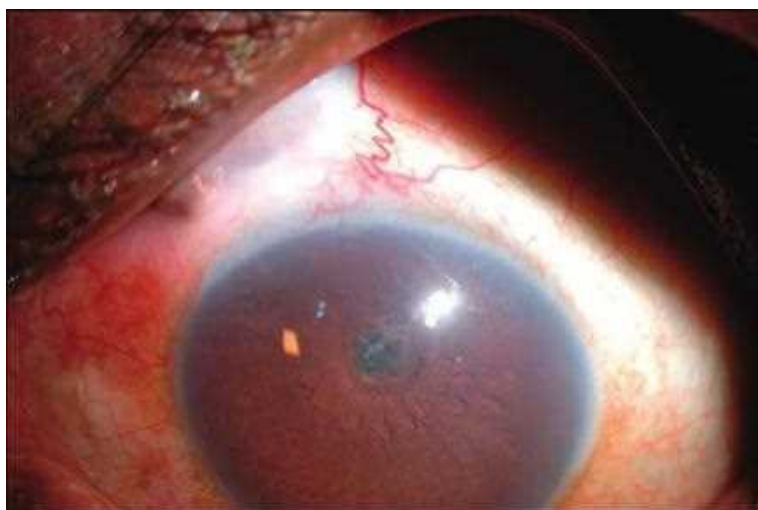
### Late Bleb Failure

Late bleb failure may result from heavy vascularization and healing around the bleb as well as episcleral fibrosis.<sup>31,32</sup> Digital pressure applied by the patient to the inferior globe through the inferior lid (Fig. 10.32.8) may be useful in such cases because this helps maintain flow through the drain

## DIGITAL PRESSURE FOR EYE WITH FAILING FILTERING BLEB



**Fig. 10.32.8** Digital pressure for eye with failing filtering bleb. (Reproduced with permission from Shields MB. Textbook of Glaucoma. 3rd ed. Baltimore, MD: Williams & Wilkins, 1992.)



**Fig. 10.32.9** Small pupil after maximal dilation resulting from posterior synechiae after trabeculectomy surgery.

and keeps the subconjunctival space expanded. If this is insufficient, needle revision of the bleb may re-establish effective filtration.<sup>33,34</sup>

### Cataract Formation

Cataracts are very common in the older population. The cataracts often get worse because of the effect of glaucoma medications<sup>35</sup> and after trabeculectomy surgery.<sup>36</sup> Cataracts can progress secondary to postsurgical events, such as shallow anterior chamber. Cataract surgery may be complicated in these patients because of small pupils caused by posterior synechiae (Fig. 10.32.9) or pseudo-exfoliation. Various techniques to open the pupil during cataract surgery have been described and are usually associated with good visual recovery.<sup>37-39</sup> One technique of opening the pupil involves the use of the I-Ring (Beaver Visitec, Waltham, MA) (Video 10.32.1). One concern, however, is the long-term success of the filtering bleb after the cataract surgery. Klink et al.<sup>40</sup> showed that IOP increased about by 2 mm Hg at 12 months postoperatively in patients who had phacoemulsification after trabeculectomy.

### Late Bleb Leaks

It is predicted that the incidence of late bleb leaks will increase over time because of the increased use of antimetabolites. Initial management of these leaks involves patching, aqueous suppression, antibiotics, and bandage contact lenses. There are numerous additional options, including glue, autologous blood injection, trichloroacetic acid application, cryotherapy, and Nd:YAG laser remodeling. If these less invasive alternatives are not successful, a return to the operating room is necessary to excise the ischemic bleb from the eye and advance the posterior conjunctival edge to the limbus<sup>14</sup> (Video 10.32.2).

### Blebitis and Endophthalmitis

As many as 1 per 100 patients/year may develop infection of the bleb. The cystic thin blebs seen after antimetabolite application are believed to have a higher risk. Blebitis is differentiated from conjunctivitis by the presence of a chalky white bleb with surrounding conjunctival injection often associated with a bleb leak. If the vitreous is quiet, prompt treatment with hourly topical antibiotics may save the bleb and prevent true endophthalmitis. Topical corticosteroids after 48 hours of treatment are useful to treat the inflammation. The prompt treatment of blebitis is generally effective. However, if endophthalmitis with vitreous involvement is diagnosed, intra-vitreous cultures and antibiotics and possible vitrectomy are required. The prognosis for salvaging such eyes is guarded. Organisms frequently seen in these eyes include *Hemophilus*, streptococci, and staphylococci. Thus, coverage is best initiated with fortified topical cefazolin or vancomycin and tobramycin. Intravitreal antibiotic injections of choice include vancomycin and amikacin. It is very important to instruct patients about early recognition of infection and to seek medical attention promptly if there is any suspicion of infection.

### GLAUCOMA DRAINAGE IMPLANTS

With the introduction of newer designs and the publication of studies, such as the Tube Versus Trabeculectomy (TVT) trial, drainage implants are gaining wider acceptance in the ophthalmology community.<sup>41,42</sup> The TVT trial showed that at 5 years after surgery, in eyes with previous incisional surgery, the IOP-lowering effect of Baerveldt (Abbott Medical Optics, Irvine, CA) drainage implantation is equivalent to that of trabeculectomy surgery. The filtration blebs associated with drainage devices are located more posteriorly compared with those seen with trabeculectomy surgery, which may decrease bleb-related concerns, such as infection and discomfort. Some complications associated with glaucoma drainage tube implantation include diplopia, corneal decompensation, tube exposure (Fig. 10.32.10), and glaucoma drainage plate exposure.

Development of new devices and technologies for glaucoma surgery was spurred by the realization that the standard surgeries performed today for glaucoma have unacceptably high failure and complication rates even when performed as primary surgeries.<sup>43</sup> Minimally invasive glaucoma surgery (MIGS) aims to provide a safer, less invasive means of reducing IOP compared with traditional surgery, with the goal of reducing dependency on topical medications. To date, the current MIGS procedures offer more modest IOP-lowering results compared with traditional glaucoma surgery, but with the benefit of a safer risk profile. Thus, these procedures are indicated in patients with mild-to-moderate glaucoma. MIGS can be defined as any glaucoma procedure avoiding conjunctival dissection and thus approached via an ab interno incision. Although safer than traditional surgery, hyphema is fairly common after these procedures, but it usually resolves spontaneously. Contraindications to performing these procedures include inability to stop anticoagulation medication, bleeding diathesis, closed angle, and inability to identify trabecular meshwork.



See clip:  
10.32.1



See clip:  
10.32.2



**Fig. 10.32.10** Exposed glaucoma drainage tube.

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# Genes Associated With Human Glaucoma

Janey L. Wiggs

10.33

**Definition:** The genetic component underlying the pathogenesis of many of the heterogeneous diseases referred to as *glaucoma*.

**Key Features**

- Congenital or juvenile onset.
- Familial predisposition.

**Associated Feature**

- Possibility of diagnostic testing to predict glaucoma risk.

INTRODUCTION

For many years, a family history of glaucoma has been recognized as an important disease risk factor. Some forms of glaucoma are inherited as mendelian dominant or recessive traits, including juvenile open-angle glaucoma, congenital glaucoma, developmental glaucomas (Rieger’s syndrome and aniridia), and pigmentary glaucoma. Other types of glaucoma, such as adult primary open-angle glaucoma (POAG), have a heritable susceptibility.<sup>1</sup> At least one gene has been identified for most types of glaucoma (Table 10.33.1).

The identification of genes that contribute to glaucoma and characterization of the normal and abnormal biological function of the protein products of these genes can provide important new information about the pathophysiology of the disease. Current treatment for glaucoma is directed toward the regulation of aqueous humor formation by the ciliary body and increased outflow of aqueous humor through the trabecular meshwork or alternative pathways created by surgical procedures. Current therapy does not actually treat the cause of the disease because the molecular and cellular basis of disease in most cases is unknown. Identifying genes responsible for glaucoma and determining the functions of the normal and abnormal protein products will define the underlying molecular processes contributing to disease. This information could lead to the development of novel treatments, including gene-based therapies. The isolation of genes responsible for glaucoma will also lead to new methods for diagnosis based on the DNA sequence changes that result in defective genes and protein products. Such DNA-based diagnostic tests can identify individuals at risk for the disease before any visual deterioration has occurred.

TABLE 10.33.1 Genes Causing Glaucoma With Mendelian Inheritance (Autosomal Dominant and Autosomal Recessive)

Condition	Gene
Juvenile open-angle glaucoma	MYOC
Congenital glaucoma	CYP1B1
	LTBP2
	TIE2 (TEK)
Developmental glaucoma	FOXC1
	PITX2
	PAX6 (aniridia)
Familial normal-tension glaucoma	OPTN
	TBK1
Nanophthalmos	MFRP

CONGENITAL GLAUCOMA

Congenital glaucoma can be inherited as an autosomal recessive or autosomal dominant trait. Two genes responsible for autosomal recessive disease have been identified: *CYP1B1*, coding for cytochrome *P450**1B1*<sup>2,3</sup> and *LTBP2*, coding for latent transforming growth factor-beta (TGF-β)–binding protein 2.<sup>4</sup> Subsequently, mutations in *CYP1B1* have been identified in patients worldwide, whereas *LTBP2* appears to be more localized to specific populations where consanguineous marriages are common.<sup>5–7</sup> Glaucoma-associated *CYP1B1* mutations disrupt protein functional domains, implying that loss of function (LOF) of the protein results in the phenotype.<sup>8</sup> Variability in the phenotypic expression of mutant forms of *CYP1B1* has led to the suggestion that modifier genes may also influence the severity of the disease resulting from mutations in this gene.<sup>9</sup> One study indicated that patients carrying *MYOC* mutations in addition to *CYP1B1* mutations have more severe disease, suggesting that the proteins of these two genes may interact in the same biochemical pathways.<sup>10</sup> Disease severity has also been shown to be modified by tyrosinase in a *CYP1B1* knockout model; however, tyrosinase does not appear to be a major modifier gene in humans with *CYP1B1* mutations.<sup>11,12</sup>

TIE2 (TEK) LOF mutations can cause congenital glaucoma with autosomal dominant inheritance and variable expressivity.<sup>13</sup> Homozygous *Tie2* knockout mice without functional TEK (tunica interna endothelial cell kinase) have high intraocular pressure and buphthalmos secondary to absence of Schlemm’s canal.<sup>14</sup> Humans with heterozygous loss function *TIE2* mutations have a range of glaucoma phenotypes extending from congenital onset to adult onset. Presumably, the variation in glaucoma onset correlates with the extent that Schlemm’s canal developed.

DEVELOPMENTAL GLAUCOMA

In humans, primarily three genes—*PITX2*, *FOXC1*, *PAX6*—have been associated with abnormal anterior segment development and glaucoma.<sup>15–17</sup> Mutations in *PITX2* located on chromosome 4q25 cause Rieger’s syndrome, which is an autosomal dominant disorder of morphogenesis that results in abnormal development of the anterior segment of the eye. Typical clinical findings may include posterior embryotoxon, iris hypoplasia, iridocorneal adhesions, and corectopia. Approximately 50% of affected individuals develop a high–intraocular pressure (high-IOP) glaucoma associated with severe optic nerve disease. Although the elevation of IOP is likely to result from abnormal development of the anterior structures of the eye, a direct correlation between the severity of the anterior segment dysgenesis and the incidence of glaucoma has not been observed. Presumably, the structures that are involved in the elevation of IOP in these patients are not readily visible clinically. *PITX2* is a bicoid homeobox transcription factor that plays an important role in ocular development.<sup>18</sup> Mutations responsible for Rieger’s syndrome are LOF mutations and missense changes that interfere with critical protein domains. Interestingly, among family members carrying the same mutations, there can be extensive variation in the severity of the phenotype. The underlying mechanism responsible for this phenotypic variability is not known.

*FOXC1*, a member of the forkhead family of regulatory proteins, is located on chromosome 6p25. Mutations in this gene are associated with iris hypoplasia and glaucoma, as well as cardiovascular developmental abnormalities.<sup>17</sup> *FOXC1* gene dosage is important for normal function, as both deletions and duplications can result in abnormal phenotypes. The importance of the *FOXC1* gene in ocular development is demonstrated by a mouse knockout model that lacks the *FOXC1* gene product and has

abnormal development of the anterior segment of the eye.<sup>19</sup> Various anterior segment structures are abnormally formed in the *FOXC1*-deficient mouse, including the iris and Schlemm's canal.<sup>20</sup>

*PAX6* is a member of the paired box homeodomain proteins and mutations in this gene have been reported to cause aniridia, Peters' anomaly, and anterior stromal keratitis.<sup>21</sup> Aniridia and Peters' anomaly are both associated with glaucoma, presumably as a result of abnormal development of aqueous humor drainage structures.<sup>22</sup>

## PRIMARY OPEN-ANGLE GLAUCOMA: JUVENILE ONSET

Juvenile POAG is a rare disorder that develops during the first two decades of life. Affected individuals typically present with high IOP, which frequently requires surgical therapy. Juvenile glaucoma can be inherited as an autosomal dominant trait. Large pedigrees used for genetic linkage studies led to the identification of the *MYOC* gene, coding for myocilin as a causative gene.<sup>23</sup> Some mutations in this gene also cause of adult-onset POAG, in particular the GLN368X nonsense mutation.<sup>24</sup> The role of myocilin in glaucoma development is not completely understood; however, studies have indicated that mutant forms of the protein are retained in the cellular endoplasmic reticulum, preventing normal function of the cell and ultimately causing cell death.<sup>25</sup> Studies of patients who have genetic abnormalities resulting in a reduction of myocilin suggest that mutations in the gene cause gain of function or a dominant negative effect rather than LOF or haploinsufficiency.<sup>26–28</sup>

The protein contains several important functional domains, including a region with strong homology to the olfactomedin family of proteins. Although the function of the olfactomedin domain in myocilin is unknown, nearly all the mutations associated with glaucoma occur in this region.<sup>29</sup>

Only 10%–20% of patients with juvenile POAG have mutations in the *MYOC* gene. Using large pedigrees without *MYOC* mutations for genetic linkage studies, two additional juvenile POAG loci have been identified at chromosomes 9q and 20q.<sup>30</sup>

## PIGMENT DISPERSION SYNDROME AND GLAUCOMA

Pigment dispersion syndrome, a common disorder in young adults, is associated with the development of pigmentary glaucoma. Studies have shown that up to 2%–4% of Caucasian Americans 20–40 years of age may be affected by this disorder with characteristic features that include loss of iris contour and loss of pigment granules from the iris. The released pigment is deposited on the structures of the anterior segment of the eye, which include the trabecular meshwork. Although generally it is accepted that the dispersed iris pigment contributes to the development of glaucoma in affected individuals, the pathogenesis of pigmentary glaucoma remains unknown.

In humans, pigment dispersion can be inherited as an autosomal dominant trait, which suggests that specific gene defects may be responsible. One locus for this syndrome has been found on 7q35–q36,<sup>31</sup> but the responsible gene has yet to be isolated. The high prevalence of this condition indicates that more than one gene may be responsible for this disorder. Two genes that contribute to a form of pigment dispersion syndrome and glaucoma in the DBA/2J mouse have been identified.<sup>32</sup> These genes, *TYRP1* and *GNPMB*, are involved in pigmentation and melanosome metabolism and do not appear to contribute to the disease in humans.<sup>33</sup>

## ADULT-ONSET PRIMARY OPEN-ANGLE GLAUCOMA

Adult-onset POAG is a common disorder with complex inheritance. The prevalence of POAG in first-degree relatives of affected patients has been documented to be as high as 7–10 times that of the general population.<sup>34</sup> Using family-based linkage approaches, three genes have been identified as factors that can contribute to POAG: (1) certain mutations in *MYOC* (GLC1A), which can cause high-tension adult-onset open-angle glaucoma<sup>24</sup>; (2) a missense mutation in *OPTN* (GLC1E) coding for optineurin, which can cause familial low-tension glaucoma (see below)<sup>35,36</sup>; and *WDR36* (GLC1G) mutations, which may influence disease severity but do not appear to be causative.<sup>37,38</sup>

Genome-wide association studies (GWAS) have successfully identified 16 genes and loci statistically associated with POAG:

- *CAV1/CAV2*.<sup>39,40</sup>
- *CDKN2B-AS1*.<sup>41–43</sup>
- *TMCO1*.<sup>42,44</sup>
- *SIX1/SIX6*.<sup>42,43</sup>
- *8q22*.<sup>43</sup>
- *ABCA1*.<sup>45,46</sup>
- *AFAP1*.<sup>45</sup>
- *GMD5*.<sup>45</sup>
- *PMM2*.<sup>46</sup>
- *FNDC3B*.<sup>47</sup>
- *TGFBR3*.<sup>48</sup>
- *ARHGEF12*.<sup>49</sup>
- *GAS7*.<sup>50</sup>
- *FOXC1*.<sup>50</sup>
- *ATXN2*.<sup>50</sup>
- *TXNRD2*.<sup>50</sup>

The proteins encoded by these POAG-associated genes are beginning to identify biological processes and pathways that underlie disease development, including autophagy (*GMD5*, *PMM2*), ocular development (*SIX6*, *FOXC1*), lipid metabolism (*CAV1*, *ABCA1*, *ARHGEF12*), and mitochondrial function (*TXNRD2*). More research is needed to fully define the genetic architecture of POAG. In addition to the contributions of these susceptibility alleles, the complex genetic architecture of POAG is likely to include gene–gene and gene–environment interactions and epigenetic effects.<sup>51</sup>

## NORMAL-TENSION GLAUCOMA

Familial normal-tension glaucoma (NTG) can be caused by a missense mutation (Glutamine50Lysine) in *OPTN*, coding for optineurin.<sup>35,36</sup> Optineurin has important roles in autophagy and in the tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) signaling pathway. Both TNF- $\alpha$  and autophagy can impact apoptosis in retinal ganglion cells in patients with glaucoma.<sup>52–55</sup> Interestingly, a duplication of the *TBK1* gene, which codes for Tank1-binding protein, influences optineurin activity and also causes familial NTG.<sup>56</sup> Mutations in both *OPTN* and *TBK1* can also cause familial amyotrophic lateral sclerosis (ALS).<sup>57</sup> and a recent GWAS identified significant POAG association with *ATXN2*, another gene related to ALS risk.<sup>50</sup>

GWAS have identified *CDKN2B-AS* and a genomic region on 8q22 as risk factors for NTG.<sup>43</sup> Both *CDKN2B-AS* and the 8q22 region appear to impact TGF- $\beta$  signaling. The 8q22 region includes an enhancer with strong activity in choroid plexus and nonpigmented ciliary body epithelium, suggesting that this region could contribute to variation in cerebral spinal fluid pressure observed in NTG.<sup>58</sup>

## EXFOLIATION SYNDROME AND GLAUCOMA

Exfoliation is common in certain geographical regions, including Scandinavia, Russia, Nova Scotia (Canada), Scotland, northeastern United States, Saudi Arabia, and Greece, and among the Bantu population in Africa; the disease has a low prevalence in the Inuit population, Germany, the United Kingdom, and southern United States. The high prevalence of the condition in certain regions suggests a genetic founder effect, and this finding supports a genetic etiology. A GWAS conducted in Iceland initially identified *LOXL1*, coding for lysyl oxidase-like protein 1, as a genetic risk factor for pseudo-exfoliation syndrome. *LOXL1* is an enzyme necessary for elastogenesis and elastic fiber maintenance.<sup>59</sup> Subsequently, *LOXL1* has been associated with exfoliation syndrome worldwide; however, although the risk alleles are present in over 90% of cases, they have also been observed to be prevalent in controls (up to 85%) suggesting that *LOXL1* is necessary but not sufficient for disease development and that other genetic and/or environmental factors also contribute to disease risk.<sup>60</sup> A subsequent GWAS for exfoliation syndrome has identified association with *CACNA1A*,<sup>61</sup> coding for a protein that forms a calcium channel. In addition to genetic factors, environmental risk factors also significantly contribute to exfoliation syndrome, especially residence in northern latitudes.<sup>60,62,63</sup>

## ANGLE-CLOSURE GLAUCOMA

Angle-closure glaucoma is highly heritable, suggesting that specific genes can contribute to the condition.<sup>64</sup> Frequently, angle-closure glaucoma is



associated with hyperopia or nanophthalmos. One gene for nanophthalmos has been located on chromosome 11.<sup>65</sup> Also located on chromosome 11, defects in the *MFRP* gene have been shown to be responsible for some cases of nanophthalmos.<sup>66</sup> This gene is selectively expressed in the eye and encodes a protein with homology to Tollid proteases and the Wnt-binding domain of the Frizzled transmembrane receptors. These proteins are involved in signaling pathways, and *MFRP* appears to be primarily devoted to regulating axial length of the eye.

GWAS for angle-closure glaucoma have also been completed and have identified eight genetic risk loci:

- PLEKHA7.
- COL11A1.
- PCMTD1-ST18.
- EPDR1.
- CHAT.
- GLIS3.
- FERMT2.
- DPM2-FAM102A.<sup>67,68</sup>

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## Evidence-Based Medicine in Glaucoma

10.34

Henry D. Jampel, Guadalupe Villarreal, Jr.

**Definition:** Evidence-based medicine is the use of the highest-quality medical data currently available to assist in clinical decision making.

## Key Features

- Five levels of evidence: the Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence<sup>1</sup> proposes the following hierarchy for levels of evidence:
  - Systematic review of randomized controlled trials.
  - Randomized controlled trials.
  - Cohort study.
  - Case series.
  - Mechanistic reasoning.

## INTRODUCTION

The practice of medicine will always be a combination of science and art. We learn the artistic aspects from our teachers and from our own experiences. The scientific parts of medicine involve using evidence that has been gathered through the rigorous observations of others in the course of clinical research.

Physicians have always attempted to use the best available medical knowledge to make decisions about the care of their patients. During the early part of the twentieth century, the best available knowledge mainly consisted of techniques and approaches that had been passed on from other physicians. These techniques and approaches were rarely scrutinized for effectiveness in a rigorous and systematic way. Most of medical practice was eminence based (“driven by really charismatic and thoughtful, probably, to some degree, leaders in medicine”),<sup>2</sup> rather than evidence based. A movement toward improving the quality of medical practice with well-designed clinical trials began in the 1970s–1980s.<sup>3–5</sup>

The term *evidence-based medicine* (EBM) gained popularity in the 1990s. Several authors have offered definitions for the term. Sackett defines EBM as the “conscientious, explicit and judicious use of current best evidence in making decisions about the care of individual patients.”<sup>6</sup> Most agree that the first step in practicing EBM is to recognize a clinical problem or question that needs to be answered. For example, one might ask, “Does medical therapy work to prevent glaucoma in patients with elevated intraocular pressure (IOP)?” The next step is to find the available best scientific evidence that addresses the problem or question. When there are conflicting data, it can be difficult to draw an appropriate conclusion if all of the data are weighed equally. To find the most reliable answer to a clinical question, it helps to focus on the higher-quality sources of evidence, such as appropriately conducted and analyzed randomized clinical trials (RCTs) and case-control studies.<sup>7,8</sup> However, in all instances, the reader must be aware of the inherent weaknesses and strengths of these studies.

## TOOLS OF EVIDENCE-BASED MEDICINE

Published reports of clinical experience are the foundation of EBM. A common scenario for the development of increasingly stronger evidence is for a clinician to formulate an impression about a disease process or an intervention and then review and publish his or her experience as a retrospective case series. This, then, leads to a prospective study that can be observational or interventional. Finally, promising results from a non-randomized prospective study can lead to an RCT.

## Randomized Clinical Trials

An RCT is a study in which participants are randomly assigned to one or more groups. The process of randomization eliminates bias in the allocation of subjects to one treatment or another.<sup>9</sup> The results of RCTs are often considered the highest-quality evidence and hence are the backbone of EBM. For instance, the Cochrane Collaboration, a leading proponent of EBM, largely limits its reviews to the analysis of RCTs.

A properly designed RCT has the potential to demonstrate a cause-and-effect relationship between a treatment and a specific patient response. For the results from an RCT to be useful, several conditions need to be met. The hypothesis of the trial has to be narrow in scope and clinically relevant. The appropriate number of patients has to be included in the study to ensure that a negative result is truly negative. Biases in the study have to be minimized. The Ocular Hypertension Treatment Study (OHTS)<sup>10</sup> is an example of an RCT that was sufficiently focused, appropriately powered, and sufficiently free of bias to answer the question “Does medical therapy work to prevent glaucoma in patients with elevated intraocular pressure?”

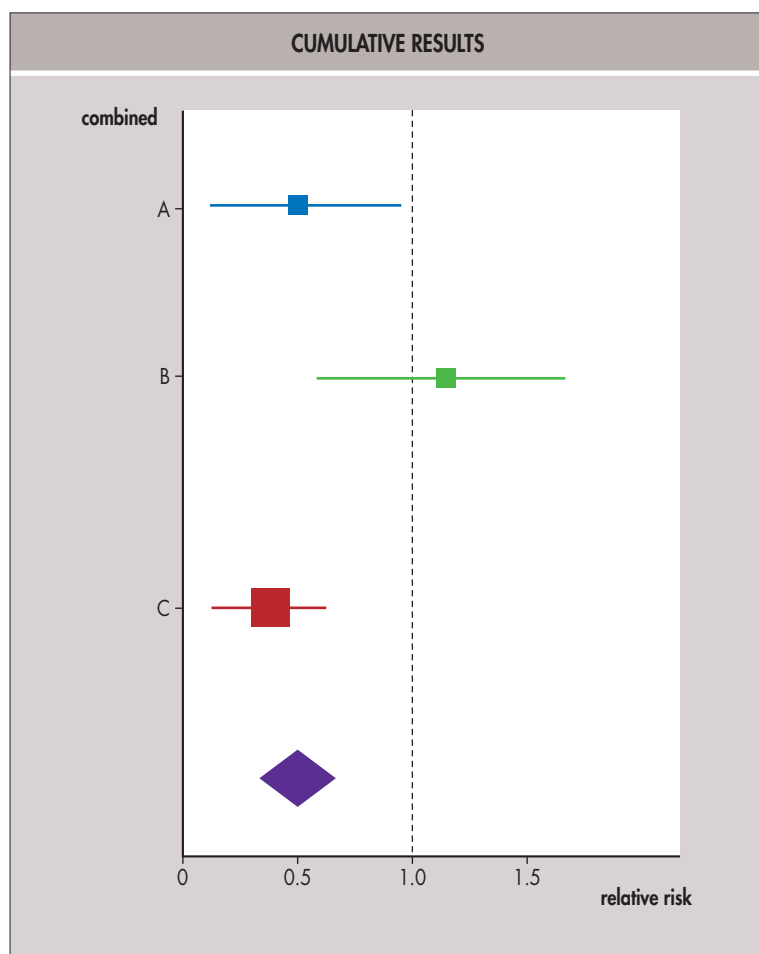
Although considered a robust study design, RCTs vary widely in their quality, depending on their sample size, inclusion and exclusion criteria, rigor in randomization, masking of observers and subjects, loss to follow-up, and data presentation. Adherence to the CONSORT (Consolidated Standards of Reporting Trials) guidelines for reporting clinical trials ensures a minimal quality of an RCT,<sup>11</sup> but even the best RCTs have some inherent weaknesses.<sup>6</sup> For instance, inclusion and exclusion criteria associated with the studies may result in findings that are not applicable to a patient who would not have qualified for the study.<sup>12</sup> For example, the OHTS specifically did not address the question of whether treatment was advantageous for patients with IOP of 21–24 mm Hg.<sup>13</sup> In addition, RCTs may not uncover all of the possible problems and adverse events associated with a particular therapy. An example of this can be found in the Collaborative Initial Glaucoma Treatment Study (CIGTS), a multicenter RCT in which individuals with newly diagnosed open-angle glaucoma were randomized to initial medical or surgical treatment.<sup>14</sup> The number of subjects who underwent trabeculectomy in the CIGTS, although sufficient to compare the success of initial medical treatment versus initial surgical treatment of newly diagnosed open-angle glaucoma, precluded obtaining useful information about the rare, but serious, complication of bleb-related infection.

Another disadvantage of RCTs is that depending on the endpoint, they may take a long time to reach completion.<sup>15</sup> When the time frame of an RCT is several years or more, it is not unusual for the therapies that are being evaluated to have been replaced by seemingly better treatments by the time the findings of the trial are published. For example, the Glaucoma Laser Trial (GLT) compared argon laser trabeculoplasty with medical therapy in the treatment of patients with newly diagnosed glaucoma and found that laser and medications to be equally effective.<sup>16</sup> However, the medical therapies available at the time included only those with timolol, epinephrine, pilocarpine, and acetazolamide pills. Some have questioned the applicability of the study today, with the availability of prostaglandins, alpha-agonists, and topical carbonic anhydrase inhibitors. Finally, the literature is replete with RCTs that did not include enough participants to determine the answer to the posed clinical question.

## Meta-Analyses and Systematic Reviews

When multiple RCTs have been conducted on a given topic, a meta-analysis can be employed. In a meta-analysis, statistical techniques are used to measure and compare the outcomes of multiple studies. By combining the outcomes of multiple studies, the overall sample size and statistical power are increased.<sup>17</sup> Meta-analyses are particularly useful when there





**Fig. 10.34.1** Systematic reviews often include a forest plot, which shows the variation in trial results and estimates the cumulative result of the included trials. Shown in the figure are the results of a hypothetical meta-analysis of three studies (A–C) looking at the relationship between use of topical glaucoma medications and risk of developing glaucoma. The results are shown in terms of estimated relative risk of developing glaucoma. The relative risk associated with each study is shown with a point estimate; the horizontal line on which the point lies represents the confidence interval. Because the use of topical medications is expected to reduce the risk of glaucoma, the relative risk should be less than 1.0. Study B yielded a relative risk greater than 1.0, which indicates that using topical drops increases the risk of glaucoma. This finding in study B does not agree with the results from studies A and C, which show that using topical drops does decrease the risk of glaucoma. The confidence intervals are an indication of the precision of each study. Study A has the narrowest confidence interval (highest precision) and study C has the widest confidence interval (lowest precision). The combined results of the three studies are indicated by the diamond at the bottom of the chart. The side points of the diamond represent the confidence interval. The upper and lower points of the diamond represent the point estimate of the relative risk for the combined studies. (From Greenberg R, Daniels S, Flanders W, et al. *Medical epidemiology*, 4th ed. New York: McGraw-Hill Medical, 2004.)

are small clinical trials that are inconclusive, perhaps because of size, and when different RCTs come to different conclusions. The averages of the study results are often weighted, placing more emphasis on larger studies. Forest plots are a convenient way of summarizing the statistical analyses performed on the studies used for the meta-analyses (Fig. 10.34.1).<sup>18</sup> Meta-analyses can be useful for reducing the biases and improving the precision that is associated with RCTs.<sup>8</sup>

An example of a meta-analysis in glaucoma therapy is the study by Maier et al.,<sup>13</sup> which addressed whether lowering of IOP delays the progression of visual field defects in patients with open-angle glaucoma. This study is of particular note because it was published in the *British Medical Journal*, not in an ophthalmology journal. It gives us insight into the limited conclusions that nonophthalmologists are willing to draw from our ophthalmological data. Maier et al. were willing to only conclude that lowering IOP in patients with ocular hypertension or manifest glaucoma lowers the risk of visual field loss and has unclear effects in patients with normal-tension glaucoma, whereas the glaucoma community has drawn more widespread conclusions from these data regarding IOP lowering in glaucoma.

Another meta-analysis compared the effectiveness and adverse effects of adding a second IOP-lowering agent to an eye already being treated with a topical prostaglandin.<sup>19</sup> The authors of that meta-analysis appropriately followed established guidelines (Quality of Reporting of Meta-analyses [QUORUM]) for the performance of a meta-analysis, used predetermined inclusion and exclusion criteria for selecting trials, and reported on how well the included studies met the quality criterion. They found that the effectiveness of the three classes of medications was similar but that they each had different side-effect profiles. Li et al.<sup>20</sup> performed a systematic review and network meta-analysis of 114 RCTs comparing the effectiveness of first-line IOP-lowering eyedrops in patients with ocular hypertension or primary open-angle glaucoma (POAG). Those authors found that prostaglandin medications were the most efficacious class, with within-class differences being small and probably not clinically meaningful.<sup>20</sup> Mean reductions in IOP (mm Hg) at 3 months compared with that in placebo group were as follows: bimatoprost (5.61), latanoprost (4.85), travoprost (4.83), levobunolol (4.51), tafluprost (4.37), timolol (3.70), brimonidine (3.59), carteolol (3.44), levobetaxolol (2.56), apraclonidine (2.52), dorzolamide (2.49), brinzolamide (2.42), betaxolol (2.24), and unoprostone (1.91).<sup>20</sup>

Although meta-analyses can put our clinical decision making on a firmer footing, they have their own limitations. First, bias and errors associated with the included studies may become magnified in the meta-analysis. Second, they often do not include negative studies because these studies may never have been published. When this is the case, the meta-analysis will yield a result that is more positive than the aggregate of all data, published and unpublished. Thus, when evaluating meta-analyses, it is important to ask what the authors did to minimize potential bias.

For most clinical questions, multiple, high-quality RCTs have not been conducted, and it is not possible to carry out a true meta-analysis. In these instances, a systematic review of the literature can be conducted. Systematic reviews include a well-defined and carefully executed review of the literature, an algorithm for determining which types of studies to include in the review, and an assessment of the quality of the manuscripts reviewed. Because studies with different designs are included, the authors generally cannot make more than qualitative statements about the answers provided by the aggregate of studies.

The Cochrane Collaboration has been at the forefront of performing meta-analyses of RCTs. In the area of glaucoma, the Cochrane Collaboration has reported on optic nerve head and fiber layer imaging for diagnosing glaucoma,<sup>21</sup> laser peripheral iridoplasty for angle closure,<sup>22</sup> laser trabeculoplasty for open-angle glaucoma,<sup>23</sup> 5-fluorouracil (5-FU) for glaucoma surgery,<sup>24</sup> intraoperative mitomycin C (MMC) for glaucoma surgery,<sup>25</sup> fornix-based versus limbal-based conjunctival trabeculectomy flaps,<sup>26</sup> needling for encapsulated blebs,<sup>27</sup> interventions for late trabeculectomy bleb leak,<sup>28</sup> combined surgery versus cataract surgery alone for eyes with cataract and glaucoma,<sup>29</sup> and medical versus surgical interventions for open-angle glaucoma.<sup>30</sup>

One organization in the United States that provides funding for systematic reviews is the Agency for Health Research and Quality (AHRQ). Within the field of ophthalmology, the AHRQ has funded systematic reviews in anesthesia for cataract surgery,<sup>31</sup> treatments for open-angle glaucoma,<sup>32</sup> surgical management of coexisting cataract and glaucoma,<sup>33</sup> and the effects of omega-3 fatty acids on eye health.<sup>34</sup> As part of the process of formulating its Preferred Practice Patterns,<sup>35</sup> the panel of experts chosen by the American Academy of Ophthalmology (AAO) carefully reviews the literature and assigns each study a quality rating and an importance to clinical care rating. The AAO, through its Ophthalmic Technology Assessments, has published systematic reviews in glaucoma, such as the effect of phacoemulsification on IOP in patients with glaucoma.<sup>36</sup>

## Other Study Designs

Clinicians who base their decisions solely on the results of RCTs, meta-analyses, and systematic reviews will be left with many situations for which they will have no guidance. As can be found upon opening any clinical ophthalmology journal, the bulk of articles rely on study designs generally considered less rigorous. These study designs include case reports, case series, cross-sectional studies, cohort studies, and case-control studies. These studies are still useful as long as the reader is aware of their limitations.

## Case Reports

Case reports are descriptions of individual patients with new diseases, conditions of interest, or of interventions in individual patients. Their main value is to encourage further investigation of the disease or intervention.

Case series contain multiple case reports and may provide summary statistics concerning results. They provide a stronger impetus to further study compared with a single case report.

### Cross-Sectional Studies

Cross-sectional studies are used to determine the prevalence of a disease or problem and are also commonly used to evaluate diagnostic tests. The Blue Mountains Eye Study used a cross-sectional design to determine the prevalence of open-angle glaucoma and ocular hypertension in the Australian population. They found that the prevalence of open-angle glaucoma was 3% and that of ocular hypertension was 3.7%.<sup>37</sup> A disadvantage of this study design is that its findings cannot be used to determine temporal sequence or cause and effect.<sup>38</sup>

### Case-Control Studies

Case-control studies are used to determine risk factors for a disease or a complication. They are particularly useful in situations where a disease or complication is rare. Individuals with a given condition (cases) are carefully matched to individuals who do not have the condition (controls). The cases and controls are then compared in terms of their previous exposure to possible risk factors. An odds ratio is calculated to quantify the higher likelihood of cases having been exposed compared with the controls.<sup>39</sup> For example, Jampel et al.<sup>40</sup> used a case-control study to look at late-onset infection after glaucoma filtration surgery and found that risk factors for infection included full-thickness procedures, filtration surgery performed without cataract surgery, MMC use, and chronic postoperative use of antibiotics. It should be emphasized that case-control studies can identify associations but cannot prove cause and effect. One of the most important pitfalls of case-control studies is the inappropriate selection of controls.

### Cohort Study

In a cohort study, a group of individuals is followed up over time. Cohort studies can be prospective or retrospective and are used to study the natural history and incidence of diseases. For instance, as a part of the Blue Mountains Eye Study, Chandrasekaran et al.<sup>41</sup> used a cohort study to show that eyes with elevated IOP at presentation treated with topical glaucoma medications had a twofold increased risk of 5-year incident nuclear cataract development.

### Other Limitations

The validity of the results of clinical studies can be limited by selection bias and information bias.<sup>42</sup>

#### Selection Bias

Selection bias occurs when the investigator's methods of obtaining subjects for the study affects the relationship between risk factors and outcomes. For instance, patients who are referred to an investigator as potential study subjects and who agree to participate in a study may not be representative of all individuals in the population of interest. The investigator's inclusion and exclusion criteria can also add to selection bias. Loss to follow-up is another significant contributor to selection bias.<sup>17</sup>

#### Information Bias

Information bias results from inaccurate measurement of risk factor or disease presence. When information bias results from errors in the subject's ability to report risk factors and exposures accurately, it is called *recall bias*. For example, when asked about family history of glaucoma, individuals already diagnosed with glaucoma may be more likely to search their memory for distant relatives who could possibly have had glaucoma compared with individuals who believe their eyes are healthy. This kind of recall bias would affect the results of a study looking at the role of family history as a risk factor for glaucoma.

## EVALUATION OF DIAGNOSTIC TESTING IN GLAUCOMA

Diagnostic testing in glaucoma serves two purposes: first, to assess whether glaucoma is present and, second, to determine if there has been progression of disease. There is no consensus about what constitutes progression, and developing a consensus is a major focus for clinical researchers. The evaluation of diagnostic testing in determining progression will therefore not be discussed further, except to make the following generalizations: Progression can be determined by (1) a change in structure or function; (2)

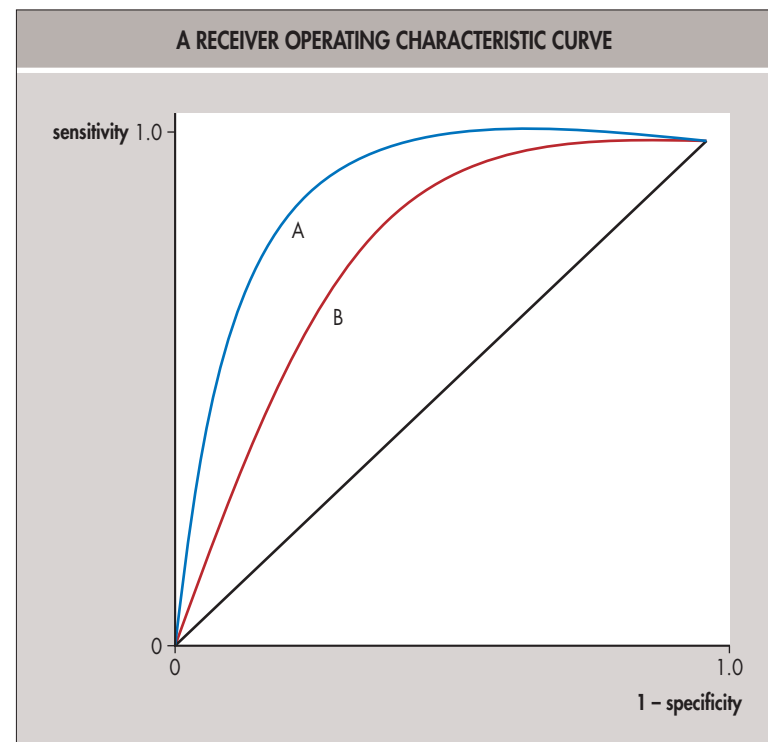
a change that signifies progression must exceed the variability inherent in performing a test repeatedly over time; and (3) the ability of a diagnostic modality to detect progression is dependent on the severity of the disease (e.g., it is generally assumed that at the later stages of disease, evaluation of perimetry is more valuable than evaluation of the optic disc or retinal nerve fiber layer). The emphasis in this section will, instead, be on the use of diagnostic tests to diagnose glaucoma, that is, to separate persons with disease from persons without disease.

Using diagnostic tests to detect glaucoma occurs in two settings—(1) in the community to “screen” and (2) in the doctor's office in patients deemed to be at risk for glaucoma, such as those with elevated IOP or a family history of glaucoma. Community screening for glaucoma is important because population-based studies have repeatedly demonstrated that a large proportion of individuals with glaucoma are undiagnosed. These are two distinct situations that call for different diagnostic tests.

The literature on diagnostic tests is peppered with technical terms, such as *sensitivity*, *specificity*, *positive predictive value*, *negative predictive value*, *likelihood ratios*, and *receiver operating curves* (see below). A brief review of some of these concepts is presented below.

Every diagnostic test is designed to determine whether a patient has a distinct condition or disease. Although the test may yield data points that lie within a wide range of values, the test results are ultimately interpreted as being either positive or negative for the disease of interest. The defining value at which the test result changes from positive to negative is called the *cutoff point*. Before diagnostic test performance can be quantified, some definitions are necessary. The sensitivity of a test is defined as the percentage of patients with positive test results who have the disease (sensitivity = patients with positive results and disease/total number of patients with disease).<sup>43</sup> The specificity of a test is defined as the percentage of patients with negative test results in the group of patients who do not have the disease (specificity = patients with negative results and no disease/total number of patients without disease).<sup>43</sup>

Sensitivity and specificity are affected by the choice of the cutoff point for the test. A high cutoff point is associated with higher test specificity and lower sensitivity, whereas a lower cutoff point is associated with higher test sensitivity and lower specificity. The performance of a diagnostic test can be estimated by plotting sensitivity against (1 – specificity) using values generated over a range of cutoff points. The resulting plot is called a *receiver operating characteristic (ROC) curve* (Fig. 10.34.2).<sup>17</sup> The area under the curve (AUC) for a test or device is a measure of its utility. An AUC of 1.0 is perfect, and a test with an AUC of 0.5 has no diagnostic utility.



**Fig. 10.34.2** A receiver operating characteristic (ROC) curve. The area under the ROC curve is 1 for an ideal or perfect diagnostic test. The area under the ROC curve is 0.5 for a test that does not distinguish between patients with or without the disease. In this figure, test A has better diagnostic value than curve B. (From Greenberg R, Daniels S, Flanders W, et al. Medical epidemiology, 4th ed. New York: McGraw-Hill Medical, 2004.)

The likelihood ratio (LR) is the likelihood that a given test result would be expected in a patient with a disease compared with the likelihood that the same result would be expected in a patient without the disease. The LR, like the ROC curve, is used to assess how good a diagnostic test is. The LR for a positive test result is (sensitivity)/(1 – specificity) and for a negative test result is (1 – sensitivity)/specificity. The LR is less likely to change with disease prevalence compared with sensitivity and specificity. Furthermore, the LR can be used, as illustrated in the example that follows, to calculate the post-test probability of a patient having the disorder in question.

The way that the LR is used is as follows: First, the LR is calculated as (sensitivity/1 – specificity). Second, the pretest odds of the condition being present, which is given by the formula: (pretest probability)/(1 – pretest probability), are calculated. Third, the post-test odds, the product of the pretest odds and the LR, are calculated. Finally, the post-test probability is calculated by dividing the post-test odds by (1 + post-test odds).

As an example, suppose you have a test with a sensitivity of 80% and a specificity of 90% for the detection of glaucoma: the LR for your test is 8 (80% ÷ 10%). Assume that the prevalence of glaucoma in your study population is 10%: the pretest odds ratio of a person having glaucoma is 1/9 (10% ÷ 90%). The post-test odds that a person testing positive has glaucoma are then 8 × 1/9, or 8/9. The post-test probability of the patient having the disease is (8/9 ÷ 17/9) or 8/17 (47%). A nomogram is available that allows a direct conversion from pretest to post-test probability if one knows the likelihood ratio (Fig. 10.34.3).

Many studies reported in the recent literature have described the utility of vision tests and imaging devices for diagnosing glaucoma. When designing a diagnostic accuracy study, it is important to determine the

purpose of the diagnostic test.<sup>44</sup> As one of the roles of spectral-domain optical coherence tomography (SD-OCT) is to determine whether those at risk for glaucoma have structural damage, design of a diagnostic accuracy study for OCT would therefore focus on evaluating glaucoma suspects.<sup>44</sup> An example is the study by Banister et al.,<sup>45</sup> which was a multicenter, prospective study performed in the United Kingdom comparing the diagnostic performance of Heidelberg Retina Tomograph III (HRT; Heidelberg Engineering, Germany) with Moorfields regression analysis (MRA) and glaucoma probability score (GPS) classification algorithms, scanning laser polarimetry (GDx; Carl Zeiss Meditec, Dublin, CA), and Spectralis SD-OCT (Heidelberg Engineering) in newly referred glaucoma suspects. A total of 943 patients were included in the analysis, 17% of whom had been diagnosed with glaucoma in at least one eye based on clinical assessment and automated perimetry. Amongst the four imaging test algorithms, HRT MRA had the highest sensitivity (87%) with the lowest specificity (64%), and GDx had the lowest sensitivity (35%) with the highest specificity (97%). HRT GPS and Spectralis SD-OCT had intermediate levels of sensitivity (82% and 77%, respectively) and specificity (68% and 79%, respectively).<sup>45</sup> On the basis of these results, the authors of the study concluded that automated imaging tests remain an adjunct to clinical assessment and perimetry and that reliance solely on imaging technologies is not advisable.<sup>45</sup>

In evaluating the usefulness of a diagnostic test, the reader must always keep the following points in mind. First, it is logical to evaluate a new diagnostic technique in a clinical setting, but one must not extrapolate the performance of a diagnostic test in a clinic to its performance as a screening test in the community. As a rule, specificity is lower in the community than in the clinic. Second, the amount of damage in the glaucoma group greatly influences the performance of any test. It is easier for a test to distinguish between severe disease and the normal state than to distinguish between early disease and the normal state. Third, the defining criteria for the diagnosis of glaucoma can affect the performance of the test. The ability of an optic disc imager to distinguish the normal state from glaucoma may vary, depending on whether the diagnosis of glaucoma was made on the basis of optic disc findings, visual field findings, or both.

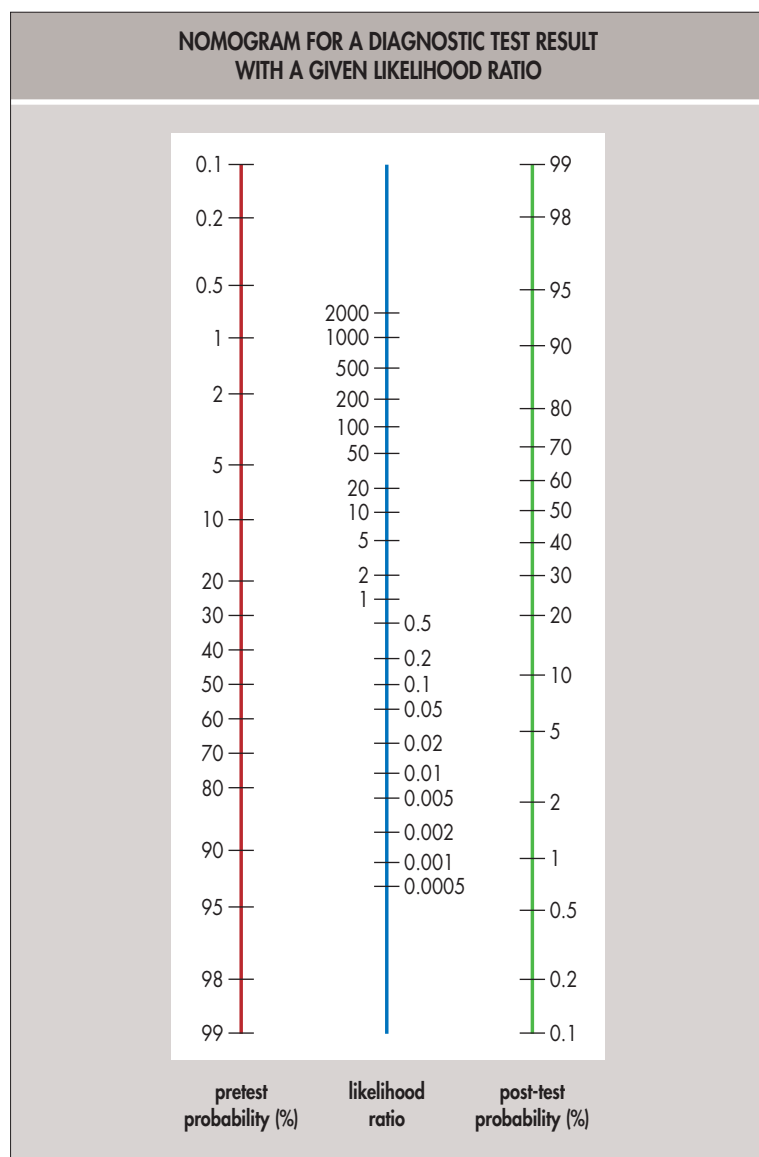
Above and beyond the preceding comments, conducting, reporting, and interpreting studies on diagnostic accuracy can be difficult. The Standards for Reporting of Diagnostic Accuracy (STARD) initiative was established to improve the quality of studies of diagnostic accuracy. One result of this initiative is a checklist of 25 items that should be included in a diagnostic accuracy study. Four publications suggested that the adherence to the STARD criteria by published studies of imaging devices and automated perimetry for the diagnosis of glaucoma is suboptimal and warrants improvement.<sup>46–49</sup> Readers must interpret the reports on diagnostic tests with caution.

## EXAMPLES OF EVIDENCE-BASED MEDICINE IN GLAUCOMA THERAPY

Several clinical trials have been conducted over the years to evaluate the treatment of glaucoma (Boxes 10.34.1 through 10.34.9). Here, examples of important issues in glaucoma management and several of the relevant clinical trials that influence how we treat glaucoma today are highlighted.

A critical question that is confronted daily is “Does medical reduction of IOP prevent or delay the onset of optic nerve damage and visual field loss in patients with ocular hypertension?” Prior to the OHTS, three small RCTs had failed to demonstrate a beneficial effect of IOP lowering in subjects with ocular hypertension.<sup>50–52</sup> However, the OHTS convincingly demonstrated that medical reduction of IOP could reduce the incidence of glaucoma from approximately 10% to 5% over a period of 5 years (see Box 10.34.1).<sup>10,53–55</sup> Unlike the OHTS, the European Glaucoma Prevention Trial failed to find an effect of medical lowering of IOP on the rate of incident glaucoma.<sup>56</sup> Possible explanations for the lack of effect in this trial are eloquently enumerated in a letter to the editor.<sup>57</sup> The OHTS also determined the risk factors predisposing to the conversion of subjects to glaucoma damage. This determination has formed the basis for glaucoma risk calculators.<sup>58,59</sup> A meta-analysis of trials of medical treatment of elevated IOP reached the same conclusion as that by the OHTS.<sup>13</sup>

A crucial related question is whether lowering IOP in patients who already have glaucoma damage could decrease the likelihood of worsening of damage. This question was addressed in the Early Manifest Glaucoma Trial (EMGT) (see Box 10.34.2).<sup>60,61</sup> Patients with newly diagnosed, early glaucoma damage were randomized to treatment with betaxolol eyedrops and laser trabeculoplasty or observation. This protocol differed from other treatment trials in that no specific amount of IOP lowering



**Fig. 10.34.3** Nomogram for converting pretest probabilities to post-test probabilities for a diagnostic test result with a given likelihood ratio. (Reproduced with permission from the Oxford Centre for Evidence-Based Medicine. Available at: <http://www.cebm.net>.)



**BOX 10.34.1 Ocular Hypertension Treatment Study (OHTS)**<sup>10,53–55</sup>

**Clinical question:** Does medical reduction of IOP prevent or delay the onset of optic nerve damage and visual field loss in patients with ocular hypertension?

**Study type:** Multicenter randomized clinical trial

**Number of patients:** 1636

**Duration:** Patients followed up for a minimum of 5 years

**Eligibility:** Men and nonpregnant women with normal visual fields and optic discs, between the ages of 40 and 80, with IOP  $\geq 24$  mm Hg but  $\leq 32$  mm Hg in one eye and IOP  $\geq 21$  mm Hg but  $\leq 32$  mm Hg in the fellow eye

**Methods:** Patients were randomized to observation or treatment with topical ocular hypotensive medications. Patients receiving treatment had target IOP that was a minimum of 20% below baseline and that was also  $\leq 24$  mm Hg. Patients were followed up every 6 months. Proportional hazards models were used to identify risk factors for POAG

**Results:** After 60 months, the probability of developing POAG was 4.4% in the group receiving medication and 9.5% in the group that did not receive medication

**Conclusions:** Patients receiving topical medications had a lower risk of developing POAG than patients receiving no medication

*IOP, Intraocular pressure; POAG, primary open-angle glaucoma.*

**BOX 10.34.2 Early Manifest Glaucoma Trial (EMGT)**<sup>60,61</sup>

**Clinical question:** How is the progression of OAG affected by immediate IOP-lowering therapy when compared with late IOP-lowering therapy or no treatment?

**Study type:** Randomized clinical trial

**Number of patients:** 255

**Duration:** Patients were followed for a minimum of 4 years

**Eligibility:** Swedish men and women between the ages of 50 and 80 years with newly detected and untreated OAG and repeatable Humphrey visual field defects

**Methods:** Patients were randomized to observation or treatment with topical betaxolol and ALT. Visual field progression was determined using HVF 30-2 fields and by evaluating three consecutive glaucoma change probability maps. Optic disc progression was determined using disc photos and flicker chronoscopy

**Results:** After 6 years, 53% of patients had experienced disc and field progression. In a multivariate analysis, untreated patients had twice the glaucoma progression risk of patients who received treatment

**Conclusions:** Untreated patients had twice the glaucoma progression risk of patients who received treatment

*ALT, Argon laser trabeculoplasty; IOP, intraocular pressure; OAG, open-angle glaucoma.*

was required. Subjects randomized to IOP-lowering treatment were less likely to sustain further glaucoma damage compared with the untreated group. A startling finding of the EMGT was the rate of progression in both the untreated and treated groups. At 6 years, 45% of treated patients and 62% of untreated patients had progressed to glaucoma damage.<sup>61</sup> Why the rate of progression was so much higher than that estimated in other studies is unclear, but it is not simply the result of a looser definition of progression.<sup>62</sup> Similar to the OHTS, risk factors for progression included exfoliation syndrome, older age, bilateral disease, higher baseline IOP, and worse mean deviation.

Additional RCTs have addressed the relative merits of different methods of lowering IOP. The Glaucoma Laser Trial (GLT) (see Box 10.34.3)<sup>16,63–65</sup> addressed the question of whether medical therapy or argon laser trabeculoplasty (ALT) was more effective at controlling IOP in patients with glaucoma.<sup>16</sup> Its authors concluded that ALT was at least as effective in the management of newly diagnosed glaucoma as medical therapy, but its conclusions were immediately called into question because of the perceived flaws in the study.<sup>66,67</sup> The GLT illustrates one of the hazards of prolonged clinical trials—the results becoming obsolete by the time the study is completed. The GLT permitted the use of currently available medications for lowering IOP, which were beta-blockers, adrenergic agents, miotics, and oral carbonic anhydrase inhibitors. Currently, a number of more effective

**BOX 10.34.3 Glaucoma Laser Trial (GLT) and Glaucoma Laser Trial Follow-Up Study (GLTFS)**<sup>16,63–65</sup>

**Clinical question:** Is ALT a safe and effective treatment for newly diagnosed POAG?

**Study type:** Randomized clinical trial

**Number of patients:** 271 (542 eyes)

**Duration:** Median follow-up of 7 years

**Eligibility:** Men and women 35 years of age or older with IOP of  $\geq 22$  mm Hg in each eye and glaucomatous optic nerve injury in at least one eye

**Methods:** One eye was randomized to laser treatment and the other eye to topical medication

**Results:** Eyes treated initially with ALT as opposed to medication had IOPs that were on average 1.2 mm Hg lower, had a 0.6 dB greater improvement in the visual field, and had a change in cup-to-disc area ratio that was 0.01 less than the change in cup-to-disc area ratio for eyes treated initially with medication

**Conclusions:** Patients treated initially with ALT had lower IOPs, better visual fields, and less glaucomatous optic nerve damage than patients treated initially with medications

*ALT, Argon laser trabeculoplasty; IOP, intraocular pressure; POAG, primary open-angle glaucoma.*

**BOX 10.34.4 Advanced Glaucoma Intervention Study (AGIS)**<sup>68–72</sup>

**Clinical question:** How are outcomes in OAG patients affected by the sequence of treatment with ALT and trabeculectomy?

**Study type:** Multicenter randomized clinical trial

**Number of patients:** 591 (789 eyes)

**Duration:** Patients followed up for a minimum of 4 years; study ongoing

**Eligibility:** Men and women between the ages of 35 and 80 years with POAG not controlled with medications

**Methods:** Eyes were randomized to receive either ALT followed by trabeculectomy 1 and trabeculectomy 2 (ATT sequence) or trabeculectomy 1 followed by ALT then trabeculectomy 2 (TAT sequence)

**Results:** In black patients, the average percent of eyes with VF loss was less in the ATT sequence than in the TAT sequence. In white patients, conversely, after 18 months the average percent of eyes with VF loss was less in the TAT sequence

**Conclusions:** Although race was not considered when the hypothesis of the study was generated, post hoc analysis suggests that long-term visual function outcomes were better for the ATT sequence in black patients and better for the TAT sequence in white patients

*ALT, Argon laser trabeculoplasty; POAG, primary open-angle glaucoma.*

**BOX 10.34.5 Collaborative Initial Glaucoma Treatment Study (CIGTS)**<sup>74–76</sup>

**Clinical question:** Are patients with OAG best managed with initial topical medication or by initial filtration surgery?

**Study type:** Multicenter randomized controlled clinical trial

**Number of patients:** 607

**Duration:** Patients were followed up for a minimum of 5 years

**Eligibility:** Men and women 25 years of age and older with OAG, IOP  $\geq 20$  mm Hg and visual field loss or glaucomatous optic nerve damage in one or both eyes

**Methods:** Patients were randomized to receive initial treatment with medications or trabeculectomy

**Results:** There was no significant difference in visual field loss between the two groups. Subjects randomized to trabeculectomy had more ocular symptoms during the first 2 years than those randomized to medications

**Conclusions:** Initial medical treatment and initial filtering surgery were both effective at preserving vision; there was a slight advantage for medications in terms of comfort

*IOP, Intraocular pressure; OAG, open-angle glaucoma.*

**BOX 10.34.6 The Fluorouracil Filtering Surgery Study (FFSS)<sup>79</sup>**

**Clinical question:** Does postoperative subconjunctival 5-FU increase the success of trabeculectomy in patients at risk for trabeculectomy failure?

**Study type:** Multicenter randomized clinical trial

**Number of patients:** 213

**Duration:** 5 years

**Eligibility:** Men and women with IOP >21 mm Hg in one or both eyes despite maximum-tolerated therapy and previous cataract surgery or failed trabeculectomy

**Methods:** Patients were randomized to trabeculectomy alone or trabeculectomy with postoperative subconjunctival 5-FU injections

**Results:** After 5 years, 51% of the eyes that received 5-FU and 74% of the eyes that did not receive 5-FU had failed trabeculectomies

**Conclusions:** Trabeculectomy success rates with 5-FU were improved over standard trabeculectomy success rates for 5 years

5-FU, 5-fluorouracil; IOP, intraocular pressure.

**BOX 10.34.7 The Tube Versus Trabeculectomy (TVT) Study<sup>84</sup>**

**Clinical question:** Is tube shunt surgery or trabeculectomy safer or more effective in eyes with prior ocular surgery?

**Study type:** Multicenter randomized clinical trial

**Number of patients:** 212 (145 reported on with 5 years of follow-up)

**Duration:** 5 years

**Eligibility:** Individuals between 18 and 85 years of age, with a history of previous trabeculectomy and/or cataract extraction with intraocular lens implantation, and intraocular pressure (IOP) between 18 and 40 mm Hg on maximum tolerated medical therapy.

**Methods:** Patients were randomized to receive either a Baerveldt 350 mm<sup>2</sup> aqueous drainage device or a trabeculectomy with mitomycin C 0.4 mg/ml for 4 minutes

**Results:** With failure defined as IOP >21 mm Hg or not reduced by 20%, IOP <5 mm Hg, reoperation for glaucoma, or loss of light perception vision, the failure rate was lower at 5 years in the tube group (30%) than in the trabeculectomy (47%) group ( $P = 0.002$ ).

**Conclusions:** In eyes with previous cataract surgery and/or trabeculectomy, Baerveldt aqueous drainage device implantation had a higher success rate than trabeculectomy with mitomycin C. One proviso is that although not statistically significant, eyes undergoing trabeculectomy had a lower intraocular pressure ( $12.6 \pm 5.9$  mm Hg) compared with eyes undergoing Baerveldt implantation ( $14.4 \pm 6.9$  mm Hg).

medications are available, and if the GLT is performed again today, its results may very well favor medical therapy.

The Advanced Glaucoma Intervention Study (AGIS) is one of the most frequently cited and discussed RCTs in glaucoma (see [Box 10.34.4](#)).<sup>68-72</sup> It sought to answer the question as to whether performing trabeculoplasty or trabeculectomy next in patients already on maximum medical treatment was the more effective approach for preserving vision. The answer to that question in the AGIS was that trabeculoplasty (followed by trabeculectomy, if necessary) and trabeculectomy (followed by trabeculoplasty if necessary) were equally effective. However, this conclusion has been overshadowed by analyses performed after dividing the subjects on the basis of race (black or white).<sup>68-70</sup> When this is done, it appears that overall vision preservation is better in black patients if trabeculoplasty is performed first and in white patients if trabeculectomy is performed first. However, there are those who question the validity of such “post hoc” analyses that were not planned for at the inception of the study. The AGIS data set has also been used to emphasize the importance of maintaining consistently low IOPs in patients with glaucoma<sup>71</sup> and the importance of IOP fluctuation<sup>73</sup> in glaucoma progression. The reader must realize that conclusions drawn from data and analyses that were not specifically designed for an RCT to address its specific aims cannot be given the same weight as the primary outcome data.

The CIGTS was another RCT comparing modalities of treating glaucoma (see [Box 10.34.5](#)).<sup>74-76</sup> In the CIGTS, subjects with newly diagnosed open-angle glaucoma were randomized to initial medical treatment or

**BOX 10.34.8 Five-Year Pooled Data Analysis of the Ahmed Baerveldt Comparison (ABC) Study and the Ahmed Versus Baerveldt (AVB) Study<sup>85-87</sup>**

**Clinical question:** What is the efficacy of the Ahmed FP7 glaucoma valve (AGV) implant compared to the Baerveldt 350 mm<sup>2</sup> glaucoma implant (BGI)?

**Study type:** Pooled analysis of two multicenter randomized clinical trials

**Number of patients:** 514

**Duration:** 5 years

**Eligibility:** Individuals 18 years and older with uncontrolled glaucoma defined as IOP greater than target despite maximum tolerated medical therapy, prior failed trabeculectomy or high-risk glaucoma, including neovascular and uveitic glaucoma

**Methods:** Patients were randomized to receive either an Ahmed FP7 or Baerveldt 350 mm<sup>2</sup> aqueous drainage device

**Results:** Cumulative failure at 5 years was lower in the BGI group (37%) than in the AGV group (49%) ( $P = 0.007$ ), with failure defined as IOP >18 mm Hg or reduced less than 20% from baseline, IOP <6 mm Hg, de novo glaucoma surgery, removal of the implant, loss of light perception vision, or severe vision loss

**Conclusions:** Baerveldt 350 mm<sup>2</sup> aqueous drainage device implantation had a higher cumulative success rate than the Ahmed FP7 drainage device, with a lower mean IOP, less glaucoma medication use, and lower rate of de novo glaucoma surgery. Rates of hypotony however were higher with BGI group (4.5%) as compared with the AGV group (0.4%).

**BOX 10.34.9 Effectiveness of Early Lens Extraction for the Treatment of Primary Angle-Closure Glaucoma (EAGLE) Study<sup>88</sup>**

**Clinical question:** Is early clear lens extraction more efficacious, safer, and cost-effective compared to LPI as first-line treatment for patients with newly diagnosed primary angle closure (PAC) with elevated IOP or primary angle-closure glaucoma (PACG)?

**Study type:** Multicenter randomized controlled clinical trial

**Number of patients:** 419

**Duration:** 3 years

**Eligibility:** Individuals aged 50 years or over, clear lens, and newly diagnosed PAC with IOP  $\geq 30$  mm Hg or PACG with IOP >21 mm Hg on at least one occasion.

**Methods:** Patients were randomized to treatment with either clear lens extraction or LPI and glaucoma drops (standard care).

**Results:** Mean IOP was lower (1.18 mm Hg), glaucoma medication use was lower (0.338 medications), and visual acuity was improved (three ETDRS letters) at 3 years in the clear lens extraction group as compared with standard care. European Quality of Life-5 Dimensions scores, NEI-VFQ-25, and Glaucoma Utility Index scores were significantly higher in the clear lens extraction group at 3 years. No serious adverse events occurred in either group and irreversible vision loss was noted in one patient in the clear lens extraction group and three patients in the standard care group. The incremental cost-effectiveness ratio for the clear lens extraction group versus standard care was £14,284 per QALY gained.

**Conclusions:** Early clear lens extraction resulted in greater clinical efficacy and was cost-effective compared with LPI as the initial treatment for patients with newly diagnosed PAC and elevated IOP or PACG.

IOP, Intraocular pressure; NEI-VFQ-25, National Eye Institute Visual Functioning Questionnaire 25; QALY, quality-adjusted life-year.

initial trabeculectomy. The CIGTS came on the heels of two RCTs in the United Kingdom comparing initial treatments for glaucoma: the Scottish Glaucoma Trial<sup>77</sup> and the Moorfields Primary Treatment Trial.<sup>78</sup> These studies suggested that initial trabeculectomy might be as good as any other initial treatment. The CIGTS, however, was more standardized, had a more heterogeneous patient population, and was of longer duration. Although visual function was the primary outcome, the designers of the CIGTS placed great emphasis on quality-of-life differences between the two groups. The investigators realized that even if the visual outcomes

were similar, one modality might result in better preservation of quality of life. Five-year results of the study, however, showed that to a first approximation, both groups did equally well on both the visual and quality-of-life outcomes.<sup>74,75</sup>

Although the use of MMC as an adjunct to glaucoma filtration surgery has become routine for many surgeons, the largest RCT in the area of antifibrosis agents remains the Fluorouracil Filtering Surgery Study (FFSS) (see Box 10.34.6).<sup>79</sup> The FFSS was the first multicenter clinical trial in glaucoma supported by the National Eye Institute, and it demonstrated the benefit of postoperative 5-FU injections in conjunction with trabeculectomy in eyes at high risk for failure. However, as with many reports of better efficacy of one treatment over another, one must not let the relative efficacy obscure the absolute efficacy. The 3- and 5-year success rates (defined as the “cumulative proportion of patients without reoperation or IOP failure”), 56% and 48%, respectively, for trabeculectomy with 5-FU in this group were disappointing.<sup>79</sup> Furthermore, the regimen of repeated 5-FU injections used in the study protocol is not used at all. This study did spark an interest, which continues to this day, in antifibrosis agents as adjuvants in filtration surgery.

Other important studies addressing antifibrosis agents in filtration surgery include, but are not limited to, studies by Skuta et al.<sup>80</sup> and Kitazawa et al.<sup>81</sup> Both groups performed small, RCTs comparing intraoperative MMC with postoperative 5-FU injections in eyes at high risk for filtration surgery failure and found that MMC lowered IOP more compared with 5-FU. These studies provided the rationale for MMC’s predominant role today as an adjunctive agent in glaucoma filtration surgery.

Two important RCTs have compared intraoperative 5-FU and MMC in “primary” trabeculectomies, that is, in eyes with no previous intraocular surgery. Both Singh et al.,<sup>82</sup> in a multicenter study, and Palanca-Capistrano et al.,<sup>83</sup> in a single-center study, randomized patients to either intraoperative MMC or 5-FU and concluded that both agents were equally effective.

The 5-year results of the Tube Versus Trabeculectomy (TVT) Study were published in 2012.<sup>84</sup> This multicenter RCT set out to determine whether tube shunt surgery or trabeculectomy is safer or more effective in eyes with prior ocular surgery. Patients were randomized to receive either a Baerveldt 350 mm<sup>2</sup> aqueous drainage device or a trabeculectomy with MMC 0.4 mg/mL for 4 minutes. With failure defined as IOP >21 mm Hg or not reduced by 20%, IOP <5 mm Hg, reoperation for glaucoma, or loss of light perception vision, the failure rate was lower in the tube group (30%) than in the trabeculectomy (47%) group ( $P = 0.002$ ) (see Box 10.34.7).<sup>84</sup> The results of a similarly designed multicenter RCT comparing tube versus trabeculectomy in eyes without previous surgery (The Primary Tube Versus Trabeculectomy Study) are expected to be available soon.

Another important set of multicenter RCTs were the Ahmed Baerveldt Comparison (ABC)<sup>85</sup> and Ahmed Versus Baerveldt (AVB)<sup>86</sup> studies, comparing the Ahmed FP7 glaucoma valve (AGV) implant to the Baerveldt 350 mm<sup>2</sup> glaucoma (BGI). A recent pooled analysis of the 5-year data from the ABC and AVB studies demonstrated lower cumulative failure in the BGI group (37%) compared with the AGV (49%) group ( $P = 0.007$ ), with failure defined as IOP >18 mm Hg or reduced by less than 20%, IOP <6 mm Hg, de novo glaucoma surgery, loss of LP or severe vision loss, or removal of the implant (see Box 10.34.8).<sup>85–87</sup>

The Effectiveness of Early Lens Extraction for the Treatment of Primary Angle-Closure Glaucoma (EAGLE) study was a large multicenter RCT comparing the efficacy, safety, and cost-effectiveness of clear lens extraction with those of LPI as first-line treatment in patients with newly diagnosed primary angle-closure glaucoma or primary angle closure with IOP of 30 mm Hg or greater.<sup>88</sup> The 3-year results of the study demonstrated that those randomized to early clear lens extraction had lower mean IOP, less glaucoma medication use, and higher quality of life scores compared with those receiving LPI as standard of care (see Box 10.34.9).<sup>88</sup> There were no significant differences in the rate of irreversible vision loss between the two groups. Economic evaluation of the EAGLE trial by Javanbakht et al.<sup>89</sup> suggested that early lens extraction is likely to be cost-effective over 3 years and may even become cost-saving by 10 years.

## BARRIERS TO THE PRACTICE OF EVIDENCE-BASED MEDICINE

The expanding volume of the medical literature is becoming increasingly difficult for clinicians to keep up with and apply to specific clinical situations. In a 1998 survey of general practitioners in the United Kingdom, most respondents cited lack of time as the primary barrier to practicing EBM.<sup>90</sup> Other barriers mentioned in the survey included lack of financial

gain in using EBM, lack of hard evidence, and patient expectations. A similar survey conducted in Denmark found that only 4.4% of responding hospital-based physicians could define and explain 12 commonly used EBM terms and that only 18% claimed to always practice EBM.<sup>91</sup> Many of the conclusions of these types of surveys are applicable to the ophthalmology community. Because no two patients are exactly alike, how can the practitioner be sure that the conclusions of an RCT are really applicable to the individual patient? Factors that must be considered include patient physiology, socioeconomic background, comorbidities, and risks of adverse outcomes.<sup>92</sup> As mentioned previously, because RCTs can take years to complete, the risk of their findings becoming obsolete may also deter clinicians from applying their conclusions.

How are clinicians really getting their evidence? The average practitioner will get the most exposure to evidence through secondary sources, which summarize the findings. These sources include journal editorials, the Cochrane Library, continuing medical education activities, in-clinic drug representative presentations, and “throwaway” journals. Faced with so many sources of information, clinicians seemingly are most likely to absorb the evidence that is presented in the clearest manner and is accompanied by straightforward clinical guidelines.

## FUTURE DIRECTIONS

The application of EBM to glaucoma may be improved in the future by better planning and organization of clinical trials combined with improved utilization of computers. Clinical trials in glaucoma have benefited from the organizational structure provided by such groups as the Ocular Hypertension Treatment Study Group. In the future, there may be further centralization of such groups into organizations that focus on broad glaucoma issues. The Pediatric Eye Disease Investigator Group (PEDIG) is one model of what such an organization might look like. PEDIG was created to coordinate pediatric clinical trials that feature streamlined protocols used by both academic and private practice clinicians.<sup>93</sup> The PEDIG coordinating center has made it less costly for the group to carry out multiple clinical trials in a timely and organized manner. Glaucoma research may someday benefit from similar efforts.

Neural networks make up a category of computer programs that hold promise as glaucoma clinical management tools. These networks are designed to be functionally similar to the human brain. One advantage that neural networks have over traditional programming methods is the potential to learn from prior examples. These networks also tend to use problem-solving approaches similar to those that humans use.<sup>94</sup> Lin et al.,<sup>95</sup> Bengtsson et al.,<sup>96</sup> Asaoka et al.,<sup>97</sup> and Andersson et al.,<sup>98</sup> among others, have separately had success with using neural networks to identify glaucomatous visual field defects and visual field progression. Neural networks are playing an increasing role in a broader category of computer-based tools for physicians, which are called *clinical decision support systems* (CDSSs).

The term *clinical decision support system* refers to software that is used to assist physicians with clinical decision making.<sup>99,100</sup> Glaucoma risk calculators are a type of CDSS that have been gaining increasing attention. Weinreb et al.<sup>101</sup> have discussed the potential value of a global risk calculator that would be based on variables, including age, IOP, cup-to-disc ratio, and central corneal thickness. A validated model estimating a patient’s 5-year risk for the development of POAG was subsequently developed<sup>59</sup> on the basis of the Ocular Hypertension Treatment Study and the European Glaucoma Prevention Study. This free online tool (<http://ohts.wustl.edu/risk>) calculates a patient’s 5-year risk of developing glaucoma, on the basis of the patient’s age, IOP, central corneal thickness, vertical cup-to-disc ratio, and pattern standard deviation. Glaucoma risk calculators are just one example of the many computer-based tools that may one day be available to clinicians to help with clinical decision making.

## CONCLUSIONS

Much lip service has been paid to EBM in the past few decades, but once one gets beyond the hype, the concept is valid and should be the fundamental underpinning of how we practice medicine. We should, to the best of our ability, perform tests, prescribe medications, and do procedures whose beneficial effects have been demonstrated in the literature. When information is lacking in the medical literature, the medical community should do its best, when feasible, to generate information to improve how we practice.

The last few decades have seen tremendous inroads into EBM for glaucoma treatment. In the mid-1980s, no large RCTs existed to guide practice, but today the results of several larger RCTs are available and their results



can be used daily in providing care to patients. The RCT has become our yardstick for making solid clinical decisions.

Barriers to the generation of good evidence-based information do exist. First, studies that address the important clinical questions have to be performed, and these studies must be designed and executed and their results analyzed correctly. Data from studies with negative results need to be captured, and new requirements for clinical trial registry may help in this regard. When there is more than one study on the same research question, appropriate meta-analyses need to be performed. Fortunately, such groups as the Cochrane Eye and Vision Group US are available to provide resources and expertise to guide the performance of this highly specialized task. Finally, dissemination and acceptance of findings remain daunting challenges in these times when “keeping up with the literature” is made difficult by increasing clinical volumes.

Fortunately, improvements in technology may help in the incorporation of evidence into practice. The Internet can make collaboration between multiple sites in a clinical trial easier. It has never been easier to access the medical literature, which is now, in larger part, available electronically. Computerized CDSSs may further improve the quality of clinical decisions and thus the care of patients.

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# Anatomy and Physiology of the Extraocular Muscles and Surrounding Tissues

## 11.1

Joseph L. Demer

**Definition:** Muscles and associated tissues that provide eye movements and allow for binocular vision.

## Key Features

- Unique muscle type with specialized structure, metabolism, and innervation.
- Connective tissue gimbal supporting the eyeball and regulating its rotational properties.

## EMBRYOLOGY

The development of extraocular muscles, which are of mesodermal origin, begins at 3–4 weeks' gestation.<sup>1,2</sup> Early in gestation, neural crest cells divide and encircle the mesodermal cells destined to become primary myoblasts of individual extraocular muscles, guiding them to their appropriate positions and forming their connective tissue pulleys. Later, after the myoblasts develop through the primary and secondary stages, cranial nerves migrate to them from the brain and form neuromuscular junctions. The extraocular muscles and their surrounding tissues are present, and in their final anatomic positions by 6 months' gestation, but they mature later, even after birth.<sup>1</sup>

## GENERAL STRUCTURE OF EXTRAOCULAR MUSCLES

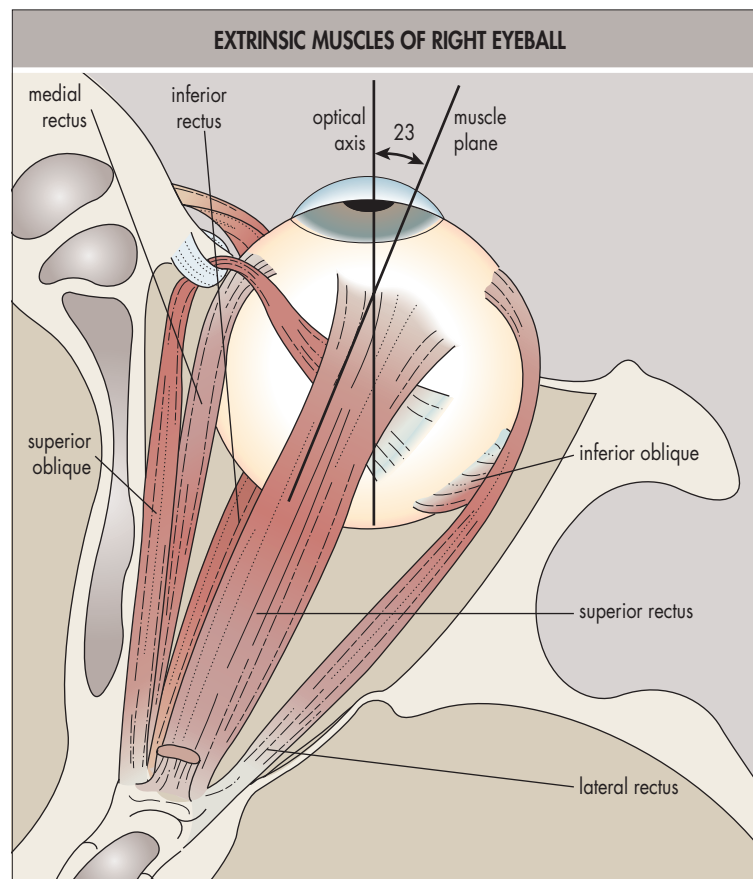
Extraocular muscles<sup>3,4</sup> and their terminal tendons<sup>5</sup> are composed of long, generally parallel fibers that transmit tension from end to end with little mechanical interaction between adjacent fibers. Each motor nerve axon in an extraocular muscle innervates only one or a few muscle fibers,<sup>1</sup> permitting extremely precise neural control of individual fibers according to their specific insertions on the sclera.

## GROSS ANATOMY OF THE EXTRAOCULAR MUSCLES

The orbits are oriented approximately 23° temporal to the midsagittal plane (Fig. 11.1.1).

### Origins of the Extraocular Muscles

All extraocular muscles except the inferior oblique originate at the orbital apex. The superior, inferior, medial, and lateral rectus muscles arise from a fibrous ring called the *annulus of Zinn*, and the optic nerve; the superior and inferior divisions of the oculomotor nerve; the abducens and nasociliary nerves; and the ophthalmic artery pass through it (Fig. 11.1.2). The superior oblique muscle arises from the orbital wall superonasal to the annulus of Zinn. The inferior oblique muscle originates from the maxillary bone in the orbital floor, adjacent to the lacrimal fossa, and posterior to the orbital rim.

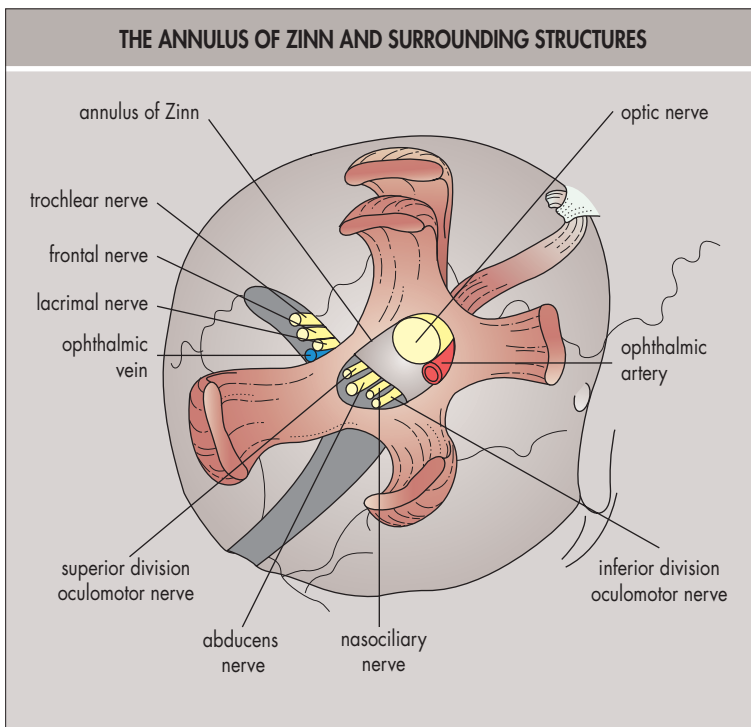


**Fig. 11.1.1** The extrinsic muscles of the right eyeball in central gaze, seen from above.

### Compartments of the Extraocular Muscles

Each of the extraocular muscles contains multiple, specialized compartments that have independent functions. Each muscle has an orbital layer and a global layer.<sup>1</sup> The global layer is oculorotatory, passing through its pulley and ultimately inserting on the sclera. The orbital layer inserts on the inner surface of its connective tissue pulley, not on the globe, so that when the muscle contracts, the orbital layer retracts the pulley along the axis of the muscle, changing the muscle's functional origin and pulling direction.<sup>6–9</sup> The orbital layer of the superior oblique muscle is concentrically located on its exterior surface and is contiguous with a connective tissue sheath surrounding the superior oblique tendon, which, in turn, represents the extension of the centrally located global layer.<sup>10,11</sup> The inferior oblique muscle also has orbital and global layers, whose possible selective functions are unknown.<sup>12</sup> Electromyographic activity in the global layer differs from the orbital layer of rectus muscles,<sup>13</sup> but the sources of differential innervation remain unknown.

An additional, transverse compartmentalization occurs in the rectus and superior oblique muscles, subserving differential function across the widths of their broad tendinous insertions. The horizontal rectus muscles have superior and inferior transverse compartments, each innervated by a



**Fig. 11.1.2** The annulus of Zinn and surrounding structures.

separate motor nerve branch.<sup>14</sup> While one motor nerve branch innervates the entire inferior rectus muscle, a separate nerve coinnervates the lateral compartment.<sup>15</sup> The trochlear nerve divides in the orbit into medial and lateral divisions, each innervating a corresponding compartment of muscle fibers.<sup>11</sup>

## Insertions of the Extraocular Muscles

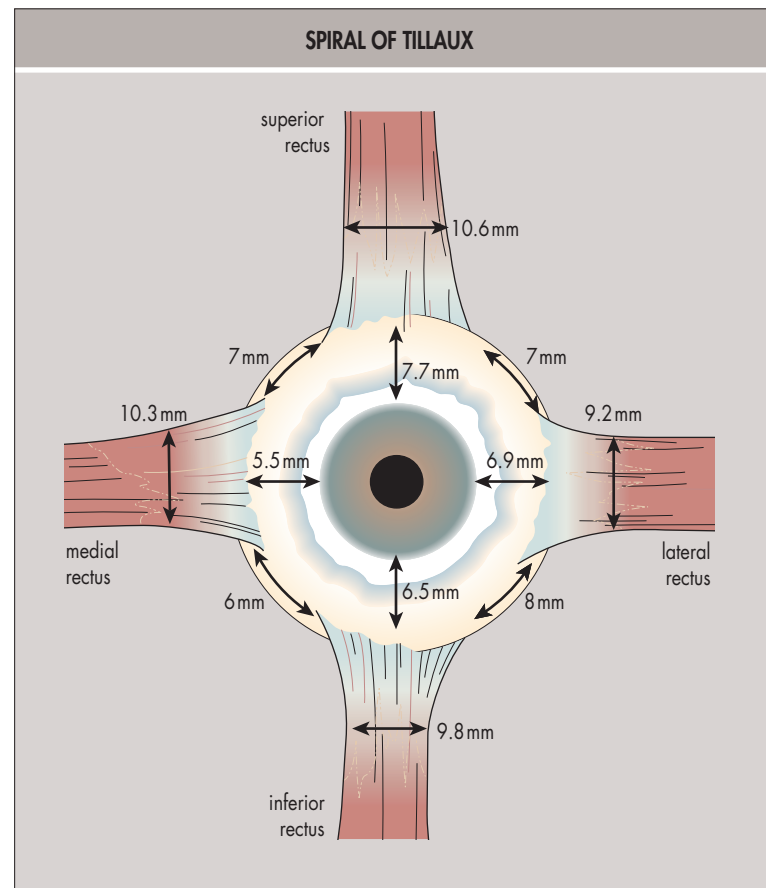
Rectus muscles transition to become tendons that insert anterior to the globe equator. The *medial rectus* inserts closest to the limbus, followed by the inferior, lateral, and superior rectus muscles in that order (MILS). The array created by connecting their insertions is called the *spiral of Tillaux* (Fig. 11.1.3).<sup>4</sup> The tendons are broad and composed of parallel fibers, so the fibers of each transverse muscle compartment insert in scleral positions corresponding to the compartment. For example, the medial rectus superior compartment acts on the superior part of the scleral insertion, whereas the inferior compartment acts about 5 mm inferiorly on the inferior part of the insertion.

The oblique muscles insert posterior to the globe equator (Fig. 11.1.4). The *superior oblique tendon* rolls into a cylindrical configuration to transit the trochlea within its sheath. Lateral to the trochlea, the sheath inserts into the nasal aspect of the superior rectus pulley, where the tendon fibers unroll into a broad, fan shape up to 18 mm wide; the lateral compartment fibers insert posterior to the equator and have a predominantly infraducting action, whereas the medial compartment fibers insert near the equator and have a predominantly incycloducting action. This distinction allows for surgical treatment of ocular torsion through manipulation of the anterior tendon fibers, such as by the Harada–Ito procedure.<sup>5</sup>

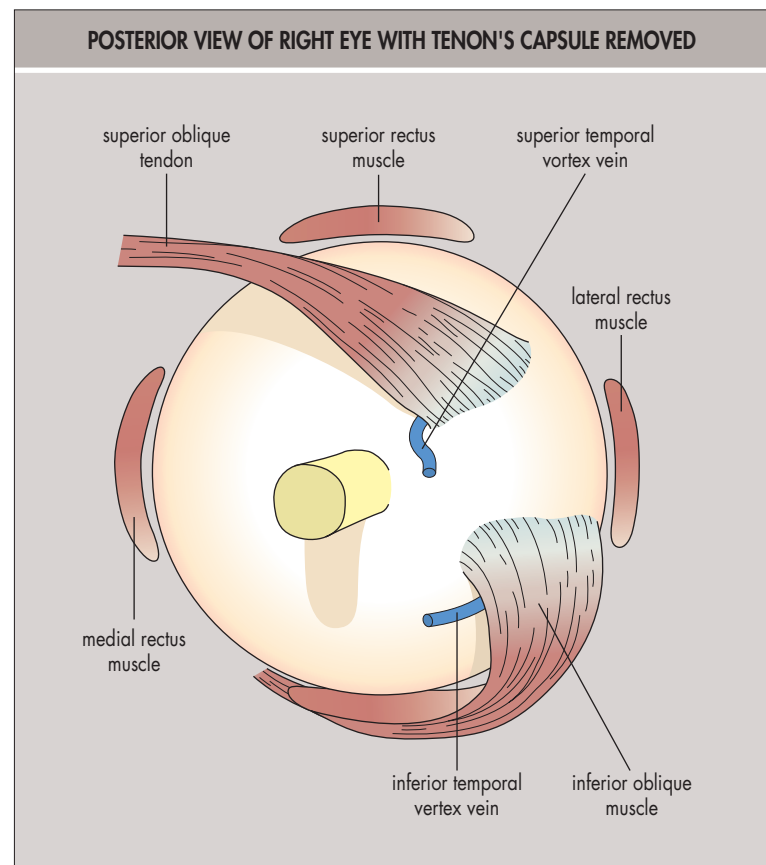
The orbital layer of the *inferior oblique muscle* inserts into the inferior rectus pulley, the inferior oblique sheath, and the inferior part of the lateral rectus pulley. The global layer inserts on the sclera in close proximity to both the macula and the inferotemporal vortex vein (see Fig. 11.1.4).

## Paths and Actions of the Extraocular Muscles

The paths of the extraocular muscles from their pulleys to their insertions determine their pulling directions; their posterior paths are relevant only to the magnitude of force generation. Through active adjustment of tensions in their orbital layers, the rectus pulley positions are maintained in positions as far posterior to globe center as their insertions are anterior to globe center. In secondary and tertiary gazes, this inflects muscle paths anterior to the pulleys so that pulling direction changes by one half of the change in eye position.<sup>9</sup> This feature of rectus muscles underlies Listing's law of ocular torsion and makes final eye position independent of the preceding sequence of horizontal and vertical rotations.<sup>8,16</sup>

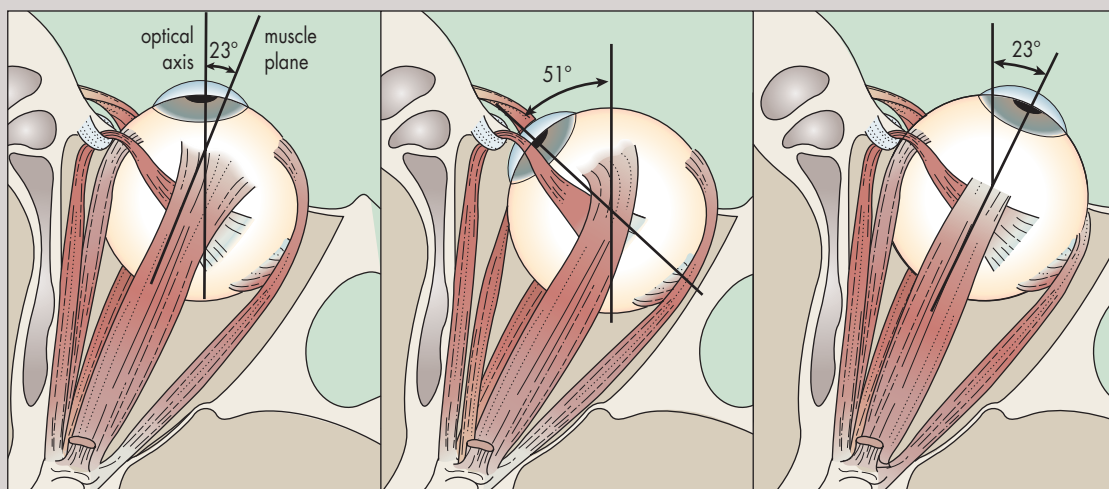


**Fig. 11.1.3** Spiral of Tillaux. The structure of the rectus muscle insertions.



**Fig. 11.1.4** Posterior view of the eye with Tenon's capsule removed. (Adapted with permission from Parks MM. Extraocular muscles. In: Duane TD, editor. Clinical ophthalmology. Philadelphia, PA: Harper & Row; 1982. pp. 1–12.)

## MAJOR ACTIONS OF THE CYCLOVERTICAL EXTRAOCULAR MUSCLES



Muscle	Primary position	Adduction	Abduction
Superior rectus	supraduction incycloduction adduction	incycloduction adduction supraduction	supraduction
Inferior rectus	infraduction excycloduction adduction	excycloduction adduction infraduction	infraduction
Superior oblique	incycloduction infraduction abduction	infraduction abduction incycloduction	incycloduction abduction infraduction
Inferior oblique	excycloduction supraduction abduction	supraduction abduction excycloduction	excycloduction abduction supraduction

**Fig. 11.1.5** Major actions of the cyclovertical extraocular muscles.

The medial rectus muscle inserts on the nasal sclera. The lateral rectus muscle inserts on the temporal sclera. The superior rectus muscle inserts on the superior sclera (see Fig. 11.1.1) and has actions depicted in Fig. 11.1.5. The superior rectus muscle courses between the tendon of the superior oblique muscle and the levator palpebrae muscle. The inferior rectus muscle inserts on the anterior globe and has actions depicted in Fig. 11.1.5. The inferior rectus muscle courses between the globe and the inferior oblique muscle. Its pulley has fascial attachments to the lower lid retractors that may lead to widening or narrowing of the eyelid fissure during inferior rectus recession or resection, respectively.

The superior oblique muscle passes through the trochlea, a rigid pulley consisting of a cartilaginous saddle attached to periorbita of the frontal bone in the superior nasal orbit. In central gaze, the superior oblique tendon forms an angle of 51° with the visual direction and has actions shown in Fig. 11.1.5. Contraction of the superior oblique orbital layer shifts the superior rectus pulley nasally during vestibulo-ocular reflexes, such as ocular counterrolling.<sup>17</sup>

The inferior oblique muscle travels through its pulley that is inferior to and partially coupled to the inferior rectus pulley<sup>18</sup> and has actions shown in Fig. 11.1.5. The inferior oblique pulley is retracted posteriorly when the orbital layer of the inferior rectus muscle contracts in infraduction but shifts anteriorly when the inferior rectus relaxes.<sup>18</sup> Shift in the inferior oblique pulley position causes its pulling direction to change by one-half of eye position, consistent with Listing's law, but contraction of the inferior oblique orbital layer shifts the inferior rectus pulley nasally and lateral rectus pulley inferiorly during vestibulo-ocular reflexes, such as ocular counter-rolling.<sup>17</sup>

## Innervation

The *oculomotor (third cranial)* nucleus is located in the midbrain. Its nerve travels through the cavernous sinus and superior orbital fissure, where it

divides into superior and inferior divisions. The superior division supplies the levator palpebrae superioris and superior rectus muscles. The inferior division supplies the medial rectus, the inferior rectus, the inferior oblique, and the ciliary ganglion. The *trochlear (fourth cranial)* nucleus originates in the midbrain and innervates the contralateral superior oblique muscle. The *abducens (sixth cranial nerve)* nucleus originates in the dorsomedial pons and innervates the ipsilateral lateral rectus muscle.

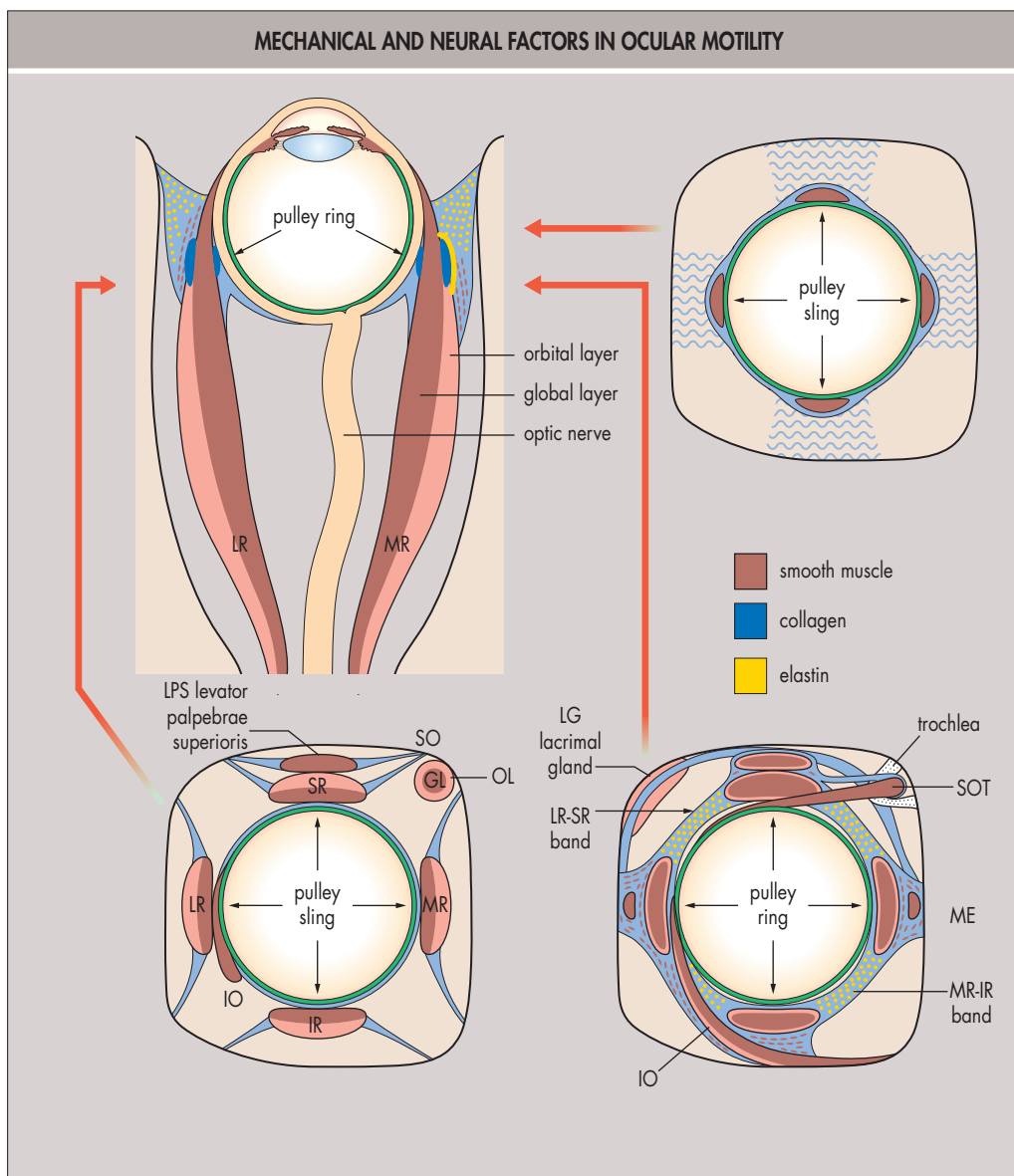
Rectus muscles are innervated from the global surface at approximately the junction of the middle and posterior third of each muscle. The inferior oblique muscle receives its innervation at the lateral border of the inferior rectus pulley.<sup>18</sup> The superior oblique muscle is innervated from its superolateral surface in the deep orbit.<sup>9</sup> Separate compartmental branches of each motor nerve divide from the main trunk posterior to the entry point in each extraocular muscle and further arborize on the global surface before traveling anteriorly to selectively enter each compartment of muscle fibers.<sup>15</sup>

## Blood Supply

The *ophthalmic artery*, a branch of the *internal carotid artery*, supplies the extraocular muscles. The lateral rectus muscle is supplied by the *lacrimal artery*, a branch of the *ophthalmic artery*. The inferior rectus muscle and inferior oblique muscles are supplied by the *infraorbital artery*, a branch of the *internal maxillary artery*, arising from the *external carotid artery*. The *anterior ciliary arteries* that supply the anterior segment of the eye travel within the rectus muscles and enter the sclera just anterior to the rectus insertions, anastomosing with conjunctival vessels at the limbus and joining the *major arterial circle of the iris*. The oblique muscles do not convey circulation to the anterior segment.

Surgical disinsertion of rectus muscles permanently interrupts the anterior ciliary arteries. If surgery is performed on multiple rectus muscles simultaneously, anterior segment ischemia may result, as discussed





**Fig. 11.1.6** The orbital pulley system. (Adapted from Demer J. Current concepts of mechanical and neural factors in ocular motility. *Curr Opin Neurol* 2006;19:4–13.)

further in Chapter 11.13.<sup>19</sup> The superior and inferior orbital veins drain the extraocular muscles.

## THE ORBITAL INFRASTRUCTURE AND ANATOMY

*Tenon's capsule* is a fibroelastic membrane that begins 1 mm from the limbus, where it is fused with the conjunctiva; it then caps the globe posteriorly to the optic nerve.<sup>14</sup> Its inner surface is smooth, which allows free gliding of the adjacent structures within it. Its equatorial region is penetrated by the extraocular muscles at their pulleys.<sup>6</sup>

Tenon's capsule thickens at and posterior to the equatorial region, where it forms a socket and is penetrated by the extraocular muscles.<sup>6</sup> At the site of penetration, a sleeve is formed around the penetrating extraocular muscle with increasing cross-linked collagen and elastin. This sleeve has significant fibroelastic attachments to the periorbita and adjacent sleeves (Fig. 11.1.6). These sleeves create compliant pulleys that redirect the extraocular muscles and act as functional origins.<sup>6,8,20</sup> The pulleys are posterior to the equator of the globe with total anteroposterior extents of 13–19 mm, although it is likely that only the middle 5–8 mm of this extent is mechanically stiff.<sup>6</sup> The pulley sleeves contain collagen, elastin, and innervated smooth muscle. The sleeves extend both anteriorly and posteriorly from the site of maximal pulley effect to form slings that stabilize the extraocular muscle paths through fibroelastic attachments to periorbita and surrounding slings (see Fig. 11.1.6).

The inferior part of the pulley system is a connective tissue sling, called the *suspensory ligament of Lockwood*,<sup>21</sup> and contains the inferior oblique pulley.<sup>18</sup> Tenon's capsule thins posteriorly, allowing free movement of the

penetrating optic nerve and vessels with globe movement. Each muscle is surrounded by a thin, fibrous muscle capsule throughout its extent.

## CLINICAL CORRELATES

Magnetic resonance imaging (MRI) has shown that pulley issues are important in strabismus.<sup>8,22,23</sup> Congenital rectus pulley malposition may produce “A” patterns (superior location of lateral rectus pulley relative to medial rectus pulley), “V” patterns (inferior location of lateral rectus pulley relative to medial rectus pulley), and incomitant hypertropia.<sup>22,24</sup> Pulley instability (e.g., produced by surgical damage or connective tissue disease) may result in an incomitant strabismus.<sup>25</sup> Pulley damage resulting in failure of pulley retraction during muscle contraction produces incomitant strabismus by restricting posterior movement of the muscle insertion.<sup>25</sup> Posterior fixation (in German *faden*, meaning “thread”) surgery works by limiting posterior pulley excursion.<sup>26</sup> The muscle pulleys redirect the rectus muscles and limit the effect of transposition surgery,<sup>27–29</sup> lessening the effective change in pulling direction that would occur if such structures were not present. Severing of the intermuscular septal connections is not necessary for rectus recession.<sup>30</sup> Posterior dissection may result in pulley damage.

## EXTRAOCULAR MUSCLE PHYSIOLOGY

Extraocular muscles are unique because of their highly specialized combination of muscle cells, which have unique structural and metabolic properties.<sup>1</sup> The oculorotatory global layer is dominated by fast twitch-generating singly innervated fibers (SIFs) with exceedingly fine motor unit size (one axon per muscle fiber). This allows for large, rapid, precise movements.

**BOX 11.1.1 Agonist–Antagonist Pairs (in the Same Eye)**

Medial rectus–lateral rectus  
 Superior rectus–inferior rectus  
 Superior oblique–inferior oblique

Orbital layer SIFs are specialized for intense oxidative metabolism, have a larger blood supply, and are fatigue resistant, allowing for more sustained pulley tension. Extraocular muscles are luxuriantly perfused, with even greater vascularity in the orbital than global layers.<sup>31</sup>

**Hering's and Sherrington's Laws**

Rotation of one eye is termed *duction*. During duction, contraction of one extraocular muscle normally results in simultaneous relaxation of its antagonist in the same eye. Agonist–antagonist pairs are listed in [Box 11.1.1](#). This relationship between agonist–antagonist pairs in one eye is termed Sherrington's law of reciprocal innervation. In Duane's retraction syndrome, Sherrington's law is violated because of cocontraction of the medial rectus and lateral rectus muscles during adduction.<sup>32</sup>

Rotation of both eyes in the same direction is termed *version*. During version, the muscles of both eyes make an equal effort to rotate them to the same gaze angles (Hering's law).<sup>33</sup> These paired agonists are called yoke muscles ([Box 11.1.2](#)). Hering's law explains the findings of primary and secondary deviations in paralytic strabismus. Innervation to the yoke muscles is always determined by the fixing eye. When the normal eye fixates, the resultant strabismus is termed *primary deviation*. When the paretic eye fixates, the resultant strabismus is larger and termed *secondary deviation*. Note that a version is composed of duction in each eye, so Sherrington's law also applies. Dissociated vertical and horizontal deviations violate Hering's law. Vergences are rotations of the two eyes in opposite directions and may be physiological as in the case of convergence to view

**BOX 11.1.2 Paired Agonists (in Opposite Eyes)**

Left medial rectus–right lateral rectus  
 Left lateral rectus–right medial rectus  
 Left superior rectus–right inferior oblique  
 Left inferior rectus–right superior oblique  
 Left superior oblique–right inferior rectus  
 Left inferior oblique–right superior rectus

near targets where yoked muscle contraction and relaxation have historically been considered symmetrically reciprocal in each eye, although evidence of some co-contraction is emerging.

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# Evaluating Vision in Preverbal and Preliterate Infants and Children

## 11.2

Kyle E. Miller, David B. Granet, Gary R. Diamond<sup>†</sup>

**Definition:** Visual acuity in preverbal infants is defined as a motor or sensory response to a threshold stimulus of known size at a known testing distance. Visual acuity in preliterate but verbal children is described as the smallest target of known size at a known testing distance correctly verbally identified by a child.

### Key Features

- In preverbal children, visual acuity may be quantified by a motor response (optokinetic nystagmus testing, forced choice preferential looking) as well as by a sensory response (visual evoked responses).
- In preliterate but verbal children, visual acuity may be quantified by verbal or motor identification of graded non-Snellen optotypes (Landolt rings, HOTV test, tumbling E test).

### INTRODUCTION

Vision screening begins in infancy and progresses to figure or letter (optotype) acuity testing by age 4 years. The American Academy of Pediatrics, the American Academy of Ophthalmology, and the American Association for Pediatric Ophthalmology & Strabismus have put forth a consensus statement regarding the evaluation of vision in children. This statement recommends attempting optotype acuity testing (standardized figures or letters) in cooperative 3-year-olds, and then repeating yearly.<sup>1</sup> Specialized techniques for visual acuity quantification are necessary when evaluating children younger than 3–4 years of age. These techniques include observation, fixation targets, optokinetic nystagmus, visual evoked potentials, forced-choice preferential looking, specially constructed graded optotypes, and digital photoscreeners.

### HISTORICAL AND OBSERVATIONAL TECHNIQUES

Much can be learned from the historical descriptions of a child's visual behavior from family members. Parents or caregivers are asked routinely whether the child responds to a silent smile, enjoys silent mobiles, and follows objects around the environment. Pertinent observations include strabismus, nystagmus, persistent staring, and inattention to objects. A younger sibling's visual behavior may be compared with that of an older child.

The pupillary light response is not equivalent to visual ability, but its presence indicates intact afferent visual neurological pathways to the level of the brachium of the superior colliculus and efferent pathways to the iris sphincter. This reflex is present in premature babies with gestational age between 30 and 32 weeks.<sup>2</sup> Visualization in very young children sometimes requires a magnifying glass, as their pupils are smaller than those of older children (decreased sympathetic tone), and the light responses are of small amplitude. Dilatation to direct illumination (paradoxical pupillary response) has been described in Leber's congenital amaurosis, optic nerve hypoplasia, congenital achromatopsia, and congenital stationary night blindness.<sup>3</sup> Nystagmus, a sign of binocular visual impairment, is absent

in cortical blindness<sup>4</sup> and often is not found in association with unilateral visual defects.

The blink to a bright light is a response noted by 30 weeks of gestational age and occasionally is present in decorticate infants. The blink to a threatening gesture is another reflex, usually present by 5 months; however, care must be taken to not push air against the child's corneas and elicit a blink by that mechanism.

### FIXATION TARGETS

Visual fixational abilities may be demonstrated in full-term newborns by using a high-contrast target. A flashlight is a poor target because it has no edges; stripes, dots, or checkerboards are preferred. Full-term infants younger than 3 months of age "follow" a small target by using hypometric saccades<sup>5</sup>; these infants may generate smooth pursuit movements to a large target, such as an optokinetic drum. Vertical saccades become identifiable by about 2 months of age, and prior to that horizontal saccades can be seen. Because saccadic palsies are common in young children who have central nervous system damage, spinning an upright child demonstrates the presence of saccades as the rapid recovery phase of the spin-induced nystagmus. If no rapid phase can be stimulated, the child's vision cannot be evaluated by his or her ability to "follow" a small target, as neither a saccadic nor a smooth pursuit system is yet available. In addition, a child who has normal fixational behavior should dampen spin-induced nystagmus in 3–5 seconds; a blind or poorly sighted child cannot use fixational dampening and beats for 15–30 seconds until mechanical dampening occurs.

In slightly older children, small, colorful, familiar toys generate the best, albeit often momentary, interest. Two methods of evaluating visual acuity using toys is with "Fix & Follow" (F&F) or "Central, Steady, & Maintained" (CSM) testing. For F&F testing, a small toy or fixation target is moved slowly in front of the child to observe the child's fixation and motility. Asymmetry in monocular testing can give an indication of amblyopia. CSM notation provides information regarding potential eccentric fixation (central), ocular motility or nystagmus (steady), and ability to keep fixation (maintained).

### OPTOKINETIC NYSTAGMUS

Evaluation of optokinetic nystagmus was the first "technological" approach to acuity measurement in preverbal children; square-wave gratings (alternating black and white stripes with sharp, distinct interfaces) placed on arcs were moved across an infant's visual field.<sup>6</sup> Standardized drums that contain stripes that subtend small fractions of the infant's visual field are available (Fig. 11.2.1) but often do not hold interest, are spun at varying and uncalibrated rates, and are bathed in variable illumination. When determination is performed binocularly, full-term infants have approximately 20/400 (6/120) acuity at birth. This method measures acuity by means of an ocular motor response technique, but using this can result in underestimation of the acuity in some children who have disturbed oculomotor systems. The horizontal saccadic system is present at term birth, whereas the vertical saccadic system does not develop until 4–6 weeks later.

### VISUAL EVOKED POTENTIALS

On the basis of the observation that visual stimuli yield a measurable electroencephalographic pattern received by occipital scalp electrodes, various methods, which include the use of bright-flash stimuli, square-wave gratings, and phase-alternating checkerboards, have been employed to evaluate

<sup>†</sup>Deceased



**Fig. 11.2.1 Optokinetic Drum Testing.** The movements of the patient's eyes are examined while they fixate on the moving stripes of the drum.



**Fig. 11.2.2 Evoked Potential Test.** The occipital electrodes are placed in position.

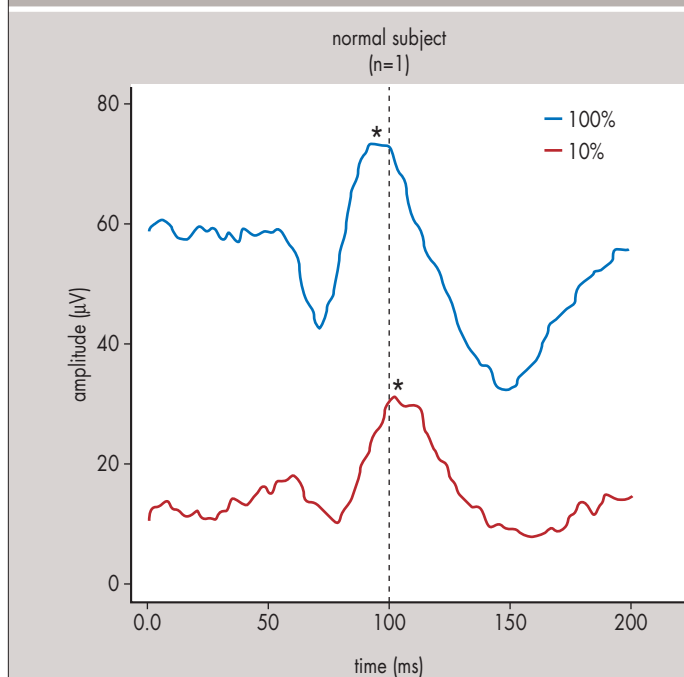


**Fig. 11.2.3 Checkerboard pattern for evoked potential test.**

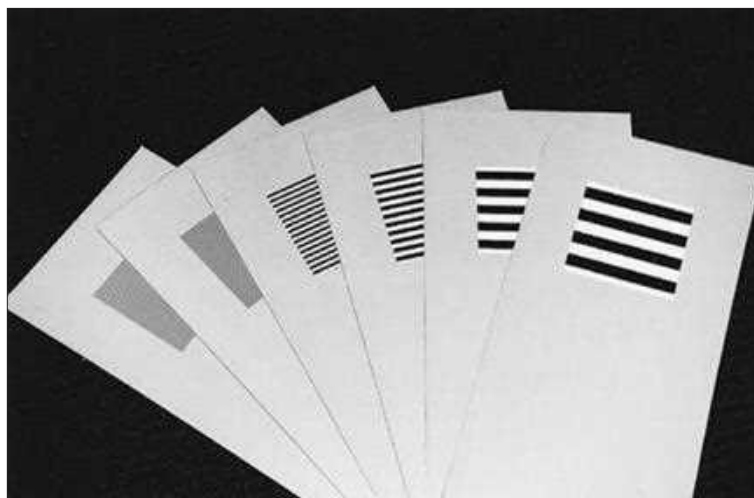
acuity. Only the last two targets can be calibrated. Many investigators using visual evoked potentials have found 20/200 (6/60) acuity in full-term newborns.<sup>7</sup> Acuity of 20/20 (6/6) may be demonstrated by 6–12 months, considerably before the age indicated by optokinetic nystagmus testing, perhaps reflecting that this electrophysiological test evaluates acuity by direct recording of sensory afferents, the only test to do so.

Visual evoked potential testing (Figs. 11.2.2 through 11.2.4) can be used to evaluate acuity in children with aphakia,<sup>8</sup> amblyopia,<sup>9</sup> or strabismus and in those who have large refractive errors. Although the test directly evaluates vision by means of a sensory process, a waveform of normal appearance has been recorded in the occasional decorticate infant who later behaves as if blind, which implies a subcortical contribution; the

#### WAVEFORM OF TYPICAL VISUAL EVOKED POTENTIAL



**Fig. 11.2.4 Waveform of Typical Visual Evoked Potential.** The amplitude of the major positive wave and elapsed time from stimulus onset to this wave are the most important features of the visual evoked potential. (From Thurtell MJ, et al. Evaluation of optic neuropathy in multiple sclerosis using low-contrast visual evoked potentials. *Neurology* 2009;73(2):1849–57.)



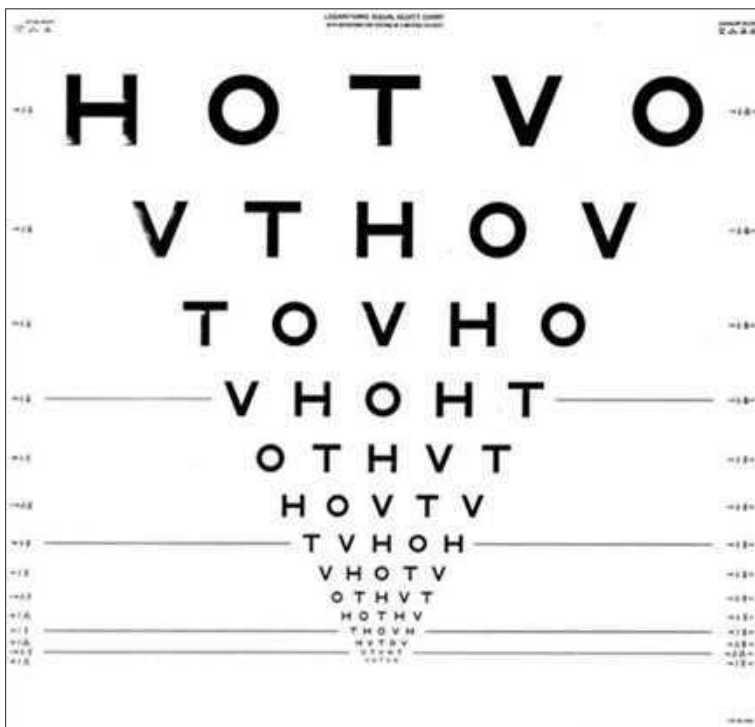
**Fig. 11.2.5 Teller acuity cards.** (Copyright© 2012 American Foundation for the Blind. All rights reserved.)

exact origin of the response remains unknown.<sup>10</sup> As the response waveform changes markedly between 1 and 6 months, care must be taken to compare waveforms with those of age-matched controls.

#### FORCED-CHOICE PREFERENTIAL LOOKING

This behavioral technique is based on the observation that infants prefer to view a pattern stimulus rather than a homogeneous field.<sup>11</sup> Using flat, calibrated, square-wave gratings, this tendency may be observed by a trained individual.<sup>12</sup> As with the optokinetic nystagmus test results, a full-term newborn differentially responds to 20/400 (6/120) gratings; the response to 20/20 (6/6) gratings occurs at 18–24 months.<sup>13,14</sup> A smaller and simpler apparatus, with the target presenter unmasked, has been devised; this is more suitable for clinical applications (Fig. 11.2.5).<sup>15</sup> Further, use in the clinical examination office has been validated with the simple use of free cards.

The child must be alert and able to generate neck and eye movements, which disqualifies many whose hypotonia and inattention prevent such



**Fig. 11.2.6** HOTV test. (From Hartmann EE, et al. Preschool vision screening: Summary of a task force report. *Pediatrics* 2000;106(5):1105–6.)

purposeful movement—a significant limitation in the evaluation of developmentally delayed infants. Thus, as with the optokinetic nystagmus technique, vision is evaluated by means of a motor response. In addition, this test presents a resolution acuity task, not a recognition acuity task, and thus may be less ideal for the detection of amblyopia than the visual evoked response test.<sup>16,17</sup> However, the testing cards are simple, are portable, and cannot lose calibration. Evidence exists of experiential effects, and because the cards can be presented with the stripes in one orientation (vertical) only, the acuities of some children with optically uncorrected astigmatism may be estimated erroneously when using this technique.<sup>18</sup> Children who have nystagmus may be more difficult to test, but shifting the cards 90° to the direction of the nystagmus can help. Additionally, those who have visual field defects may have difficulty finding the targets.

## GRADED OPTOTYPES

Rarely, children as young as 18 months can respond to Snellen optotypes, but it is uncommon for children younger than 4.5 years to read a standardized Snellen acuity chart reliably—despite their parents' confidence. Tests useful in the age range 2–5 years include Allen pictures, Lea symbols, Landolt ring test, the HOTV test, and the tumbling E test.<sup>2</sup>

Allen pictures and Lea symbols allow for testing acuity by using familiar pictures. Allen pictures include horse, cake, car, and bird, among others, and there are four Lea symbols: circle, square, house, and apple. Both have good correlation with Snellen acuity and can be performed using a matching card thereby decreasing the age at which children successfully complete the testing.

The HOTV test requires pattern recognition and matching of progressively smaller optotypes with those on a handheld card. These letters are chosen to be of average recognition difficulty and have a vertical axis of symmetry, which obviates right–left confusion common in this age group. An advantage is the exact correspondence of the target to the graded Snellen optotypes (Fig. 11.2.6).

Landolt rings are discontinuous circles; the child points to a similar ring on a handheld card. The test often confuses the younger child and perhaps is more useful for use in illiterate adults; however, its direct correspondence to Snellen is an advantage. The tumbling E test requires matching orientation of the letter “E” with a figure or the child's fingers; unfortunately, right–left disorientation is common in this age group, limiting the usefulness of this test. Its major advantage is the direct correspondence to graded Snellen optotypes.

**TABLE 11.2.1** Visual Acuity of Infant Eyes

Test	2 Months	4 Months	6 Months	1 Year	Attainment (months)
Opticokinetic nystagmus test	20/400	20/400	20/200	20/80	24–30
Forced choice preferential looking test	20/400	20/200	20/200	20/50	18–24
Visual evoked response test	20/200	20/80	20/60–20/20	20/40–20/20	6–12

## Digital Photoscreening

The use of a photoscreening device was first introduced in the 1970s; however, the introduction of digital technology has increased its use. The first digital photoscreener with on-site result interpretation was introduced in the late 1980s by a team led by David Granet at the University of California San Diego. Several versions now exist, with the most common one using infrared photography to obtain an image of each eye, and the image is analyzed for amblyogenic risk factors. These devices allow for screening of children as young as 6 months of age and are recommended to be used at the 12-month, well-child visit and annually thereafter until acuity can be tested directly.<sup>1</sup>

## MATURATION OF VISUAL ACUITY

Although the central cones function by full-term birth, acuity as measured by the preceding techniques does not approach 20/20 (6/6) until 6–30 months, depending on the examination technique (Table 11.2.1). Reasons for this delay include the incomplete development and specialization of photoreceptors, maturation of synapses in the inner retinal layers, myelination of the upper visual pathways, and maturation of the ciliary body. Foveal cones do not attain adult appearance until 4 months after full-term birth,<sup>19</sup> and true visual pathway myelination continues until 2 years of age.<sup>20</sup> Interestingly, ambient illumination increases the rate of visual system myelination.<sup>21</sup>

Occasionally, infants fail to develop visual fixational abilities until they are 6–12 months of age, but at a later age, they develop normal visual behavior, termed *delayed visual maturation* (DVM). These children, often small for gestational age or developmentally delayed, have a normal or sluggish pupillary response, no nystagmus, and normal globe structure and present challenges to the clinician. The electroretinography result is normal; the visual evoked response has been reported variously as normal,<sup>22</sup> reduced in amplitude, or absent.<sup>21</sup> These children are postulated to have a cortical synaptic developmental delay. No clear explanation exists for children who have normal visual evoked response test results but present with visual inattention and other aspects of this syndrome. The parents are reassured and the child is examined frequently during this period until visual attention reaches the expected level.

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# Examination of Ocular Alignment and Eye Movements

Faruk H. Örgü, Gary R. Diamond<sup>†</sup>

# 11.3



IN THIS CHAPTER  
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## Definitions:

- *Phoria*: a latent visual axis deviation held in check by fusion.
- *Tropia*: a manifest visual axis deviation (also known as *strabismus* or *squint*).
- *Intermittent tropia*: an intermittent visual axis deviation that may exist only in certain gaze positions and target distances or when the fusion is altered (when person is ill, tired, etc.).
- *Ductions*: monocular movements into various gaze positions; each eye views in the same direction.
- *Versions*: synchronous simultaneous movements of the two eyes in the same direction.
- *Vergences*: binocular eye movements into opposite gaze directions.
- *Primary position*: position of the eyes when looking straight ahead with body and head erect.

## Key Features

- Alignment of the visual axes can be evaluated by objective and subjective clinical methods.
- Evaluation of eye movements can be accomplished by objective and subjective techniques.
- Patients who have mechanical limitations of eye movements can be evaluated, if the patient is cooperative, in an outpatient setting by using forced-duction testing and active force-generation testing.

## EVALUATION OF OCULAR ALIGNMENT

### Introduction

The clinician evaluating ocular alignment must first decide what information is required—the eye alignment during everyday binocular viewing, or the maximal deviation of the visual axes under conditions of disrupted binocular vision, or both. Subjective methods are useful in cooperative, communicative older patients, but objective methods must be used in younger patients or those less cooperative. Finally, some testing methods are useful only under research laboratory conditions.

### Laboratory Methods

Most laboratory tests are objective. The absolute position of the eye in space may be determined by measurement of the quantity of light reflected by the sclera of a deviated eye. The electro-oculogram (EOG) is generated by alterations in direct current between the front and back of the eye as the eye rotates; this voltage change is detected by suitably placed electrodes. Finally, insulated wire placed in a silicone rubber limbal annulus (eye coil) generates a current in response to a magnetic field; this very precise technique is limited by irritation caused by the device but may be used to detect horizontal, vertical, and torsional changes in eye position.

### Clinical Methods

The examination of the patient starts as soon as the patient enters the clinic. The way the patient moves, interacts, and navigates around the room and the presence or absence of anomalous head positioning should be evaluated, especially when the patient is comfortable in his or her own setting. In the examination room, the patient may be stressed enough to hide such problems as intermittent strabismus and phorias. Ideally, the clinician should accompany the patient from the waiting room to the examination chair and carefully note the position of the patient's head when it is mobilized in free space. Anomalous head positions may indicate restrictive or paralytic strabismus, the presence of a null point in a patient who has nystagmus, or alphabet-pattern strabismus. But it also can be present in other conditions, such as refractive errors, neck musculoskeletal system anomalies, and so on. Usually, a patient places the head in a position that provides comfortable single binocular vision for the straightened view, but occasionally the head is placed to separate diplopic images maximally or to suppress the less desired second image. The examiner must distinguish head turns, tilts, and vertical head positions and attempt to quantitate these to within 5°.

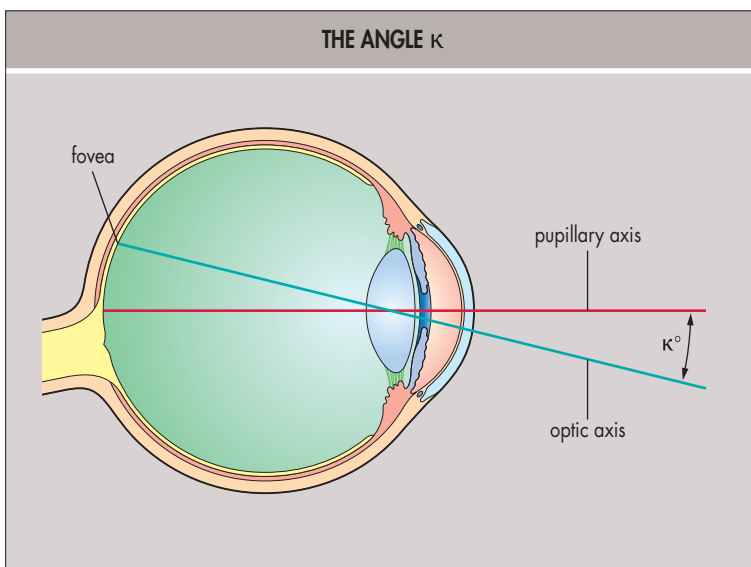
Once the patient is seated in the examination chair, the patient's lid position is noted; lid asymmetry is usually present in patients who have vertical strabismus. In cases of hypotropia, there is often associated pseudoptosis of the eyelid because of the downward rotation of the eye. Once the eye is straightened, the lid is no longer ptotic. Other soft tissue and bone structures that surround the eye may give false impressions about ocular alignment to the patient's family and the examiner. Epicanthal skin folds that extend over the nasal sclera in a small child may simulate esotropia; this is noted by parents, particularly in pictures and/or when the child looks with a head turn. Unilateral or asymmetrical lower lid retraction may give the impression that one eye is higher than the fellow eye. Vertical displacement of an orbit may simulate vertical strabismus, and hypertelorism may simulate exotropia. The examiner can diagnose strabismus only after the appropriate alignment testing has been performed.

The optic axis can be determined accurately only with alignment of the Purkinje images with a coaxial light through a telescope; this light intersects the retina between the disc and the fovea.<sup>1</sup> For clinical purposes, the optical axis may be assumed to strike the fovea. An observer considers the eye as viewing along its *pupillary axis*, a line through the pupillary center perpendicular to the cornea. The visual axis outside the eye is usually nasal to the pupillary axis ("positive angle Kappa ( $\kappa$ )") at an average angle of 5° in emmetropic eyes, 7.5° in hyperopic eyes, and 2° in myopic eyes (Fig. 11.3.1).<sup>2</sup> In some myopic eyes, the visual axis is temporal to the pupillary axis, which gives a "negative angle  $\kappa$ ." In some children who have cicatricial retinopathy of prematurity, the fovea is dragged temporally, which results in large positive angle  $\kappa$  and pseudo-exotropia.

### Objective Clinical Methods

Objective clinical methods to determine and measure deviations of the visual axes include corneal light reflex tests, cover tests, and haploscopic tests (i.e., synoptophore, etc.). These tests do not require any response by the patient and thus are independent of the patient's ability to interpret the testing environment.

<sup>†</sup>Deceased



**Fig. 11.3.1 The Angle  $\kappa$ .** This is the displacement in degrees of the pupillary axis from the optical axis. The positive angle  $\kappa$  provides the illusion of exotropia in this left eye.

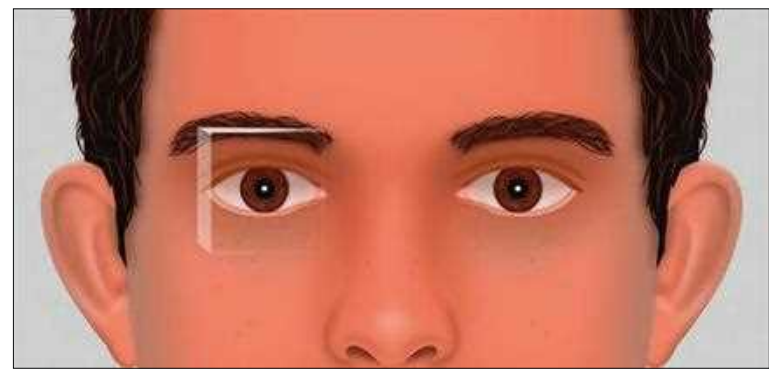


**Fig. 11.3.2 Hirschberg Light Reflex Method.** The patient has a left esotropia. Note the corneal light reflex at the temporal pupillary border of the left eye while the reflex is centered in the pupil of the right eye.

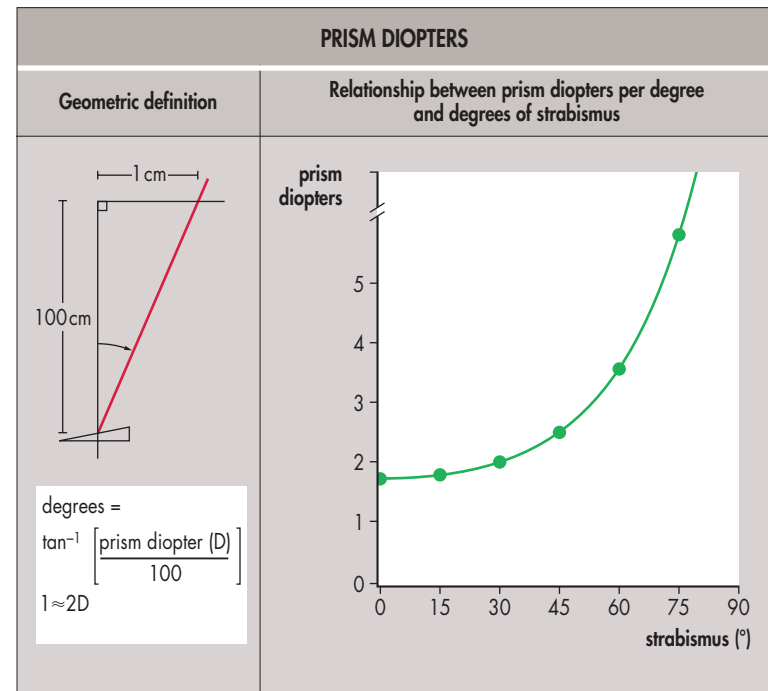
### Corneal Light Reflex Tests

Corneal light reflex tests, the oldest testing methods, are suitable for all patients. They do not take into account the angle  $\kappa$  and do not require both eyes to discern a fixation target or to be able to move into a given position to take up fixation of the target. The Hirschberg method relies on a pupil size of 4 mm and assumes each millimeter of light displacement across the cornea is equivalent to  $7^\circ$  of decentration or  $15\Delta$ . A light reflection signifies a  $15^\circ$  or  $30\Delta$  deviation at the pupillary border (Fig. 11.3.2), a deviation of  $30^\circ$  or  $60\Delta$  at the midiris, and a deviation of  $45^\circ$  or  $90\Delta$  at the limbus. Studies indicate that 1 mm of light displacement is equal to  $18^\circ$  of strabismus, and  $21^\circ$  if referred to the frontal plane by photographic techniques.<sup>3</sup> The test should be performed with the light centered in each eye's pupil to detect the presence of secondary deviations (see later). The disadvantages of this test are the estimations necessary to measure the eye deviation and the inability to control accommodation when testing at near fixation because the measuring light serves as the fixation target. Distance testing is difficult because of the dimness of the target light reflected in the corneas. The test again requires pupils to be 4 mm, and will give wrong estimations if the pupil size is drastically different from 4 mm.

The Krimsky test quantifies the light reflex displacement using appropriately held prisms. The original description suggested placing the prism before the aligned eye (Fig. 11.3.3), but most users today find it easier to hold the prism before the deviating eye.<sup>4</sup> The results are identical unless a secondary deviation (measurement taken with the paretic or mechanically restricted eye fixing) exists. An arc perimeter may be used to measure larger deviations by alignment of a light in the deviated eye, with the deviation read in degrees from the arc perimeter scale. The Maddox tangent scale at 3.3 ft (1 m) or 16.5 ft (5 m) testing distance may be used in a manner similar to that with the arc perimeter. Using the major amblyoscope, a light may be projected on each cornea and the tubes moved to center the light reflexes.



**Fig. 11.3.3 Krimsky Light Reflex Method (Same Patient as in Fig. 11.3.2).** The strength of a base-out prism over the fixing right eye sufficient to center the pupillary light reflex in the esotropic left eye is defined as the amount of left esotropia.



**Fig. 11.3.4 Prism Diopters.** Geometric definition of the prism diopter, a tangent function. The relationship between prism diopters per degree and degrees of strabismus is nonlinear ( $90^\circ$  represents an infinite number of prism diopters).

Prisms must be appropriately handled to yield accurate measurement of strabismus (Video 11.3.1).<sup>5</sup> They deflect light toward the base, but the patient views the light as deflected toward the prism apex. The prism diopter is defined as the strength of prism necessary to deflect a light beam 0.4 inches (1 cm) at 3.3 ft (1 m) distance (Fig. 11.3.4). As a tangent function, the prism diopter is not linear and increases in size as the deviation increases, but for small deviations  $1^\circ$  approximates  $1.7\Delta$ . Glass prisms are manufactured rarely today but are calibrated to be held in the Prentice position with the back-surface perpendicular to the visual axes. Plastic prisms, whether loose or in bar form, must be held with the rear surface in the frontal plane to approximate closely the position of minimal deviation of light through the prism. Prisms cannot be stacked base to base, as the sum prism strength is much greater than the sum of the individual prism strengths, but they may be stacked with bases  $90^\circ$  apart. Large deviations are best neutralized with the prisms divided between the two eyes. For measurements when patients view in eccentric gaze positions and in those undergoing the head tilt test, care is required to ensure that the prisms are held in the frontal plane.

### Cover Tests

These objective tests detect and measure horizontal and vertical strabismus, but they cannot measure torsional deviations and detect only some and not all torsional deviations. All cover tests demand the ability of each eye to discern the fixation target and to move to take up fixation upon that target.

The cover test detects tropias—constant visual axis deviations. The examiner observes the uncovered eye for movement as its fellow is







See clip:  
11.3.2  
to  
11.3.5

covered with a paddle, thumb, or remote occluder (Video 11.3.2). Nasal movement implies exotropia (Video 11.3.3), temporal movement esotropia (Video 11.3.4), upward movement hypotropia, and downward movement hypertropia (Video 11.3.5) of the uncovered eye.<sup>6</sup> Each eye is covered in turn. An accommodation-controlling fixation target of about 20/40 (6/12) size is presented to the patient, who ideally describes the target (Video 11.3.1). Small toys are suitable to be used in young children, but bright white lights are avoided because these patients cannot accommodate on the contours of a light. Tropias established by the cover test may be measured by using the simultaneous prism and cover test; a prism of appropriate strength held in the appropriate direction is introduced before one eye as its fellow is covered. Prism strength is increased until eye movement ceases; this prism strength corresponds to the size of the strabismus (Videos 11.3.6 and 11.3.7). The test is then repeated with the prism before the other eye.



See clip:  
11.3.6  
and  
11.3.7

The uncover test requires observation of the covered eye as the cover is removed (Video 11.3.2). If that eye is deviated under cover, it may regain fixation or may remain deviated. The former implies the presence of *phoria*, a latent deviation held in check by sensory fusion, or *intermittent tropia* (Video 11.3.8); the latter implies tropia with fixation preference for the fellow eye (Video 11.3.2).



See clip:  
11.3.2  
and  
11.3.8

Phorias may be detected more directly by using the alternate cover test, in which each eye is occluded alternately to dissociate the visual axes maximally. Care must be taken to permit time for each eye to reside behind the cover (the cover must not be “fanned” before the eyes) (Video 11.3.9). Appropriately held prisms enable quantitation of the phoria or the tropia (Video 11.3.6). Some patients have poorly defined endpoints and a range over which eye movements shift from one direction to the opposite as prism strength is increased; the strabismus measurement may be estimated as the midpoint between clearly defined movements in each direction. For most clinical purposes, measurements within 2 D are sufficiently accurate. Cover test measurements are influenced by the presence of eccentric fixation; its presence must be investigated in patients who have severe amblyopia.



See clip:  
11.3.6  
and  
11.3.9

The eye behind the prism should be the “fixing” eye. If the cause of strabismus is paralytic or restrictive, patients may have greater cover test measurements when the paretic or restricted eye fixes in a given gaze position (secondary deviation) than when the sound eye fixes (primary deviation). This phenomenon arises from Hering’s law, which demands equal innervation to yoke muscles; thus, the yoke of a paralyzed or restricted muscle receives excess innervation when the pathological eye is fixing.

Strabismus should be detected and measured in primary position at distance and near fixation and in gaze up, down, right, and left 30° from primary position. The nine “diagnostic gaze positions” include the above plus up and right, up and left, down and right, and down and left; these are useful to measure cyclovertical muscle palsies. For patients who have oblique muscle dysfunction, measurements are taken with the head tilted 30° right and left at distance fixation.

### Subjective Clinical Methods

Subjective clinical methods include diplopia tests and haploscopic tests, which require patient cooperation, intelligence, and ability to communicate the sensory perception to the examiner.

The red glass test requires the patient to alert the examiner when the red light viewed behind a red filter before the right eye and a white light viewed with the left eye are superimposed or displaced one from the other. Fusion is disrupted by the red glass, and thus, horizontal and vertical phorias are uncovered and measured; torsional deviations are not detected by this method. The gaze position of maximal image separation is a clue to the identity of paretic or restricted muscles. This is a useful bedside test, but accommodation is not controlled.

The Maddox rod consists of closely aligned, powerful glass or plastic cylinders. When illuminated, these cylinders project a line on the patient’s retina perpendicular to the groove orientation. The line is aligned horizontally to detect and measure horizontal phorias (accommodation cannot be controlled with this test). Torsional diplopia also may be detected and quantified using the “double Maddox test”; the Maddox rod is placed in a trial frame scaled in degrees. It is common to place two Maddox rods of different colors (red and white) in each trial frame cell and permit the patient to rotate each to his or her perception by using the trial frame dial. An easy method is to align the grooves at 90° on the trial frame, shine the light into one eye at a time, covering the fellow eye to orient the patient to the individual red and white lines. Then distort either one of the rods to be off by about 25° by turning the knob of the trial frame to make the angle difference between the lines obvious. Then, the patient is asked to

turn either rod by using the dialing knob to make them “parallel” again. The torsional position of each eye may be read directly in degrees from the angular scale used for cylinder axes. This test should be repeated three times to check the patient’s consistency.

Haploscopic devices, such as the major amblyoscope, present each eye with a significantly different target from its fellow eye. These devices measure horizontal, vertical, and torsional deviations by alternately illuminating the fixation targets presented to each eye; the tubes are positioned appropriately until no eye movements occur.

Diplopia tests also present different images to the two eyes. These images may be identified by red–green (anaglyph) glasses or by mirrors. The Lancaster red–green test uses a screen marked in 2° increments viewed from a distance of 6.6 ft (2 m). The examiner projects a red or green line on the screen; the patient views through the anaglyph glasses and projects the appropriate colored line upon the examiner’s projected line. The results are recorded and the glasses reversed or the projecting wands switched. Torsion also could be evaluated by asking the patient to hold the projected line parallel to the examiner’s projected line; the plot will allow detection of torsional deviations along with horizontal and vertical deviations in different gazes.

The Hess screen contains illuminated red lights at fixed distances on a black screen; the patient places a green pointer light on the red lights while wearing anaglyph glasses. The glasses are reversed to test the other eye. Torsion cannot be detected with this test.

## EYE MOVEMENT EXAMINATIONS

### Introduction

Evaluation of ductions, versions, and vergences is essential to understand a patient’s eye movement system completely. A commonly accepted terminology system is given in [Table 11.3.1](#). *Ductions* are monocular eye movements, generally evaluated with the fellow eye occluded. Extreme gaze positions are investigated. In full and normal abduction, the temporal limbus touches the lateral canthus. Full adduction brings the junction of the nasal and middle corneal thirds to a position above the inferior tear punctum.<sup>7</sup> Each eye elevates 10 mm and depresses 5–7 mm. Tertiary gaze positions are also evaluated and compared with those in the fellow eye.

Measurements of eye movements may be performed by estimation or quantification by using the arc perimeter, Goldmann perimeter, or tangent screen. Rotations of 50° in all directions are considered normal.

*Versions* are binocular movements in which the eyes view in the same direction. They are used to enlarge the field of view and to bring the object of attention onto the fovea. Versions are either voluntary or involuntary. *Vergences* are binocular movements in which the eyes gaze in opposite gaze directions; these are slow movements made as part of the near synkinesis or to achieve better alignment to facilitate sensory fusion. Fusional vergence amplitudes (convergence amplitudes to correct an exodeviation,

TABLE 11.3.1 Eye Movement Terminology

	Terminology	Movement
Ductions	Adduction	Nasal rotation
	Abduction	Temporal rotation
	Depression	Downward rotation
	Elevation	Upward rotation
	Intorsion	Upper corneal pole rotates inward
	Extorsion	Upper corneal pole rotates outward
	Dextrocycloduction	Upper corneal pole rotates rightward
	Levocycloduction	Upper corneal pole rotates leftward
Versions	Dextroversion	Both eyes rotate to patient’s right
	Levoversion	Both eyes rotate to patient’s left
	Supraversion	Both eyes rotate upward
	Infraversion	Both eyes rotate downward
	Dextrocycloversion	Upper corneal poles of both eyes rotate to patient’s right
	Levocycloversion	Upper corneal poles of both eyes rotate to patient’s left
Vergences	Convergence	Both eyes rotate nasally
	Divergence	Both eyes rotate temporally
	Positive vertical vergence	Right eye rotates higher than left
	Negative vertical vergence	Left eye rotates higher than right
	Incyclovergence	Upper corneal poles of both eyes rotate inward
	Excyclovergence	Upper corneal poles of both eyes rotate outward



**Fig. 11.3.5 Forced Duction Testing.** The patient has left esotropia and limited abduction. The patient is abducting her left eye from a position of maximal adduction, and the examiner is attempting to abduct the eye farther than the patient can.

**TABLE 11.3.2 Normal Fusion Vergence Amplitudes**

Testing Distance (m)	Convergence (D)	Divergence (D)	Vertical Vergence (D)
6	14	6	2.5
0.025	38	16	2.5

divergence amplitudes to correct an esodeviation, etc.) may be measured by the introduction of increasingly strong prisms before one eye of the patient, who views an accommodation-controlling target. The patient reports when the image doubles or the examiner notes the sudden appearance of strabismus. The power of prism necessary to reach this “break” point is the vergence amplitude at a given testing distance in a given direction. The prism power is then reduced until the patient “recovers” fusion, usually within 2–4 D of the break point. The patient may generate accommodative convergence to aid fusion, especially at near fixation; the patient is asked to report target blur to the examiner, a signal that accommodative convergence is being generated.

Normal fusional vergence amplitudes are listed in Table 11.3.2.<sup>8</sup> Mellick studied fusional amplitudes in relation to age with two separate methods (prism stereoscope and synoptophore [a form of major amblyoscope]) and two targets. He found no significant influence of age.<sup>9</sup> To test fusional convergence, the prism is held base out before a patient’s eye; to test fusional divergence, the prism is held base in. Positive vertical vergence requires a base-down prism placed before the right eye, and negative vertical vergence requires one placed before the left eye.

## Mechanical Tests of Eye Movement Limitation

Patients who have duction limitations may suffer from paralysis or paresis, or mechanical restriction of full duction movement, or both. Forced duction testing and active force generation testing may help to differentiate these. In cooperative patients, these tests may be performed in the office, but in young or uncooperative patients, these tests are reserved for the operating room (see Chapter 11.13), when the patient is under local or general anesthesia.

### Forced Duction Test

The forced duction test is an attempt by the examiner to move a patient’s eye farther in a given direction than the patient can move it. Topical anesthetic is placed on the appropriate limbal location (generally 180° away from the duction limitation) with a small cotton swab, and the limbal conjunctiva is grasped firmly with a toothed forceps. The patient is asked to rotate the eye fully in the direction of the limited duction. An attempt then is made by the examiner to rotate the eye beyond the position attained by the patient while avoiding globe retraction (Fig. 11.3.5). Care must be taken not to abrade the cornea. Patients who have pure nerve palsy exhibit no restriction to full movement by the examiner; patients who have pure



**Fig. 11.3.6 Active Force Generation Test.** The patient has left esotropia and limited abduction. The patient abducts her left eye from a position of maximal adduction, and the examiner estimates the force of abduction through the forceps.

restriction (dysthyroid orbitopathy, entrapment of ocular contents after blowout fracture) exhibit restricted movements (termed *positive forced duction test*). Some patients initially have a pure nerve palsy, but contraction of the antagonist muscle results in secondary mechanical restriction of movement. Suction cup devices have been developed for examiners who are wary of using toothed instruments at the limbus; a cotton swab may be a sufficient tool in some patients, but because the tendency with use of the cotton swab is to push the eye posterior in the eye socket, this may relax the rectus muscles and hence give wrong impression of the duction test.

Forced duction testing of oblique muscles may be performed, but two forceps are used, and the globe is depressed forcibly into the orbit. This depression toward the orbit puts the oblique muscles on stretch while relaxing the rectus muscles. To test tension in the superior oblique tendon, the globe is grasped in the limbal meridian of the tendon (the 2:30 o’clock position in the right eye, the 10:30 position in the left) and 180° away. The globe is rocked clockwise and counterclockwise over the taut tendon and the tendon tension is evaluated; experience with normal tendons is essential to obtain an accurate evaluation. To test tension in the inferior oblique muscle, the globe is grasped at the 4:30 position limbus and 180° away in the right eye, at the 7:30 position limbus and 180° away in the left eye; the globe is rocked similarly and the muscle tension evaluated.

### Active Force Generation Test

Active force generation testing may be used to evaluate the ability of a muscle to move the eye against a resisting force. The forceps is placed at the limbus of the anesthetized globe in the meridian of the muscle whose duction is limited, and the patient requested to rotate the eye in the direction of the limited duction; the examiner judges through the forceps the relative amount of force generated. Strain gauges have been devised that enable quantitation of this force. Fig. 11.3.6 shows a patient who has maximal adduction in the left eye. The examiner can gauge the relative abduction strength as the patient attempts to move her eye to the left.

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## Sensory Adaptations in Strabismus

## 11.4

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**Definition:** Physiological adaptations to strabismus in order to avoid visual confusion or diplopia.

## Key Features

- Suppression.
- Monofixation syndrome.
- Anomalous retinal correspondence.

## VISUAL CONFUSION AND DIPLOPIA

## Introduction

Normal binocular vision is a process of fusing retinal images from each eye into a single three-dimensional visual perception. If binocular visual development is established early in an infant's life, it is maintained unless sight is lost in either eye. When an individual develops strabismus, the corresponding retinal elements in the two eyes are no longer directed toward identical objects. This puts the individual at risk for development of two specific visual phenomena, visual confusion and diplopia, both potentially quite uncomfortable. Visual confusion is the simultaneous perception of dissimilar objects that project on corresponding retinal elements (e.g., the two foveas). Diplopia is the perception of one object that projects on two different (noncorresponding) retinal areas (Fig. 11.4.1).

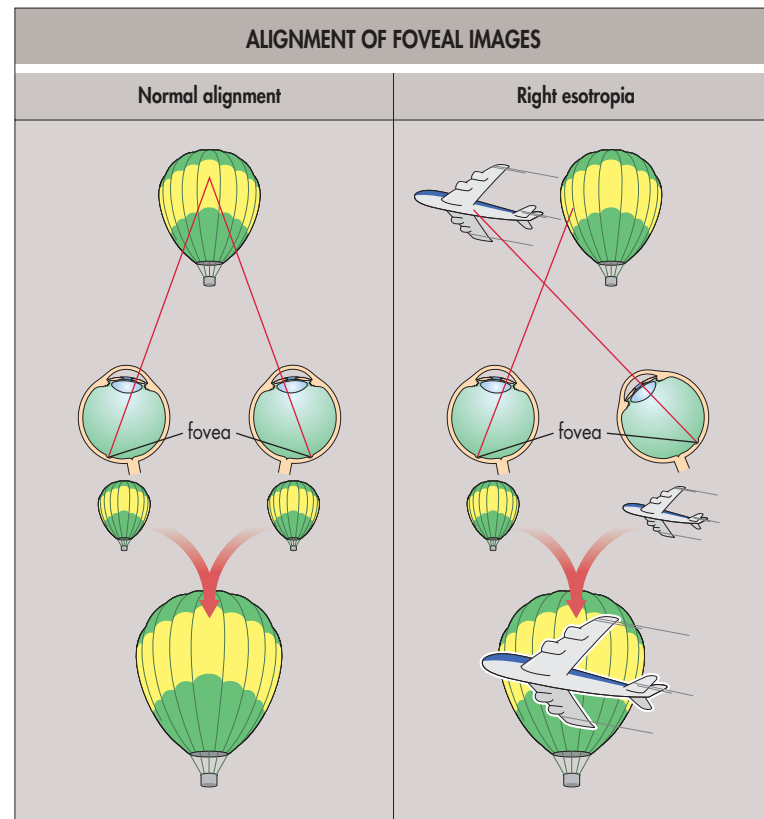
## Ocular Manifestations

Central confusion is physiologically eliminated in individuals of any age as the rod-free retinal areas cannot simultaneously perceive disparate targets. The fovea in the strabismic eye is immediately enveloped in a scotoma of roughly 2.5° diameter.<sup>1</sup> This can be demonstrated in oneself by manual displacement of one eye with a finger; there is an immediate decrease of visual acuity in that eye.

The onset of a new strabismus in children older than 7–9 years of age and in all adults causes diplopia. A patient with diplopia will fixate with the fovea of the straight eye and cortically inhibit the fovea of the deviated eye. The diplopic image results from a nonfoveal point being stimulated in the deviated eye and the image being localized to its corresponding visual field. If retinal correspondence is normal, patients with exotropia will experience heteronymous (crossed) diplopia, and patients with esotropia will experience homonymous (uncrossed) diplopia.

## Treatment, Course, and Outcome

Clinically, reports of visual confusion are rare, as the deviated fovea is suppressed. Acquired strabismus in the visually mature patient will experience diplopia unless it is controlled successfully by the fusional vergence system or by the occlusion of one eye or severely decreased visual acuity is present in one eye. Even patients who have acuity as low as 2/200 (0.6/60) may experience severe symptoms from visual confusion and diplopia. The ideal outcome for a patient with diplopia is the restoration of binocular single vision in all gaze positions. Nonsurgical interventions, such as eye exercises, prisms, optical blurring and/or occlusion, can be used indefinitely, if successful, or as a temporizing measure until strabismus surgery is needed. Botulinum toxin injections to the extraocular muscles to temporarily correct the strabismic deviation also have been used to eliminate diplopia.

<sup>†</sup>Deceased

**Fig. 11.4.1 Alignment of Foveal Images.** Normal alignment of a typical patient who has straight eyes fuses foveal targets. Right esotropia in a binocular patient results in visual confusion of foveal targets. This does not exist clinically, as the fovea in the turned eye cannot accept an image disparate from that seen by the fovea in the straight, fixing eye.

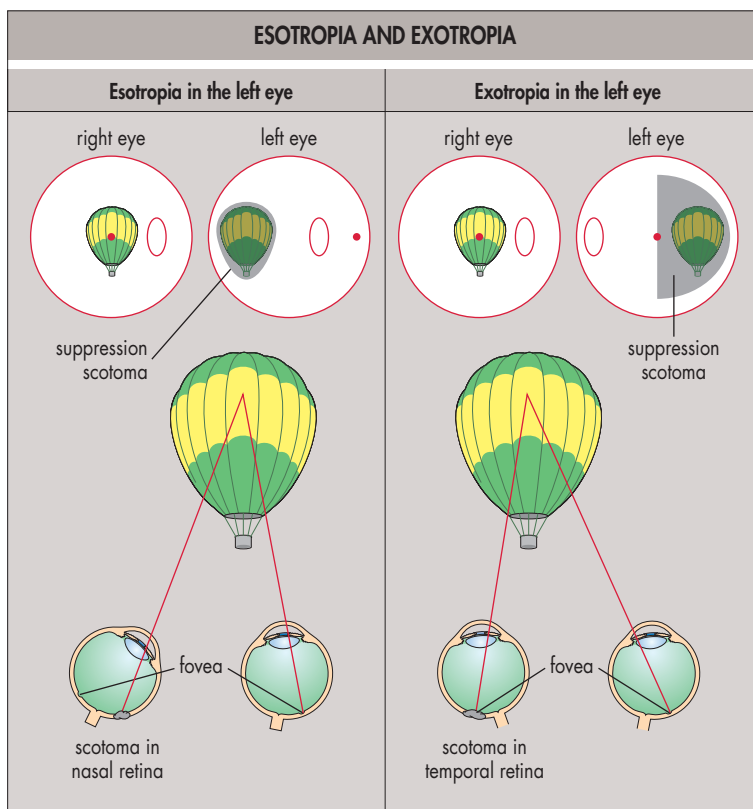
## SUPPRESSION AND ANOMALOUS RETINAL CORRESPONDENCE

## Introduction

Children younger than 7–9 years of age whose visual systems are still developing are usually able to achieve the sensory adaptations of suppression and anomalous retinal correspondence (ARC).<sup>2</sup> Suppression is the cortical mechanism used to eliminate the diplopic image caused by strabismus. Anomalous retinal correspondence is the adaptation to misaligned visual axes where the foveas are no longer functionally linked together in the visual cortex. Cortical reorganization of retinal relationships such that a peripheral retinal area of the deviating eye now shares a common visual direction occurs with the fovea of the straight eye. The foveas are no longer corresponding retinal points. These adaptations may develop rapidly or slowly after the appearance of strabismus.

## Ocular Manifestations

The cortical mechanism of suppression prevents diplopia from reaching consciousness during binocular visual activity and develops only during an immature visual system. Facultative suppression exists when the eyes are in the deviated state. As in the case of intermittent exotropia, suppression exists when the eyes are divergent and is not present when the eyes are



**Fig. 11.4.2 Esotropia and Exotropia.** Esotropia in the left eye—a nasal retinal suppression scotoma obviates central diplopia. Exotropia in the left eye—a temporal retinal suppression scotoma obviates central diplopia.

straight. In contrast, obligatory suppression is present at all times, whether the eyes are deviated or aligned. Constant monocular suppression not only results in poor binocular vision but may increase the risk of amblyopia.

Interestingly, the shape and size of the suppression scotoma are different in an esotrope compared with an exotrope.<sup>3</sup> An esotrope usually exhibits a small, round scotoma that envelops only the nasal retinal area within which the foveally viewed image in the aligned eye projects, although occasionally a somewhat larger, suppressed retinal area is demonstrated. Suppression scotoma in a patient with exotropia is much larger and encompasses the temporal retinal area on which the foveally viewed image in the aligned eye projects and, in addition, the entire area that extends to a vertical line that bisects the fovea (Fig. 11.4.2). Postulated explanations for this difference include developmental and teleological differences between the nasal and temporal hemiretinas, the intermittent and variable amplitude of many exodeviations, the constant nature of many esodeviations, and others; no explanation, however, is entirely convincing.

Anomalous retinal correspondence restores some sense of binocular cooperation with limited fusion and stereoscopic capabilities in the presence of a heterotropia. Therefore, patients with ARC do not experience diplopia. In the development of ARC, the normal sensory development is replaced only gradually and not always completely.

## Diagnosis and Ancillary Testing

There are a variety of tests to assess a patient's sensory status and to help identify the type of sensory adaptation, if present. It is important to note that the degree of the dissociative nature of the tests may influence a patient's response and perhaps give varying responses regarding the state of retinal correspondence. Tests that are least disruptive to the symmetry of binocular input (i.e., minimal dissociation) are more likely to give evidence of ARC. For example, a positive ARC response may be shown using the Bagolini lenses but may not persist with the more dissociative after-image test. The inconsistency of responses on the sensory tests has been interpreted as how firmly established the cortical adaptation is.<sup>4</sup> Because the depth of the sensory rearrangement can vary widely, an individual can test positive for both normal retinal correspondence (NRC) and ARC.

## Treatment, Course, and Outcome

Suppression is a barrier to fusion. Management of suppression, therefore, involves the treatment of the strabismus itself via refractive error

### BOX 11.4.1 Features of Monofixation Syndrome

#### Consistent With Normal Retinal Correspondence

- Presence of measurable fusional vergence amplitudes
- Presence of stereopsis (to 67 arc seconds) in many
- Relatively stable alignment
- Demonstrable peripheral fusion
- No measurable heterotropia in many

#### Consistent With Anomalous Retinal Correspondence

- Small heterotropia in some
- Lack of stereoscopic appreciation in some

### BOX 11.4.2 Older Terms for Monofixation Syndrome

Monofixational phoria  
Microtropia  
Microstrabismus  
Esotropic flick strabismus  
Small-angle strabismus

correction, occlusion, or pharmacological penalization to overcome any amblyopia that may be present and alignment of the visual axes to permit simultaneous stimulation of corresponding retinal elements. Antisuppression exercises are contraindicated if the patient does not elicit fusional potential in an effort to prevent intractable diplopia.

Anomalous retinal correspondence is a sensory adaptation to abnormal ocular alignment in an attempt to recover binocular cooperation. It should be noted that the quality of binocularity of a patient with ARC is inferior to that of the binocular interaction in NRC. The presence of ARC is of clinical significance when planning strabismus surgery. Patients may become aware of paradoxical diplopia if the surgical target angle does not take into account the patient's ARC status. (i.e., crossed diplopia in patients with esotropia and uncrossed diplopia in patients with exotropia). This postoperative paradoxical diplopia is usually transient. Nowadays, ARC is rarely seen clinically because of the early screening and treatment of childhood strabismus.

## MONOFIXATION SYNDROME

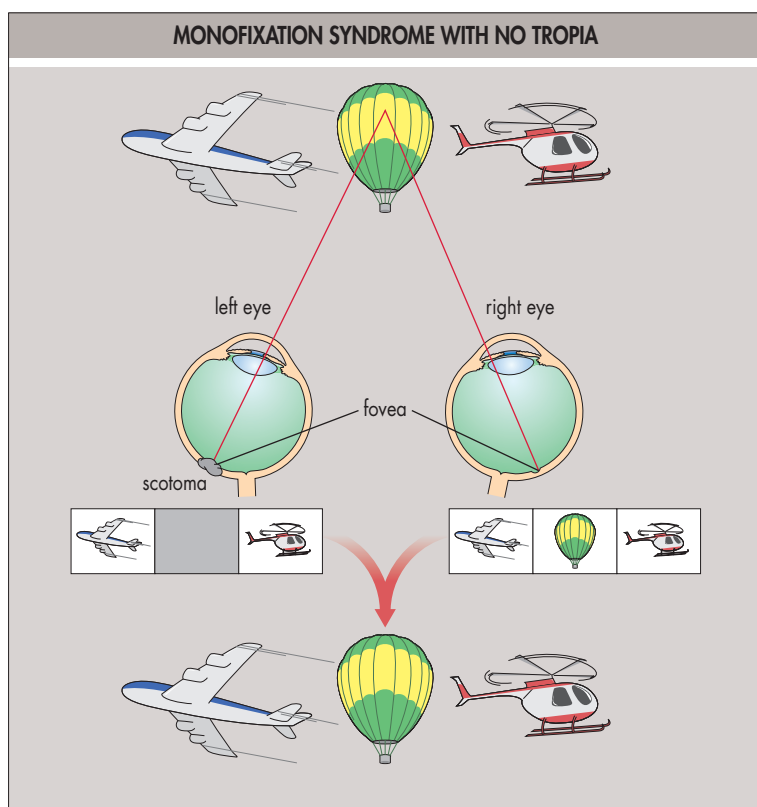
### Introduction

Many binocular patients who have a small or absent heterotropia (up to 8Δ esotropic or exotropic and 2Δ vertically up or down) and possible superimposed heterophoria exhibit monofixation syndrome (MFS), show a sensory state that comprises features of both normal retinal correspondence and ARC (Box 11.4.1). Initially known by many terms, each of which explains one sensory or motor component of the complete syndrome (Box 11.4.2), the generally accepted name MFS emphasizes the essential feature of this syndrome, the presence of peripheral fusion without central fusion.<sup>5</sup> This means that only one rod-free retinal area (fovea) views at a given time.

Tychsen<sup>6</sup> has shown in cortical area V1 of macaque monkeys that horizontal axons of about 7 mm in length could join receptive fields about 2.5° or 4.4 prism diopters apart. Two neurons could join fields about 5.0° or 6.6 prism diopters apart. Thus, the maximal tropia that permits peripheral fusion is explicable as a combination of V1 neuron reach and V1 topography.<sup>6</sup>

The syndrome may develop spontaneously by unknown means, may be caused by anisometropia, is the best-expected sensory state in almost all patients who have infantile strabismus after successful surgical alignment, and is found in patients who have acquired unilateral organic foveal lesions (e.g., toxoplasmosis), although in the last instance, the scotoma is usually larger. The absence of bifoveal fusion and reduced stereoacuity also has been reported in adults with long-standing constant strabismus,<sup>7</sup> long-standing surgically induced monovision,<sup>8</sup> and in the delayed removal of dense adult onset cataracts.<sup>9</sup>

Central fusion (bifoveal viewing with the possibility for superb stereoscopic appreciation) may occur in the presence of very minimal deviation of the visual axes, less than that detectable by cover testing, and is termed fixation disparity; it measures roughly 14 minutes of arc (perhaps 0.5Δ) and is present in most individuals.<sup>10</sup> It should not be confused with MFS.



**Fig. 11.4.3 Monofixation Syndrome With No Heterotropia.** Note the central scotoma that envelops the area seen by the left fovea and fusion of peripheral information.

## Ocular Manifestations

Patients who have MFS demonstrate an absolute, facultative, central scotoma that usually measures  $2.5^{\circ}$ – $3^{\circ}$  in diameter, and, like a suppression scotoma seen in binocular patients who have childhood-onset strabismus and larger heterotropias, it is present only when a given fovea is not fixing (Fig. 11.4.3).

## Diagnosis and Ancillary Testing

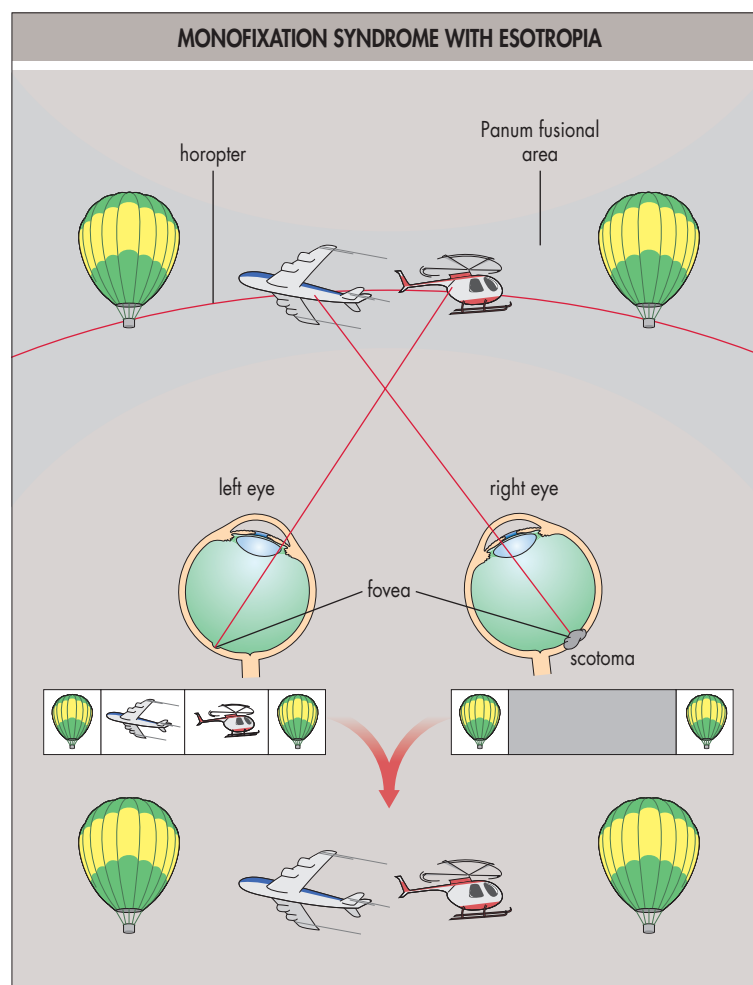
Peripheral fusion and demonstrable fusional vergence amplitudes (often of a normal amount) usually are demonstrable in patients who have MFS and provide generally stable alignment.<sup>11</sup> Presumably, the expanded nature of the peripheral Panum's fusional area permits peripheral fusion to develop despite a small heterotropia (Fig. 11.4.4). Perhaps this reflects the greater than one-to-one linkage between peripheral retinal photoreceptors and ganglion cells. Stereoscopic ability often is found but is rarely better than 67 seconds of arc, as only one fovea is used in binocular viewing.<sup>12</sup> Note that the sensory status of patients who have MFS is the same whether or not a small heterotropia exists, although those who have large, superimposed heterophorias may sometimes have asthenopic symptoms.

Sensory testing shows peripheral without central fusion, possible stereoscopic appreciation (although never to normal limits), and generally normal fusional vergence amplitudes. If the patient has a heterophoria superimposed on a small heterotropia, alternate cover testing demonstrates larger strabismus than does cover/uncover or simultaneous prism-and-cover testing.<sup>13</sup>

Patients who have MFS exhibit sensory characteristics closer to normal retinal correspondence than ARC, that is, the presence of fusional vergence amplitudes and possible gross stereoscopic appreciation, although those who have a small heterotropia do not have precise alignment of corresponding retinal elements.<sup>14</sup> Cover testing shows roughly 22% without a manifest or latent deviation, 34% with heterophoria only, and 44% with heterotropia and superimposed heterophoria, occasionally up to  $20\Delta$ . Only MFS permits the existence of a measurable heterotropia and superimposed heterophoria.<sup>15</sup>

## Course and Outcome

The absence of simultaneous foveal viewing means that young patients are at risk for the development of amblyopia, and approximately two-thirds do become amblyopic—90% if they also have a heterotropia. In the absence of



**Fig. 11.4.4 Monofixation Syndrome With  $4\Delta$  Right Esotropia.** Note the right central scotoma that prevents perception of the plane and helicopter under binocular viewing conditions and fusion of peripheral information (balloons). The horopter is an infinitely thin surface in space that contains all the object points that project to corresponding retinal points. It is surrounded by Panum's fusional area, within which objects in space can be fused, even though they project onto noncorresponding retinal points.

anisometropia, three-fourths of patients with MFS have amblyopia. In the case of successfully aligned infantile esotropes, of those who have MFS, one-third have amblyopia. As in the treatment of all amblyopia, the earlier the treatment is started the better the outcome in improving vision.

Once MFS is present, it is not possible to advance to bifoveal fusion via eye exercise, prisms, surgery, or any other methods. Despite being relatively stable, this condition may decompensate, causing an increase in heterotropia resulting in diplopia. Reducing the angle of strabismus to within "monofixation" range, by optical or surgical means, will eliminate the diplopia.

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# Sensory Status in Strabismus

Gary R. Diamond<sup>†</sup>, Nicola Freeman

# 11.5

## Definitions:

- **Fusion:** cortical integration of slightly dissimilar images perceived by the two eyes into a unified percept.
- **Horopter:** the locus in space representing the intersection of all points that stimulate corresponding retinal points.
- **Panum's fusional area:** area in space surrounding the horopter in which objects can be fused.
- **Stereopsis:** a form of depth perception that demands binocular vision and usually sensory fusion.
- **Monofixation syndrome:** a form of binocular vision found in many patients who have small amounts of strabismus that permits peripheral fusion, stereopsis, and alignment stability.

## Key Features

- Subjective tests for binocular vision and retinal correspondence are an important part of every patient's examination.
- Monofixation syndrome can be reliably diagnosed only with sensory testing.

## INTRODUCTION

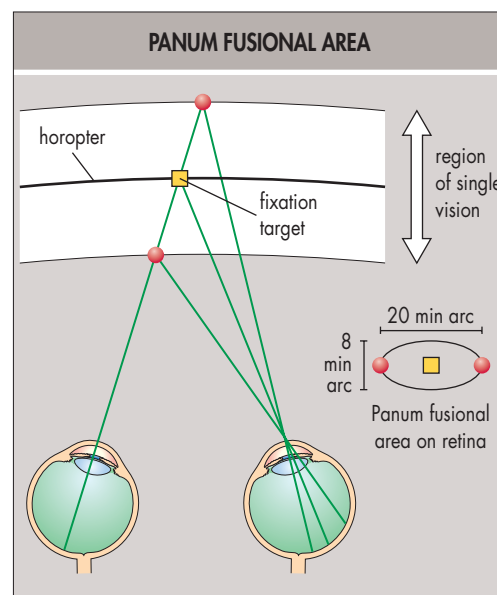
Binocular patients who develop strabismus before the age of 7–9 years usually develop the sensory adaptations of suppression and anomalous retinal correspondence to obviate diplopia and visual confusion (see Chapter 11.4). Older patients who develop strabismus for the first time suffer from diplopia and visual confusion as long as vision remains in both eyes, until the eyes are aligned or the patient learns to ignore one image. Nonbinocular patients (or those who perceive vision with one eye at a time) are not troubled by symptoms of double vision if their eyes become strabismic.

Clinical testing of sensory status in patients with strabismus is easier to understand after the basic physiology of sensory fusion and stereopsis has been understood.

## SENSORY FUSION

Sensory fusion is the cerebral cortical integration of the slightly dissimilar images perceived by the two eyes into a unified perception. If images are sufficiently dissimilar, they cannot be fused; examples are red and green variants of the same object or lines seen vertically by one eye and horizontally by the other. Binocular rivalry usually occurs under these conditions, and a varying perception is obtained. Motor fusion with vergence amplitudes, and even stereopsis, may be produced by rivalrous stimuli in the absence of sensory fusion. Such stimuli are fortunately uncommon in daily life but are most useful when assessing the sensory status of the visual system.

A retinal element is a small retinal patch that has an associated directional value. The fovea's directional value is defined subjectively as straight ahead; peripheral retinal elements possess directional values in other orientations. Corresponding retinal points are a pair of retinal elements, one in each eye, that have the same directional value. Comfortable single binocular vision occurs when objects in the binocular field stimulate corresponding retinal points and the higher cortical function—termed *sensory fusion*—occurs.



**Fig. 11.5.1 Panum's Fusional Area.** The left eye fixates a square target, and a search object visible only to the right eye is moved before and behind this target. The ellipse of retinal area, for which typical dimensions are given for the parafoveal area, is the projection of the Panum's fusional area. Diplopia is not perceived for two targets within this area.

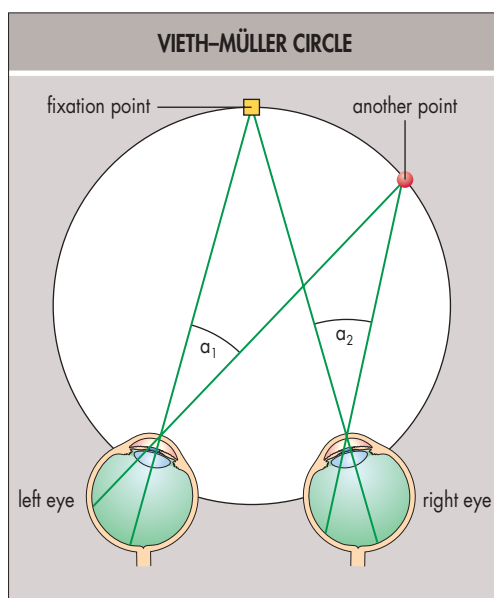
The locus in space that represents the intersection of all points in space that stimulate corresponding retinal points is termed the *horopter*. Interestingly, sensory fusion still occurs if the object that projects on a retinal element in one eye projects on a range of elements that surrounds the corresponding retinal element in the second eye. The area in space that projects from this range of elements in the second eye that intersects with the projection from the retinal element in the first eye is termed *Panum's fusional area* (Fig. 11.5.1). Panum's fusional area surrounds the horopter anteriorly and posteriorly; it permits fusion to take place when exact retinal correspondence does not occur. The binocularly perceived object imaged on noncorresponding retinal loci, but fused within Panum's fusional area, is perceived to have one subjective visual direction. The foveal Panum's area is circular, of diameter about 14 minutes of arc; thus, an object projected on the fovea of one eye may be displaced by this amount, and the patient still maintains bifoveal vision. The size of Panum's fusional area increases toward the retinal periphery (see Fig. 11.5.1), but the ultimate size and shape depend on the temporal and spatial frequency of the patient's alignment drift when fixing on a stationary target.<sup>1</sup>

Objects in front of or behind Panum's fusional area stimulate physiological diplopia, which is not usually noted but may, in turn, stimulate fusional vergence eye movements. The horopter shape may be defined in a pair of perfectly spherical eyes that have refractive seats at the nodal points of each eye as the locus of points of zero vertical disparity relative to the fixation points. In a horizontal plane, the horopter, which includes the fovea, is the Vieth–Müller circle (Fig. 11.5.2).<sup>1–3</sup> In a living animal visual system, the horopter is flatter (the Hering–Hellebrand horopter deviation). The vertical horopter tilts away from the observer, who stands on the horopter; the inclination is a function of fixation distance.<sup>3,4</sup>

## DEPTH PERCEPTION AND STEREOPSIS

Depth perception may occur without binocular vision because it is dependent on both monocular and binocular clues. Stereopsis is a form of depth perception that demands binocular vision and usually sensory fusion but, under certain conditions, may be stimulated by rivalrous objects whose images cannot be fused. Stereopsis is the perception of depth stimulated by objects that possess horizontal disparity, with one object usually located

<sup>†</sup>Deceased



**Fig. 11.5.2 Vieth-Müller Circle.** If the eyes are assumed to be spherical with rotational centers at the nodal points, all points in space that have a zero disparity fall on this circle. Angle  $\alpha_1$  = angle  $\alpha_2$ ; thus, equal retinal distances map into equal angles in space in this idealized system.

in front of or behind the fixation point. Horizontal disparity alone is sufficient to stimulate the stereoptic perception. Visual contours are not necessary, and disparity may be stimulated by random dots.<sup>5-7</sup> *Stereoacuity*, the disparity threshold at which a depth difference may just be appreciated, is best at the fovea and depends on the level of visual acuity in each eye. Stereoacuity dissipates rapidly into the peripheral visual field and with increasing object distance<sup>8</sup> and is proportional to interpupillary distance. Under ideal conditions, human foveal stereoacuity may be 10 seconds of arc.<sup>9,10</sup>

## CLINICAL TESTING

The clinician must determine the sensory status of each patient, specifically whether the patient is binocular and if so, whether the patient has normal retinal correspondence (NRC) or anomalous retinal correspondence (ARC) and suppression (see Chapter 11.4). Binocular patients who have constant tropias measurable on cover testing may exhibit NRC with diplopia and visual confusion, ARC and suppression, or monofixation syndrome (MFS). MFS possesses features of both NRC and ARC but is considered closer to the former.

Asymptomatic patients who have tropias  $>8\Delta$  horizontally or  $>4\Delta$  vertically usually have ARC and suppression, although these may be difficult to demonstrate. Asymptomatic binocular patients who have smaller tropias, or a smaller tropia with superimposed phoria, usually have MFS.

Many sensory tests are available to the busy clinician, but access to and understanding of just a few enable evaluation of the patient's sensory status. It is important to perform sensory testing at the beginning of the examination; prolonged monocular occlusion to evaluate visual acuity may dissociate the eyes and confound determination of the patient's ambient sensory status.

## Testing for Binocularity (Simultaneous Perception)

Many tests require simple tools to demonstrate binocularity. Holding a red lens before one eye and presenting a white light detects perception of two lights, red and white, in patients who have NRC and diplopia. Prisms may be used to project one light beyond the bounds of a suppression scotoma in patients who have ARC and suppression or NRC-MFS. Commercially available Polaroid projection slides, when viewed through polarized lenses, present one-half of an optotype line to each eye; binocular patients view the entire line, whereas nonbinocular patients view the half perceived by the foveating eye only. Prismatically, overcorrection of a patient with strabismus elicits diplopic symptoms, which proves the presence of binocular vision.

The Worth four-dot test is an array of four round targets ("dots"), usually presented with the red dot above two green dots that, in turn, are above one white dot. Distance (Fig. 11.5.3) and Near (Fig. 11.5.4) Worth four-dot targets are used. The diameter of the target array subtends  $1.25^\circ$  at 6 m and  $6^\circ$  at 33 cm. The targets are viewed through red-green (anaglyph) glasses, and the patient describes the perception to the examiner or simply counts the lights viewed. Binocular patients perceive red and green lights



**Fig. 11.5.3 Distant Worth Four-Dot Target.** This is fixed to a wall, traditionally with the red dot placed at the top.



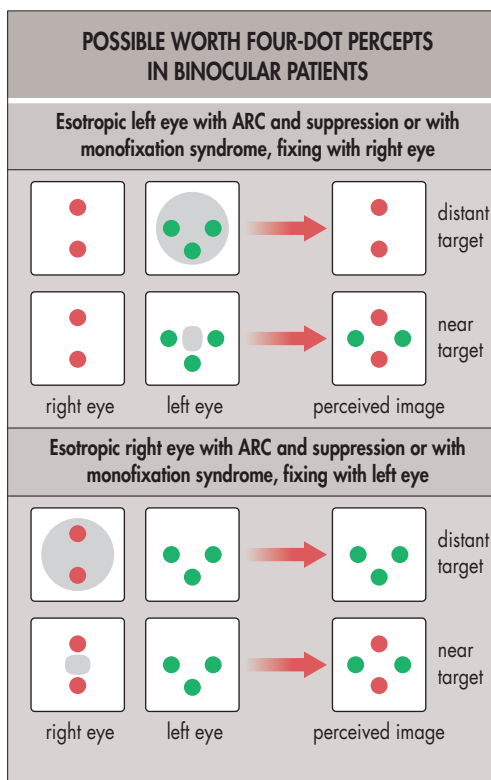
**Fig. 11.5.4 Near Worth Four-Dot Target and Anaglyph Glasses.** The near target is brought to the face to elicit a binocular response in patients who have strabismus and large scotomas.

simultaneously, but the near wand must be held very close to a patient with a large strabismic deviation to project the target beyond the bounds of a suppression scotoma (Fig. 11.5.5). Nonbinocular patients see two red or three green lights at all testing distances (Fig. 11.5.6).

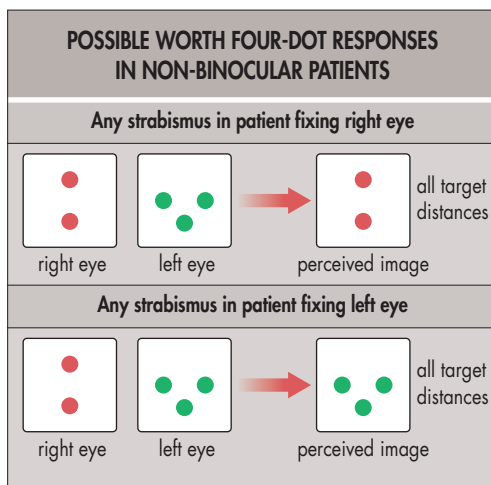
Baglioli lenses are finely ruled plano lenses that give a streak appearance to a point light source perpendicular to the ruled direction. The lenses are placed in orthogonal orientation (traditionally at  $135^\circ$  right eye and  $45^\circ$  left eye; Fig. 11.5.7) in a trial frame, and the patient views a light at distance fixation. Binocular patients perceive an "X" figure or, if a suppression scotoma exists, one complete line and the peripheral elements of the second. Nonbinocular patients see only one entire line.

Haploscopes, for example, the major amblyoscope, may present slightly different but fusible images to each eye; if portions of each image are perceived, the patient is binocular. The viewing tubes may be displaced to the strabismic angle, if such exists, or the tubes may be kept in the straight position and targets used that are large enough to project beyond the suppression scotoma.





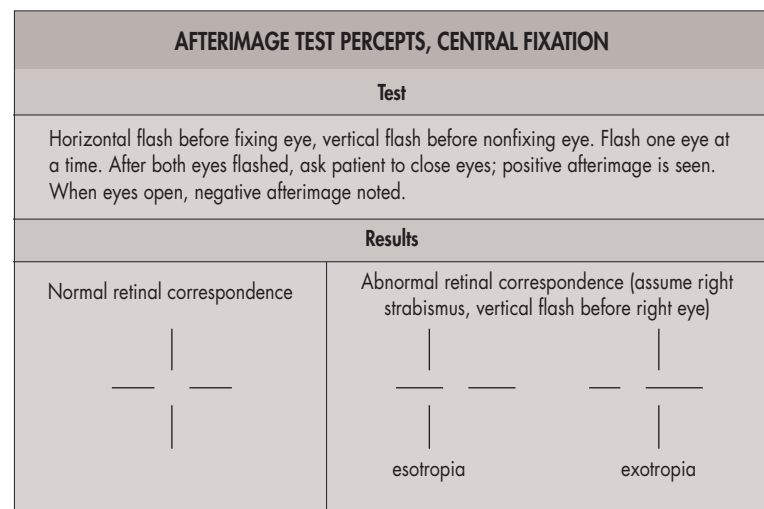
**Fig. 11.5.5 Possible Worth Four-Dot Percepts in Binocular Patients.** Note the similar distant responses in patients who have esotropia with abnormal retinal correspondence (ARC) and suppression and in those who have monofixation syndrome. Patients who have exotropia with ARC and suppression give the same responses, but the suppression scotoma is larger and shaped somewhat differently (see Fig. 11.4.2). The red lens is over the right eye and the green lens over the left eye.



**Fig. 11.5.6 Possible Worth Four-Dot Responses in Patients Who Do Not Have Binocularity.** The red lens is over the right eye and the green lens over the left eye.



**Fig 11.5.7 Bagolini Lenses in a Trial Frame.** Striations placed at 75 degrees right eye and 135 degrees left eye.



**Fig. 11.5.8 Afterimage Test Percepts, Central Fixation.** Shown are those possible in patients who have central fixation and binocular vision.

### BOX 11.5.1 Retinal Correspondence Tests (Listed Most Sensitive to Least Sensitive)

Bagolini striated lenses  
Synoptophore (major amblyoscope)  
Worth four-dot test  
Afterimage test

## Tests of Retinal Correspondence

Many of the preceding tests may be used in binocular patients to diagnose ARC and suppression, NRC bifoventality, or NRC-MFS at a given testing distance at a given moment. As ARC exists only under binocular testing conditions, some tests may yield an ARC response at a given moment, whereas other tests yield an NRC response, depending on the room illumination and the length of time ARC has been present. Tests that confound correctable single binocular vision and that poorly reproduce ordinary binocular viewing conditions demonstrate ARC later compared with tests that closely simulate typical binocular viewing conditions. Retinal correspondence tests more commonly used in clinical practice are listed, by depth of abnormal correspondence, in [Box 11.5.1](#).

The afterimage test is most removed from ordinary binocular viewing and the most dissociating of all commonly performed retinal correspondence tests; an ARC response on this test declares the ARC to be deep seated. An afterimage (positive in dim illumination, negative in bright) is imprinted on each retina in turn with a photographic flash device. The fellow eye is covered during the flash. Usually, a vertical flash is presented to one eye and a horizontal flash to the other. The fovea is protected by a central mask with fixation target and thus “labeled” as the center of an afterimage line. An NRC response yields a cross pattern ([Fig. 11.5.8](#)) because the fovea in each eye retains the straight-ahead directional value. A crossed heteronymous localization occurs in ARC with esotropia, as the straight-ahead directional value lies in the nasal retina of the strabismic eye; the fovea has a temporal directional value.<sup>11</sup> In patients who have ARC and exotropia, the afterimage perception is an uncrossed homonymous localization.

In patients who have ARC, suppression, and NRC-MFS, the Worth four-dot test demonstrates suppression of one eye when presented with a distant Worth target and fusion of lights of the near Worth target (see [Fig. 11.5.5](#)). The Worth four-dot test thus cannot be used to differentiate ARC from NRC easily.<sup>12</sup>

Clinicians who have access to a major amblyoscope (synoptophore) may set the tubes at the objective angle of strabismus; if the targets are superimposed, NRC exists. Crossed diplopia occurs in patients who have ARC and esotropia and uncrossed diplopia in patients who have ARC and exotropia. An “angle of anomaly” is defined when the patient moves the tubes until the targets are superimposed; this subjective angle equals the objective angle in “harmonious” ARC and is less or greater in “unharmonious” ARC.

The Bagolini lens test most closely simulates ordinary viewing and is the least dissociating of all retinal correspondence tests.<sup>13</sup> Central (foveal)

POSSIBLE BAGOLINI LENS PERCEPTIONS, CENTRAL FIXATION				
Test				
Right eye lens at 135 in trial frame, left eye lens at 45. Fixate on distant light in semidarkened room.				
Closest sensory test to normal viewing, first to exhibit abnormal retinal correspondence (ARC) strabismus, first to revert to normal retinal correspondence (NRC) when eyes aligned.				
Results				
Cover–uncover test irrelevant	No binocularity, right eye fixing		No binocularity, left eye fixing	
No shift on cover–uncover testing (no tropia)	NRC bifoveal		NRC monofixation, left eye fixing	
Shift on cover–uncover testing (tropia)	$\leq 8\Delta$ NRC monofixation, left eye fixing		$> 8\Delta$ ARC, left eye fixing exotropia	
	$> 8\Delta$ ARC, left eye fixing esotropia			
		$> 8\Delta$ NRC, esotropic diplopia		NRC, exotropic diplopia

Fig. 11.5.9 Possible Bagolini lens perceptions, central fixation.



Fig. 11.5.10 Titmus stereotest with polaroid glasses.

fixation must be assumed and the alignment of the eyes known; possible outcomes are given in Fig. 11.5.9.

Stereopsis Tests

Clinically useful stereopsis tests provide slightly different views of the same target to each eye. A unique view is created by either Polaroid filters (e.g., Titmus, Lea symbols Butterfly Stereo Acuity, Wirt, Randot) or anaglyph (red and green) glasses (e.g., TNO test).

The Titmus stereotest (Fig. 11.5.10) provides disparity in the range 3000 seconds of arc at 40 cm testing distance (fly wings above background) to 40 seconds of arc (ninth circle). Younger children may respond to the depth



Fig. 11.5.11 TNO stereotest with anaglyph (red and green) glasses.



Fig. 11.5.12 Lang stereotest.



Fig. 11.5.13 Frisby stereotest.

illusion of three sets of five animals, one of which appears to float above the background (400, 200, 100 seconds of arc). The TNO stereotest (Fig. 11.5.11) uses random-dot stereograms viewed through anaglyph glasses and contains disparities in the range 480–15 seconds of arc. Children who reject polaroid or anaglyph glasses may be tested by using the Lang test<sup>14</sup> (Fig. 11.5.12), in which random-dot stereograms are presented through a cylinder grating that overlies the target or the Frisby stereotest (Fig. 11.5.13), which consists of three plates that permit stereoacuity measurement in the range of 600–20 seconds of arc.

TABLE 11.5.1 Synopsis of Sensory Testing in Strabismus

Test	NRC–Bifoveal	NRC–Monofixation	Abnormal Retinal Correspondence	Diplopia	No Binocularity
Worth four-dot, distance (6 m)	4 dots	2 or 3 dots	2 or 3 dots	5 dots	2 or 3 dots
Worth four-dot, near (40 cm)	4 dots	4 dots	4 dots	5 dots	2 or 3 dots
Stereo	None to 14 sec arc	None to 67 sec arc	None	None	None
The Worth four-dot test and stereotest can be used to define a patient's sensory status. Appreciation of four lights on the Worth test at any testing distance signifies binocular vision. Appreciation of four distant lights demands normal retinal correspondence (NRC) and bifoveality, as does recognition of less than 100 seconds of arc stereoacuity. Any level of stereoptic appreciation signifies NRC at that moment at that testing distance.					

Test for Monofixation Syndrome

One feature of this syndrome (see Chapter 11.4) is a small, round scotoma that surrounds the fovea of one eye under binocular viewing conditions. As the patient views a distant target, a 4Δ prism, usually held base out, is introduced before one eye. If held before the fixing eye, both eyes will saccade to the new target position in the direction of the prism's apex. A slower fusional vergence movement in the fellow eye in the opposite direction follows. However, when the prism is held before the nonfixing eye, there is no saccade because the displaced image falls within the scotoma and, therefore, is not perceived.<sup>15</sup> The test must be performed with the prism held before each eye. It is possible that some patients may switch fixation as the prism is introduced, and in this case no saccadic shift will then be observed.

In summary, the busy clinician may best determine the sensory status of most patients by using two straightforward and easily available tests—the Worth four-dot test and the Titmus stereotest. A summary of sensory testing interpretation using these commonly available testing devices is given in Table 11.5.1.

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Access the complete reference list online at [ExpertConsult.com](https://www.expertconsult.com)



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# Esotropia

Michael Kinori, Shira L. Robbins

# 11.6

**Definition of Infantile Esotropia:** Inward deviation of the visual axes, with an onset before age 6 months.

## Key Features of Infantile Esotropia

- Esotropia typically greater than  $30\Delta$  present before 6 months of age.
- Cross-fixation.
- Little to no binocular vision.
- Normal refractive error for age (between +0.50 and +3.00).
- Initially, similar deviation at distance and near fixation.

## Associated Features (Often Appear After the First Year of Life)

- Inferior oblique muscle overaction.
- Dissociated vertical deviation.
- Fusion maldevelopment nystagmus (previously known as *latent nystagmus*).
- Amblyopia in about one-third of patients.

**Definition of Accommodative Esotropia:** Inward deviation of the visual axes caused by the focusing efforts of the eyes as they try to see clearly. Patients typically have hyperopia and/or high accommodative convergence-to-accommodation (AC/A) ratio.

## Key Features of Accommodative Esotropia

- Initially intermittent acquired esotropia.
- Esotropia larger at near than distance fixation.
- Age of onset usually between 18 months and 3 years.

## Associated Feature

- Typically hyperopic, but patients who have a high AC/A ratio may have any refractive error.

**Definition of Duane's Syndrome:** Congenital miswiring of the medial and/or lateral rectus muscles.

## Key Features of Duane's Syndrome

- Retraction of the affected globe(s) on attempted adduction.
- Limitation of abduction, adduction, or both.
- Abnormal head posture.
- Present from birth; however, often noticed later in infant/toddler years.

## Associated Features of Duane's Syndrome

- Elevation (upshoot) or depression (downshoot) of the globe on attempted adduction.
- Esotropia (or exotropia in some patients), rarely larger than  $30\Delta$ .

## INTRODUCTION

Esotropias represent the most common form of strabismus and include infantile, accommodative, cyclical, and nonaccommodative forms. They also are seen more frequently in children with neurological impairment or vision deficit (sensory esotropia) and in some patients who have Duane's and Moebius' sequence, sixth cranial nerve palsy, and thyroid disease associated strabismus.

## INFANTILE ESOTROPIA

### Introduction

Infantile esotropia was previously termed *congenital esotropia*. "Congenital esotropia" is a misnomer because in very few cases, if any, esotropia is present at birth.<sup>1</sup> Infantile esotropia is defined as esotropia that presents before 6 months of age (Fig. 11.6.1). Many normal infants will have an intermittent esotropia or exotropia in the first weeks of life that is thought of as developmental and disappears between ages 2 and 4 months. Prospective studies have determined that this is the age at which infantile esotropia is first noted. Among younger infants, it cannot be predicted who will develop infantile esotropia by age 2–4 months.<sup>1</sup>

### Epidemiology and Pathogenesis

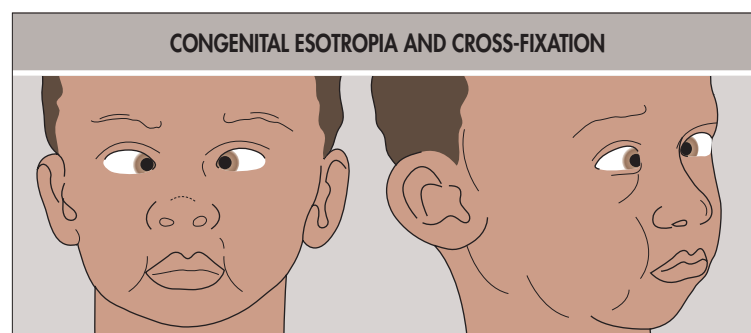
The incidence of infantile esotropia is roughly 1% in most series and may be more common in children who have neurological disorders.<sup>2</sup> Gender and racial distributions are equal. Concordance in one series was 81% in monozygous twins and 9% in dizygous twins.<sup>3</sup> It is common to find some form of strabismus in other members of the proband's family.

### Ocular Manifestations

Amblyopia occurs in 25%–40% of patients, but the majority "cross-fixate" (i.e., use the right eye to fix across the nose to view objects to the left of the patient, and vice versa) (Fig. 11.6.2).<sup>4</sup> A child who does not have amblyopia



**Fig. 11.6.1 Infantile Esotropia.** The child is fixing with her left eye; note the temporally decentered light reflex in the right eye.



**Fig. 11.6.2 Congenital Esotropia and Cross-Fixation.** The infant uses the right eye to view left, and vice versa. Note that the infant uses his left eye to fix across the nose to view objects on his right side.



**Fig. 11.6.3 Bilateral Overelevation in Adduction.** Although the patient has orthophoria in primary gaze, she has bilateral overelevation of the globe in adduction caused by inferior oblique imbalance.



**Fig. 11.6.4 Dissociated Vertical Deviation in the Right Eye.** The patient's right eye drifts upward with dissociation. When the patient fixates with the right eye, no hypodeviation is seen in the left eye. (Reproduced with permission from Cheng KP, Biglan AW, Hiles DA. Pediatric ophthalmology. In: Zitelli BJ, Davis HW, eds. Atlas of Pediatric Physical Diagnosis. 2nd ed. New York: Gower Medical Publishing; 1992. p. 19.1.)

#### BOX 11.6.1 Dissociated Vertical Deviation Compared With Inferior Oblique Overaction

##### Dissociated Vertical Deviation

Present in all gaze positions  
Does not obey Hering's law  
Slow floating elevation, abduction,  
excyclotorsion movement  
Not associated with A- or V-pattern

##### Inferior Oblique Overaction

Present in adduction only  
Obeys Hering's law  
Rapid elevation and abduction  
movement  
Often associated with V pattern

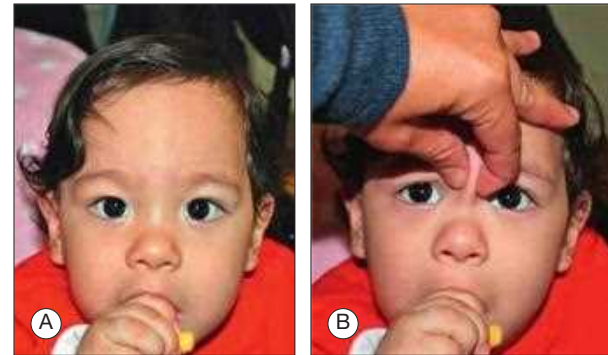
switches fixation at the midline as an object is brought from one side to the other and does not maintain fixation or adopt a progressive head turn. This phenomenon might cause the examiner to believe that a true abduction deficit exists and pursue an unnecessary workup for sixth cranial nerve palsy. In most cases, however, when one eye is covered, full abduction can be elicited in the uncovered eye.<sup>5</sup> The “doll's head” maneuver is helpful to demonstrate true abduction ability. Generally, the deviation is greater than 30Δ and comitant, measuring roughly the same in all gaze positions, both distant and near gazes.

Inferior oblique muscle involvement is noted in up to 75% of patients, with an onset most frequently during the second year of life; it may be unilateral or bilateral (Fig. 11.6.3).<sup>6</sup> Early surgical correction of esotropia does not prevent the later development of inferior oblique imbalance. This should be differentiated from dissociated vertical deviation (DVD), which also occurs in roughly 75% of these patients and has similar onset patterns<sup>7</sup> (Fig. 11.6.4). DVD may be manifest or latent, can be very asymmetrical, and may present as any combination of slow elevation, abduction, and excyclotorsion (Box 11.6.1). Less commonly, the dissociated abduction is more prominent than elevation, and in that case, it is termed *dissociated horizontal deviation* (DHD). A dissociated torsional deviation (DTD) can be seen as a few nystagmus beats. Although its cause is unknown, DVD may represent a primitive eye movement pattern uncovered by deficient fusion.

Fusion maldevelopment nystagmus (FMN), formerly known as *latent nystagmus* with fast phase toward the unoccluded eye, is found in approximately 50% of patients.

Asymmetrical monocular pursuit is a feature of infantile esotropia, as measured by optokinetic nystagmus (OKN). Temporal-to-nasal pursuit is favored; patients who have infantile esotropia show poor nasal-to-temporal OKN regardless of the degree of stereopsis or the timing of surgery.<sup>8</sup>

Many young children sent to ophthalmologists by pediatricians for esotropia have pseudo-esotropia, an illusion caused by a wide and flat nasal bridge, wide epicanthal folds, and the ability to converge to very close distances (Fig. 11.6.5A).<sup>9</sup> In the Asian population, where a flat nasal bridge and wide epicanthal folds are more common features, pseudoesotropia is



**Figure 11.6.5 Pseudoesotropia.** (A) Wide flat nasal bridge with prominent epicanthal folds covers the nasal sclera giving the impression of an esotropia. However, the corneal light reflexes are centered in each eye. (B) Patient does not appear cross-eyed with elimination of the prominent epicanthal folds.

#### BOX 11.6.2 Differential Diagnosis of Infantile Esotropia

Early-onset accommodative esotropia  
Nystagmus blockage syndrome  
Moebius' sequence  
Duane's syndrome  
Congenital sixth cranial nerve palsy  
Cyclic esotropia  
Esotropia associated with visual loss in one eye (sensory esotropia)  
Neurological impairment  
Strabismus fixus and other fibrosis syndromes

more likely. A recent study found that the positive predictive value of referral for infantile esotropia in children of Chinese descent was only 5.9% (as opposed to 36% in non-Chinese children).<sup>10</sup>

### Diagnosis

Cover test measurements to measure the angle of strabismus may be difficult in very young children. The light reflex tests (Hirschberg and Krimsky) are easier to perform in infants. A variation of the light reflex test in which the deviation is neutralized by prisms held apex to apex before both eyes may be required if the angle of strabismus is very large. The deviation tends to be constant but may vary; spontaneous resolution may occur if the deviation is small (<40Δ) or intermittent.<sup>11</sup> Refractive errors are typically similar to those of normal children of the same age.

In older children with surgically corrected or uncorrected infantile esotropia, FMN may confound attempts at monocular acuity measurement; fogging one eye with plus lenses, a translucent occluder, or anaglyph (red-green) lenses may provide a more accurate acuity measurement in the face of FMN.

Side-gaze observations by nonophthalmologists may be particularly deceptive in the case of pseudo-strabismus, as the adducted eye is buried easily under the skin fold. Hirschberg's light reflexes may demonstrate alignment to the parents, as can elevation of the nasal bridge skin away from the face to alter the facial appearance temporarily (see Fig. 11.6.5B).

### Differential Diagnosis

The differential diagnosis of infantile esotropia (Box 11.6.2) includes the entities discussed in detail later. The nystagmus blockage (compensation) syndrome, in the opinion of some investigators, accounts for a significant segment of the young population with large-angle, early-onset esotropia.<sup>12</sup> These patients have a large esotropia and nystagmus at a young age. The nystagmus is of minimal amplitude in adduction and maximal in abduction.<sup>13</sup> Therefore, the patient makes a continuous effort to maintain both eyes in adduction through the use of convergence, and it may be



impossible to neutralize the esodeviation by using prisms held before one or both eyes. This is in contrast to nystagmus associated with the common form of infantile esotropia (FMN), which presents in equal degrees in all gaze positions. Various series imply that nystagmus blockage syndrome affects 10%–12% of patients with infantile esotropia, but many investigators believe that it is much less common. Sixth cranial nerve palsies need to be considered in the transient newborn form, which often resolves spontaneously over a few days or weeks as well as the more common acquired postviral or postimmunization form.

Treatment

The theoretical goals of treatment include the following:

- Excellent visual acuity in each eye.
- Perfect single binocular vision in all gaze positions at distance and near.
- A normal aesthetic appearance.

All of the above are obtainable except for perfect single binocular vision (with rare exceptions)<sup>14</sup> because these patients, even with early treatment, do not view with both foveae simultaneously. However, as discussed later, most obtain peripheral fusion with the monofixation syndrome and generally stable alignment. Other reported benefits of successful surgical alignment include improvement in fine motor skills, enlarged binocular visual field, and even heightened bonding between the parents and the child.

Amblyopia traditionally is treated preoperatively for multiple reasons: (1) Compliance is usually better as families are more motivated to treat when they can see the strabismus; (2) visual behavior may be evaluated more easily (the eye moves to take up fixation in the presence of a large strabismus); (3) amblyopia responds more quickly in a younger child; and (4) postoperative occlusion treatment would interfere with the potential development of binocularity. Amblyopia associated with infantile esotropia is amenable to treatment. With the appropriate optical correction and occlusion therapy (or equivalent) adjusted throughout the first years, 20/20 vision can be achieved in most patients.<sup>15</sup> The impact of treatment of refractive errors less than +2.00 D usually is minimal. Larger refractive errors are corrected, and the deviation is remeasured because postoperative exotropia may occur if surgery is performed on uncorrected, highly hyperopic eyes denoting an accommodative esotropic component.

When infantile esotropia is left untreated, patients do not display binocular vision of any type when they become old enough to cooperate for testing of their visual sensory status. The primary goal of surgical treatment at this age is to align the eyes sufficiently to stimulate the development of some binocularity. This binocularity usually fulfills the criteria for monofixation syndrome, as defined by Parks,<sup>16</sup> and is generally a stable alignment.<sup>17,18</sup> The works of Birch<sup>19</sup> and Ing<sup>20</sup> revealed that the time windows during which stereopsis and fusion develop are during years 1 and 2 of life, respectively. This binocular function timeline favors early surgical correction. Some studies suggested that surgical correction by age 1 year is more effective than that performed later.<sup>21,22</sup> Some even suggested very early surgical correction (at the age of 2–4 months) to develop better binocularity.<sup>14,23</sup> However, this is typically unrealistic because most patients are not presented this early to a strabismus specialist.

Advocates of surgery after age 2 years are concerned about the later development of inferior oblique muscle overaction and DVD, which require separate surgical procedures, and the difficulty of measuring acuity in children who have aligned visual axes. They are unconvinced about the benefits of the monofixation syndrome (peripheral fusion without central fusion). Given the reproducible strabismus measurements, informed and supportive parents, the availability of safer pediatric anesthesia, and the absence of amblyopia, most strabismus surgeons in the United States opt for attempts to achieve horizontal alignment during the patient’s first year of life.

Most ophthalmologists in the United States will choose symmetrical medial rectus muscle recessions on both eyes (possibly adding a monocular or binocular lateral rectus muscle resection or plication for very large deviations). However, monocular surgery is often preferred when one eye has poor vision to avoid the risk of surgical complication in the good eye. Monocular surgery is typically recession of the medial rectus muscle and resection or plication of the ipsilateral lateral rectus muscle. Some surgeons prefer a limbal incision because of the ease of access and orientation as well as the ability to recede contracted conjunctiva and to thus augment the effect of the medial rectus muscle recession. Many prefer the fornix approach popularized by Parks because it avoids proximity to the cornea and results in rapid patient mobilization. It also may have better early cosmesis. Some surgeons prefer to perform recessions measured from the limbus, rather than the original muscle insertion, because of increased

TABLE 11.6.1 Surgery for Infantile Esotropia<sup>a</sup>

Deviation* (Δ)	Symmetrical	Asymmetrical (One Eye)	
	Recess Medial Rectus, Both Eyes (mm)	Resect Lateral Rectus (mm)	Recess Medial Rectus (mm)
30	4.5	5.5	4.5
35	5.0	6.0	5.0
40	5.5	6.5	5.5
50	6.0	7.0	6.0
60	6.5	7.5	6.5
70	7.0	8.0	7.0

\*There are many surgical dosage tables. This one is commonly used around the world.

uniformity. A common protocol for surgical treatment is given in Table 11.6.1. Some variability occurs in certain patient populations. Recently, Park and Oh found that in preterm infants with infantile esotropia, the overcorrection rate was greater than in full-term children, even though the extent of surgery was reduced by 0.5 mm per muscle in preterm patients.<sup>24</sup>

A novel approach to infantile esotropia is the use of botulinum toxin, originally popularized by Scott.<sup>25</sup> In a retrospective study comparing botulinum toxin to surgical bilateral medial rectus muscle recession for esotropia in patients younger than 2 years of age, no statistically significant difference existed in terms of alignment and stereopsis between the groups.<sup>26</sup> Advocates of botulinum toxin argue that reduced anesthesia time gives it a distinct advantage. Many patients, however, require more than a single injection, and because the anesthesia risk primarily occurs during induction and emergence, this advantage may disappear. Potential side effects from the toxin, such as ptosis and the induction of vertical strabismus, are to be considered because these young patients are in the amblyogenic age range.<sup>27</sup>

Patients with DVD usually exhibit no binocularity when DVD is present. The treatment of DVD generally is surgical. The surgery can be symmetrical or asymmetrical and may involve significant recessions of the superior rectus muscles or inferior oblique muscles in the presence of overaction. When there is inferior oblique muscle over action, the most common inferior oblique muscle weakening procedures are myectomy and recession. In mild cases, some recommend a “z” myotomy.<sup>28</sup> Anteriorization of the oblique muscle insertion into the margin of the inferior rectus muscle significantly weakens the muscle and may be an effective treatment for simultaneous DVD. Clear separation between DVD and inferior oblique muscle overaction is necessary, however, because weakening of a normally functioning inferior oblique muscle may cause limitation of elevation in adduction, compensatory head postures, and all the signs and symptoms of cyclovertical muscle palsy.

Course and Outcome

Children who have surgery for infantile esotropia require long-term follow-up because of the possible development of DVD, inferior oblique muscle overaction, FMN, and amblyopia. An optimal result is alignment within 8Δ of orthophoria. Residual esotropia of greater than 10Δ found 4–6 weeks after initial surgery may respond to antiaccommodative measures if the patient has significant hyperopia, with a repeat strengthening procedure likely necessary. This might consist of bilateral lateral rectus muscle strengthening procedure for those who initially underwent bilateral medial rectus muscle recessions, and a recess-resect/plication procedure on the unoperated eye for those who underwent a unilateral procedure. A surgical correction for DVD or inferior oblique muscle overaction may be indicated as well. Thus, it is not uncommon for a patient with infantile esotropia to undergo two to three surgical procedures during childhood. A significant fraction of patients who initially achieve alignment later develop accommodative esotropia and require treatment with glasses.<sup>29</sup> Preoperative parental education regarding these common postoperative scenarios cannot be overemphasized. Asymmetrical monocular pursuit as measured by OKN testing persists indefinitely and may be a perpetual marker for infantile esotropia.

ACCOMMODATIVE ESOTROPIA

Introduction

Accommodative esotropia is the most common esodeviation in children and is characterized by two mechanisms simultaneously occurring in the

same individual. The first mechanism is high hyperopia, with an average of +4.50 D, and the second is a tendency for larger esodeviation at near fixation. This mechanism is called a *high AC/A ratio* and will be discussed in further detail later.

## Epidemiology and Pathogenesis

Accommodative esotropia is characterized by an intermittent esotropia that appears at age 2–3 years; however, earlier onset is not rare. Parents usually note it toward the end of the day or when the child is very tired, ill, or daydreaming (especially at near fixation distances, e.g., across the dinner table). At onset, the child may experience asthenopia as fusional divergence amplitudes are stressed and may rub the eyes or squint; an older child may complain of headaches or diplopia and close one eye. As the esotropia becomes more frequent, abnormal retinal correspondence and suppression, when extant, relieve asthenopic symptoms at the possible expense of fusional divergence amplitudes. Some children maintain intermittent esotropia for long periods, whereas in others the condition degrades quickly to constant esotropia, especially at near fixation, leading to a risk of development of strabismic amblyopia.

## Ocular Manifestations

Patients who have high hyperopia must generate a large, accommodative effort to see clearly at distance and an even larger effort for clear vision at near. They may “choose” blurred vision and straight eyes to maintain comfortable single binocular vision (but at the risk of developing bilateral ametropic amblyopia if high hyperopia is present). Alternatively, they may “choose” clear vision and risk asthenopia and esotropia. Those patients who have high hyperopia, but do not develop esotropia and maintain excellent acuity, often have low AC/A ratios.

Patients with high AC/A ratios have greater deviation at near because of overactive convergence response to a given accommodation requirement. This ratio can be calculated by using two methods—the *heterophoria* method and the *gradient* method—as described in [Box 11.6.3](#). A ratio up to 6/1 is considered normal. An accurate calculation of the AC/A ratio generally is not required in a clinical setting, and some have suggested treating the AC/A ratio as a concept, rather than a quantity.<sup>5</sup> The rule of thumb is if the esotropia at near is greater than the esotropia at distance by 10Δ or more, a high AC/A ratio exists. Patients who have low hyperopia or myopia can also have a high AC/A ratio and develop an esodeviation greater at near.

## Diagnosis and Ancillary Testing

Alignment at distance and near, together with upgaze and downgaze (to detect A/V patterns) will provide most of the valuable information for the examiner. In patients who have a V-pattern esotropia with greater deviation in downgaze, it is important to measure near deviations in primary position to avoid confusion with V-pattern esotropes.

The other crucial information is the accurate cycloplegic refraction to determine the full degree of hyperopia. Historically, atropine has been considered essential to obtain the maximal hyperopic refractive error; however, its use requires a return visit (typically after 2–3 days of atropine instillation), its cycloplegic effect is prolonged and may be associated with systemic side effects. Nowadays, the standard cycloplegic agent is cyclopentolate with or without tropicamide. It permits short onset and, in most patients, provides results within +0.50 D of the refractive error obtained using atropine. Children with dark irides might have residual esotropia because of latent uncorrected hyperopia, and atropine refraction should be considered to uncover the full hyperopic refraction.

If the esodeviation cannot be found on initial attempts, occlusion of one eye for 45 minutes to 3 hours may be carried out, or cycloplegia can be induced and cover testing performed by using suitably large targets. An esodeviation after cycloplegia provides strong confirmation of parental observations and may be sufficient to warrant initiation of treatment.

## Differential Diagnosis

Infrequently, a child presents with sudden diplopia and comitant esotropia—acute acquired comitant esotropia (AACE). Although many cases are nonneurological, comitance does not rule out the possibility of an underlying neurological condition, such as intracranial tumors, Chiari malformation, and hydrocephalus. In a recent series of 48 children with AACE, 6% had intracranial disease. Imaging may be warranted, especially

### BOX 11.6.3 Accommodative Convergence-to-Accommodation Ratio Calculations

#### Heterophoria Method

Determine the distance and near deviation in prism diopters and the interpupillary distance in centimeters.

$$AC/A = IPD(\text{cm}) + \frac{(\Delta_2 - \Delta_1)}{F}$$

where

AC/A ≡ accommodative convergence to accommodation

IPD ≡ interpupillary distance

Δ<sub>1</sub> ≡ distance deviation (eso is +, exo is −)

Δ<sub>2</sub> ≡ near deviation

F ≡ near fixation distance in diopters of accommodation (1/2 meter ≡ 2 D, 1/3 meter ≡ 3 D)

#### Example

IPD ≡ 60 mm or 6 cm

Δ<sub>1</sub> ≡ 3 ET

Δ<sub>2</sub> ≡ 30 ET

F ≡ 1/3 m ≡ 3 D

$$AC/A = 6 + \frac{30 - 3}{3} = 15 \text{ (high)}$$

#### Gradient Method

Determine eye deviation in prism diopters at a fixed distance with and without a supplemental lens correction (generally +3 D lens).

$$AC/A = \frac{\Delta_1 - \Delta_2}{D}$$

Δ<sub>1</sub> ≡ ocular deviation without lens

Δ<sub>2</sub> ≡ ocular deviation with lens

D ≡ power of lens used

#### Example

Δ<sub>1</sub> ≡ 25 ET

Δ<sub>2</sub> ≡ 16 ET

D ≡ +3.00

$$AC/A = \frac{25 - 16}{3} = 3 \text{ (normal)}$$

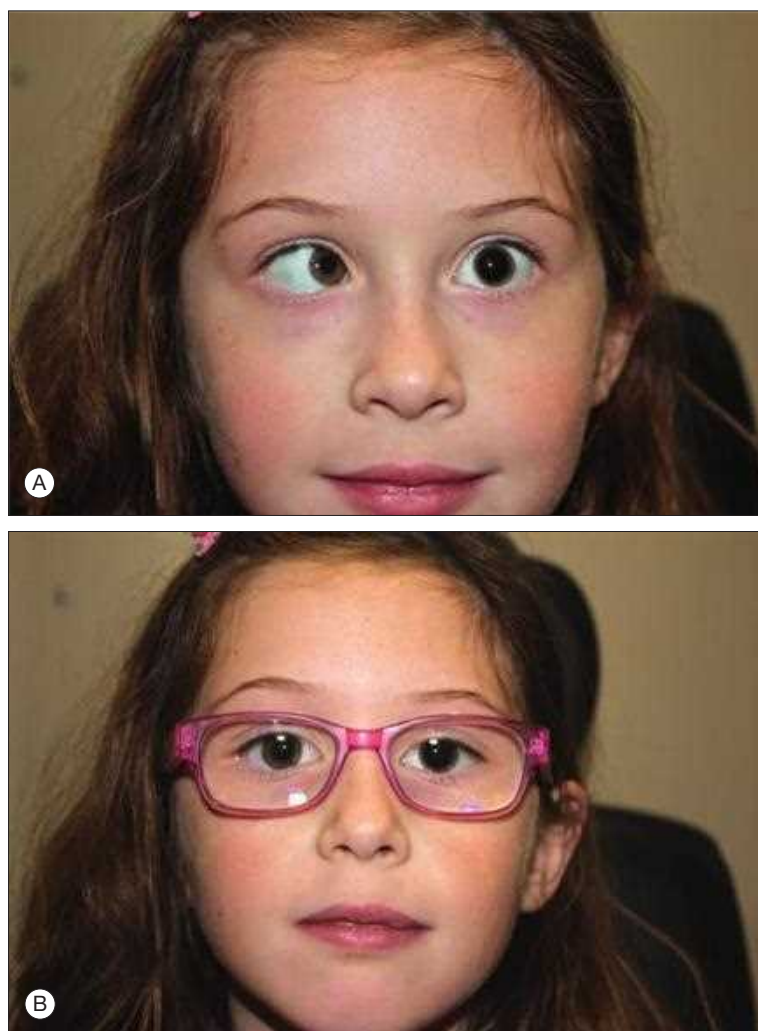
in the setting of greater deviation at distance than near, age greater than 6 years at presentation, recurrent AACE, or other neurological signs.<sup>30</sup> Other entities are listed in [Box 11.6.2](#).

## Treatment, Course, and Outcome

Treatment consists of antiaccommodative measures, primarily the prescription of most or all of the patient's hyperopic refractive error (to do the focusing for the child so accommodation and thus convergence are not stimulated) ([Fig. 11.6.6](#)). Parents must be warned that once glasses are prescribed, the child may exhibit larger and more frequent esodeviations when glasses are removed.

The fit of eyeglasses for infants and toddlers is challenging because of the frame weight, flat nasal bridge, lack of cooperation, and small face but is imperative for adequate treatment. The child is re-evaluated after a month's full-time wear of the prescription. If the distance and near esodeviations are reduced to within the monofixational range (≤8Δ of esotropia) and the child has a comfortably controlled phoria and no asthenopic signs or symptoms, the treatment is considered initially successful and the patient is re-evaluated 3–6 months later, depending on age. Assessment of visual acuity at distance and near, assessment of alignment at distance and near, and sensory testing are monitored. Cycloplegic refractions are repeated periodically. If the distance tropia is greater than the above limit, the cycloplegic refraction is repeated. If the greater deviation persists despite full hyperopic prescription, the patient becomes a candidate for surgery. If the distance deviation is controlled but an esotropia greater than the above limit is present at near fixation, or if a symptomatic phoria at near fixation persists, the patient can be given bifocal glasses.

The height of the bifocal segment needs to be high enough to split the pupil in primary position to be functional in young children. The initial bifocal strength may be estimated from measurement of the near esodeviation by using various strengths of trial frame lenses or arbitrarily given as



**Figure 11.6.6 Accommodative Esotropia.** (A) Without hyperopic correction there is prominent right esotropia. (B) Eyes are straight with full hyperopic correction. This patient is dilated in the left eye from amblyopia penalization treatment of the better seeing left eye.

+2.50–3.00 D. The patient is asked to wear the bifocals with re-evaluation to be done in 1–2 months. One study found that despite their widespread use, bifocals did not improve the outcomes in children with accommodative esotropia with high AC/A.<sup>31</sup>

When the successfully treated child is about 5 years of age, the parents may note less esodeviation without glasses; at about 6 years of age, the power of the glasses often can be weakened progressively, roughly 0.50–0.75 D every 6 months, beginning with the bifocals. A common practice is to place the weaker correction in a trial frame and perform cover testing; occasionally, a patient appears to have alignment during this office evaluation but develops significant esodeviation, asthenopic symptoms, or both, when the weaker correction is worn. In such cases, the patient should return to the previous stronger prescription. It often is possible to eliminate bifocals by age 8 or 9 years and the mild to moderate hyperopic correction by the early teenage years. Patients who have high hyperopia, significant astigmatism, or anisometropia may require optical correction for acuity purposes after their accommodative esotropia has resolved, and this can sometimes be done with contact lenses.

Patients whose treatment is initiated after age 4 years may not accept their full hyperopic correction without a period of cycloplegia (e.g., one drop of atropine in both eyes). Ideally, the minimal correction necessary to provide and maintain comfortable single binocular vision and (in the case of high hyperopia) good visual acuity is prescribed. After age 6 years, the AC/A ratio tends to normalize, but hyperopia may increase. Rarely, treatment of accommodative esotropia with miotics, such as ecthiopate iodide 0.125%, may be indicated. This cholinesterase inhibitor causes pharmacological accommodation (and miosis), which results in reduction of the accommodative effort and, therefore, less associated convergence. The ideal candidate for this treatment would be a patient with high AC/A ratio; or it can be used as a temporary measure in older children when wearing glasses is not desired, such as during sports or social events. V-pattern esotropia with the greatest deviation in downgaze is another condition

where miotics can be employed. One of the most common side effects are iris cysts along the pupillary margin; these cysts typically regress when the drop is discontinued or when topical 2.5% phenylephrine is added. Other notable side effects include brow ache and prolongation of respiratory paralysis in patients undergoing general anesthesia with succinylcholine. Miotics are less popular now, partly because it is difficult to obtain in the United States.

At any time after a period of successful antiaccommodative treatment, a patient may develop esotropia that cannot be controlled with glasses.<sup>32</sup> Repeat refraction is carried out, and if greater hyperopia is found, the full hyperopic correction is prescribed. It is difficult to predict the effect of even as little as +0.50 D additional correction on a decompensated accommodative esotrope. If no effect is obtained after a few weeks' trial, the patient is said to have partially accommodative esotropia and should undergo strabismus surgery.

For most ophthalmologists, bimedial recession classically directed toward the nonaccommodative component of the esodeviation is the procedure of choice. The target angle, however, is debatable and includes correcting for the residual deviation at distance and at near or the average deviation between distance and near. Some surgeons empirically add 1 mm recession per medial rectus muscle for a high AC/A ratio. Others believe that posterior fixation sutures combined with medial rectus muscle recessions benefit patients with high AC/A ratios.<sup>33</sup> In general, patients with high AC/A ratios are more difficult to manage.<sup>34</sup> Some utilize the prism adaptation test to reduce the underresponse rate—that is, prescribing base-out prisms for the residual esotropia over the full hyperopic correction until no esotropia is present and operating for that angle.<sup>35</sup> Parents must be warned about the continual need for antiaccommodative treatment even after strabismus surgery, which typically consists of eyeglasses. Hyperopic laser in situ keratomileusis (LASIK) has been effective mainly in older patients (ages 10–52 years)<sup>36</sup> but is not commonly used for accommodative esotropia in the United States for many reasons, including the usual shift toward emmetropization over time. Studies have shown that around 60% of children can be weaned out of spectacles during their grade school years.<sup>37,38</sup>

A difficult group of patients consists of teenagers who have their condition well controlled with bifocals or high hyperopic correction but who have aesthetic concerns. A switch to contact lenses places less accommodative demand on the patient and may enable comfortable single binocular vision at near fixation without the need for separate reading glasses. Bifocal contact lenses may be tolerable to some patients; few are satisfied with “monovision” fitting of one lens for distance and another for near. Progressive bifocals may be tolerated by some teenagers and permit persistent bifocal treatment without the dysaesthetic impact of a bifocal line. Finally, cautious single medial rectus muscle recession or small bimedial rectus muscle recession may be performed in those patients who fuse at distance when wearing single-vision lenses and who wish to be rid of their bifocals.

The effective management of accommodative esotropia demands a long period of cooperation among patient, physician, and parents and is as much art as science. Nowhere else in strabismus management are communication skills more important than in the management of accommodative esotropia.

## CYCLIC ESOTROPIA

This rare form of strabismus, first reported by Burian<sup>39</sup> in 1958, is a condition of intermittent esotropia most commonly presenting as alternate 12- to 36-hour periods of perfect alignment followed by constant, usually large-angled (30–40Δ) esotropia. The age of onset is generally 3–4 years. When the eyes are aligned, excellent fusional abilities and stereopsis are found; when esotropia is present, patients exhibit abnormal retinal correspondence and suppression. Some patients who have cyclic esotropia display irritability and emotional withdrawal during periods of strabismus. The incidence of cyclic esotropia has been estimated to be 1 in 5000 cases of strabismus. Aids to diagnosis include a strong suspicion and a log of the strabismus periods kept by the parents. This condition differs from early intermittent accommodative esotropia because cycles are strictly repetitive, and during the aligned periods, little or no strabismus may be elicited despite prolonged occlusion.

The cause is unknown but may be related to the “biological clock” phenomenon popularized by Richter.<sup>40</sup> Some patients develop cyclic esotropia after head trauma, a neurosurgical procedure, strabismus surgery, or infection. Most patients eventually decompensate to a constant strabismus and require surgery.



Antiaccommodative measures usually have little effect during periods of strabismus and are not needed during aligned periods. Surgical treatment is successful in 75%–90%<sup>41</sup> of cases in attaining alignment with one operation, whether performed during aligned or strabismic periods.

## MOEBIUS' SEQUENCE

Moebius' sequence consists of unilateral or bilateral facial nerve palsy with abduction limitation. It may be associated with other cranial nerve palsies, orofacial dysmorphism, distal limb or axial malformations, and intellectual impairment.<sup>42,43</sup> Some young infants have difficulty suckling, as well as abnormal phonation. The upper motor neuron seventh cranial nerve palsies cause smooth facies, lagophthalmos, absent nasolabial folds, rounded mouth, and decreased facial emotional responses. In a series of 46 patients with Moebius' sequence, three patterns of ocular motility occurred: (1) orthotropia in primary position with complete abduction and adduction deficits (41%), (2) large-angle esotropia with cross-fixation (50%), and (3) large-angle exotropia with torticollis, absence of convergence, and vertical eye misalignment (9%).<sup>43</sup> Most, if not all, patients lack binocular function. When cross-fixation is present, it is similar to infantile esotropia; as a rule, however, abduction to the midline cannot be performed.<sup>43</sup> Patients who have esotropia generally have tight medial recti on forced duction testing<sup>44</sup>; those who have gaze palsy and straight eyes in primary gaze do not.

The cause of the esotropia may include both involvement of sixth cranial nerve fascicles and nuclei, as well as an aberrant medial rectus muscle insertion because some patients have medial recti that insert quite close to the limbus. No treatment is necessary or highly successful in patients who have gaze palsies alone. Those who have esotropia and are unable to abduct to the midline require medial rectus muscle recessions. These recessions may be technically quite challenging because the muscles are very tight and difficult to hook, suture, and safely detach from the globe. Double-overlapping marginal myotomies may be safer in some situations. Resections of the nonfunctioning lateral recti are avoided, as they are generally ineffective.

## DUANE'S SYNDROME

### Epidemiology and Pathogenesis

Duane's syndrome, or Duane's retraction syndrome, which accounts for 1% of all strabismus, is a congenital, usually sporadic miswiring of the medial and lateral rectus muscles, resulting in abnormal horizontal eye movements. The most common variant of this syndrome is Duane type 1 (85%) being more common in girls (60%) and affecting the left eye (60%). It is characterized by limited abduction of the involved eye and often has a "tether" phenomenon, which consists of overelevation or overdepression on attempted adduction as the retracted globe escapes from its horizontal rectus muscle restrictions<sup>45</sup> (Fig. 11.6.7). This specific pattern can distinguish between Duane's syndrome and sixth cranial nerve palsy.

### Ocular Manifestations

Neuropathologically, this disorder has been shown to be caused by an absent sixth cranial nerve nucleus and nerve and innervation of the lateral rectus muscle by a branch from the inferior division of the third cranial nerve.<sup>46,47</sup> Thus, classic electromyographic findings of absent lateral rectus muscle firing upon attempted abduction, and firing of both horizontal recti upon attempted adduction, are explained.<sup>48</sup> Simultaneous contraction

of both muscles will cause globe retraction and decreased palpebral fissure on adduction. No mechanism exists to improve the abduction limitation. Typically, patients who develop esotropia and tight medial rectus muscles adopt a head turn toward the affected eye (e.g., a left head turn in a left type I Duane) to maintain single binocular vision (Fig. 11.6.8), or they maintain a straight head but accept esotropia, abnormal retinal correspondence, and suppression, if extant. In general, since these patients develop an abnormal head posture to maintain binocularity, amblyopia is uncommon.

Duane's syndrome is bilateral in roughly 20% of cases; less common forms include type II (14%), with limitation of abduction and a tendency toward exotropia, and type III (1%), with limitation of both abduction and adduction and any form of horizontal strabismus.

### Treatment

The indications for surgical correction are chronic abnormal head posture, manifest deviation in primary position, significant upshoots or downshoots and disfiguring globe retraction. The amount of esotropia in monocular Duane's syndrome type I is rarely greater than 30Δ. The examiner should make sure that alignment in primary position is measured without any head turn, otherwise esotropia will be underestimated. Recession of the ipsilateral medial rectus muscle aligns the eye but does not improve abduction beyond primary position. Rarely, very large weakening procedures on the medial rectus muscle result in consecutive exotropia, but the mechanisms are unclear. A small medial rectus muscle recession in the opposite eye can help stabilize the pathological eye in primary position by application of Hering's law.<sup>49,50</sup> Resection of the lateral rectus muscle generally is avoided, as it increases retraction and may not improve abduction. Various surgical options of lateral transposition of the vertical rectus muscles has been shown to improve abduction of the affected eye.<sup>51,52</sup>

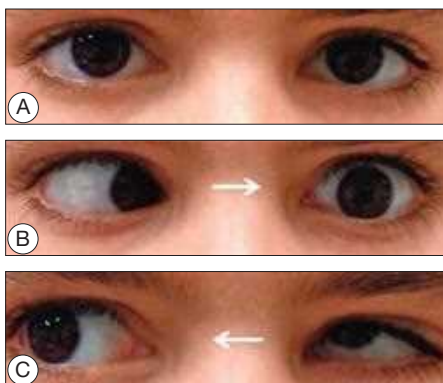
The tether phenomenon may be improved surgically by using posterior fixation sutures for the horizontal rectus muscle or by horizontal splitting of the lateral rectus muscle into a "Y" structure, with resuturing of the muscle above and below the axis of the lateral rectus muscle. If extreme retraction with pseudoptosis is dysaesthetic, both horizontal recti may be recessed to relieve the retraction.

### Systematic Associations

Systemic associations in 30% of cases include: Goldenhar's syndrome (also known as *oculo-auriculo-vertebral syndrome* or *facio-auriculo-vertebral dysplasia*); Klippel-Feil syndrome; a rare autosomal dominant form; the Wildervanck association of Duane's syndrome, and congenital labyrinthine deafness. Brainstem auditory evoked responses occasionally are abnormal, which suggests widespread neurological abnormalities.

## STRABISMUS FIXUS

This rare, congenital, stationary, very large-angle esotropia of unknown cause may represent a form of congenital fibrosis of the medial rectus muscles. The condition differs from strabismus fixus seen in adults, which typically occurs in the presence of high myopia ("heavy eye syndrome," discussed later in this chapter). Usually, no abduction is possible, and strabismus surgery on these very tight muscles often is of little benefit.



**Fig. 11.6.7 Versions in Duane's Syndrome Type I.** This child has Duane's syndrome type I in his left eye. (A) Very mild esotropia in primary gaze. (B) On left gaze (direction of arrow), there is no abduction of the left eye beyond the midline. Lid fissure widens on attempted abduction. (C) On right gaze (direction of arrow), the lid fissure of the left eye narrows, and the globe displays an upshoot on attempted adduction of the left eye.



**Fig. 11.6.8 Head Posture in Left Duane's Syndrome Type I.** This child has a face turn to the left to compensate for deficient abduction in the left eye. (Reproduced with permission from Fells P, Lee JP. Strabismus. In: Spalton DJ, Hitchings RA, Hunter PA, eds. Atlas of clinical ophthalmology. London, New York: Gower Medical Publishing; 1984. p. 6.7.)

## ESOTROPIA IN THE NEUROLOGICALLY IMPAIRED

The incidence of strabismus is higher in the population of neurologically impaired children than in the general population. In addition to the previously mentioned categories, children with neurological impairment may have a variable intermittent esotropia that is unresponsive to antiaccommodative measures; it may be stable, worsen to a constant tropia, or disappear with maturity. Surgery is avoided unless measurements of the deviation are reproducible, the patient is intellectually capable of benefiting from improved binocular function, and the effects of any neurotropic medications, especially sedatives, are considered. Surgical outcome may be less successful in these patients, but antiaccommodative measures may be helpful.<sup>53</sup> The population of patients with Down syndrome with strabismus are an exception and appear to respond better than most groups of children with neurological impairment.<sup>54</sup> In addition, a patient under significant emotional stress occasionally presents with temporary esotropia, sometimes related to accommodative spasm. Transient esotropia and diplopia during vigorous exercise also have been reported,<sup>55</sup> but the mechanism is poorly understood.

## ESOTROPIA ASSOCIATED WITH VISUAL DEFICIT (SENSORY ESOTROPIA)

Children who have impaired vision in one or both eyes are at risk for the development of strabismus. Esotropia develops in a high proportion of infants younger than age 2 years who have decreased acuity secondary to congenital cataract, corneal opacity, retinal pathology, or other devastating media clarity impairment. Early surgery for media diseases has a low prognosis for the development of stable single binocular vision. In cases of unilateral blindness and esotropia, the surgical approach often is best limited to the involved eye. Strabismus surgery outcomes in this population are guarded and likely correlate with the poor fusion and the dense amblyopia associated with this condition.<sup>56</sup>

## THE “HEAVY EYE SYNDROME” AND THE “SAGGING EYE SYNDROME”

In some patients who have acquired esotropia with high myopia, the lateral rectus muscle shifts inferiorly and the superior rectus muscle shifts nasally, leading to esotropia and hypotropia.<sup>57</sup>

A different group of patients with acquired esotropia have divergence insufficiency or divergence paralysis esotropia. These older patients do not have high myopia. They have comitant esotropia and diplopia at distance fixation and fusion at near fixation with minimal abduction deficit.<sup>58</sup> Orbital imaging studies of these patients have shown degeneration of the lateral rectus–superior rectus band, which results in an inferior displacement of the lateral rectus muscle. Therefore, the term “sagging eye syndrome” has been suggested for the condition in this group of patients.<sup>59</sup> Both medial rectus recession and lateral rectus resection/plication are effective surgical options.<sup>58,60</sup>

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# Exotropia

Daniel J. Salchow

# 11.7

**Definition:** Divergent misalignment (outward deviation) of the visual axes of the eyes, which may manifest constantly or intermittently. It may be acquired or congenital, most often its etiology is unknown (primary forms of exotropia) but may be secondary to other underlying causes.

## Key Feature

- Outward deviation of one eye.

## Associated Features

- History of closing one eye in bright sunlight (intermittent exotropia).
- Amblyopia, if present, usually mild unless exotropia constant.
- Inferior or superior oblique muscle overaction may be present.
- A, V, or other “alphabet” patterns in some cases.

## INTRODUCTION

Exotropia is a manifest divergent misalignment of the visual axes of the eyes. A latent outward deviation is called *exophoria*.

Intermittent exotropia (IXT; Fig. 11.7.1) is the most frequent cause of exotropia. It is a primary exotropia, and its cause remains unknown. In many patients, IXT may be considered a progressive disease; an exophoria may decompensate to an intermittent exotropia and finally to a constant exotropia.<sup>1,2</sup> Von Noorden reported that in 75% of patients, the condition progressed, in 9%, it did not progress, and in 16%, it improved with time.<sup>2</sup>



**Fig. 11.7.1 Intermittent Exotropia.** (A) Eyes straight. (B) A few moments later, the exotropia has become manifest. (Courtesy Howard Eggers.)

This highlights the need for regular observation, particularly in children with IXT.

Infantile exotropia, another primary exotropia, is very rare.<sup>3</sup> It presents with constant exotropia in the first 6 months of life.

Exotropia also may be secondary to oculomotor palsy, Duane's syndrome, craniofacial disorders, internuclear ophthalmoplegia (INO), and other disorders. Sometimes an exotropia develops after surgery for esotropia, which is termed *consecutive exotropia*, or it even develops spontaneously in patients who had infantile esotropia. The distinction between primary and secondary exotropia usually is straightforward because of characteristic findings in cases of secondary exotropia. Sensory exotropia denotes an exotropic eye with severely reduced vision.

## EPIDEMIOLOGY AND PATHOGENESIS OF INTERMITTENT EXOTROPIA

IXT makes up about 50% of exotropias in children<sup>4</sup>; its incidence in the United States is 32.1 per 100 000 in persons under 18 years.<sup>5</sup> IXT is more common in Asian populations<sup>6–10</sup> and possibly also in women.<sup>10–12</sup> Patients with IXT may more frequently develop other disorders, such as attention deficit hyperactivity disorder (ADHD) and adjustment disorder.<sup>13</sup> The distribution of refractive errors in patients with IXT is similar to that in the general population.<sup>14</sup> A positive family history increases the risk for exotropia. Inheritance is probably polygenetic.<sup>15,16</sup>

## OCULAR MANIFESTATIONS OF INTERMITTENT EXOTROPIA

IXT typically presents between ages of 2 and 4 years with a gradual onset of exodeviation, more frequently noted when the child fixes on a distant target. Squinting (closing) of the deviating eye and eye rubbing in bright sunlight are noted frequently and may be the presenting complaint. Contracture of lateral recti in long-standing cases of constant exotropia, true overaction of oblique muscles, lateral gaze incomitance, and alphabet patterns may be associated. In many patients with IXT, normal retinal correspondence is present when their eyes are aligned and anomalous retinal correspondence when the eyes deviate; these patients rarely complain of diplopia.<sup>17</sup> When the deviation has been latent for a long time, these sensory adaptations may not develop, and these patients experience diplopia when they have exotropia. The angle of the deviation often is stable until secondary contracture of the lateral recti ensues.

## Classification of Intermittent Exotropia According to Distance/Near Angle

In basic-type IXT, the difference between the distance and near angles is 10 prism diopters (PD) or less. In divergence excess type IXT, the distance angle exceeds the near angle by greater than 10 PD, in convergence insufficiency-type IXT, the near angle exceeds the distance angle by greater than 10 PD.<sup>18</sup> Diagnostic monocular occlusion ( $\geq 1$  hour) may be helpful, particularly in divergence excess-type IXT, which may convert to basic-type IXT. After diagnostic occlusion, if the distance angle still exceeds the near angle by more than 10 PD, the accommodative convergence-to-accommodation (AC/A) ratio should be determined by using the gradient method. If the exotropia at distance decreases by more than 12 PD when  $-2$  D lenses are placed before both eyes, the AC/A ratio is increased. Patients with divergence excess-type IXT and increased AC/A ratio are at risk for

TABLE 11.7.1 “Office Control Score” to Assess Control of Intermittent Exotropia<sup>18</sup>

5	Constant exotropia
4	Exotropia manifests >50% before dissociation
3	Exotropia manifests <50% before dissociation
2	Exotropia manifests only after dissociation, fusion in >5 seconds
1	Exotropia manifests only after dissociation, fusion in 1–5 seconds
0	Exotropia manifests after dissociation, fusion in <1 seconds (phoria)

Note: The examiner takes the score for distance and near fixation and uses the average. The higher the score, the poorer the control.  
From Mohnney BG, Holmes JM. An office-based scale for assessing control in intermittent exotropia. *Strabismus* 2006;14:147–50.

TABLE 11.7.2 “Revised Newcastle Control Score” for Assessment of Control of Intermittent Exotropia in Children<sup>15</sup>

	Score
Home control	
XT or monocular eye closure seen:	
Circle appropriate score	
Never	0
<50% of time fixing in distance	1
>50% of time fixing in distance	2
>50% of time fixing in distance + seen at near	3
Clinic control	
Circle appropriate score near and distance	
Near	
Immediate realignment after dissociation	0
Realignment with aid of blink or re-fixation	1
Remains manifest after dissociation/prolonged fixation	2
Manifest spontaneously	3
Distance	
Immediate realignment after dissociation	0
Realignment with aid of blink or re-fixation	1
Remains manifest after dissociation/prolonged fixation	2
Manifest spontaneously	3
Total NCS: (Home + Near + Distance) =	

Scores range 0–9 points. The higher the score, the poorer the control.  
From Buck D, Clarke MP, Haggerty H, et al. Grading the severity of intermittent distance exotropia: the revised Newcastle Control Score. *Br J Ophthalmol* 2008;92:577.

postoperative overcorrection (esotropia) at near and may require bifocal spectacles postoperatively, and this should be discussed before surgery.

Control of Intermittent Exotropia

Patients with IXT are able to intermittently align their eyes (control of IXT). If control is poor and exotropia manifests frequently, the risk for visual complications increases. Although often subjectively judged by the examiner (“good” – “fair” – “poor”) control can be assessed in standardized ways by using “control scores” (Table 11.7.1<sup>19</sup> and Table 11.7.2<sup>20</sup>). Since control may be variable, these scores also can vary even during one examination.<sup>21</sup>

Complications of Exotropia

Amblyopia occurs in 3%–4.5% of children with IXT.<sup>4,22</sup> Loss of binocular function (stereopsis) may complicate IXT, especially in children, particularly if phases of manifest exotropia increase. Generally, the better the control, the lower is the risk for these complications.

Contracture of the lateral recti may occur in patients with long-standing IXT and in those with constant exotropia. Adduction may be limited, and the tight lateral recti may act as tethering cords. On attempted elevation and depression in adduction, the globe may overelevator or overdepress, and this may be confused with oblique muscle dysfunction. However, both the inferior oblique and superior oblique muscles rarely may become truly overactive in patients with IXT. Forced duction testing of the oblique muscles differentiates those with true oblique muscle overaction from those with merely tight lateral recti.<sup>23</sup>

Some patients with IXT have less misalignment on side-gaze than in the primary position and have been considered at greater risk for surgical overcorrection.<sup>24</sup> Many patients have greater deviations in upgaze, downgaze, or both, than in the primary position; some have oblique overaction,

BOX 11.7.1 Differential Diagnosis of Exotropia

- Pseudo-exotropia from large, positive angle  $\kappa$  or hypertelorism
- Intermittent exotropia
- Decompensated exophoria
- Third cranial nerve palsy with medial rectus weakness
- Duane’s syndrome type II
- Synergistic divergence
- Infantile exotropia
- Exotropia in craniofacial syndromes (secondary to orbital anomalies)
- Convergence insufficiency/paralysis (e.g., in Parkinson’s disease)
- Exotropia consecutive to surgery for esotropia

which may explain the incomitance. All “alphabet patterns” may be found, from the common A (greatest deviation in downgaze) and V (greatest deviation in upgaze) patterns to the X, Y, and  $\lambda$  patterns discussed in depth in Chapter 11.8.

DIAGNOSIS AND ANCILLARY TESTING FOR EXOTROPIA

A family history of strabismus should be sought, as well as an estimation of age of onset, progression in frequency and severity, and recognition by family, friends, and teachers. Previous treatment for strabismus should be noted.

The ophthalmologist should study the alignment of the eyes as the patient enters the room and during the medical history to gain insight into the alignment under ordinary viewing conditions. Sensory tests for the presence of anomalous retinal correspondence, suppression, and stereopsis are performed first and evaluated, as discussed in Chapters 11.4 and 11.5, followed by the assessment of control in patients with IXT.

The cover test is used to detect exotropia, and the uncover test and alternate cover test are used to detect exophoria. The angle should be measured with the alternate cover test and prism test by using an accommodation-controlling target in the primary position at distance (ideally 20 ft [6 m]) and at near (1 ft [0.3 m]) fixation and in gazes right, left, up, and down at distance fixation. Ductions and versions are evaluated to search for oblique muscle dysfunction or contracture of the lateral recti. Evaluation of alignment at far distance fixation (horizon seen through a window or at the end of a long hallway) may uncover larger angles by minimizing the influence of accommodative convergence.

Sometimes, parents of children with IXT note strabismus at home, but the physician cannot detect misalignment with typical cover tests. Diagnostic occlusion may be used to disrupt fusion, and the eye is uncovered at the moment of alternate cover testing.

DIFFERENTIAL DIAGNOSIS

Only rarely is IXT confused with another form of strabismus; should it decompensate to constant exotropia, it must be differentiated from infantile exotropia and exotropia associated with other entities (Box 11.7.1). Inferior oblique muscle overaction and dissociated vertical deviation are common in infantile exotropia, but latent nystagmus is rare. Spontaneous alignment sometimes occurs by age 1 year; surgical correction by age 2 years provides alignment with monofixation syndrome as a satisfactory outcome in most cases.<sup>25</sup>

TREATMENT

Correction of Refractive Errors

Successful treatment of intermittent exotropia requires correction of any significant refractive error. Myopia is corrected fully to improve visual acuity at distance and to stimulate accommodative convergence. Significant hyperopia (greater than +3.00 D) is partially corrected as well because uncorrected high hyperopia may be associated with hypoaccommodation and poorer control of IXT.<sup>26</sup> Treatment of amblyopia alone rarely improves alignment, but treatment compliance before surgery is often better, and it is easier to follow visual acuity levels in each eye in nonverbal children before the eyes are aligned.

### BOX 11.7.2 Features Considered in the Decision on Surgical Treatment

Increasing frequency of strabismus (manifest 50% of the time or more)  
Decreasing binocularity (e.g., stereopsis)  
Decompensation from intermittent to constant exotropia  
Increasing symptoms of squinting and rubbing of eye(s), asthenopia, accommodative spasm  
Strabismus noted by friends, teachers, strangers  
Cosmetic deformity if obvious manifest deviation

## Orthoptic Treatment

Orthoptic training is based on the concept of deficient motor fusion and has been performed in some fashion for more than 80 years. Fusional vergence amplitudes may be enhanced, when deficient, by using a major amblyoscope or fusional training exercises in free space. Other techniques utilize monocular targets or stereograms.<sup>27</sup> Results vary, depending on the success criteria; long-term results, however, are lacking.

## Therapeutic Occlusion

Part-time monocular occlusion (alternating if amblyopia is absent) may improve control of IXT in some. Evidence of its long-term effectivity in the treatment of IXT is lacking.<sup>28</sup> It is sometimes used as a measure to delay strabismus surgery.

## Overcorrecting Minus Lenses

Overcorrecting minus lenses (−2.00 to −4.00 D over the habitual distance prescription) can stimulate accommodative convergence and may improve fusional control of IXT. The angle of the deviation decreases and control improves in most IXT patients in response to overcorrecting minus lenses.<sup>29–31</sup> These lenses usually are reserved for children because children have a larger accommodative reserve. Adverse effects include asthenopic complaints (eye strain, headache). Randomized trials on this topic are lacking.

## Optical Treatment

Use of therapeutic (base-in) prisms has been attempted in some patients with IXT, with questionable long-term efficacy. Typically, about 50% of the maximal distance deviation is corrected with prisms. In most younger patients, fusional convergence is relaxed in response to the prism (“eat” the prism), and the physician has to increase the prism strength progressively; older patients who have more constant exotropia and limited fusional amplitudes may respond more positively. IXT may become more constant when the prism glasses are removed. Prisms greater than 10 PD are difficult to incorporate into lenses; thus, Fresnel membrane prisms are more useful for larger deviations, although they cause a blurring effect (see Chapter 11.12).

## Pharmacological Treatment

By injecting pharmacological agents, extraocular muscles can be strengthened or weakened. Botulinum toxin weakens a muscle, and injection of 2.5 IU into both lateral recti can reduce the angle from 30 PD to 6–10 PD in children. The success rate after 6 months ranges from 40% to 70%; retreatments are frequently required (37.5%).<sup>32,33</sup> Adverse effects include upper lid ptosis and persistent consecutive esotropia.

To strengthen an extraocular muscle, bupivacaine (a calcium channel blocker) may be injected. Preliminary reports have shown encouraging results.<sup>34</sup>

## Surgical Treatment

Strabismus surgery is appropriate after conservative approaches have been attempted without satisfactory results. Patients with IXT become reasonable surgical candidates when many of the features listed in Box 11.7.2 are present. Patients with exotropia under 10Δ associated with the monofixation syndrome do not usually benefit from surgery unless a symptomatic latent component is present.

Children operated before age 7 years, and those in whom the deviation is present for less than 5 years may have better surgical results.<sup>35</sup> However,

TABLE 11.7.3 Advantages and Disadvantages of Bilateral and Unilateral Surgery for Exotropia

	Advantages	Disadvantages
Bilateral surgery (recession of both lateral recti or resection/plication of both medial recti)	Does not create lid fissure anomalies on side-gaze Recessions do not sacrifice muscle tissue Does not alter refractive error	Bilateral surgery may be difficult to explain to patients who note monocular strabismus Monocular surgery lends itself more readily to local anesthesia techniques
Unilateral surgery (recession of one lateral rectus and resection/plication of one medial rectus)	Preferred if one eye deeply amblyopic Preferred if patient demands surgery on one eye Monocular surgery lends itself more easily to local anesthetic techniques	Resections/plications involve disposal of muscle tissue Often leads to subtle lid tissue anomalies on side-gaze (wider in abduction than adduction)

TABLE 11.7.4 Suggested Extent of Surgery for Patients With Exotropia

Deviation (Δ)	Recess Lateral Rectus by (mm)	Resect Medial Rectus by (mm)
12	3.5	2.5
15	4.0	3.0
20	5.0	4.0
25	6.0	5.0
30	7.0	6.0
35	7.5	7.0
40	8.0	8.0
45	8.5	9.0
50	9.0	10.0
60	10.0	
70	11.0	

The amounts require the suture to be placed 1.0–1.5 mm from the lateral rectus insertion. Adapted from data from Marshall M. Parks, MD.

timing of surgery is an individual decision and should take into account the patient's (and parents') needs and wishes.

The surgeon must decide between bilateral surgery (bilateral lateral rectus muscle recession or bilateral medial rectus muscle resection or plication) and unilateral surgery (recession of one lateral rectus muscle combined with resection or plication of the ipsilateral medial rectus muscle). Historically, bilateral lateral rectus muscle recession was reserved for patients with divergence excess type IXT. Patients with convergence insufficiency type IXT received resection or plication of both medial recti, all others received unilateral surgery. The question whether unilateral or bilateral surgery yields better results has not been settled; both are effective. The advantages and disadvantages of bilateral and unilateral surgery are listed in Table 11.7.3. For exotropias larger than 40–50 PD, more than two muscles should be operated on.

Suggestions for the surgical amounts for given deviations are provided in Table 11.7.4. Most surgeons operate for the maximal deviation at distance fixation except in patients with convergence insufficiency; in those patients, some surgeons operate for the maximal deviation at near fixation, whereas others choose a more cautious approach and only correct the maximal deviation at distance fixation to avoid overcorrection. Patients whose deviation decreases by greater than 10Δ in lateral gaze from primary position should have 1 mm less lateral rectus muscle recession performed on the side of the lesser deviation. All patients should be warned of the possibility of postoperative diplopia.

## COURSE AND OUTCOME

Consecutive esotropia is a complication of surgery for exotropia, but recurrent exotropia is significantly more common. Reconstructive success may be defined as an esotropia or exotropia of less than 15Δ, and functional success is often defined as a small asymptomatic phoria or constant tropia less than 10Δ with peripheral fusion, or small residual intermittent exotropia. Published success rates after one operation are 70%–95% for reconstructive success and 44%–90% for functional success. Patients should be warned of the smaller lateral visual field expanse that occurs after successful surgery, and the potential for pseudo-ptosis as the vertical eyelid fissures may not be artificially widened as they are with large angle exotropias.



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# Torsional Strabismus

Scott K. McClatchey, Linda R. Dagi

# 11.8

**Definition:** Strabismus related to ocular torsion.

## Key Features

- A- and V-pattern deviations.
- Oblique overactions and underactions.
- Torsion of the globe.

## INTRODUCTION

### Definitions of Inferior Oblique Overaction, Superior Oblique Overaction, A-Pattern, and V-Pattern

“Oblique muscle overaction” and A- or V-pattern strabismus, are defined on the basis of clinical examination findings. Inferior oblique overaction (IO OA) is an elevation of the adducting eye in side gaze, whereas superior oblique overaction (SO OA) is a depression of the adducting eye in side gaze. In the extreme limits of gaze, the adducting eye may demonstrate exodeviation as well as a hypertropia (IO OA) or hypotropia (SO OA). The term “overaction” implies hypertonicity or excess neural stimulation; this clinical appearance, however, does not necessarily mean the oblique muscles are truly overacting. Instead, the term “oblique overaction” is used because the oblique muscles have their greatest vertical action when the eye is adducted. A common system for grading oblique overaction is 0 (normal) to 4+ (extreme).

A- and V-patterns are defined by the difference in horizontal deviation in upgaze compared with downgaze, where the patient is fixing on an

accommodative distance target, and the vertical gaze angle is about 30° from the primary gaze:

- A-pattern—at least 10 prism diopter (PD) lesser exodeviation or greater esodeviation in gaze up than down (Fig. 11.8.1).
- V-pattern—at least 15 PD greater exodeviation or lesser esodeviation in upgaze than downgaze (Fig. 11.8.2).

Precise head positioning when measuring deviation in side-gaze or up- or downgaze is difficult,<sup>1</sup> especially in children. Thus, the incomitant deviation in up- and downgaze may vary inadvertently, depending on the variable direction of gaze. Because of this, many clinicians simply label A- and V-patterns as mild, moderate, or large.

### The Three Axes of Strabismus

To understand these types of strabismus, it is important to understand the three axes of ocular motion. Each globe has 3° of freedom, and thus the motions of the eye fall into three orthogonal axes: horizontal, vertical, and torsional. Misalignment in the horizontal axis is seen as esotropia or exotropia (XT), whereas misalignment in the vertical axis is seen as hypertropia. But torsional misalignment is invisible to the clinician when the eyes are in primary position: Detection usually depends on observing the relatively skewed ocular deviations in various gaze directions, or on funduscopy by noting the incyclorotated or excyclorotated fundus appearance. Incyclotorsional misalignment is often attributed to SO OA, whereas excyclotorsion is often attributed to IO OA.

In human eyes, the actions of the extraocular muscles (EOMs) are not so cleanly separated along these axes. The horizontal recti are pure in their direction of action: Even in eccentric gaze, their muscle paths are constrained by the pulley system of the orbit. Because they originate on the nasally displaced orbital apex, the superior rectus muscle is responsible for modest intorsional effect, and the inferior rectus muscle for a modest extorsional effect. As a result, increased or decreased action of either

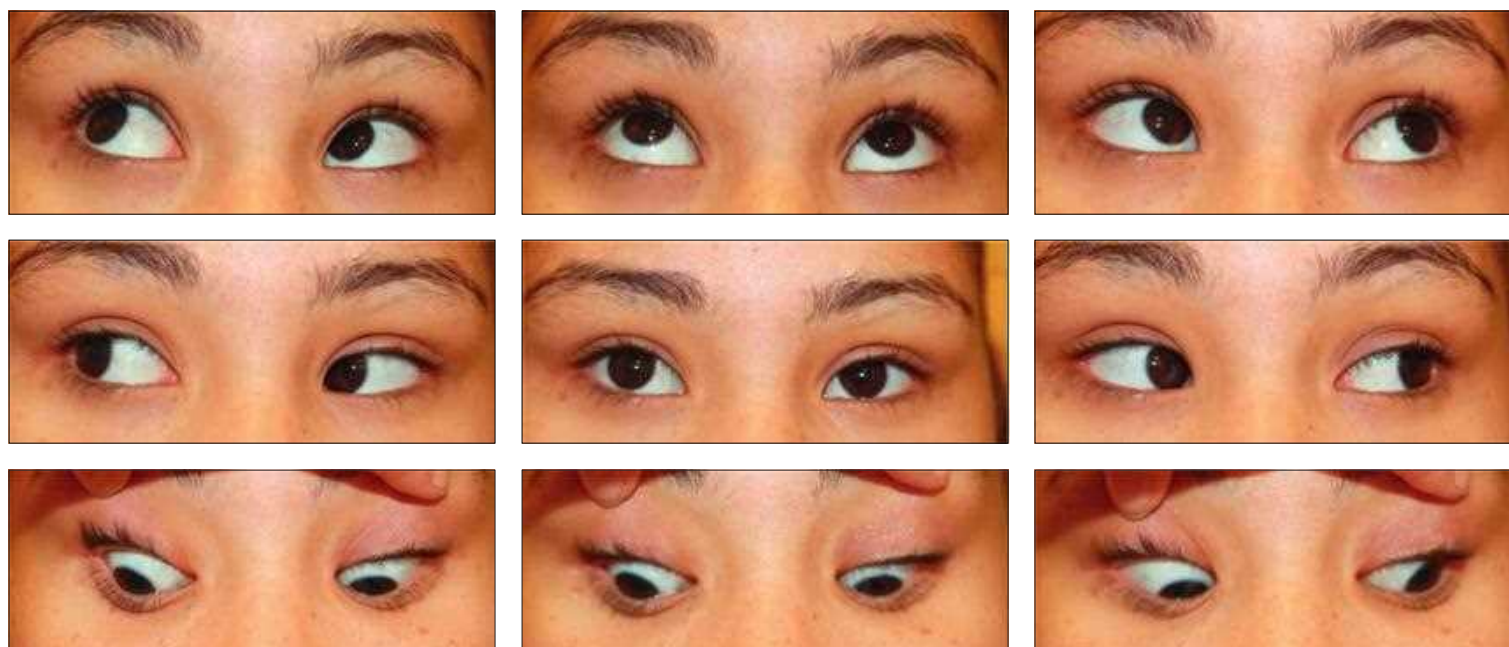
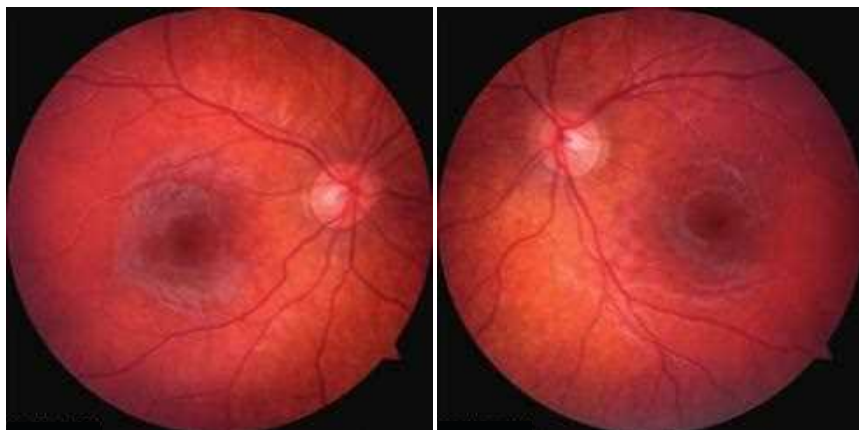


Fig. 11.8.1 A-pattern with superior oblique overaction (SO OA). (Courtesy L. R. Dagi, MD.)





**Fig. 11.8.2** V-pattern with inferior oblique overaction (IO OA) and superior oblique underaction (SO UA). (Courtesy L. R. Dagi, MD.)



**Fig. 11.8.3** Bilateral excyclotorsion. (Courtesy S. K. McClatchey, MD.)

vertical rectus muscle secondary to, for example, local toxicity from an anesthetic injection or inflammatory hypertrophy from thyroid eye disease can sometimes result in symptomatic torsional diplopia.<sup>2,3</sup>

The oblique muscles insert at an angle  $39^\circ$  from that required to be purely torsional, with the spread of SO insertion causing its effect to vary even more with ocular position. In addition, the passive action of orbital tissues and the elasticity of the EOMs have significant impact on the ocular position in eccentric gaze.

Each of the EOMs passes through a pulley of connective tissue that constrains its path, forming an effective point of origin for the action of the muscle as it inserts at the globe. These pulleys are connected in an array that encircles the globe. This array is actively shifted by the orbital layers of the EOMs and by smooth muscle. It has been demonstrated that rectus muscle transposition procedures have little impact on rectus muscle trajectory behind the globe because of the stabilizing effect of the pulley system. Thus, the very presence of this pulley system modulates the impact of transposition procedures and likely explains why such procedures leave the original function of the transposed muscle reasonably intact.<sup>4</sup>

In most patients, torsion is a key to understanding clinical observations.<sup>5,6</sup> However, pathology in any of these components, including neural control, muscles, soft tissues, and the pulley arrays, and, in some cases, even the bony orbital anatomy can produce strabismus, in particular, pattern strabismus and oblique overaction.<sup>7</sup> Recent work has identified neurally separate compartments of some of the extraocular muscles, which also may play a role in some cases.<sup>8</sup>

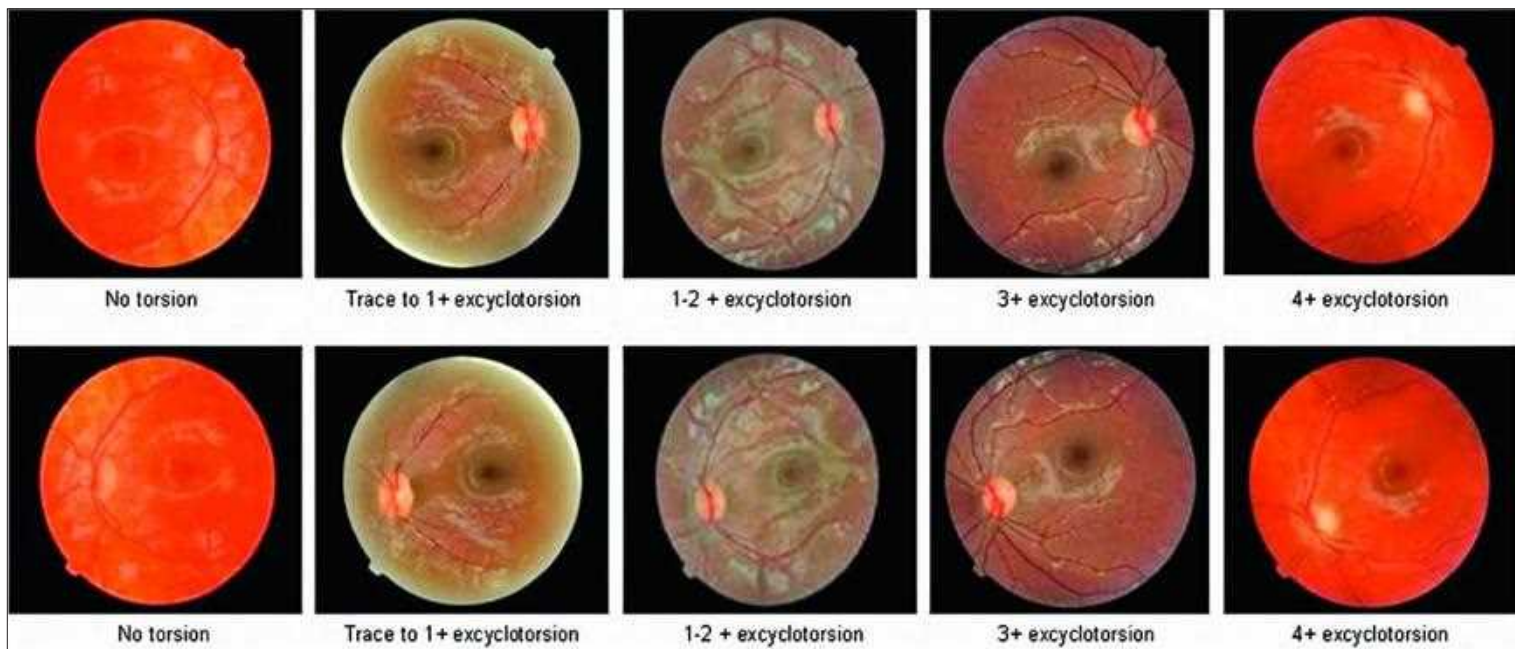
### Example: Child With Accommodative Esotropia Who Develops a V-Pattern

As an example of primary overaction of the inferior obliques, let us consider a common case of a 2-year-old child with hyperopia of  $+4.5$  D both eyes (OU) presenting with accommodative esotropia. Initial examination shows no oblique overaction, pattern strabismus, or fundus torsion, and wearing of glasses fully correct his deviation. The child is lost to follow-up, and over 2 years, he fails to wear the glasses. He presents again at age 4 years with now partially accommodative esotropia. When wearing glasses to correct his full cycloplegic refraction, his ET cc = 25 PD. He also has 3+ inferior oblique both eyes (IO OU), a moderate V-pattern, and approximately  $15^\circ$  of excyclotorsion in both eyes (Fig. 11.8.3). Because no apparent cause exists for IO OA, such as fourth cranial nerve palsy or craniosynostosis, it is diagnosed as primary IO OA. Surgery is performed: recess medial rectus (MR) 5.0 mm OU and recess IO 14 mm OU. At his 2-month postoperative examination, he is ortho in all positions of gaze, with no IO overaction, no V-pattern, and no torsion on fundus exam.

Why did this patient develop a V-pattern with apparent IO OA, and how did recession of IO correct both conditions?

### Summary of Upcoming Sections

Many causes occur for oblique overactions and pattern strabismus. In this chapter, we will show how ocular torsion and heterotopy of the pulley arrays



**Fig. 11.8.4** The top row displays fundus photographs of the direct view of anatomical (fundus) torsion progressing from no torsion to 4+ excyclotorsion. Below each photo the image is inverted to illustrate the view seen by the examiner with indirect ophthalmoscopy. (With permission from MacKinnon S, Rogers GF, Gregas M, Proctor MR, Mulliken JB, Dagi LR. Treatment of unilateral coronal synostosis by endoscopic strip craniectomy or fronto-orbital advancement: ophthalmologic findings J AAPOS 2009;13(2):155–60.)

are the keys to understanding many cases of oblique muscle dysfunctions and V- and A-pattern strabismus. We will discuss clinical observations, the place of torsion within the three axes of strabismus, how torsion of the rectus pathways results in pattern strabismus and the appearance of oblique overaction, how lack of fusion can lead to torsional strabismus in many, and other causes of oblique dysfunctions.

## CLINICAL OBSERVATIONS

### Epidemiology

In a study by Wilson and Parks,<sup>9</sup> IO OA was observed to develop in about 72% of patients with congenital esotropia, 34% of those with accommodative esotropia, and 32% of those with intermittent exotropia, who were followed up for longer than 5 years. The incidence of IO OA in patients with congenital esotropia was not related to age at strabismus onset, time from onset to surgery for the esotropia, age at first surgery, or decompensation of horizontal alignment; it was, however, related to the number of surgeries necessary to align the eyes horizontally. The mean age of onset or detection was 3.6 years with many demonstrating pattern deviation much before.

Eustis and Nussdorf<sup>10</sup> studied infants undergoing bilateral medial rectus muscle recession for esotropia and found that of the eyes with excyclotorsion observed at surgery, all demonstrated IO OA at follow-up. Of those with no torsion at the time of surgery, only nine of 21 demonstrated IO OA at follow-up.

Of children with SO OA, there is a higher rate of concurrent neurological disease, up to 40% in one series.<sup>11</sup>

### Age of Observation

Oblique overactions and A- and V-patterns rarely are observed clinically in very young infants with esotropia, perhaps because of their limited efforts. It is difficult to get an infant to follow an object into far side-gaze or to precisely measure alignment in chin-up or chin-down posture. Many patients either develop or are found to have these signs of torsional strabismus when they are 2–6 years of age.

### How to Observe or Measure Torsion

#### Directly With Fundoscopy or Photography

Clinical fundoscopy can be used to estimate the degree of fundus torsion, based on a 1– to 4+ scale,<sup>5</sup> a protractor,<sup>12</sup> or estimation of the angle, as is done for free-lens retinoscopy refractions. Torsion also can be documented by fundus photography in cooperative patients (Fig. 11.8.4) or at surgery.

### Correlation of the Appearance of Oblique Overaction, Pattern Strabismus, and Fundus Torsion

Clinically significant fundus torsion can vary from 10° to 20°. In general, 10° of bilateral fundus excyclotorsion corresponds to 2+ IO OU and a moderate V-pattern; 20° of excyclotorsion corresponds to 4+ IO OU and a large V-pattern. The same is true for incyclotorsion: 10° of bilateral fundus incyclotorsion corresponds to 2+ superior oblique both eyes (SO OU) and a moderate A-pattern; 20° of incyclotorsion corresponds to 4+ IO OU and a large A-pattern. With large angles of torsion, the eyes also appear to have underaction of the antagonist of the “overacting” oblique: thus a child with 20° of excyclotorsion may appear to have a 2– SO OU as well as 4+ IO. Of note, some children with craniosynostosis can have substantially larger torsion as a result of orbital torsion; the authors have seen up to 40° of excyclo-torsion in this setting.<sup>13</sup>

### Blind Spot Mapping

In eyes with ocular torsion, the relative position of the nerve and macula are rotated. Visual fields in such eyes show displacement of the blind spot, with the blind spot below the horizontal meridian in excyclo-torsion and above in incyclotorsion.<sup>6</sup>

### Location of Rectus Muscle Insertions at Surgery

An eye with significant excyclo-torsion maintains that torsion under anesthesia. Thus, a surgeon who makes an inferotemporal conjunctival incision will do so directly over the inferior border of the lateral rectus muscle insertion instead of over the sclera.

### Forced Ductions

Forced ductions at surgery of eyes with torsional strabismus can demonstrate limitations because of short oblique muscles.<sup>14</sup>

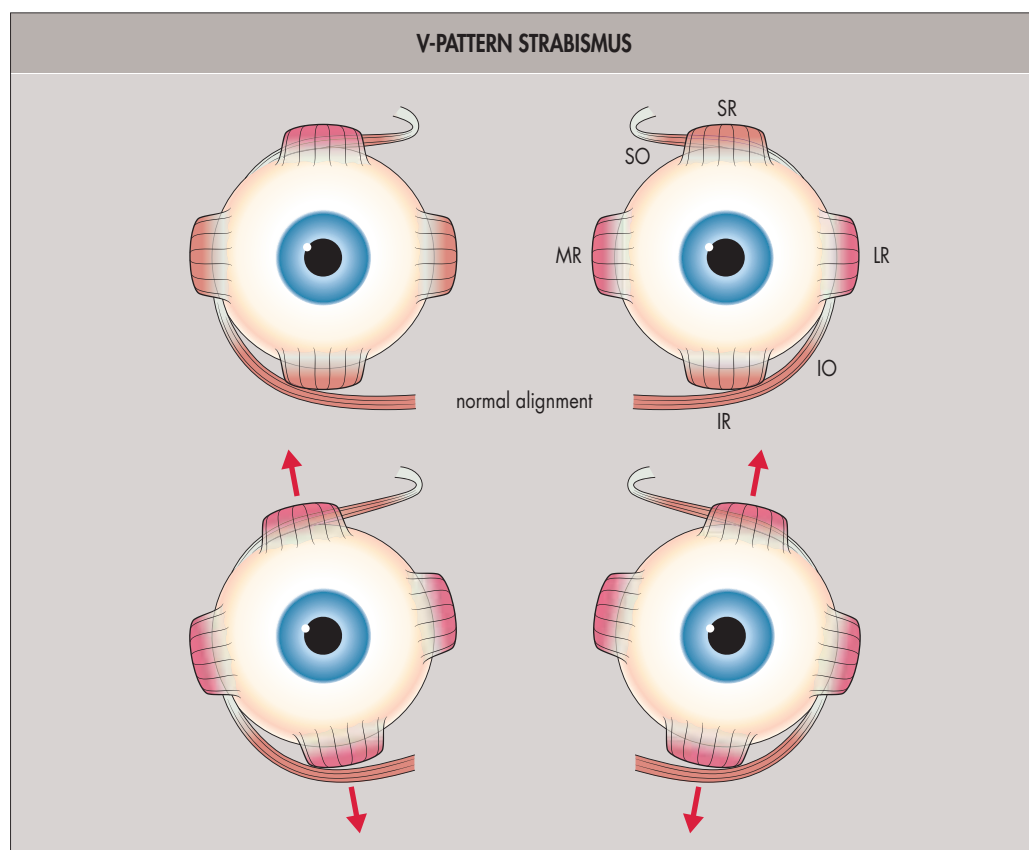
### Double Maddox Rod

An adult with acquired fourth cranial nerve palsy from injury to the trochlear nerve will show subjective excyclo-torsion on a Double Maddox rod (DMR) test. However, as shown by Guyton and von Noorden,<sup>15</sup> patients who develop torsion before age 6 years do not show this subjective finding. Analogous to anomalous retinal correspondence for horizontal strabismus, sensory adaptations occur in childhood torsional strabismus.

### Lancaster Red-Green Test

The Lancaster red-green test provides a clear plot of strabismus in these patients; in some, there is a clear torsional pattern.





**Fig. 11.8.5** Extorsion in both eyes (OU) resulting in V-pattern strabismus in attempted up- and downgaze. (Courtesy S. K. McClatchey, MD.)

### Magnetic Resonance Imaging of the Orbits

The fine detail of high-quality surface-coil magnetic resonance imaging (MRI) has been used to extensively document the muscle paths and connective tissue of the orbits. In some patients, such as those with craniosynostosis and pattern strabismus, the pulley array has been shown to be tortorted, incylo-tortorted for A-patterns and excylo-tortorted for V-patterns, or with certain pulleys displaced (heterotopy).<sup>16,17</sup> In other patients, especially those with high myopia, older adults, or those with connective tissue aging laxity, the pulley or muscle pathway pathology varies and is key to understand the resulting strabismus.

### Parks' Three-Step Test

The late Dr. Marshall Parks said that his three-step test was useful to identify the offending cyclovertical muscle only for an isolated cyclovertical paresis. In practice, this test works best with some patients who have an SO palsy, but when used in isolation, it sometimes does not help accurately diagnose even a palsied SO; other cyclovertical muscles are rarely paretic in isolation. There are many factors that confound the results of this test, such as skew deviation, pulley heterotopy, thyroid eye disease, and strabismus surgery; it can be frankly misleading.<sup>2,8</sup>

### Torsion Is Sufficient to Cause the Appearance of Oblique Dysfunction

#### A- and V-Patterns From Excyclotorsion of the Globe Absent Primary Oblique Dysfunction

As the vector forces of the vertical recti are tortorted along with globe and pulley torsion, excyclotorsion in upgaze results in simultaneous exodeviation and in downgaze results in esodeviation, producing a V-pattern (Fig. 11.8.5).

On right gaze in a patient with excyclotorsion OU, the left eye is adducted and elevated, and the right eye is abducted and depressed. However, this is elicited clinically by asking the patient to “follow” an object. Typically, a patient will fixate with the abducted eye, which can only be maintained if the patient also makes an effort to elevate that eye. This elevation affects both eyes, resulting in the right eye fixating on the object of regard, and the left eye appears to have an exaggerated elevation in adduction: this may be interpreted by the clinician as IO OA even if that is not the primary cause (Fig. 11.8.6).

If one eye sees poorly because of amblyopia or another cause, on abduction it will go up (in incyclotorsion) or down (in excyclotorsion) to allow the adducting eye to remain in the horizontal position.

The corresponding “underactions” on version testing are more difficult to observe but are nearly always present with large degrees of torsion. Typically, a patient with 20° of excyclotorsion will have the appearance of 4+ IO OU and 2– SO OU.

### The Observation of Normal Version Testing After Denervation and Extirpation (D&E) of the IOs

Thus, the appearance of oblique over- or underaction may not be completely dependent on the oblique muscles themselves. Sometimes, it is caused primarily by cyclorotation of the pulleys and associated rectus muscles. However, surgery on the oblique muscles, in many cases, can resolve the abnormal torsion of the globe and the A- or V-pattern. As an example, in some patients with extreme excyclotorsional strabismus (4+ IO, large V-pattern, 20° of excyclotorsion), some surgeons perform a denervation and extirpation (D&E) of the IOs.<sup>18</sup> Subsequent version testing shows no oblique dysfunction at all, either over or underaction. Because the IO has no active effect on the globe or on the pulley array after this surgery, the recti must themselves be responsible for producing the normal versions: the net effect of the D&E is to relieve the excyclotorsional effect of the shortened IOs.

## ETIOLOGY

### Sensory Torsion

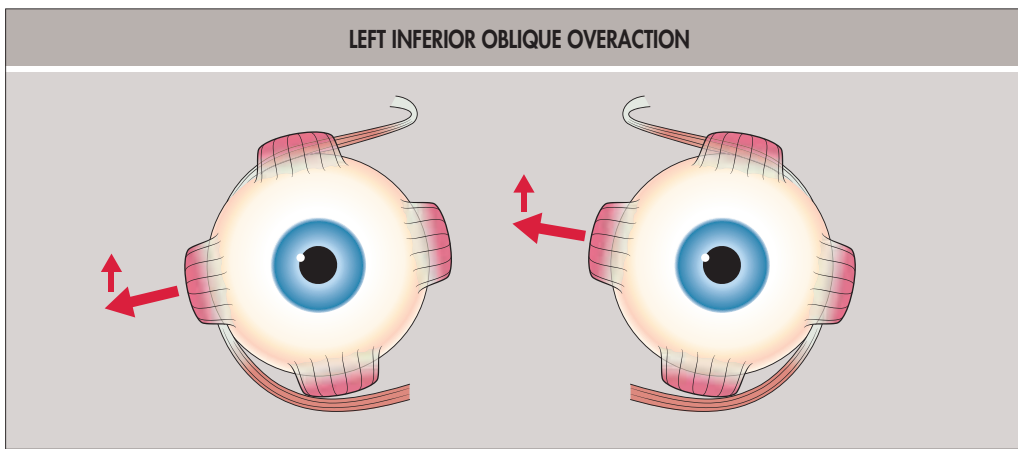
#### Well-Known Examples of Sensory Esotropia or Sensory Exotropia

Children or adults who have poor vision in one eye often lose good binocularity and develop strabismus. For example, children with unilateral cataract in the Infantile Aphakia Treatment Study (IATS) had a 39% rate of strabismus surgery.<sup>19</sup> This is often called *sensory strabismus*. It is thought that the patient's underlying alignment tendency (bias) toward eso- or exodeviation results in gradually increasing esotropia or exotropia, respectively, through muscle length adaptation.<sup>20</sup>

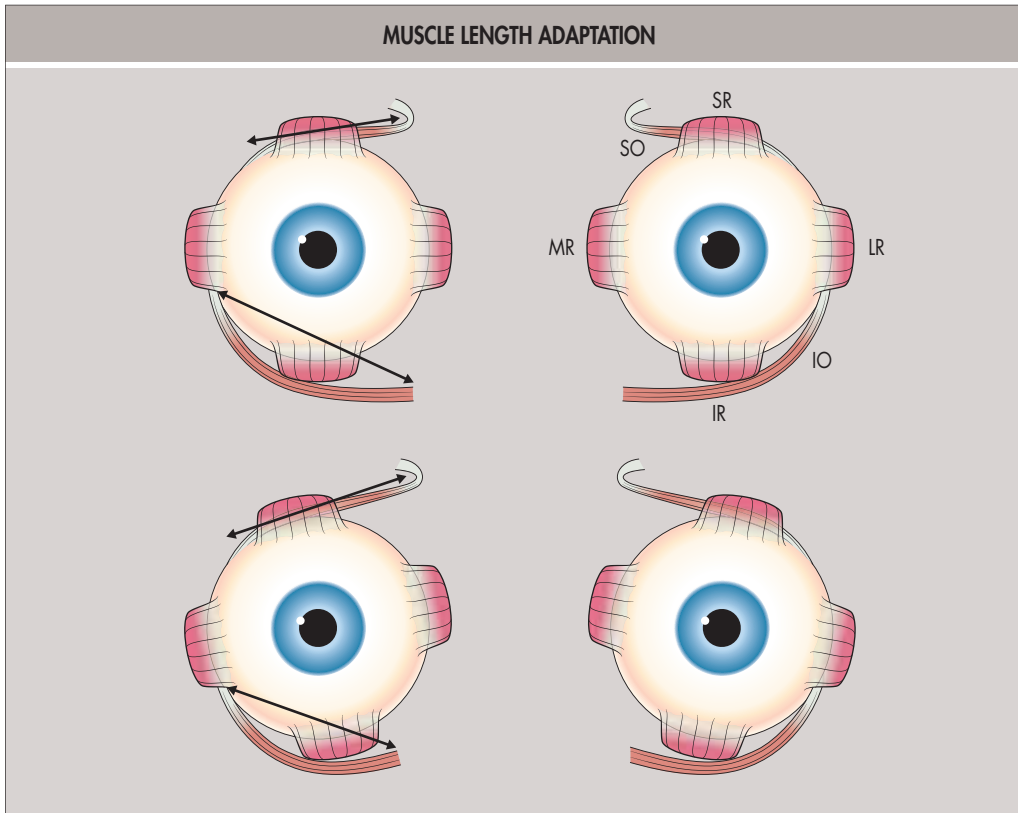
### Muscle Length Adaptation

Muscles throughout the body continually remodel to conform to their average length, and the EOMs likewise lengthen and shorten in response to chronic ocular position.<sup>20</sup> This adaptation occurs by addition or subtraction of sarcomeres at the tendon–muscle connection.<sup>21</sup> In effect, a muscle that is chronically extended lengthens over time; muscles that are chronically





**Fig. 11.8.6** Extorsion in both eyes (OU) results in “left inferior oblique overaction” in attempted right gaze. (Courtesy S. K. McClatchey, MD.)



**Fig. 11.8.7** Muscle length adaptation results in the length of the inferior oblique being shorter when the eye is chronically extorted; the antagonist superior oblique is likewise lengthened. (Courtesy S. K. McClatchey, MD.)

in a shortened state shorten over time. Muscle length adaptation allows the muscles to grow as the body grows in childhood and has a large role in many pathological states, such as muscle contractures in cerebral palsy.

Thus, there is some sense to the admonition, “Don’t cross your eyes like that, or they’ll get stuck!” Because of muscle length adaptation, the extraocular muscles of eyes that are chronically misaligned lengthen or shorten to match their chronic position; this explains the development of nonaccommodative esotropia over time in a patient with uncorrected accommodative esotropia. Some other examples of this include normal development (the muscles lengthen to match the growing orbit), the lengthening of a recovered muscle 3 months after Botox injection, and spread of comitance over time in chronic fourth cranial nerve or sixth cranial nerve palsies.

### Bias

People with binocular fusion maintain alignment through a feedback process. Any misalignment of the eyes whether horizontal, vertical, or torsional is detected by the brain and corrected through a vergence reflex; in turn, the EOMs adapt to this normal alignment through muscle length adaptation. However, loss of fusion often allows any underlying bias to result in a freewheeling progressive misalignment in any of the three axes of strabismus, again reinforced through muscle length adaptation.

### Sensory Deprivation or the Lack of Fusion Leads to Tropia

If a patient has a bilateral horizontal outward bias, loss of fusion will result in exotropia over time, and inward bias results in esotropia. Vertical bias

tends not to cause tropia because the yoke vertical recti tend to be biased equally. Oblique bias, in turn, causes intorsion or extorsion through the same mechanism (Fig. 11.8.7). This oblique bias becomes manifest whenever fusion is lost because of any cause; most commonly, this occurs in horizontal strabismus and is called *primary oblique overaction* but is better termed *sensory torsion* in analogy to *sensory esotropia*.<sup>5</sup> Although these biases can be in any direction, in children, notably, sensory esotropia and sensory excyclotorsion tend to develop more frequently compared with exotropia and incyclotorsion.

Therefore, in patients who develop constant strabismus, such as congenital esotropia or partially accommodative esotropia, the lack of fusion allows the freewheeling obliques to steadily shorten or lengthen, depending on their inherent oblique bias, resulting in torsional strabismus.

### Pulley Arrays

Pioneering computer modeling by Joel Miller<sup>22</sup> demonstrated that muscle paths must be constrained by a pulley system, which has been identified by histological studies, high-resolution MRI, and studies in animals. The constraints of pathologically torted pulley arrays result in pattern strabismus in certain patients, such as those with craniosynostosis.

Each of the six extraocular muscles passes through a pulley before inserting on the globe. The trochlea of SO is fixed to the orbit, but the other pulleys consist of soft tissue condensations with a connecting ring of collagen and smooth muscle that serve as an array to constrain the path of

the muscles as they approach the globe. These pulleys are located behind the equator of the eye and are located close to where the muscle penetrates Tenon's capsule; it is coupled to the orbit by connective tissue. Each of the recti and oblique muscles have an active orbital layer that inserts on the pulley array so that on muscle contraction the array is shifted by the recti or torted by the obliques along with ocular motion, although less so than the globe itself.<sup>8</sup> This active pulley array enforces Listing's law and greatly simplifies the effect of neural input to the EOMs in various gaze positions. The pulley array also can be adversely affected by aging, high myopia, and other pathology; the discussion of these conditions is beyond the scope of this chapter.

The whole array can be excyclotorted in patients with craniosynostosis, resulting in large V-patterns, the appearance of large IO or SO overactions, and a tilt of the palpebral fissure matching the torsion. In V-patterns, the palpebral fissures are temporally down-slanted; those who present with the less common A-patterns may demonstrate upward slanting of the fissures.

Although the cyclovertical muscles may have oblique pathways in the primary or off-axis position, the pulleys constrain their actions in all gaze directions. In secondary or tertiary gaze, these pulleys are the inflection points of the muscle paths. To a great degree, the superior and inferior recti act vertically, and the primary action of the SO and IO is torsional. These constraints greatly simplify the brain's task in maintaining fusion as the eyes move together.

## Other Causes of Oblique Dysfunctions and Pattern Strabismus

Often these are called *secondary oblique overactions*.

### Superior Oblique Muscle Palsy

Congenital SO "palsy" can either be from a true SO underdevelopment, as seen on orbital MRI, or from a laxity of the tendon found by forced ductions or direct observation at surgery. Fourth cranial nerve palsies may also be acquired, from trauma, tumor, or myasthenia gravis. DMR testing in acquired cases shows subjective torsion. The antagonist muscle (the IO) shortens over time, and the excyclotorsion from both causes appears as IO overaction and SO underaction.

### Brown's Syndrome

Patients with Brown's syndrome have an outward deviation of the Brown eye in far upgaze, simulating a V-pattern. There is, however, no predictable pattern of torsion for either eye in primary position.

### Duane's Syndrome

Eyes with Duane's syndrome can simulate IO or SO overaction because of a tight lateral rectus muscle or because of abnormal neural stimulation of the vertical recti—again, as such, small amounts of fundus torsion may be noted on examination.

### Dissociated Vertical Deviation

Dissociated vertical deviation (DVD) can appear similar to IO OA on version testing and often appears in the same patient population, but several distinguishing features occur. As opposed to excyclotorsion, DVD is apparent in the primary position and is usually accompanied by latent nystagmus. No true hypertropia of the adducting eye exists in side-gaze, although often DVD will appear when the visual axis of the adducting eye is blocked by the nose. Unless there is a coexisting torsional strabismus, no V-pattern or fundus torsion occurs.

### Craniosynostosis

Many patients with craniosynostosis, such as those with Crouzon's or Apert's syndrome, have congenitally excyclorotated orbits, resulting in large V-patterns and corresponding oblique overactions. A-patterns are less commonly seen. Most commonly the pulley array is excyclotorted,<sup>23</sup> and the appearance of seeming IO OA and superior oblique underaction (SOUA) is seen. It is, however, important to note that the exaggerated V-patterns seen in some forms of craniosynostosis also may be the result of seemingly absent,<sup>24</sup> but most likely underdeveloped extraocular muscles, and iatrogenic disinsertion of the SO at the trochlea during primary craniofacial repair (fronto-orbital advancement).<sup>25</sup> Particularly exaggerated V-patterns associated with exceptional amounts of fundus torsion and, in some cases, inability to elevate the abducted eye above midline (the "see-saw" V-pattern), may be secondary to alteration in the bony anatomy of the orbital apex.<sup>13</sup> This causes primary excyclotorsion of the rectus muscles initiating at the very origins of the rectus muscles near

the orbital apex, and likely reinforced by secondary pulley heterotopy.<sup>13</sup> Of note, oblique muscle surgery by itself often has only modest effect in such patients because of the multifactorial origin of the V-pattern.<sup>26</sup>

## Pseudo-Oblique Overaction Occurs in Patients With a Large Quantity of Exotropia

As shown by Capo et al.,<sup>27</sup> patients with large-angle exotropia can appear to have simultaneous SO OA and IO OA on both sides. No torsion exists in such patients, and the oblique overactions normalize with horizontal rectus surgery for the exotropia alone. This occurs as a result of the mechanics of the soft tissues in the orbit, which limit rotation of the globe.

## MANAGEMENT

### Observation

Small or moderate torsional strabismus may have little effect on the patient's function or appearance. Patients with a moderate V-pattern but otherwise straight eyes will have esotropia on downgaze, but most patients are fixating at near when looking down, so this can be a physiological alignment.

Some patients adopt a head posture to maintain binocularity; this posture usually indicates a need for surgical treatment. For example, a child with good binocularity and a V-pattern esotropia might develop a chin-down posture to maintain fusion.

### Oblique Muscle Surgery

Surgical management of torsional strabismus often is undertaken simultaneously with surgery for horizontal misalignment. Correction generally involves moving the insertion of the IO for excyclotorsion, or operating on the SO tendon to increase or diminish incyclotorsion. In surgery for horizontal strabismus, the recti are neither strengthened nor weakened. To a good approximation, the muscles are cut off, the globe is repositioned, and the muscle insertions are replaced in the new position.<sup>28</sup> In the same way, one common treatment for extorsion consists of cutting the IO, returning the globe to its normal position, and replacing the oblique insertion passively (myectomy) or actively (via recession). The SO with its broad insertion has a more complex mechanical effect than the IO, varying more with globe position. Although an SO recession can be performed,<sup>29,30</sup> intorsion is sometimes treated with SO tendon lengthening via a graded expander.<sup>31,32</sup> Likewise, extorsion or insufficient intorsion can be treated with an SO tuck (e.g., in congenital "SO palsy" caused by a lax tendon) or a Harada-Ito procedure.

Bilateral symmetrical SO or IO surgery typically has no effect on the horizontal alignment.<sup>11,33</sup>

Any surgery that affects ocular torsion in a patient with stereopsis will cause a postoperative sensation of everything appearing to be tilted toward or away from the patient. This occurs because the change in torsion results in a relative horizontal displacement between the two eyes, of objects above or below the object of regard—the same phenomenon used by the stereopsis system to judge distance. The same phenomenon occurs when a patient is given spectacles that correct oblique astigmatism with opposing directions in the right and left eyes. In these cases, it is useful to provide a warning to the patients that they will experience such symptoms for about 2 weeks after surgery.

### Surgical Variations

IO surgery has several variations. The IO can be recessed along its path: 10 mm for 2+ IO OA and 14 mm for 3+ IO OA. A myectomy of the IO allows the globe to untort and has proven suitable for a remarkably wide range of IO OA in a self-correcting manner. In large V-patterns and 4+ IO OA, a D&E eliminates the active effect of the muscle. In patients with combined DVD and moderate V-pattern or 2+ IO OA, anterior transposition of the insertion to a station just temporal to the lateral border of the inferior rectus muscle can both correct the torsion and reduce the DVD.

Surgery on the SO is more complex but also has several variations. For large A-patterns in nonbinocular patients, tenotomy or tenectomy will collapse the pattern; this must be avoided in patients with binocularity because it may produce intractable diplopia. Other variants to treat incyclotorsion that permit a more controlled "weakening" of SO tone and incyclotorsion include Z-split lengthening of the tendon, graded recession of the SO,<sup>29,30</sup> silicone tendon expander,<sup>31</sup> and intraoperative adjustable suture expander,<sup>32</sup> among others. A tuck of the SO works well to correct

congenital SO palsy, where forced ductions reveal a laxity of the tendon. Harada–Ito advances or tucks the anterior fibers of the SO tendon and can successfully increase incyclotorsion or reduce excyclotorsion in a measured or adjustable manner.

## Rectus Transpositions

Rectus muscle transposition may be used to resolve A- or V-patterns. For example, for a V-pattern, the medial recti would be transposed inferiorly or the lateral recti transposed superiorly. In the absence of primary oblique dysfunction, vertical transposition can be effective; such transposition may, however, worsen torsion and, in that regard, is less suitable for the patient with good stereopsis.<sup>34</sup>

## SUMMARY

The young boy, in our example, with partially accommodative exotropia, IO OA, V-pattern, and excyclotorsion can best be understood as having strabismus in two axes, horizontal and torsional. Accommodation to see through uncorrected hyperopia forced his eyes inward via the near triad reflex. The excyclotorsion developed when his eyes crossed and lost fusion as a result of this accommodative esotropia. The loss of fusion allowed his underlying excyclotorsional bias to drive a progressive shortening of his IOs and lengthening of his SOs through muscle length adaptation, just as his medial recti shortened through muscle length adaptation to their chronically shortened position. Thus, this strabismus caused by loss of fusion that allows the freewheeling torsional bias to gradually induce bilateral ocular torsion through muscle length adaptation is best termed *sensory torsion*. The main surgical effect of bilateral recession of the medial recti and bilateral recession of the IOs is, thus, to address each of these component axes separately.

The clinician must keep in mind that there are many causes of ocular torsion, pattern strabismus, and the appearance of oblique dysfunction. Careful measurements in the three axes of strabismus and a search for all potential causes can yield a better understanding of the nature of the strabismus and guide surgical treatment.

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# Paralytic Strabismus

Hilda Capó, Steven E. Rubin

# 11.9

**Definition:** Strabismus resulting from partial or complete paralysis of the third, fourth, or sixth cranial nerve.

## Key Features

- Incomitance—magnitude of deviation is gaze dependent.
- Secondary deviation—magnitude of deviation increases when paretic or restricted eye is fixating on a target.

## Associated Features

- Third nerve palsy—ipsilateral exotropia, hypotropia, ptosis, and pupillary findings.
- Fourth nerve palsy—ipsilateral hypertropia with head tilt to the opposite side.
- Sixth nerve palsy—ipsilateral esotropia with head turn to the affected side.

## INTRODUCTION

The most common type of strabismus is the comitant variety—in which the angle of deviation does not vary with direction of gaze. Less commonly, oblique muscle dysfunction causes an alphabet-pattern strabismus, as discussed in Chapter 11.8. Least common are the disorders that result from paresis or restriction of the extraocular muscles. This chapter discusses only paralytic strabismus.

In contrast to the straightforward evaluation of comitant strabismus, an expanded array of diagnostic techniques must be employed in patients with paralytic strabismus. Accurate classification of strabismus requires measurements in the cardinal positions of gaze (as discussed in Chapter 11.3) to detect the characteristic incomitance of paretic or restrictive disorders. In general, the measured deviation is greatest in the field of action of the paretic muscle(s).

With comitant strabismus, prism measurements are independent of the fixating eye, even in patients with a fixation preference for one eye. If the measurements change when the fellow eye takes up fixation, a paretic or restrictive etiology is usually the cause. The deviation is larger when the affected eye is used for fixation and is termed *secondary deviation*.

Restriction can be confirmed by forced duction testing, whereby the anesthetized perilimbal conjunctiva of the affected eye of a cooperative patient is grasped with forceps and the eye moved into the affected field; resistance indicates mechanical restriction (pointing to contracture of the antagonist muscle) rather than, or in addition to, muscle weakness as the cause of the strabismus. To confirm a paretic process, force generation testing to assess the relative strength of a muscle is useful. The anesthetized perilimbal conjunctiva is grasped with forceps and the patient instructed to look in the affected field<sup>1</sup> as the examiner feels the pull of the affected muscle. Similar information can be gained from careful observation of saccades into the limited field. A steady but slow movement into the gaze direction in question suggests a paretic cause, in contrast to an initially rapid and abruptly ending movement (like a dog running to the end of its leash), which suggests a restrictive cause. A Tensilon test also should be considered, as myasthenia gravis can mimic any isolated or combined extraocular muscle palsy.

Diplopia in adults and cooperative children can be assessed with binocular visual fields. This technique utilizes a standard Goldmann perimeter

or tangent screen to identify and quantify the extent of the diplopic areas of gaze.<sup>2</sup>

Patients with extraocular muscle palsies require consideration for more extensive evaluation. Comitant strabismus is rarely secondary to a neurological or systemic disease, whereas paralytic strabismus can result from other disorders. Congenital palsies are the main cause in children and can be the cause of fourth nerve palsies in adults, who may maintain their deviation latent for many years.

Management of paralytic strabismus follows the same general guidelines as for many difficult conditions—less invasive and less risky remedies are tried first. Hence, patients with a mild or slowly improving paresis can be offered occlusion or prism therapy before surgery is considered. Surgical treatment should be deferred until more than 6 months have passed after onset and serial examinations yield stable results. Before proceeding with surgery, the precise goals of treatment must be made exceedingly clear to the patient. The primary goals are to attain good ocular alignment in the primary position and downgaze, improve the incomitance, expand the field of single binocular vision, and improve compensatory head postures. Achieving good alignment in all fields frequently is unfeasible. When surgery is planned, the muscle(s) at work in the field(s) of greatest deviation must be targeted. Although advocated by some for routine use in all cooperative patients undergoing strabismus surgery, adjustable sutures have an even greater potential role in surgery for paralytic strabismus. The great variability in the degree of weakness of affected muscles makes published tables of graded recessions and resections somewhat less reliable in nerve palsies. Appropriate informed consent for surgery requires a discussion about alternative treatments, including the option of no treatment. Details of surgical strategies are discussed with the individual nerve palsies.

## THIRD NERVE PALSY (OCULOMOTOR)

### Introduction

Because the third cranial nerve innervates the inferior oblique, inferior rectus, and medial rectus muscles (by its inferior division) and the superior rectus and levator muscles (by its superior division), palsy of this nerve can affect ocular motility in all three planes (horizontal, vertical, and torsional).

### Ocular Manifestations

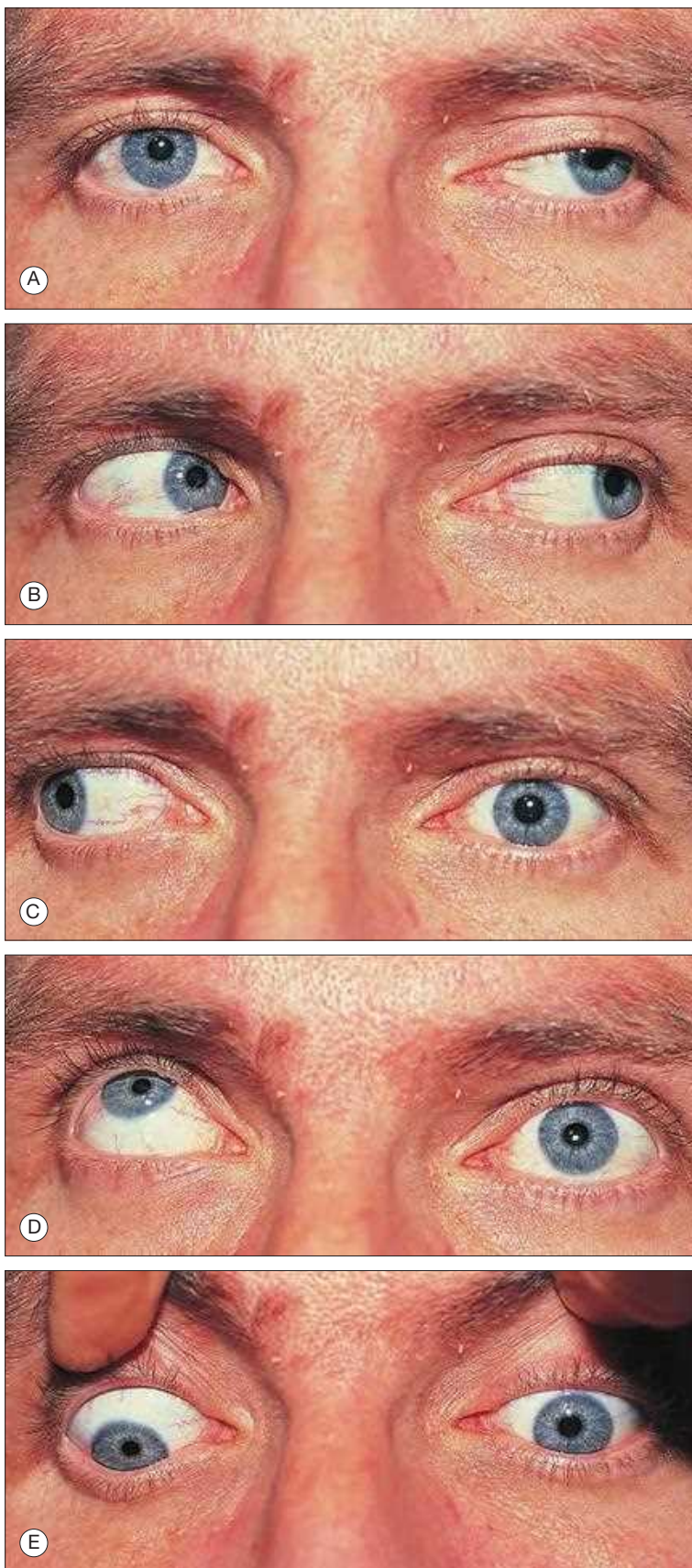
Third nerve palsies typically manifest ipsilateral exotropia and hypotropia with ptosis and pupillary findings. They can be congenital or acquired and can be partial, affecting one or more muscles (Fig. 11.9.1) or complete (Fig. 11.9.2). Cyclic palsies also have been reported.<sup>3</sup>

Aberrant regeneration is a phenomenon peculiar to third nerve palsies, hence the alternative term *oculomotor synkinesis*. After a paretic event, the extramedullary axons can heal and regenerate, but not necessarily to their original locations.<sup>4</sup> Therefore, action potentials that previously resulted only in adduction may now produce depression, retraction (from simultaneous vertical rectus muscle contraction), globe elevation, lid elevation, or pupillary constriction. The two most common manifestations are lid elevation (pseudo-Graefe sign) and pupillary constriction, each of which occurs on adduction, downgaze, or both.

### Congenital Third Nerve Palsies

Congenital third nerve palsies (generally idiopathic) are rare. Affected children most often have unilateral involvement and no other neurological abnormalities.<sup>4</sup> Some of the latter have been reported<sup>5</sup> but are thought to represent concurrent injury rather than a cause of the palsy. These cases

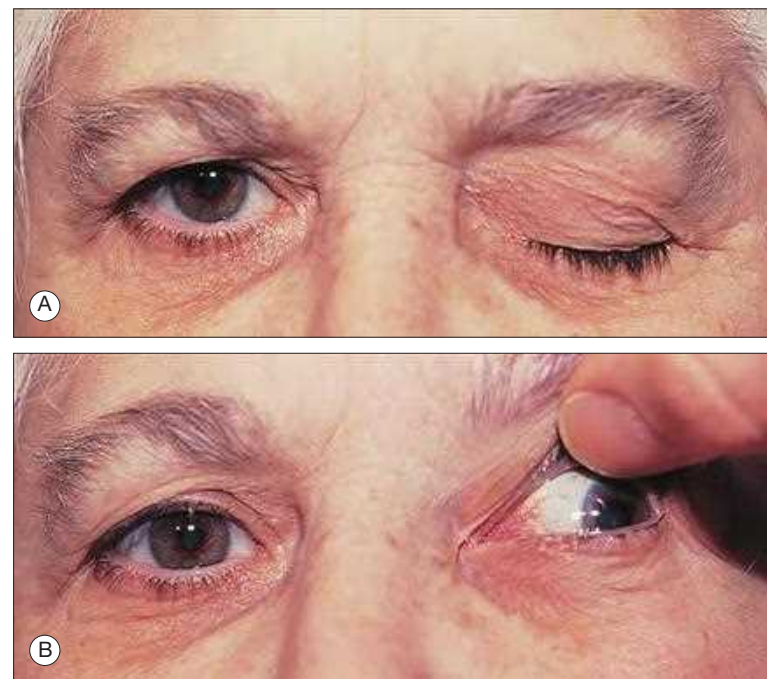




**Fig. 11.9.1 Adult With a Partial Left Third Nerve Palsy.** (A) Primary gaze showing slightly larger pupil, mild ptosis, left exotropia, and left hypotropia. (B) Normal left gaze. (C) No adduction of the left eye on right gaze. (D) Poor elevation. (E) Poor depression.

are not considered traumatic in origin as excessive birth trauma is not consistently found.

Most often, in congenital palsies all the extraocular muscles innervated by the third cranial nerve are affected, resulting in exotropia, hypotropia, and ptosis of varying amounts. Pupillary involvement can result from either a primary manifestation of the palsy (a larger pupil from deficient sphincter innervation) or aberrant regeneration (pupillary constriction



**Fig. 11.9.2 Older Woman With Complete Left Third Nerve Palsy.** (A) Complete ptosis, left eye. (B) Left exotropia and (small) left hypotropia.

**TABLE 11.9.1 Causes of Acquired Third Nerve Palsy by Age Group**

Cause	Children (%)	Adults (%)
Trauma	40	14
Neoplasm	14	11
Aneurysm	0	12
Vascular/diabetic	0	23
Other	29	16
Undetermined	17	24

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with adduction or downgaze). Pupillary sparing is not a reliable indicator of congenital origin as its presence in congenital cases is inconsistent.<sup>4,6,7</sup> Most children suffer loss of binocular function and amblyopia from ptosis or constant exotropia. When ptosis is either absent or incomplete, to optimize their binocularity, affected children may develop an abnormal head posture (torticollis) consisting of chin elevation or a contralateral face turn to neutralize the hypotropia, ptosis, or exotropia.

### Acquired Third Cranial Nerve Palsies

Acquired third nerve palsies, although more common than their congenital counterpart, are still unusual. They are rarely bilateral. Possible causes are age dependent (Table 11.9.1). The incidence is low among children and young adults, in whom trauma is the most common cause, but increases in middle-aged adults (1.7 per 100,000).<sup>8</sup> Patients older than 60 years have the highest incidence (12.5 per 100,000), predominantly because of a large increase in microvascular third nerve palsies.<sup>8</sup> Acquired palsies of the oculomotor nerve produce an incomitant exotropia and/or hypotropia and/or ptosis. In addition, visually mature adults report diplopia and visual confusion unless they also have significant ptosis. Torticollis (contralateral face turn and/or chin-up posture) develops if the posture neutralizes the diplopia.

Patients with an acquired third nerve palsy require further neurological evaluation as the palsy may be an ominous sign, especially in younger patients,<sup>9,10</sup> although exceptions occur.<sup>11</sup> Once thought indicative of benign and non-life-threatening microvascular disease, pupillary sparing can occur even in cases caused by intracranial aneurysms.<sup>12–14</sup> Pain and pupil involvement are unreliable in differentiating a microvascular from aneurysmal compression (see Chapter 9.16, for specific details and recommendations for evaluating these patients). Isolated pareses of individual muscles innervated by either branch of the third cranial nerve have been described<sup>15</sup> and generally defy neuroanatomic localization. They are almost never indicative of serious pathology elsewhere, and manifestations depend on the affected muscle. Brown's syndrome must be considered



in a patient with an apparent isolated inferior oblique muscle palsy; the three-step test (discussed later) and forced duction testing usually can distinguish between these two conditions. In patients who have craniofacial disease, isolated pareses may be caused by congenital absence of a rectus or oblique muscle.<sup>16</sup> Abnormal horizontal insertions also have been reported.<sup>17</sup>

## Nonsurgical Treatment

Third nerve palsy is the most challenging of the paralytic strabismus syndromes because of the number of muscles and different motility planes involved. Definitive treatment is almost never immediately required because many cases exhibit some degree of improvement, either spontaneously or when the underlying cause is managed.

In visually immature children, careful attention must be paid to both monocular and binocular visual development during this period because amblyopia can develop rapidly and require aggressive patching. In visually mature individuals without complete ptosis, diplopia may be alleviated with occlusion during the period of expectant observation. Even incomplete occlusion, accomplished by applying translucent tape to a spectacle lens, may be sufficient. When the horizontal or vertical deviation is small, prisms may be beneficial to keep binocular development on track in children and alleviate diplopia in adults. Prisms may be a permanent solution when the residual deviation is small. Although prisms work best in small comitant deviations, success in incomitant strabismus is possible if the magnitude of the prism is chosen to match the functionally important primary and downgaze positions.

Botulinum toxin therapy can be a useful adjunct treatment in the acute phase. Injecting the antagonist muscle(s), either by direct surgical visualization or transconjunctivally under audible electromyographic control, can prevent permanent contracture, which would otherwise interfere with recovery or complicate subsequent surgical treatment, or both.<sup>18–20</sup>

## Surgical Treatment

Restoration of normal motility generally is not attainable except in the mildest cases, so realistic surgical goals should be made clear to the patient in the early stages of treatment. Surgical treatment should be undertaken when little if any expectation of additional recovery exists, usually at least 6–12 months after onset. When some medial rectus muscle function is present, a large recess–resect procedure may produce acceptable results for the horizontal deviation<sup>21,22</sup>; this has been advocated in some patients with complete paralysis if combined with a traction suture.<sup>23,24</sup> The resected medial rectus can be supra-placed or infra-placed to improve an associated vertical deviation.

Resections of completely nonfunctional muscles have limited long-term effect as the nonfunctioning muscle stretches with time. Therefore, when no demonstrable medial rectus function exists, some other method to generate passive adducting force is necessary in addition to functional inactivation of the lateral rectus muscle. The latter requires supra-maximal recession of the lateral rectus muscle to at least 16 mm from the original insertion,<sup>25</sup> fixation of the lateral rectus muscle to the periosteum of the lateral orbital wall,<sup>26</sup> or extirpation or large myectomy of the lateral rectus muscle. Passive adducting force can be accomplished by transposition of the superior oblique tendon<sup>27</sup> insertion to a position adjacent to the medial rectus insertion, either with<sup>28</sup> or without<sup>29</sup> its removal from the trochlea. Additional alternatives include nasal orbital fixation and nasal transposition of the lateral rectus muscle. Nasal orbital fixation of the eye globe may be accomplished utilizing various materials, including an orbital bone periosteal flap,<sup>30,31</sup> a nonabsorbable suture anchored to the medial orbital wall periosteum,<sup>32–34</sup> or a T-plate titanium anchoring system fixated to the medial orbital wall.<sup>35</sup> Transposition of the lateral rectus muscle to the superior and inferior borders of the medial rectus muscle,<sup>36</sup> in combination with adjustable sutures<sup>37</sup> or augmented fixation sutures,<sup>38</sup> may generate adducting force and eliminate the opposing force of the lateral rectus muscle. Adequate splitting of the lateral rectus muscle is critical when performing nasal transposition to avoid compromising the optic nerve.

An accompanying ptosis generally is addressed after ocular alignment has been optimized. If done in reverse order, raising the lid of a hypotropic eye unable to utilize Bell's phenomenon to protect the cornea may produce exposure keratitis and worsen diplopia. This strategy may, however, have to be followed in visually immature children to prevent the development or worsening of amblyopia.

With isolated muscle palsies, the prognosis for an acceptable outcome is greater because only one muscle is affected. Such pareses are generally

treated by weakening the antagonist muscle along with strengthening (resection) of the affected muscle, provided some of its function remains. In the case of isolated inferior oblique muscle paresis, antagonist weakening (of the superior oblique muscle) must be done with caution because of the resulting effects on ocular torsion. In such cases, vertical rectus muscle weakening also can be effective.<sup>39</sup>

Whenever performing surgery on multiple rectus muscles on the same eye, anterior segment ischemia (ASI) is a possible complication. This condition may result when perfusion of the anterior segment is abruptly compromised by sudden loss of the contribution made from the anterior ciliary arteries that normally accompany the rectus muscles and penetrate the sclera at the muscle insertions. The vertical rectus muscles generally contribute more than the horizontal rectus muscles do. With time, perfusion to the anterior segment is restored by augmented circulation from the posterior ciliary circulation. This lends support to the strategy of staging surgery and waiting several months to operate on additional muscles on the same eye. ASI can occur years after the initial extraocular surgery<sup>40</sup> or even after surgery on only two muscles.<sup>41</sup> Acute manifestations of ASI include pain, corneal edema, Descemet's membrane folds, and anterior chamber inflammation. Late effects include iris atrophy, an eccentric pupil, and sometimes visual loss.<sup>42</sup> Although ASI usually arises only with surgery on three or four rectus muscles, circumstances such as circulatory disorders or advanced age can increase the risk with surgery on fewer muscles. Preservation of the anterior ciliary circulation during rectus muscle surgery, either with<sup>43</sup> or without<sup>44</sup> the use of the operating microscope, has been proposed to reduce if not eliminate the risk of this complication (discussed in Chapter 11.13).

## FOURTH NERVE PALSY (TROCHLEAR)

### Introduction

Palsies of the fourth (and sixth) cranial nerves generally are less complex clinical pictures because these two cranial nerves each innervate only one extraocular muscle. The fourth cranial (trochlear) nerve controls the superior oblique muscle, which acts as a depressor and is the major intorter of the eye.

### Epidemiology and Pathogenesis

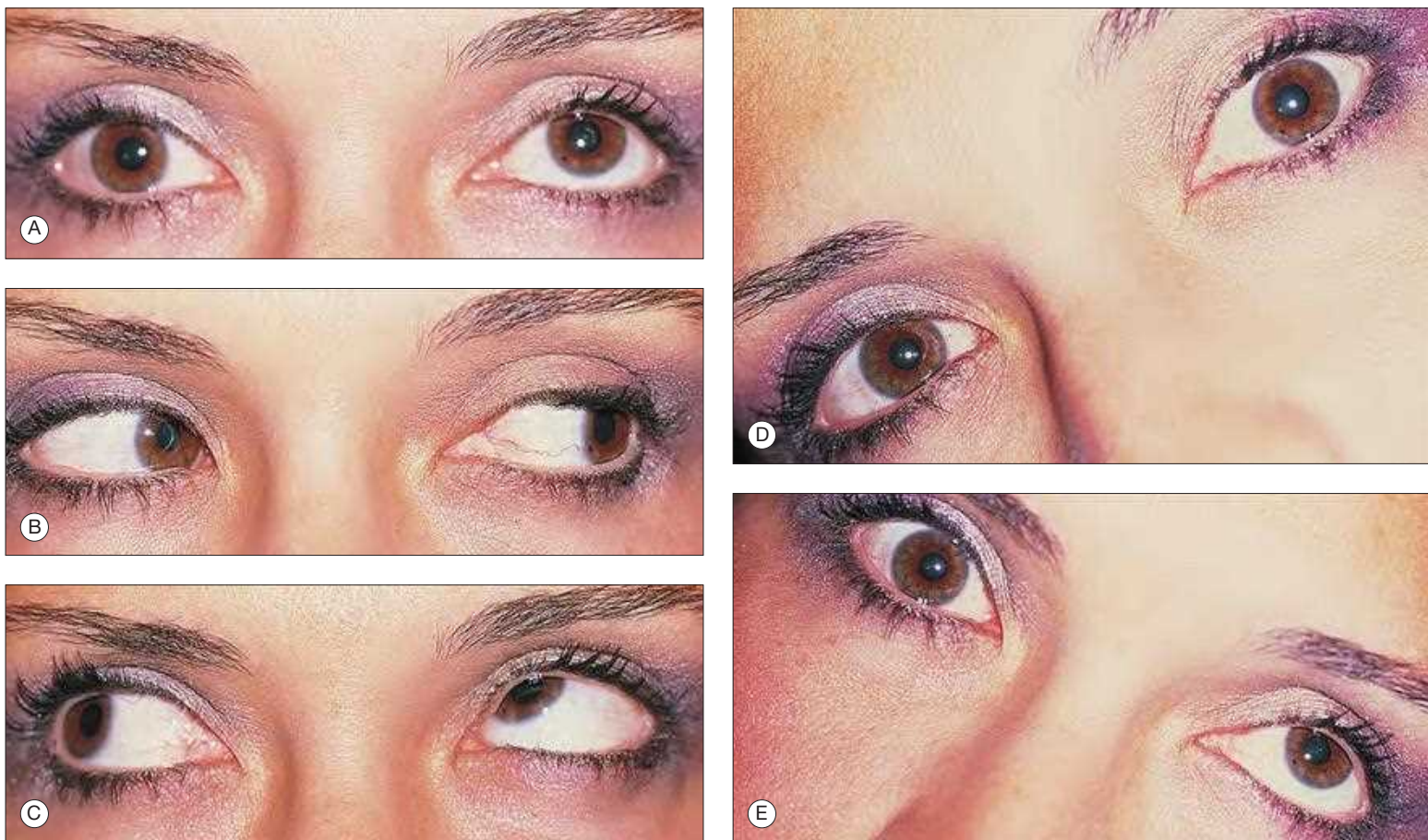
Although incidence data are age dependent, large series generally indicate that palsies of the fourth cranial nerve occur less often than those of the third cranial nerve<sup>21,45–47</sup>; pediatric studies show that order reversed.<sup>48</sup> Data from a practice based on strabismus surgery, however, might indicate that fourth nerve palsies are the most common.<sup>15</sup> The ability of patients to maintain latency of fourth nerve palsy (as a result of development of large vertical fusional amplitudes) probably influences the reported statistics.

Fourth nerve palsies rarely have a neurological etiology. Most cases are congenital (idiopathic) or posttraumatic in origin.<sup>4,49</sup> The fourth cranial nerve is uniquely susceptible to trauma<sup>50</sup> because it is the only cranial nerve with a dorsal exit from the brainstem, which results in the longest intracranial course of any cranial nerve. A patient who has a “unilateral” palsy, especially in traumatic cases, should be meticulously examined for evidence of bilateral involvement, which may not become evident until after surgery.<sup>15</sup> When a history of recent major trauma is lacking, a neurological workup may be considered but is usually unproductive.

Congenital fourth nerve palsy is almost always sporadic; only rare reports of familial occurrence exist.<sup>51,52</sup> Although the diagnosis in many patients is not made in childhood or youth, inspection of old photographs often reveals a consistent characteristic head tilt. Patients also commonly exhibit facial asymmetry, as discussed below. Amblyopia almost never is a complication in congenital or early acquired cases.<sup>53</sup> In rare cases, fourth nerve “palsy” results from congenital absence of the superior oblique tendon or muscle,<sup>54</sup> especially in patients who have craniofacial disorders.<sup>16</sup> This can be suspected preoperatively on finding an associated horizontal deviation, amblyopia, a large primary-position hypertropia, spread of comitance, and/or pseudo-overaction of the contralateral superior oblique muscle.<sup>55</sup>

### Ocular Manifestations

Weakness of the superior oblique muscle allows unopposed action of its direct antagonist, the inferior oblique muscle, which results in an ipsilateral hypertropia and excyclotorsion. Vertical diplopia and difficulty reading in downgaze are the most common complaints vocalized in fourth nerve



**Fig. 11.9.3** Young woman with idiopathic (presumed congenital) left fourth nerve palsy. (A) Primary position left hypertropia from loss of the depressor effect of the paretic left superior oblique muscle. (B) Normal motility in left gaze, away from the fields of action of the paretic left superior oblique muscle. (C) Compensatory overaction of the antagonist left inferior oblique muscle in its field of action in right gaze. (D) No vertical deviation on contralateral head tilt, when reflex excyclotorsion of the affected left eye is accomplished by the unaffected inferior rectus and inferior oblique muscles. (E) Large left hypertropia on ipsilateral head tilt, when reflex incyclotorsion recruits the superior rectus muscle and the paretic superior oblique muscle, and the vertical effect of the unaffected superior rectus muscle cannot be neutralized by the paretic superior oblique muscle.

palsy. Some observant patients also report excyclotorsion; affected engineers even draw the equivalent of Lancaster screen findings, including the effect on torsion.

The classic sign of unilateral fourth nerve palsy is a contralateral head tilt (an ocular torticollis). It is exhibited by most patients and is usually the presenting sign in children, although nonophthalmological causes also must be considered.<sup>56</sup> With a contralateral head tilt, reflex compensatory ocular countertorsion of the affected eye recruits the inferior oblique and inferior rectus muscles to produce excyclotorsion and avoids stimulation of the paretic superior oblique. When the inferior oblique and inferior rectus muscles produce this reflex countertorsion, their opposite vertical effects are mutually neutralized and no vertical deviation results, allowing the patient to maintain fusion. However, with an ipsilateral tilt (to the side of the paretic eye), the countertorsion of the affected eye recruits the incyclotorters, the superior rectus and paretic superior oblique muscles. The vertical effect of the normal superior rectus muscle, which produces elevation, is insufficiently neutralized by the weakened superior oblique muscle, resulting in an ipsilateral hypertropia<sup>57</sup> (Fig. 11.9.3). Paradoxically, some patients maintain a head tilt to the ipsilateral side, presumably to increase the vertical separation between the images and make it easier simply to ignore one of them.<sup>58</sup>

The Bielschowsky three-step head-tilt test<sup>59</sup> can be used to confirm the presence of an isolated cyclovertical muscle palsy if vision in each eye is adequate for fixation and no restrictions on either globe exist. It must be performed with the patient erect, otherwise the vestibular input, which this test is heavily dependent on, will be eliminated. The test was modified by Parks<sup>60</sup> and is now termed the *three-step test* (summarized in Table 11.9.2). Each of the three steps consists of an alternate cover test measurement of the deviation in the indicated gaze position(s): primary position for step 1, right and left gaze for step 2, and 45° head tilt to each side for step 3. Table 11.9.3 summarizes the eight possible outcomes of the three-step test as well as which of the eight cyclovertical muscles is the culprit. It is important to remember that a positive result of the three-step test does not prove the existence of an isolated muscle paresis<sup>61</sup>—it may be positive because of other causes, such as Brown’s syndrome. Torsion can be noted subjectively

**TABLE 11.9.2** The Three-Step Test for Diagnosis of an Isolated Single Cyclovertical Muscle Palsy

Step	Determine Whether:
1	There is a right or left hypertropia in primary gaze
2	The hypertropia worsens with right or left gaze
3	The hypertropia increases with right or left head tilt

**TABLE 11.9.3** Characteristic Three-Step Test Patterns and Their Interpretation

Test Outcome (Step 1–Step 2–Step 3)	Affected Cyclovertical Muscle
R–L–R	Right superior oblique muscle
L–R–L	Left superior oblique muscle
L–L–L	Right inferior oblique muscle
R–R–R	Left inferior oblique muscle
L–L–R	Left inferior rectus muscle
R–R–L	Right inferior rectus muscle
L–R–R	Right superior rectus muscle
R–L–L	Left superior rectus muscle

This test requires each eye to have vision sufficient for fixation and no restrictions. The test is not helpful in patients who have more than one weak cyclovertical muscle in each eye and may be positive in patients with Brown’s syndrome, muscle entrapment, or other causes of restricted eye movement.

through Maddox rod testing or objectively by comparing the spatial relationship of the fovea to the optic nerve on retinal examination.

Patients with bilateral palsy often have “reversing” hypertropias (e.g., a right hypertropia on left gaze and a left hypertropia on right gaze) and a bilaterally positive third step of the three-step test (right hypertropia on right head tilt and left hypertropia on left head tilt). A bilateral palsy often causes a chin-down head position in response to a V-pattern esotropia,



resulting from the loss of the superior oblique muscle's tertiary abducting action in downgaze and large degrees of excyclotorsion in downgaze.

Although symptoms of cyclotropia should be evident in any acquired fourth nerve palsy, it is often not a significant problem except in acquired bilateral cases, which typically result from closed head trauma. In congenital or early acquired cases, sensory reorientation of the retinal meridians develops to eliminate subjective cyclotropia.<sup>62,63</sup> When both superior oblique muscles are weak or completely paralyzed, their opposing hypertropias can neutralize each other, but their excyclodeviations are additive. This effect is maximized in downgaze, the field of greatest action of both superior oblique muscles. When the excyclotorsion (as measured by double Maddox rod [DMR]) exceeds 10°<sup>64</sup> or 15°, <sup>65,66</sup> a bilateral fourth nerve palsy is strongly suggested, although smaller amounts of torsion do not rule out a bilateral palsy.<sup>49</sup> Such affected patients, having no hypertropia to cause them to develop a compensatory head tilt, may adopt a chin-down head position to keep their eyes in the upgaze position where the paretic superior oblique muscles contribute least to ocular alignment, minimizing the excyclotropia and V-pattern esotropia. Observation of the relative positions of the disc and fovea with indirect ophthalmoscopy can be used to objectively assess torsion.<sup>67,68</sup>

Congenital or long-standing fourth nerve paresis can cause physiological and anatomical changes that help determine the time of onset. These patients are constantly challenged to maintain fusion despite a slowly increasing vertical deviation, allowing very large vertical vergence amplitudes to develop; 15–20 prism diopters (PD) are not unusual in these patients, a normal value being 3 to 4 PD.<sup>69</sup> In addition, the constant head tilt is strongly associated with facial asymmetry; the ipsilateral side is vertically shortened and hypoplastic. In such patients, a line drawn through both pupils and another line drawn through the corners of the mouth intersect near the face on the side of the tilt instead of running parallel as in patients with symmetrical facies. The asymmetry was once thought to result from ipsilateral carotid artery compression, but more recent work suggests that it is caused by deformational molding from monotonous ipsilateral positioning during sleep.<sup>70</sup> Early surgery in congenital cases is thought to prevent this asymmetry.<sup>70,71</sup>

## Nonsurgical Treatment

General principles of treatment apply in fourth nerve palsies—small, asymptomatic deviations usually can be observed until they produce a bothersome head tilt or other discomfort. In children, a persistent head tilt can even induce scoliosis.<sup>72</sup>

Small, symptomatic deviations, in some cases, may be successfully treated with the use of prisms. Even though incomitant deviations are not ideal indications for prism treatment, some palsies exhibit spread of comitance that makes them amenable to prism therapy. In cases without spread of comitance, prisms still may be successfully used by addressing the primary position and downgaze deviations and by taking advantage of the patient's large vertical fusional amplitudes.

As with other nerve palsies, acquired fourth nerve palsies, usually traumatic, should initially be nonsurgically treated during a period of observation lasting at least 6 months; improvement or even complete resolution frequently occurs. However, unlike their third nerve counterparts, congenital fourth nerve palsies almost always progress to the point where surgery becomes necessary.

## Surgical Treatment

Surgical treatment of fourth nerve palsies follows the general principles of treatment for any incomitant deviation in that the muscle(s) selected for manipulation must be the one(s) active in the field of largest deviation, especially when the primary position and downgaze (reading position) are concerned. One approach is to assume that the antagonist inferior oblique muscle always overacts to some degree and that weakening the inferior oblique muscle (recession, myectomy, myotomy) resolves up to approximately 15 PD of primary position hypertropia. Patients who have larger primary position hypertropias may require additional muscle surgery, usually a recession of the contralateral inferior rectus muscle (the yoke of the paretic superior oblique muscle) with or without an adjustable suture technique.

A comprehensive surgical management plan for this difficult problem was codified by Knapp<sup>73</sup> in 1974 and is summarized in [Box 11.9.1](#); it accounts for the observed spread of comitance and follows the general principles already outlined.

In classes 1 and 2, where only one gaze field has a large deviation, the muscle whose field of greatest action lies within that gaze field is operated

### BOX 11.9.1 Knapp's Classification of Superior Oblique Paresis

#### Class

1. Greatest deviation is with the affected eye elevated in adduction, the field of the ipsilateral (antagonist) inferior oblique muscle.
2. Greatest deviation is with the affected eye depressed in adduction, the field of the affected paretic superior oblique muscle.
3. Greatest deviation is in all contralateral gazes (down, level, and up).
4. Greatest deviations are in all contralateral gaze and in all downgaze positions (contralateral, straight, and ipsilateral).
5. Greatest deviations are in all downgaze positions.
6. V-pattern esotropia, cyclotropia, and bilaterally positive three-step test indicates a bilateral palsy.
7. Poor elevation and depression in adduction of the affected eye, resulting from direct injury to the superior oblique muscle, causing its restriction and paresis.

Adapted from Knapp P. Classification and treatment of superior oblique palsy. *Am Orthopt J* 1974;24:18–22.

on. The overacting inferior oblique muscle is weakened in class 1, and the paretic superior oblique muscle is strengthened with a tendon tuck or plication in class 2. A mild Brown's syndrome (inability to elevate the eye in adduction) is a desirable result following strengthening of the superior oblique muscle for class 2. However, superior oblique tendon tucks should only be performed when the tendon is sufficiently lax as determined by the intraoperative exaggerated forced duction test, otherwise a severe Brown's syndrome may result.

In class 3, where all contralateral fields are affected, inferior oblique muscle weakening or superior oblique muscle strengthening can be performed alone for vertical deviations below 20 PD; larger deviations may require adding a graded recession of the contralateral inferior rectus muscle. However, it should be mentioned that undercorrections in patients with large preoperative vertical fusional amplitudes are better tolerated than, and preferred over, overcorrections.

Class 4 cases evolve from class 3 cases—the deviation extends from the lateral gaze positions to affect all three downgaze positions as well. Knapp recommended the same treatment as in class 3 and then waiting for the downgaze deviation to resolve after the lateral gaze deviation had been treated, presuming that it was caused by temporary underaction of the ipsilateral inferior rectus muscle. If it did not resolve, he advocated resection of the inferior rectus muscle. More recent analysis attributes this pattern of deviation to contracture of the ipsilateral superior rectus muscle from constant long-standing hypertropia,<sup>49</sup> which may simulate contralateral superior oblique muscle overaction. Treatment requires recession of the ipsilateral superior rectus muscle if oblique surgery alone is insufficient.

Class 5 pareses have maximum deviations in the downgaze fields and are unusual. Although Knapp originally recommended tucking the affected superior oblique muscle in combination with tenotomy of the contralateral superior oblique muscle, this strategy may convert a unilateral palsy into a bilateral one.

Bilateral superior oblique muscle palsies constitute class 6; Knapp recommended bilateral tucking of the superior oblique tendon. In these cases, the predominant deviation is excyclotropia. Successful treatment has been accomplished with bilateral transposition of the anterior fibers of the superior oblique tendon, which are primarily responsible for its torsional action, as originally described by Harada and Ito<sup>74</sup> or more recently by the Fells modification.<sup>64,75</sup> Another option in mild cases is a bilateral nasal transposition of the inferior rectus muscles, which may be combined with a recession to treat a vertical deviation.<sup>76</sup>

Combined paresis and restriction of the superior oblique muscle constitute class 7 cases; these are usually caused by trauma, especially dog bites,<sup>73</sup> directly to the trochlear region. Surgery on the frontal sinus also can be responsible.<sup>15</sup> Knapp offered no solution for this difficult situation; initial alleviation of the restriction with subsequent treatment of the paretic component has since been recommended.

The vast majority of congenital cases have a demonstrable laxity or other abnormality of the tendon, which is infrequently found in acquired cases.<sup>77,78</sup> This can be assessed by intraoperative exaggerated traction test, and when present, it suggests treatment with a tendon-strengthening procedure, perhaps combined with weakening of the antagonist inferior oblique muscle.<sup>79</sup>



**BOX 11.9.2 Possible Causes of Abduction Deficits****Congenital**

- Infantile esotropia
- Möbius' syndrome<sup>81</sup>
- Duane's syndrome
- Congenital horizontal gaze palsy

**Acquired**

- Trauma
- Neoplasm
- Meningitis
- Hydrocephalus
- Benign recurrent sixth nerve palsy<sup>86–88</sup>
- Pseudotumor cerebri
- Gradenigo's syndrome<sup>89</sup>
- Demyelinating disease
- Vascular disease
- Aneurysm
- Postmyelography
- Postimmunization
- Postviral

**SIXTH NERVE PALSY****Introduction**

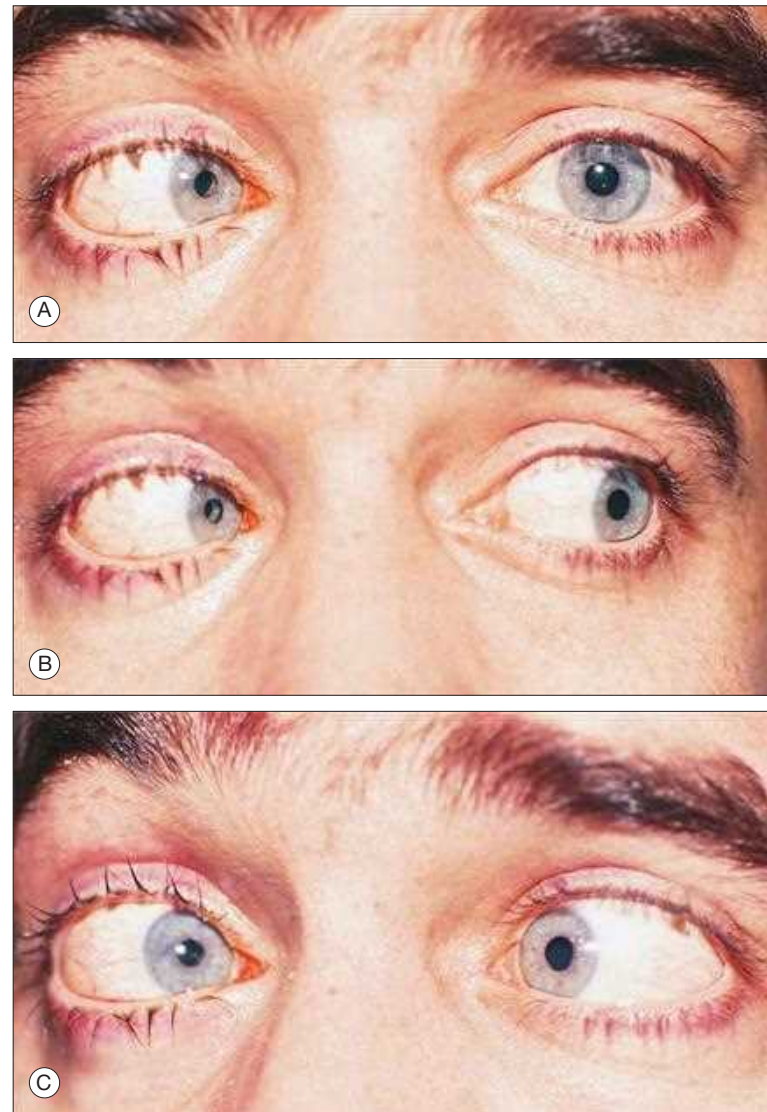
Because only the lateral rectus muscle is affected, palsies of the sixth cranial nerve have presentations that are much less complex than those of the third or fourth cranial nerves. A deviation in the horizontal plane alone is produced, with no torsion or lid involvement, thus reducing the amblyogenic causes in susceptible children. Sixth nerve palsies are more common than either third or fourth nerve palsies in most age groups.<sup>21,45–48</sup>

**Epidemiology and Pathogenesis**

Congenital sixth nerve palsy is unusual and in many cases resolves rapidly.<sup>80</sup> If improvement is not forthcoming after serial observation, a neurological evaluation should be considered. More often, an esotropia with poor abduction of one or both eyes, dating from birth, represents another condition (Box 11.9.2), most commonly infantile esotropia. Children who have a large, constant esotropia often exhibit cross-fixation, fixating in the right field with their left eye, and vice versa, thus never having to abduct either eye. Sixth nerve palsy can be ruled out by provoking abduction, either by unilateral occlusion for a few hours or by utilizing the vestibulo-ocular reflex. The examiner holds the baby face to face at a close distance and spins around, first to one side and then to the other. If the reflex saccades in the opposite direction are brisk and the abduction full, sixth nerve palsy can be discounted. When abduction is truly limited, Duane's syndrome should be considered if there is narrowing of the palpebral fissure and eye globe retraction in adduction. Möbius' syndrome<sup>81</sup> is another possibility, although children with this disorder have other obvious problems (mask-like facies, poor feeding, hypoglossal atrophy, skeletal abnormalities) related to palsies of the seventh and twelfth cranial nerves in addition to the sixth cranial nerve. Congenital gaze palsy has also been reported<sup>82</sup> as a cause of an abduction deficit.

As it has a long intracranial course and the longest subarachnoid course of any cranial nerve, the sixth cranial nerve is prone to injuries from trauma and from nontraumatic diseases of contiguous structures, as summarized in Box 11.9.2. A benign ipsilateral recurrent palsy that follows a viral illness or immunization can affect children<sup>83,84</sup>; the adult counterpart has no known cause.<sup>85</sup> Studies indicate that in children, trauma, more than neoplasm, is a common cause of acquired sixth nerve palsy.<sup>21,45</sup> Earlier studies indicated the reverse, perhaps because of the delayed diagnosis of tumors prior to the advent of computed tomography (CT) and magnetic resonance imaging (MRI), a delay that allowed a paralytic strabismus to develop.<sup>45</sup> Acquired, bilateral palsies are more ominous than their unilateral counterpart.

Despite the lengthy list of possible causes, acquired unilateral sixth nerve weakness (Fig. 11.9.4) is often benign, even if recurrent.<sup>86</sup> However, careful examination must be performed to make sure the palsy is truly isolated and not accompanied by any other neurological findings suggesting a serious cause. Patients who have a truly isolated paresis may be initially observed with serial examinations.<sup>87</sup> However, further investigation



**Fig. 11.9.4 A 33-Year-Old Man With a Right Sixth Nerve Palsy.** (A) Right esotropia in primary position. (B) No deviation in contralateral (left) gaze. (C) Large esotropia in ipsilateral (right) gaze—the affected right eye cannot even get to midline position.

is indicated if no improvement occurs. Prompt, spontaneous resolution of sixth nerve palsy, however, does not rule out neoplasm as a cause in children or adults.<sup>88</sup> The appearance of new indicative findings or progression of the paresis demands immediate investigation. Although rare since the advent of antibiotics, children should be evaluated for otitis media as the cause. Gradenigo's syndrome occurs if contiguous inflammation of the petroclinoid ligament affects the adjacent sixth cranial nerve as it passes through Dorello's canal.<sup>89</sup>

**Ocular Manifestations**

Sixth nerve palsy manifests as esotropia, which almost always affects the primary position. The esotropia of a sixth nerve palsy initially exhibits the typical incomitance of a paralytic strabismus; the deviation is maximized in ipsilateral horizontal gaze and smallest in opposite gaze. In addition, the deviation is larger when the paretic eye is fixating (secondary deviation). However, contracture of its antagonist and yoke muscles (the ipsilateral medial rectus and the contralateral medial rectus muscles, respectively) can rapidly convert the deviation into a comitant esotropia.<sup>90</sup> In unilateral cases that have not yet developed comitance, an ipsilateral face turn may allow binocularity. In congenital palsies that result from Möbius' syndrome an esotropia may be lacking, and instead a gaze palsy may be present if the nucleus of the sixth cranial nerve is affected because the neurons that participate in horizontal conjugate gaze originate within the nucleus of the sixth cranial nerve.<sup>91,92</sup>

**Nonsurgical Treatment**

Surgical treatment of sixth nerve palsy should be deferred whenever a chance for improvement exists and at least for the first 6 months after

onset. During this period of expectant observation, young children who do not adopt the characteristic ipsilateral face turn to maintain binocularity should undergo unilateral occlusion to avoid the development of sensory adaptations. To minimize the possibility of amblyopia, the occlusion should alternate between the eyes. To minimize accommodation (which can worsen the esotropia), spectacles with full hypermetropic correction may be given. Adults also may appreciate unilateral occlusion to eliminate uncrossed diplopia.

Small deviations may be amenable to treatment with the use of prisms, especially because the originally incomitant deviation can rapidly become comitant because of contracture of both medial rectus muscles, as discussed earlier. To stimulate fusional divergence, the minimum amount of horizontal prism that allows fusion should be prescribed.

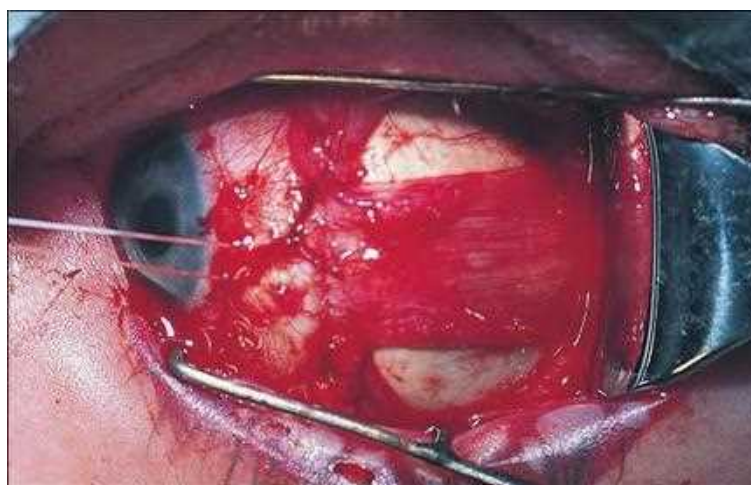
Chemodenervation with botulinum toxin can be used during the acute phase of sixth nerve palsy to prevent contracture of the antagonist medial rectus muscle while the lateral rectus muscle recovers function.<sup>17,18,93</sup> Despite its frequent lack of lasting benefit as a sole remedy for chronic palsy,<sup>18,19,93</sup> some patients may require or even prefer its repeated use as their treatment.<sup>94</sup> It is very useful as an adjunct to surgical management and sometimes essential to prevent or minimize the risk of postoperative ASI.

### Surgical Treatment

Surgical treatment should be considered when more than 6 months have passed after onset and serial examinations yield stable results. The goals of treatment are good ocular alignment in the primary position, expansion of the diplopia-free field, and improvement of the face turn. The surgical plan is largely determined by the depth of the palsy and the degree of medial rectus muscle contracture. Lateral rectus muscle function can be assessed directly by a force generation test,<sup>1</sup> careful observation of ipsilateral saccades, and modified electro-oculography.<sup>95</sup> Traditional forced duction testing estimates the degree of medial rectus contracture.

When at least some lateral rectus muscle function remains (usually with an esotropia of less than 30 D), a graded recess-resect procedure often succeeds; an undesired effect may, however, be an exotropia in the contralateral field of gaze. To avoid this situation, an alternative is a recess-resect procedure in the contralateral eye. Effective treatment when little or no abducting force remains generally requires a new source of abducting force provided by a muscle transposition procedure, together with weakening the antagonist medial rectus muscle, if contracted. Abducting force can be supplied by moving the adjacent vertical rectus muscles to the lateral rectus muscle insertion or by nonsurgical union of the adjacent halves of the lateral and vertical rectus muscles. The many variations of these techniques are reviewed elsewhere.<sup>96</sup>

The original Hummelsheim procedure<sup>97</sup> involves longitudinally splitting the superior and inferior rectus muscles and transposing each lateral half to the insertion of the paretic lateral rectus muscle. This procedure can be enhanced by resection of the transposed halves of the vertical rectus muscles.<sup>98,99</sup> Full-tendon transpositions (Fig. 11.9.5) can transfer more force, particularly if combined with a resection before reinsertion,<sup>100</sup> but have a higher risk of causing ASI. A proposed modification utilizes a posterior fixation suture to better direct the transferred force as horizontally as possible.<sup>101,102</sup> A muscle transposition of vertical recti without tenotomy and muscle splitting recently has been described<sup>103</sup> as a variation of the traditional Jensen procedure,<sup>104</sup> which entails longitudinal splitting of the lateral rectus and the vertical rectus muscles. The adjacent halves are then joined with a nonabsorbable suture, usually in conjunction with medial rectus muscle recession. Because the vertical recti are not severed from the globe, it was originally thought that this procedure would eliminate the risk of ASI, a theory that has since been disproved.<sup>105</sup> To minimize this risk and at the same time preserve the effectiveness of full-tendon transposition, adjunctive chemodenervation of the medial rectus muscle with botulinum



**Fig. 11.9.5** Full-tendon “transposition” of the superior and inferior rectus muscles to the insertion of the left lateral rectus muscle. (Courtesy R. Scott Foster, MD.)

toxin (instead of surgical recession) has been advocated<sup>106</sup> as has a lateral rectus plication along with Hummelsheim transposition (California Hummelsheim)<sup>107</sup> with or without medial rectus muscle weakening

### SUMMARY

In summary, the diagnosis and management of paralytic strabismus is complex. Patterns of incomitant strabismus must be analyzed using an array of tests and maneuvers to arrive at the correct diagnosis. Additional historical and physical findings must be sought to determine whether systemic evaluation is necessary. In spite of the multiple challenges encountered when surgically treating paralytic strabismus, results may be gratifying if surgical goals are clearly understood and surgical principles are followed.

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## Other Vertical Strabismus Forms

11.10

Mitchell B. Strominger, Howard M. Eggers

**Definition:** Vertical strabismus not paretic in origin.**Key Features**

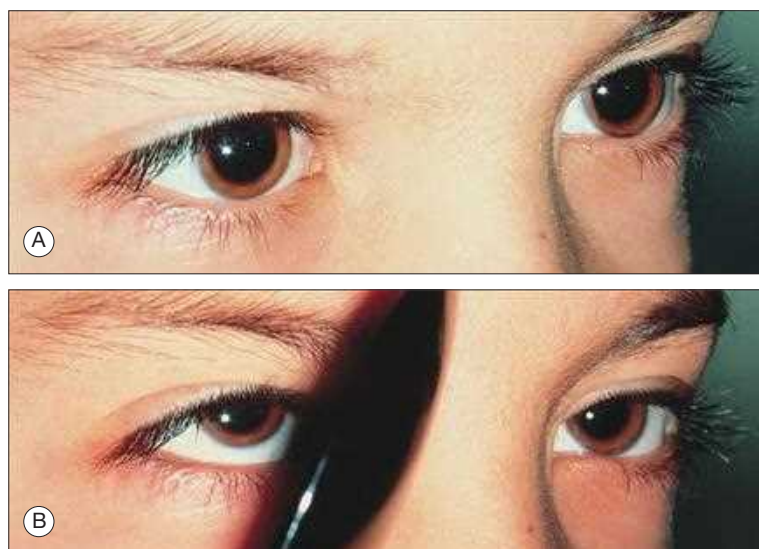
- Incomitance.
- Supranuclear or mechanical causation.

**INTRODUCTION**

The various findings in nonparetic vertical strabismus can be grouped into several clinical entities. All share incomitance as a feature. The causes are multiple and include supranuclear, strabismic, mechanical, restrictive, or muscle fibrosis.

**DISSOCIATED VERTICAL DIVERGENCE****Introduction**

Dissociated vertical divergence (or dissociated vertical deviation [DVD]) is characterized by a spontaneous upward deviation of either eye (dissociation) while the other eye fixates a target (Fig. 11.10.1).<sup>1</sup> The deviation is variable within an episode and from one dissociated episode to another. After a period of usually no more than a few tenths of a second or on a shift of gaze, the eye returns down and typically becomes transiently mildly hypotropic. The amplitude of the deviation and the frequency of spontaneous dissociation usually are not equal in the two eyes. The spontaneous deviation may occur with or without daydreaming or fatigue, although these states make the deviation worse or the spontaneous dissociation more common.



**Fig. 11.10.1 Dissociated Vertical Divergence.** (A) The eyes are approximately straight in primary position. (B) Occlusion of an eye leads to an upward drift of the covered eye. Dissociated vertical divergence is usually bilateral, although it may show asymmetrical amounts of drift. On cover testing, each eye drifts up when under cover. A measure of a simultaneous vertical deviation is the prism power that equalizes the amplitude of the vertical drift in the two eyes.

**Epidemiology and Pathogenesis**

Although DVD is most common with infantile esotropia, it can occur with any horizontal strabismus and sometimes as an isolated defect. Seldom present at birth, DVD frequently is a new finding after the age of 2–3 years and is thought to be associated with the early disruption of binocular development. Elevation in adduction, which produces an apparent inferior oblique muscle overaction, can be the initial presentation. Fusion maldevelopment syndrome (FMS; latent or manifest latent nystagmus) commonly occurs with DVD in infantile esotropia.

**Ocular Manifestations**

In cover testing, the eye drifts upward, outward, and excyclorotates behind the occluder. The eye then returns downward when the occluder is removed and fixation restored. The uncovered eye typically remains stationary. Binocular visual input thus plays a role in stabilization of the eyes in the primary position, although the deviation can occur with inattention, or be manifest. Because the deviated eye usually is suppressed, diplopic symptoms seldom occur.<sup>2</sup> Rarely, the suppression is not deep enough, and vertical diplopia occurs. Occasionally, a patient may find it physically uncomfortable for the eye to turn upward. The spontaneous deviation may also disturb psychosocial function.

Because each eye drifts upward under cover and moves downward on removal of the cover, it is difficult to measure accurately the vertical deviation of DVD. Thus, the prism power that makes the residual vertical drift symmetrical can be used as an estimate. Occasionally, the drift movement is chiefly horizontal and the term *dissociated horizontal deviation* is used.<sup>3</sup> If it is primarily torsional, the term *dissociated torsional deviation* is used.

**Diagnosis**

The cause of DVD is the subject of much speculation. The normal versions and ductions imply a defect in supranuclear control of eye position. Eye movement studies implicate an abnormal vertical vergence system.<sup>4</sup> The Bielschowsky phenomenon is a curious characteristic of DVD that must be related to the abnormal supranuclear control of vertical eye position. It is demonstrated by occlusion of one eye to make it deviate upward. Then, a neutral density wedge is placed before the opposite, unoccluded eye. The eye behind the cover makes a gradual downward movement in proportion to the attenuation of light that reaches the open eye. This phenomenon sometimes becomes manifest in a blind or significantly visually impaired eye.

**Differential Diagnosis**

The characteristic findings in DVD eliminate the need for any differential diagnosis except in cases that have minimal involvement, concurrent vertical deviation, or difficulty in examination because of the patient's young age. Overaction of the inferior oblique (primary or secondary) muscle and superior oblique muscle paresis must be ruled out. In cases of vertical strabismus, a coexisting DVD may be difficult to diagnose.

**Treatment**

Although binocular sensory and motor fusional capacity is poor in DVD, the aim of nonsurgical therapy for DVD is to strengthen the patient's fusional mechanisms. This is done by elimination of any concurrent strabismus, and optimization of vision through accurate refractive prescription and treatment of amblyopia. Indications for surgery are visual symptoms, physical discomfort from a large deviation, or disfigurement produced by

the updrift. A variety of surgical procedures have been advocated for DVD. These include resection of the inferior recti, recession of the superior recti with or without a Faden (posterior fixation) procedure, and anterior transposition of the inferior oblique.<sup>5-8</sup> If one eye is used habitually for fixation, surgery needs to be performed only on the opposite eye. If either eye is used at times for fixation, both eyes need to be operated on, but asymmetrically, each eye in proportion to its drift. Dissociated horizontal deviation can be corrected by lateral rectus recession on the involved side.

## PRIMARY INFERIOR OBLIQUE MUSCLE OVERACTION

### Epidemiology and Pathogenesis

Overelevation in adduction may be the result of primary overaction of the inferior oblique muscles. The cause is unknown, although it is associated with horizontal strabismus. An anatomical variation plays a role because it can be seen in craniosynostosis. A difference in the plane of action of the superior and inferior oblique muscles, referred to as *desagittalization*, may leave the inferior oblique with a stronger vertical action in adduction than the superior oblique muscle.<sup>9</sup> Excyclorotation of the globe or orbit may raise the insertion of the medial rectus above the horizontal midline to give it a vertical action that assists elevation in adduction and simulates inferior oblique muscle overaction.

### Ocular Manifestations

Primary inferior oblique muscle overaction refers to a marked elevation of an eye when in the adducted position under binocular viewing conditions (Fig. 11.10.2). Usually, no vertical deviation occurs in primary position. When bilateral, a right hypertropia is seen in left gaze and a left hypertropia in right gaze. The elevation in adduction may be bilaterally symmetrical or asymmetrical. The head-tilt test result is negative and depression

on adduction is normal. It is typically associated with a horizontal strabismus, either an esotropia or exotropia, and produces a V-pattern (see Chapter 11.8).

### Differential Diagnosis

The differential diagnosis includes secondary inferior oblique muscle overaction (from a paretic ipsilateral superior oblique or contralateral superior rectus muscle), Duane's syndrome, and DVD. Overaction secondary to superior oblique muscle paresis shows a positive head-tilt test. The differentiation of DVD from inferior oblique muscle overaction is important as it dictates the surgical options.

Primary inferior oblique muscle overaction commonly occurs in infantile esotropia and is frequently confused with DVD. Genuine inferior oblique muscle overaction should produce a V pattern and show measurable vertical deviations in lateral gaze. The abducted eye becomes lower as the high, adducted eye takes up fixation. The deviation is the same regardless of which eye fixates.

In DVD, dissociation of the eyes occurs by occlusion of much of the visual field of the adducted eye by the nose and eyebrow, which results in elevation of the occluded eye. If the adducted eye is the fixating eye, much less or no elevation occurs in adduction. Occlusion of the abducted eye may make that eye elevate and thus reverse the hypertropia findings. The updrift and recovery movements are slower than in a true tropia of inferior oblique muscle overaction and are frequently accompanied by torsional movements, excyclotorsion as the eye rises, and incyclotorsion during recovery.

### Treatment

When elevation in adduction genuinely results from inferior oblique muscle overaction, a weakening procedure is required for these muscles.<sup>10</sup> Surgical options include inferior oblique muscle recession, myotomy, or myectomy. If a concurrent DVD is present, inferior oblique muscle anterior transposition may reduce the upward drift. Apparent overaction of the inferior oblique muscles may disappear after surgery for esotropia.

## MONOCULAR ELEVATION DEFICIENCY (PREVIOUSLY TERMED "DOUBLE ELEVATOR PALSY")

### Introduction

Monocular elevation deficiency (MED) is an apparent paralysis of both elevators (superior rectus and inferior oblique muscles) of one eye that results in a hypotropia on the affected side that increases on upgaze. The levator palpebrae may or may not be involved. A subtype with inferior rectus muscle restriction may occur. Bell's phenomenon is usually absent but, if present, implies a supranuclear lesion. The pupil is normal, as are horizontal rotations.

### Epidemiology and Pathogenesis

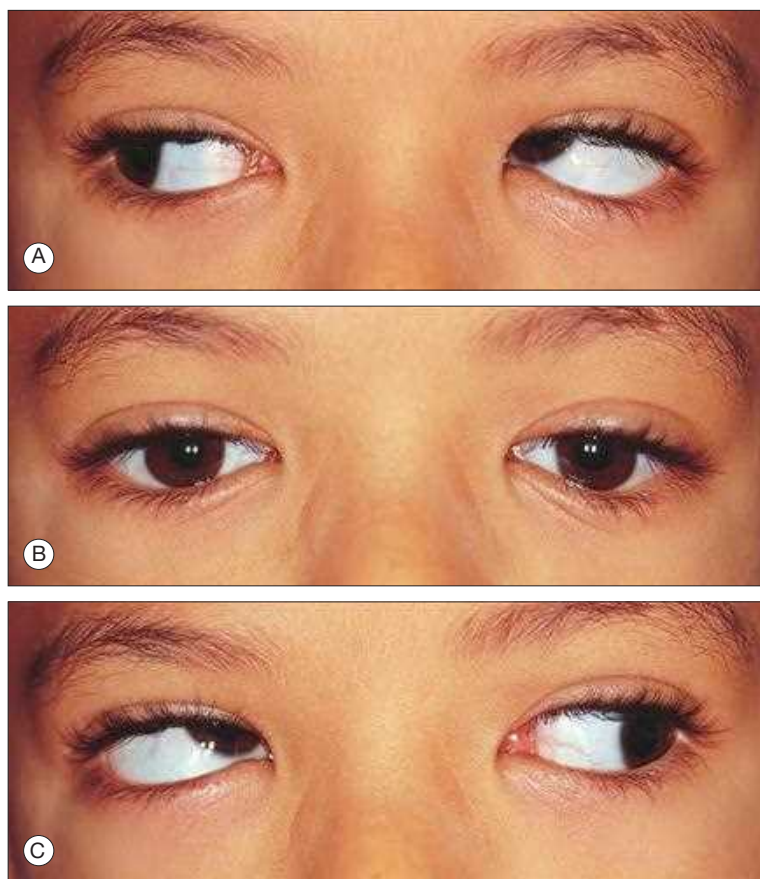
MED may be congenital or acquired. The cause of the congenital form is not known. Acquired cases have all been adults who have small lesions in the pretectum, thus necessitating neuroimaging.<sup>11</sup>

### Differential Diagnosis

The differential diagnosis includes mechanical restriction of elevation (orbital floor fracture, thyroid orbitopathy, congenital fibrosis of the extraocular muscles) and Brown's syndrome (which can sometimes affect primary position).

### Treatment, Course, and Outcome

Forced ductions should be carried out to confirm any mechanical restriction. Surgical treatment traditionally consists of transferring the entire tendon of both the medial and lateral rectus muscles to the superior rectus muscle insertion (Knapp's procedure).<sup>12</sup> Horizontal rotations are impaired only slightly, and vertical rotations are improved remarkably. If the inferior rectus is restricted, it has to be recessed, which can be done in a stepwise, staged-surgery approach evaluating alignment and the need for a second surgery after healing has occurred. Because four anterior ciliary arteries



**Fig. 11.10.2 Elevation in Adduction.** The apparent overaction of the inferior oblique muscle must be confirmed with cover testing. A dissociated vertical divergence frequently gives the same appearance on testing versions. True inferior oblique muscle overaction gives a measurable deviation in lateral gaze and may produce a V-pattern. In dissociated vertical divergence, the abducted eye may circumduct under occlusion. (A) Right gaze. (B) Gaze in primary position. (C) Left gaze. Note elevation of adducted eye in lateral gaze to either side.



are sacrificed for the transposition, it is best to allow 6 months for adaptation of the blood supply before operation on a third rectus muscle. Alternatively, dissection and preservation of the anterior ciliary arteries from the muscle may enable the third muscle to be included at the initial operation. If the lid height does not improve with the raising of eye position, lid surgery may be needed.

## BROWN'S SYNDROME

### Introduction

The motility features of the superior oblique tendon sheath syndrome were originally thought to result from a short anterior sheath of the superior oblique tendon but now are attributed to various abnormalities of the tendon–trochlea complex (Fig. 11.10.3).<sup>13</sup>

### Epidemiology and Pathogenesis

In Brown's original series, there was a 3:2 predominance of women to men and nearly twice as many cases involved the right eye as the left; 10% of cases showed bilaterality. Familial occurrence of Brown's syndrome has been reported.<sup>14</sup>

### Ocular Manifestations

The most striking clinical feature is restriction of elevation in adduction, which is limited to the horizontal plane. The lid fissure may widen when the eye is adducted. Because the limitation arises from mechanical factors, it is the same on version, duction, and forced duction testing. The maximal elevation can increase as the eye moves from adduction to abduction, in which it is normal. Divergence in upgaze from primary position is seen, but normal elevation occurs into supra-abduction (normal superior rectus muscle function), thus differentiating it from MED. The ipsilateral superior oblique muscle usually does not overact. Variable features are head tilt and tropia in all fields. Some acquired and congenital cases have been noted to resolve spontaneously.

Acquired cases arise from orbital trauma,<sup>15</sup> direct trochlear trauma, orbit or muscle surgery, scleral buckling, frontal sinusitis or sinus surgery, Molteno valve implantation, and inflammation of the superior oblique tendon or sheath. Orbital floor fractures may trap the orbital tissue in such a way as to simulate Brown's syndrome. Brown's syndrome is produced easily during surgery to tuck the superior oblique muscle if the tendon sheath is not stripped away adequately or if the surgery is carried out too close to the trochlea. Inflammation of the superior oblique tendon has occurred in rheumatoid arthritis and juvenile rheumatoid arthritis.<sup>16–18</sup> Intermittent forms of vertical retraction syndrome have been associated with a click, which occurs as the restriction is released (superior oblique click syndrome).<sup>19,20</sup>

### Treatment

If binocular vision is present and the head position is correct, treatment is not obligatory. Treatment is required for visual symptoms, strabismus, or incorrect head position. Acquired cases that have active inflammation of the superior oblique tendon may benefit from local corticosteroid injections in the region of the trochlea.<sup>16</sup> Prisms may provide some relief from diplopia in acquired forms.

The goal of surgery is to restore free ocular rotations. Intraoperative aggressive forced ductions can improve movement in some of cases but the majority requires a surgical procedure. Brown advocated that the superior oblique tendon be stripped. The results of such a procedure often are unsatisfactory because of reformation of scar tissue. A procedure of luxation of the whole trochlea, with the superior oblique tendon and orbital structures left intact, appears promising.<sup>21</sup> Tenotomy of the superior oblique tendon also can be performed.<sup>22</sup> This has the disadvantage that it frequently produces a superior oblique muscle paresis.<sup>23</sup> Furthermore, if the tendon is not tight, the tenotomy may not improve the restricted movement. Currently, insertion of an inert spacer or suture between the cut ends of the superior oblique tendon is advocated. During surgery, a traction test is repeated frequently until the globe rotations are free.

## CONGENITAL FIBROSIS

Congenital fibrosis of the extraocular muscles (CFEOM) is a group of conditions within the general category of the congenital cranial disinnervation



**Fig. 11.10.3 Brown's Syndrome.** Elevation of the left eye is impaired most in right gaze. The differential diagnosis includes inferior rectus muscle paresis. Brown's syndrome is characterized by a positive traction test for elevation in adduction, but muscle paresis is not. (A) Gaze to right and up. Note limitation of elevation of adducted left eye. (B) Gazing upward shows mild limitation of elevation of left eye. (C) Gazing left and up shows no restrictions. (D) Gazing to the right shows no vertical deviation in this case, but one may be present with additional testing. (E) Primary position shows no deviation.

disorders<sup>24</sup> (CFEOM1, CFEOM2, CFEOM3, and Tugel's syndrome). It manifests as a variable degree of fibrosis and atrophy of the extraocular muscles innervated by the third and fourth cranial nerves. This leads to a restrictive orbitopathy. Blepharoptosis and a compensatory elevated chin position occur. Attempts at upward eye movements may result in convergence. The overall prevalence is 1:230 000 and has been identified throughout the world. Tugel's syndrome is associated with hand anomalies. The differential diagnosis includes Graves' disease, Brown's syndrome, orbital floor fracture, monocular elevation deficiency, and chronic progressive external ophthalmoplegia.

Surgical treatment can relieve the extreme downward tethering of the eyes. The head position improves as a result. The lids may need to be

raised, but caution is necessary because the upward rotation of the eyes is limited and the normal Bell's phenomenon does not occur with blinking. It, therefore, is easy to produce corneal exposure with eyelid raising procedures.

## FRACTURES OF THE ORBITAL FLOOR

### Ocular Manifestations

Ocular motility may be impaired in orbital floor fractures as a result of proptosis and edema from the original trauma, muscle contusion, intraorbital hemorrhage, herniation of the orbital fascia, and muscle entrapment.<sup>25</sup> Eye movements in general, but particularly elevation and depression, may be limited. The inferior rectus is the muscle most commonly affected.

### Diagnosis

The diagnosis of inferior rectus entrapment is made on the basis of the presence of limited elevation on the affected side, which results in hypotropia, and a positive forced duction testing. Mild cases show hypotropia only in upgaze. Depression may be limited by entrapment or by damage to the nerve to the inferior rectus muscle. Because of the oculocardiac reflex, attempted upgaze in cases of inferior rectus entrapment may be accompanied by bradycardia, especially in the pediatric population. Diplopia may persist after the inferior rectus muscle has been freed.

The pathophysiology of any resultant strabismus is the herniation of the orbital contents—fat, connective tissue septa, and muscle—into the fracture and consequent tethering of the eye. If the entrapment is old, the muscle can become permanently fibrotic and inelastic, which results in a reduced range of rotation. A paresis of the inferior rectus also may occur, which presumably arises from trauma to the nerve that supplies the inferior rectus. On occasion, the inferior rectus muscle may be devitalized by compromise of its blood supply. The muscle is then found to be quite friable at the time of surgery.

### Treatment

A floor fracture does not require repair if no disturbance of motility exists.<sup>25</sup> Large fractures, however, should be repaired to prevent enophthalmos. Some clinicians treat immediately while others wait for up to 2 weeks for regression of the edema. Unfortunately, fracture repair may not free the inferior rectus muscle adequately, necessitating ocular muscle surgery for the hypotropia that remains with restriction to elevation.

## GRAVES' OPTHALMOPATHY (DYSTHYROID ORBITOPATHY)

### Introduction

Dysthyroid orbitopathy is an autoimmune inflammatory condition that involves the orbital tissues, primarily the muscles and fat, but spares the muscle tendons. The muscles are affected by an autoimmune inflammatory process of interstitial edema and round cell infiltration. The muscles enlarge and then become fibrotic and inelastic. Other findings are lid edema, proptosis, lid retraction, and compressive optic neuropathy. Proptosis results from edema and enlargement of the muscles and orbital fat.

### Ocular Manifestations

The usual motility findings are caused by a restrictive myopathy. In addition, orbital inflammation can result in diffuse adhesions of Tenon's capsule and orbital tissues to the globe. The inferior rectus muscle is the most commonly affected, resulting in limitation of elevation. When the condition is more severe, the eye may be tethered down by the inferior rectus muscle leading to a hypotropia in the primary position. The medial rectus muscle is the next most commonly involved, followed by the superior and lateral recti ( $I > M > S > L$ ). The oblique muscles also may be involved, although rarely. The orbitopathy frequently is asymmetrical between the two eyes.

## Diagnosis

The diagnosis is primarily clinical because the patient may have any level of thyroid activity. Thyroid ophthalmopathy also may recur after many quiescent years. Orbital computed tomography (CT), magnetic resonance imaging (MRI), or B-scan ultrasonography shows enlargement of the muscles with tendon sparing. Forced duction testing demonstrates restriction. Intraocular pressure becomes elevated as the eye attempts to rotate against the restriction. Usually, lid edema, proptosis, or lid retraction is present in addition to any motility disturbance.

### Treatment

Treatment of dysthyroid orbitopathy begins with correction of the thyroid state by an endocrinologist. The goal from the ophthalmic standpoint is single vision in the primary position and downgaze. Fresnel press-on prisms and/or botulinum toxin injections may provide some relief of diplopia until the deviation has stabilized. Because more than one muscle usually is involved, horizontal, vertical, and occasionally oblique deviations are present, the patient should be observed until the deviation has stabilized and the orbital inflammation has subsided. This often may take 6 months or longer. Although some improvement in motility may occur as a result of subsidence of orbital edema, the fibrotic changes in the muscles prevent resolution of the portion of the deviation that arises from restrictive muscle changes. Surgically, tight muscles are recessed to enable better movement and reduce the deviation. A secondary goal is to improve the incomitance. An untoward effect of recessing a restrictive muscle, however, is to produce an underaction in its field of action, thus potentially producing diplopia in an area not seen previously. This is especially true when recession of a tight inferior rectus muscle may produce worse diplopia in a downward reading position. Finally, resection of a fibrosed muscle may worsen the deviation and is reserved for special circumstances and then only limited to the tendon and not the infiltrated muscle belly.

## HEAVY EYE SYNDROME

Convergent strabismus fixus ("heavy eye syndrome") is an ocular motor abnormality, in which the eye is fixed in adduction. It usually also is hypotropic with limitation of elevation. Typically associated with moderate to high myopia, it is a progressive disorder that can initially mimic a paralytic strabismus but then becomes restrictive. Orbital imaging studies demonstrate a slippage or displacement of the extraocular muscle path and pulley, with the lateral rectus muscle displaced inferiorly and the superior rectus muscle displaced medially. Loop myopexy, with or without medial rectus muscle weakening, has become the treatment of choice for this disorder.<sup>26</sup>

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# Amblyopia

George S. Ellis, Jr., Cindy Pritchard

# 11.11

**Definition:** Amblyopia is a developmental defect of spatial visual processing that occurs in the central visual pathways of the eye.

## Key Features

- Decreased recognition associated with decreased vernier (determining offset) and grating acuity (distinguishing contrasted grating stripes).
- Accentuation of the “crowding” phenomenon.
- Unsteady fixation.

## Associated Features

- Decreased contrast sensitivity and spatial localization.
- Abnormal accommodation.

## Experimental Findings

- Receptive fields larger than normal.
- Functionally better under scotopic and mesopic conditions than under photopic conditions.
- Reduced reaction time.

## INTRODUCTION

Amblyopia is a “developmental defect of spatial visual processing that occurs in the central visual pathways of the brain.”<sup>1</sup> In essence, it presents as loss of visual acuity in one or, occasionally, both eyes. Amblyopia most often occurs in otherwise healthy eyes but can be an added cause of poor vision in eyes with other ocular pathology. The neurodevelopmental defects associated with amblyopia are a result of lack of use of one or both eyes or a result of a long-standing defocused image. Fortunately, the neuroplasticity that allows amblyopia to develop also permits successful treatment if the amblyopia is detected and treated early enough in the critical period of development of the visual system. Early detection is imperative for successful treatment. Therefore, clinicians must have a clear understanding of amblyopia and its clinical associations, detection strategies in infants and young children, and the armamentarium of treatment approaches. Only then is restoration of visual acuity possible in an eye with amblyopia.

## CLASSIFICATION OF AMBLYOPIA (THE THREE DS)

### Strabismic Amblyopia (Deviated Image)

Amblyopia can develop in children with manifest strabismus, with these children habitually fixating with one eye and suppressing use of the fellow eye. No correlation exists between the size of deviation and the depth of amblyopia.<sup>2</sup> Therefore, amblyopia is a concern even in the presence of very small heterotropia. Children with intermittent strabismus are less susceptible to amblyopia, but the risk is still present.<sup>3</sup>

### Anisometropic Amblyopia (Defocused Image)

Children with uncorrected anisometropia can become amblyopic. The diagnosis is made when the decreased acuity in the more ametropic eye

does not immediately improve and become normal with use of corrective lenses. This acuity loss extends to the peripheral visual field equally nasally and temporally, which implies uniform degradation of the visual system in an amount proportional to the anisometropia.<sup>4</sup> As monocular visual function in the far temporal periphery of the visual field is spared, the acuity defect found in the more central field must result, in some part, from abnormal binocular interaction.<sup>5</sup>

A study by Donahue demonstrated that the prevalence of amblyopia in very young children with anisometropia is low; however, the prevalence and depth of amblyopia increases with age.<sup>6</sup> This suggests that spectacle correction of anisometropia in the absence of amblyopia might prevent later development of amblyopia. Depth of amblyopia correlates with the degree of anisometropia.<sup>7</sup> The risk of developing amblyopia is greatest when the hyperopic refractive errors between the two eyes differ by more than about 2.00 D, when the myopic refractive errors differ by more than about 4.00 D, or when astigmatic errors differ by more than about 1.25 D.<sup>6</sup> Patients who have anisometropic hyperopia exert sufficient accommodation to provide clear visual acuity in the less hyperopic eye, leaving the other eye blurred and at risk for development of amblyopia. Essentially, with sufficient anisometropia, children will automatically choose to use the clearer (less ametropic) eye for fixation, ignoring the blurred fellow eye. For children with monocular astigmatism, the amblyopia may be confined to a meridian in which maximal defocusing occurs. This type of amblyopia, referred to as “meridional” amblyopia, has been documented in reports of experimental studies.<sup>8</sup>

## Stimulus-Deprivation Amblyopia (Deprived Image)

Any congenital or early acquired condition that results in an obscuration of the visual axis in one or both eyes can lead to stimulus-deprivation amblyopia. If the condition is left untreated, the amblyopia that develops may be devastating visually and sometimes irreversible. Common causes include cataract, corneal opacity, pupil anomalies, severe ptosis, and lid masses (Fig. 11.11.1). Another form of stimulus-deprivation amblyopia is that associated with long-standing bilateral uncorrected high refractive errors. This is commonly referred to as “refractive amblyopia” and is most often seen with bilateral high hyperopia or bilateral high myopia but can occur with bilateral high astigmatism as well. In such cases, both eyes are amblyopic. The diagnosis is made when, in the absence of other eye disease, visual



**Fig. 11.11.1 Stimulus-Deprivation Amblyopia.** A 6-month-old infant with infantile hemangioma of the right upper lid, completely covering the visual axis.

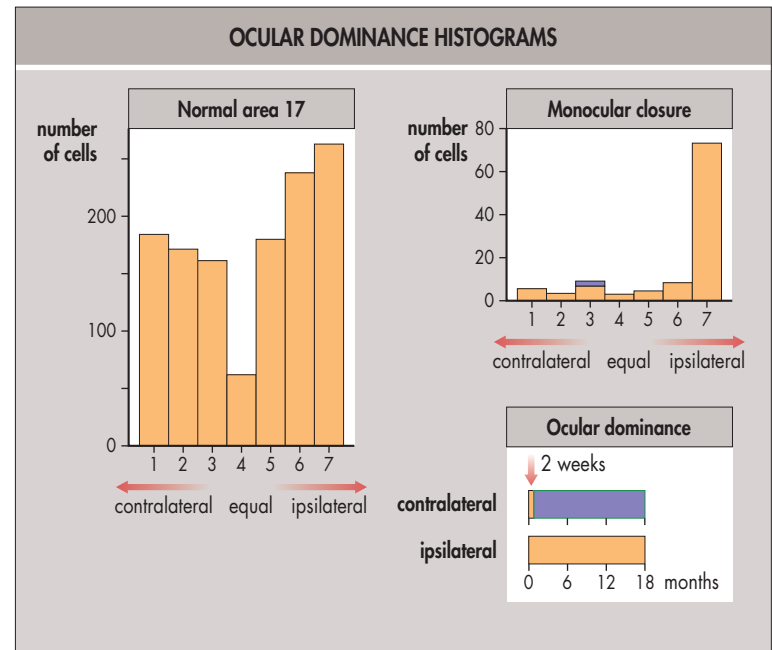
acuity bilaterally is subnormal when the appropriate refractive correction is in place.

## PATHOPHYSIOLOGY

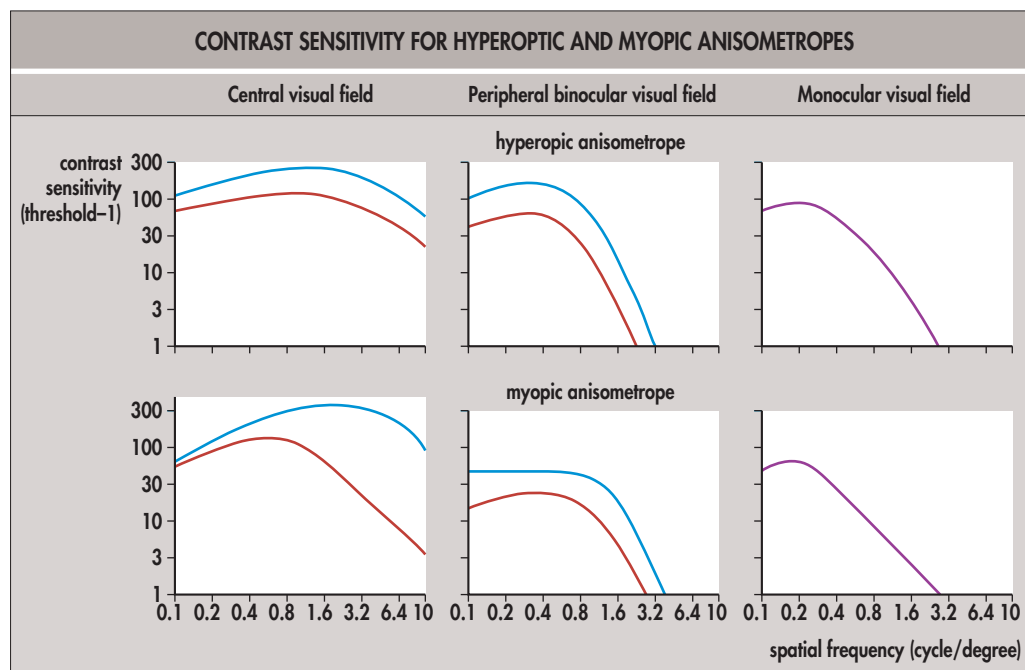
During visual development, in a period known as the *critical period*, the anatomy and physiology of the visual system are malleable. Animal experiments have provided useful insights into the physiological and anatomical processes that occur in humans. Hubel and Weisel were the first to investigate the neuroanatomical and neurophysiological effects of monocular deprivation, which eventually led to their being awarded the Nobel Prize for Physiology/Medicine in 1981. Their early studies involving monocularly deprived kittens demonstrated a reduction or shrinkage in cells responsive to stimulation of the deprived eye in the visual cortex and lateral geniculate body.<sup>9,10</sup> Projections from the lateral geniculate nucleus to the visual cortex are similarly affected. Cortical stripes from the affected eye are narrower than normal, and stripes from the sound eye wider than normal.<sup>11</sup> The effects of monocular deprivation reflect competition from the open eye as well as loss of connections with the deprived eye. Ocular dominance histograms demonstrate the changes that occur in the visual cortex (Fig. 11.11.2).<sup>12</sup> Further investigation in amblyopic monkeys demonstrated that these changes can be reversed by suturing the lid of the sound eye.<sup>13</sup> Using kittens as a model for exploring the critical period, a study showed that monocular deprivation brought on by lid closure is most devastating between 4 and 6 weeks of age, during which time 3 days of monocular closure results in most cortical cells being driven by the open eye. Susceptibility decreases from age 6 weeks to age 3 months; some susceptibility persists until age 9 months.<sup>14</sup> In addition to changes in the visual cortex and lateral geniculate body, other area of the brain have been shown to be involved in amblyopia. Diffusion tensor imaging has detected changes in the anterior visual pathways of subjects with amblyopia.<sup>15</sup> Abnormalities in the structural properties of major white matter tracts in strabismic amblyopia have been described.<sup>16</sup> In animal models with stimulus deprivation amblyopia, arbors of fine-detail cells (X cells) in the geniculate were found to be larger than normal, and arbors of movement cells (Y cells) were smaller than normal.<sup>17</sup> Evidence of retinal involvement has been reported as well, for example, abnormalities of electro-oculography implicating the pigment epithelium.<sup>18</sup> Choroidal thickening in anisometropic and strabismic amblyopia has been demonstrated in studies utilizing optical coherence tomography (OCT).<sup>19</sup>

Many studies have reported functional defects in the visual system of amblyopia in animals and humans. Although it is beyond the scope of this chapter to report all of the findings, some are especially noteworthy to exemplify the abnormal quality of vision associated with amblyopia. Some of the abnormalities can be found in one of the classifications of amblyopia (strabismic, anisometropic, etc.) but not in another classification. For example, vernier acuity is about six times more precise than grating or optotype acuity in normal eyes and in eyes with anisometropic amblyopia

but is less precise in eyes with strabismic amblyopia.<sup>20</sup> This degradation of vernier acuity occurs at both fine and coarse levels. Contrast sensitivity in eyes with strabismic amblyopia may be normal or abnormal at high spatial frequencies. However, for anisometropic amblyopic eyes, the contrast sensitivity curve shows substantial losses at high spatial frequencies only (Fig. 11.11.3).<sup>21,22</sup> Spatial localization as measured by Hess and Holliday is decreased in proportion to contrast sensitivity loss (Fig. 11.11.4).<sup>22</sup> Additional abnormalities include abnormal accommodation and reaction times. Studies have shown that when accommodation is tested in subjects with amblyopia, a reduction occurs in the slope of the stimulus/response curve for the amblyopic eye.<sup>23</sup> Amblyopic eyes also have delays in reaction time that correlates with the decrease in visual acuity.<sup>24</sup>



**Fig. 11.11.2 Ocular Dominance Histograms.** Normal area 17 depicts a normal monkey and is derived from 1256 recordings of visual cortex cells in monkeys of all ages. Monocular closure is from a monocularly deprived monkey (the right eye was occluded from 2 weeks to 18 months of age; recordings were taken from the left hemisphere). Each cell is driven solely by the ipsilateral eye (group 7), contralateral eye (group 1), both eyes (group 4), or somewhere in between (groups 2, 3, 5, and 6). (Data from Hubel DH, Weisel TN, LeVay S. Functional architecture of area 17 in normal and monocularly deprived macaque monkeys. Cold Spring Harbor Symp Quant Biol 1975;40:581–9.)



**Fig. 11.11.3 Contrast sensitivity for those with hyperopic and myopic anisometropia in binocular and monocular visual fields.** Red lines represent the amblyopic eye, blue lines the sound eye, and purple the monocular visual field. (Data from Hess RF, Pointer JS. Differences in the neural basis of human amblyopia: the distribution of the anomaly across the visual field. Vision Res 1985;25:1577–94.)

## SPATIAL LOCALIZATION TEST



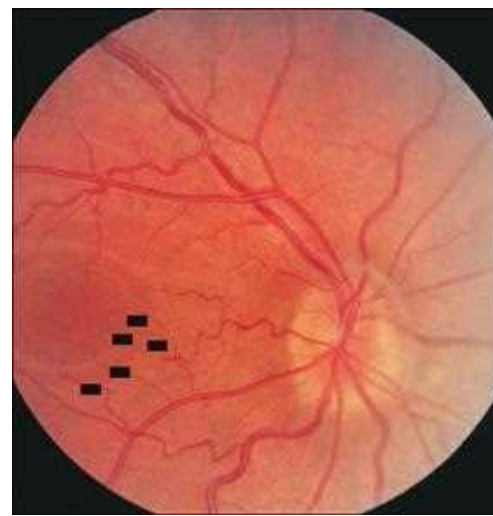
**Fig. 11.11.4 Spatial Localization Test.** The goal of this test is to align the middle grating between the upper and lower gratings.

## DIAGNOSIS

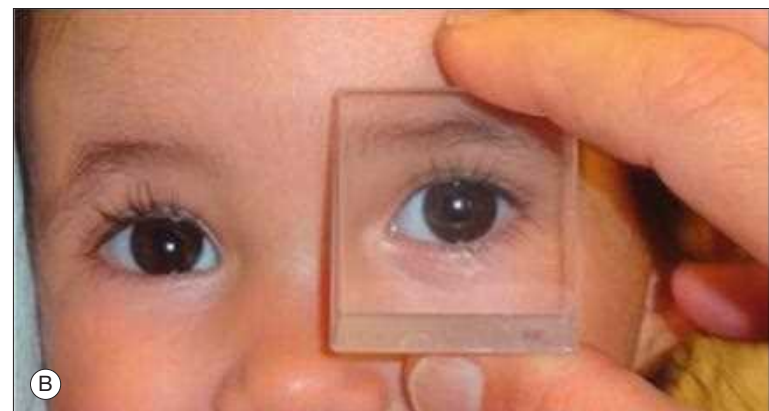
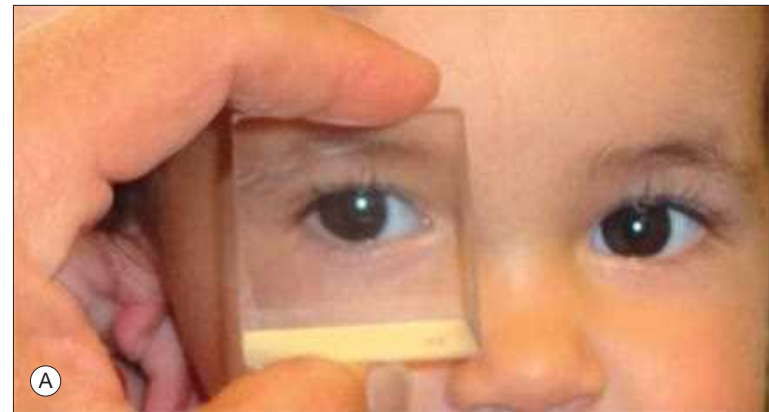
The diagnosis of amblyopia should be considered whenever subnormal acuity cannot be explained by physical findings, particularly in the presence of an amblyogenic condition (strabismus, anisometropia, bilateral high refractive error, or obstruction of visual axis). It is important to recognize that in children with strabismus, even a very small deviation of the visual axes can lead to amblyopia. Because amblyopia cannot be diagnosed solely on the basis of the results of physical examination of the eye and because it can be present when all ocular structures are normal, it is important to carefully assess the visual function for each eye in children in the amblyogenic age group.

A feature of amblyopia of any type is accentuation of the “crowding” phenomenon or spatial interference effect, in which single optotypes are discerned more easily than those in a larger array.<sup>25</sup> Thus, for verbal children, in whom acuity can be determined with Snellen letters or preliterate figures, the presence of crowding difficulty can help confirm the diagnosis. When single-letter or single-picture acuity is better than linear acuity, it is suggestive of amblyopia. Some vision charts allow for the use of “crowding bars” that can simulate linear presentation when isolated optotypes are used for testing. These bars surround the isolated figure or letter resulting in an acuity that is more consistent with linear acuity. Another characteristic of amblyopic vision involves the impact of illumination on acuity. The acuity of amblyopic eyes is better under scotopic or mesopic conditions than under photopic conditions.<sup>26</sup> If a neutral-density filter is available, acuity will remain the same or, in some cases, improve slightly when viewing through the filter with an amblyopic eye. In a normal healthy eye, the acuity will be slightly reduced through the filter. In the presence of organic disease, the neutral-density filter will cause a dramatic reduction in acuity.<sup>26,27</sup>

Determining whether or not amblyopia is present is much more challenging with preverbal infants and with nonverbal developmentally delayed older children. In such cases, acuity can be evaluated by behavior with monocular occlusion. For example, if a child does not object to occlusion of the right eye but rejects occlusion of the left eye (i.e., by moving away from the cover or by crying consistently, etc.), it can be assumed that the right eye has decreased acuity. In addition, the ability to fix and “follow” a small target with each eye can be compared and fixation evaluated with regard to two parameters: central versus eccentric fixation and steady versus unsteady fixation. Amblyopia can be associated with eccentric fixation (Fig. 11.11.5). Patients with eccentric fixation no longer fixate with their fovea, using nonfoveal points to fixate. Unsteady fixation can occur both with central and eccentric fixation and indicates amblyopia in that eye. Therefore, evaluating fixation as central or eccentric and steady or unsteady can assist in assessment for amblyopia when a subjective measurement of acuity is not possible. Another useful tool for assessing visual function when subjective measures cannot be obtained is evaluating maintenance of fixation preference in children who have manifest or induced strabismus. Alternating fixation implies equal acuity in each eye. If a child prefers fixation with one eye, determining the strength of the preference adds valuable information. The poorer the vision in the nonpreferred eye,



**Fig. 11.11.5 Diagnosis of Eccentric Fixation.** A target is projected onto the retina using a special ophthalmoscope. The observer examines where the fixation target falls on the retina relative to the fovea. The marks indicate the locations of successive fixations in a case of eccentric fixation. In general, the poorer the vision, the greater is the scatter and the greater is the distance from the fovea.

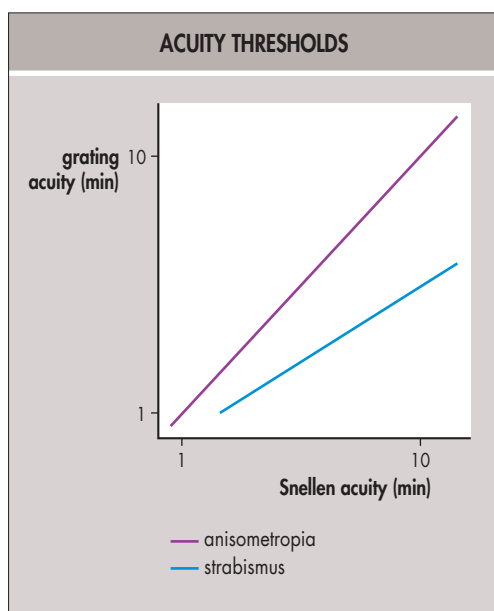


**Fig. 11.11.6** A 20 $\Delta$  base down prism test showing no preference for fixation with one eye suggesting equal vision. (A) Vertical prism is placed in front of right eye. Corneal light reflex shows that child is fixating with left eye. (B) Vertical prism is placed in front of left eye. Corneal light reflex shows that child is fixating with right eye.

the shorter the period the child will maintain fixation with the nonpreferred eye under binocular conditions. This test is performed by covering the dominant eye and forcing the child to fixate on an interesting target with the nonpreferred eye. When the cover is removed, the examiner watches to see how long the child will continue to maintain fixation with the non-dominant eye. The clinician assesses whether fixation is held through a blink-to-blink period, for a few seconds only, or momentarily before fixation is switched back to the dominant eye. Although this manner of vision testing can yield false-positive and false-negative results for amblyopia, it is widely accepted by clinicians for vision assessment in preverbal infants and children with strabismus.<sup>28</sup> Visual function can be tested in a similar manner in children without strabismus by optically inducing a vertical or horizontal deviation with a 10 $\Delta$ –20 $\Delta$  vertical or horizontal prism placed in front of one eye (Fig. 11.11.6).<sup>29</sup>

A mild afferent pupillary defect may be seen in the presence of amblyopia; this, however, implies an organic cause for decreased visual acuity.<sup>29,30</sup> It is important to keep in mind that amblyopia can occur along with ocular pathology. For example, with unilateral optic nerve hypoplasia, the acuity





**Fig. 11.11.7 Grating Acuity Thresholds versus Crowded Snellen Acuity Thresholds.** Snellen acuity is affected much more than grating acuity in strabismic amblyopia.

of the affected eye will be reduced as a result of the abnormal optic nerve. The acuity can become further degraded with superimposed amblyopia. Many clinicians treat these children for amblyopia to achieve acuity that meets the maximum potential of the involved eye.

Forced-choice preferential looking techniques (e.g., Teller acuity cards) are used by some clinicians to assess acuity in infants and preverbal children. It is important to be aware that acuity in amblyopic eyes is overestimated by grating techniques (Fig. 11.11.7).<sup>31</sup> Therefore, tests for visual acuity, such as Teller acuity cards, may be useful in the detection of moderate or severe amblyopia but may fail to detect mild amblyopia.<sup>32</sup>

## TREATMENT

Since plasticity of the visual system diminishes with age, early treatment is essential for optimal outcomes. It is important to recognize, however, that older children also can benefit from amblyopia treatment. Numerous studies describe successful improvement of visual acuity in strabismic or anisometropic amblyopia in teenagers.<sup>33</sup> In addition, patients who have abnormal structural lesions may have a superimposed amblyopia. Many patients who have abnormal structural eye lesions benefit from a trial of amblyopia therapy.<sup>34</sup>

Correction of anisometropia and significant refractive errors is an essential preparation for active amblyopia treatment. As many with amblyopia have deficient accommodation, hyperopic refraction often needs to be corrected.<sup>23</sup> Keratorefractive surgery has been performed for high degrees of anisometropic amblyopia; this treatment, however, usually is resorted to when conventional amblyopia treatment has failed.<sup>35</sup>

It is not always necessary to remove cataracts prior to amblyopia therapy. If the cataract is small or diffuse, amblyopia therapy can be initiated prior to lens extraction. The benefit of an intact natural lens with its accommodative abilities can outweigh the benefit of a perfectly clear visual axis. If, with adequate amblyopia treatment, the vision does not reach an acceptable level, cataract extraction can then be considered.

## Occlusion

Occlusion of the sound eye has long been recognized as an effective treatment for amblyopia. The most common type of occlusion is an adhesive patch (Fig. 11.11.8). Adhesive patches can, however, cause skin irritation. This can sometimes be minimized by changing to another brand with a different adhesive or varying the size of the patch so that the adhesive contacts a different area of skin. Junior-size patches often can provide adequate occlusion even in older children. Another approach to minimizing skin irritation is to create a barrier between skin and the adhesive by using tincture of benzoin or milk of magnesia. Milk of magnesia will leave a residual fine powder on skin when it dries. The patch can then be applied with the powder acting as a barrier. Parents should be forewarned that the child will likely resist the patch. Pirate-style patches are not recommended because they are easily removed, and peeking is easy (Fig. 11.11.9). Emphasizing the importance of adequate treatment will strengthen the parents' resolve when they are confronted with resistance from the child.



**Fig. 11.11.8 Adhesive Patches.** Decorative patches (left) are commercially available online. Flesh tone patches (right) are available at many stores. To make patching more fun, the child and his classmates can decorate the flesh tone patches with stickers or with drawings.

Some clinicians recommend arm restraints when all attempts for adequate patching fail. Arm restraints are commercially available, however, "floaties" for the pool secured with tape at the elbow can be useful in preventing the child from bending his arm to reach the patch for removal.

Glasses fit well over adhesive patches. When glasses are worn, however, nonadhesive patches can be utilized. Most varieties are made with heavy felt that prevents light from passing through the patch. The disadvantages of nonadhesive patches are that they are easily removed by simply removing the glasses and the child can easily peek over the patch by sliding the glasses down the nose to view over the top of the patch.

Patients who undergo full-time occlusion are re-evaluated at intervals of a week per year of life to a maximum of 4 weeks; thus, a 6-month-old child returns in 3 days, and a 4-year-old should return in 4 weeks. Part-time occlusion can be effective and safely allows longer intervals between follow-up visits.<sup>36,37</sup> Furthermore, it has been known for at least 70 years that part-time patching reduces the risk of development of occlusion esotropia, which can occur in children with no strabismus prior to patch treatment.<sup>38</sup>

When peeking over the glasses can be controlled in a cooperative older child, fogging the lens of the sound eye provides a more cosmetically acceptable form of occlusion treatment. The lens can be fogged by applying a commercially available Bangerter foil to the lens or by simply using a brand of tape that is translucent but not transparent (Fig. 11.11.10). Clear films commonly used to line kitchen shelves or drawers can be used to achieve effective lens fogging. Fogging a lens works especially well along with atropine drops placed in the sound eye in children with hyperopia. The blur caused by uncorrected hyperopia combined with atropine will discourage the child from looking over the glasses.

## Atropine Penalization

Atropine drops placed in the sound eye may encourage use of the amblyopic eye for near tasks. Atropine 1% is commonly prescribed for use once daily. An advantage of this method of treatment is that it requires no compliance on the part of the child, other than wearing any needed glasses. In uncooperative children, the drops can be instilled while they are asleep. Some children will show an improvement in acuity with drops applied just 2 days per week.<sup>39</sup> If no improvement in vision is detected, the frequency



**Fig. 11.11.9 Pirate-Style Patch.** Children can easily peek by using a face turn to look around the patch or can easily remove the patch.



**Fig. 11.11.10 Taped Lens.** Translucent tape applied to lens of sound eye is more cosmetically acceptable than adhesive patches.

of drop instillation should be increased. Parents should be informed that with daily atropine use, the drop should be instilled each day even when the pupil remains dilated because a dilated pupil is not a reliable indicator that accommodation is paralyzed. When atropine penalization fails to produce improvement in acuity, patching or fogging should be added to the treatment regime. Parents need to be educated about the potential pharmacological side effects of atropine and ensure that it is not accessible to young children who may ingest it accidentally.

## Optical Penalization

Modifying the eyeglass prescription in a way that encourages fixation with one eye for near and the other for distance also can be used as a treatment for amblyopia.<sup>40</sup> For example, the sound eye may be corrected for near fixation and the amblyopic eye for distance. This form of treatment is not commonly applied; it can, however, be effective, particularly when the amblyopia is mild.

## Systemic Pharmacological Treatment

Occlusive and penalization treatments for amblyopia can only be effective during the critical period of visual system development. The aim of systemic pharmacological treatment is to facilitate treatment during the critical period and to extend the critical period in older children with amblyopia to enable them to respond to treatment. Studies using animal models have demonstrated that neurotransmitters can perhaps make this possible.<sup>41</sup> Among the neurotransmitters studied are the anticholinesterase inhibitor donepezil, the serotonin receptor inhibitor fluoxetine, the catecholamine modulator citicoline, and the dopamine precursors carbidopa and levodopa. Some of these agents have been studied in humans. Levodopa and carbidopa, in particular, have gained much attention. Studies have shown that low doses of levodopa, alone or together with carbidopa, have been shown to augment the effect of occlusion therapy,

even in children over age 12 years.<sup>42</sup> Systemic pharmacological treatment for amblyopia, however, has not yet achieved mainstream acceptance in clinical practice, and its efficacy has been challenged by studies that have shown that no difference exists in treatment outcome between a placebo and levodopa with carbidopa.<sup>43,44</sup>

## COURSE AND OUTCOME

A key variable to the course and outcome of amblyopia treatment is the plasticity of the visual system. This plasticity can and does both help and hinder amblyopia treatment. Successful amblyopia therapy can only occur when the visual system is plastic. If treatment is too aggressive without an adequate follow-up schedule, however, this plasticity can enable the sound eye to become amblyopic (reverse amblyopia) as well. Caution must be used to avoid causing amblyopia in the previously sound eye. Very young children are especially at risk for this because their visual system is more plastic. Plasticity of the visual system can enable amblyopia to recur when treatment is discontinued. Approximately one-fourth of successfully treated amblyopic children experience a recurrence within 6 months of treatment cessation.<sup>45</sup> Therefore, even when the maximal benefit of amblyopia treatment has been reached after the most aggressive tolerated treatment, the treatment should not be discontinued abruptly. Rather, the treatment should be adjusted to maintain the achieved acuity. This can be accomplished either with a gradual reduction in the number of hours of occlusion or with a gradual reduction in the number of days per week of atropine drop instillation.

Strabismus surgery is traditionally deferred until after amblyopia has been treated successfully. The assumption is that surgical results are improved as a result. A retrospective study suggested that surgical results are not dependent on preoperative treatment of amblyopia.<sup>46</sup> Treatment of amblyopia before surgery, however, may result in better parental compliance with regard to surgery, and evaluation of visual acuity by fixation preference is easier if the eyes are strabismic. In addition, if amblyopia is successfully treated before surgery, postoperative occlusion for maintenance of acuity will be minimal and thus is less likely to disrupt peripheral fusion.

## CONSIDERATIONS

For some patients, the creation of a better-sighted “spare tire” (in case of trauma or disease claiming the sound eye) is logically all that can be promised. An interesting study showed a threefold greater risk of loss of the sound eye when the other is amblyopic.<sup>47</sup> With the consideration that vision can be improved from a level of legal blindness to 20/20 if amblyopia is detected and treated early enough, the importance of early detection and treatment becomes very clear. It is not uncommon for older patients who develop ocular disease late in life to undergo multiple surgical procedures, injections, or oral and topical medical treatments to restore or preserve vision. Yet, in a young child with amblyopia, a simple, inexpensive eye patch can permanently restore vision as long as the eye remains healthy through the child’s entire lifetime.

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# Forms of Nonsurgical Strabismus Management

Kyle E. Miller, David B. Granet, Gary R. Diamond<sup>†</sup>

# 11.12

## Definitions:

- **Orthoptics:** a wide range of techniques used to expand fusional vergence amplitudes and permit improved single binocular vision.
- **Convergence insufficiency:** a deficiency in convergence of the eyes to focus on a near target causing symptoms, such as difficulty reading.

## Key Feature

- Numerous techniques other than glasses are available to treat strabismus and should be considered before strabismus surgery is performed.

## ORTHOPTICS

The treatment of strabismus by means of orthoptics (literally “straight eyes”) has a long history, although perhaps this technique is used more extensively in Europe than in the United States. Its basic principle is the gradual expansion of fusional vergence amplitudes with exercises, either in open space or using targets viewed through devices intended to isolate the eyes—haploscopic devices—such as the major amblyoscope. Fusional vergence amplitudes also can be expanded through the use of gradually stronger prisms held in the appropriate direction before one or both eyes or through the use of spherical lenses to utilize the accommodation–convergence relationship to change ocular alignment. More recently, use of dichoptic images of increasing separation has been demonstrated to increase fusional amplitudes.

Historically, the success of orthoptic training was greatest in cooperative patients who had phorias (especially exophoria) or intermittent strabismus of comitant nature. The patients who suffered alphabet-pattern strabismus, torsional symptoms, or highly incomitant strabismus and who gave little cooperation fared less well. Patients affected by long-standing constant tropias were less likely to regain fusional vergence amplitudes despite orthoptic training. There are few published series of successfully treated patients followed up for long terms. It is unclear whether orthoptic training must be continued throughout life to be effective. It also is unclear whether preoperative fusional expansion might improve long-term surgical results.

Today, the most common indication for orthoptic training is convergence insufficiency (CI). The Convergence Insufficiency Treatment Trial randomized 221 children to four different treatment groups: (1) office-based vergence/accommodative therapy with home reinforcement (OBVAT), (2) home-based pencil push-ups (HBPP), (3) home-based computer vergence/accommodative therapy and pencil push-ups (HBCVAT+), or (4) office-based placebo therapy with home reinforcement (OBPT). Although flawed, with no randomization for children with attention deficit disorder/hyperactivity disorder (ADD/HD) and using a symptom survey tool, it remains a valuable source for qualitative information regarding treatment of CI. They found that after 12 weeks of therapy, 73% of those in the OBVAT had successful outcomes. Nearly half of those in the HBPP group and a third of those in the HBCVAT+ group also met the success criteria.<sup>1</sup> A follow-up study showed that the effects of treatment were sustained for at least 1 year in all groups.<sup>2</sup> Despite the increased success rate for office-based orthoptic therapy, the increased time and cost burden of

this therapy has left many to start with home-based therapy as a first-line treatment for CI.

Diplopia recognition (antisuppression) training for patients who have anomalous retinal correspondence and suppression is performed rarely today because of the risk of intractable diplopia.

## PRISMS

Prisms often are very useful in the treatment of certain patients who have a small degree of horizontal and vertical strabismus (especially when comitant).<sup>3,4</sup>

Patients who have superior oblique muscle palsy and a vertical deviation in the primary position may benefit from a vertical prism before the paretic eye. The usefulness of this technique is confounded by the simultaneous excyclotorsion associated with this palsy; some patients, however, cyclofuse successfully if the vertical deviation is collapsed with a prism. The minimal amount of prismatic correction necessary to provide comfortable single binocular vision is prescribed after an office and home trial with Fresnel membrane prisms, as described later in the chapter. Because many patients who suffer from this palsy have incomitant deviations when viewing from right to left, the field of single binocular vision is likely to be limited. In addition, vertical fusional vergence amplitudes are likely to wither under prism correction, and the patient becomes more strabismic when the prism is removed.

Some patients who have sixth nerve palsies and esotropia in primary position benefit from a base-out prism over the paretic eye; this may obviate the need for a face turn to view in the forward position. Some patients who have congenital nystagmus and a compensating face posture may benefit from prisms before one or both eyes to position the null point of least nystagmus and best acuity in the forward position with the head straight. In the case of a horizontal face position, the bases of the prisms are placed in the direction of the face turn. Because the amount of prismatic correction is quite large, this approach usually is impractical.

The use of prisms to treat patients who have typical intermittent horizontal and vertical strabismus often is contraindicated because they place fusional vergence amplitudes at rest and consign the patient to permanent, often increasing, prismatic correction. Certain older or debilitated patients may, however, benefit from prismatic correction when surgery is not indicated or when the deviation is small and symptomatic.

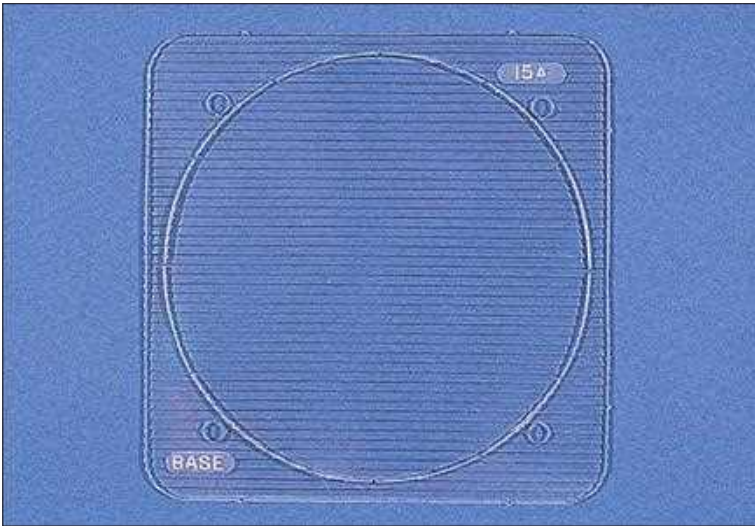
The prism adaptation test involves the preoperative use of prisms to neutralize a deviation with prisms for a given period, followed by surgery for the amount of strabismus fully neutralized by the prisms. Thus, the prism neutralization may be used to predict the outcome of surgery for a given deviation, to determine the maximum deviation, and to estimate fusion potential at that deviation (Fig. 11.12.1). In addition, some patients exhibit a different deviation with the prism adaptation test from that with cover testing. In a controlled, randomized study of patients who had acquired esotropia, 60% underwent prism adaptation, and 40% did not; of those who responded to prisms with motor stability and sensory fusion, half underwent conventional surgery, and half underwent augmented surgery based on the prism-adapted deviation.<sup>5</sup> Success rates were highest (89%) in the prism adaptation responders who underwent augmented surgery, 79% in those who underwent traditional amounts of surgery, and lowest (72%) in those who did not undergo prism adaptation.

The amount of prism to give a patient for comfortable single binocular vision may be assumed arbitrarily to be one-third to one-half of the maximal phoria obtained on cover testing, or it may be titrated to the subjective response of the patient.<sup>6</sup> The amount also can be tested using free

<sup>†</sup>Deceased



**Fig. 11.12.1 Prism Adaptation Test.** A child with esotropia is wearing a Fresnel membrane prism over the left eye, of sufficient strength to neutralize the esotropia.



**Fig. 11.12.2 A Fresnel Membrane Prism.** The prisms are prepunched in circular format, and the base is clearly marked.

prisms in space or using the prism attachment on a phoropter. Fresnel membrane prisms are obtained easily, are relatively inexpensive, and are easy to adjust in strength (Fig. 11.12.2). They are somewhat dysaesthetic, yellow, peel after about 3 months in place, and do degrade acuity (about one line per  $5\Delta$ ). Available in the range  $1\Delta$ – $30\Delta$ , they may be confined to one or both lenses (plano carriers in the case of patients who are not wearing a correction); trimmed to fit a bifocal segment, distance correction, or part of the field of a lens or may be prescribed to an oblique axis orientation for those who have both horizontal and vertical deviations. Patients are given a trial of Fresnel prism wear, and if it is agreeable with a relatively small deviation (under about  $10\Delta$ ), the prism may be ground permanently into spectacles. Some patients prefer to continue to wear the Fresnel membrane prism and simply change it, as needed.

## BOTULINUM TOXIN

The use of type A *Clostridium botulinum* toxin (Fig. 11.12.3) to temporarily paralyze human extraocular muscles by chemodenervation and thus permit the antagonist to contract and effect a permanent alignment change is credited to Scott et al.<sup>7</sup> at the Smith-Kettlewell Eye Research Foundation. The toxin interferes with acetylcholine release from nerve endings by antagonization of serotonin-mediated calcium ion release. The toxin usually is injected in the conscious patient, with the syringe needle connected to an auditory electromyography (EMG) device that amplifies the muscle action potentials (Fig. 11.12.4). Some practitioners inject through conjunctiva without EMG; however, there is no auditory or visual confirmation of placement, and this may lead to a higher rate of reinjections. Alternatively, the muscle may be injected under direct visualization under a local or general anesthetic. Within 3 days, the injected muscle becomes paralyzed, and an overcorrection is initially noted.

Many series of patients have been reported. In a series reported by Biglan et al.,<sup>8</sup> best results were found in patients who had surgical overcorrections (87.5% controlled with oculinum) and mild sixth nerve palsy (43.7% controlled) and worst results in patients who had comitant exotropia (13.3% controlled) and infantile esotropia (33.3% controlled). Significant



**Fig. 11.12.3. Vial of Reconstituted Type A *Clostridium botulinum* Toxin.** The toxin comes in a freeze-dried state and must be gently reconstituted prior to injection. (Image courtesy Erika C. Acera, O.C.[C].)



**Fig 11.12.4.** Electromyography (EMG) device for injecting intramuscular botulinum toxin in an awake patient. The syringe is attached to the dark green needle hub in this picture. As the needle is advanced into the muscle the tone made by the machine changes allowing the user to know when to inject. (Image courtesy Erika C. Acera, O.C.[C].)

complications included blepharoptosis, hypertropia, globe perforation, and subconjunctival hemorrhage. Complications reported by others include transient pupillary dilation, retrobulbar hemorrhage, spread of paralysis to noninjected muscles, missed injection site, patient disorientation, diplopia, and corneal irritation.<sup>9</sup>

Botulinum treatment appears to be most useful in patients who are not medically fit for surgery (because of illness or a history of malignant hyperthermia), who refuse surgery, who have had multiple strabismus operations, or who have acute sixth nerve palsies and mild esotropia in primary position. Botulinum use is contraindicated in patients who have a history of myasthenia gravis and is less effective in patients who have restriction of eye movement caused by scar tissue or entrapment of tissue, but it does have a role in the treatment of thyroid-related ophthalmopathy.<sup>10</sup>

## BUPIVICAINE

The use of bupivacaine (Fig. 11.12.5) has been more recently reported as a potential treatment for strabismus by Scott et al.<sup>11</sup> As opposed to the muscle relaxation created by the use of botulinum toxin, bupivacaine works on the injected muscle by causing it to remodel and shorten via hypertrophy. The method of injection is the same as in botulinum toxin. In a series of 55 consecutive patients with comitant horizontal strabismus, stable outcomes were observed for up to 5 years after injection.<sup>12</sup> As with botulinum toxin, the patients who would likely benefit the most from this treatment are those unable to tolerate general anesthesia or have other contraindications to incisional surgery.



**Fig 11.12.5.** Vial of bupivacaine. No reconstitution is necessary. (Image courtesy Kyle E. Miller, MD.)

## OCCLUSION

Although unsatisfactory to the patient and physician, occluding (or blurring) an eye for intractable diplopia related to strabismus remains an option. Sometimes this can be achieved with the use of an adhesive patch, cloth patch, blurring lens in glasses, Bangertner filter on spectacles, a blurring contact lens, or a black-centered contact lens.

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# Techniques of Strabismus Surgery

Shira L. Robbins

# 11.13

**Definition:** Strabismus surgery is physical manipulation of the extraocular muscles with the goal of therapeutic benefit.

## Key Feature

- The ideal strabismus surgery needs to merge fusional potential garnered through preoperative testing with education about realistic patient expectations and excellent surgical technique.

## INTRODUCTION

Strabismus can lead to frank diplopia, visual shadowing, visual confusion, asthenopia, headaches, dizziness, anomalous head position, decreased visual field, impaired stereopsis, and a large impact on an individual's social and economic positions. Because of the myriad symptoms and functional limitations, treatments are commonly warranted. Strabismus surgery is an important part of the treatment armamentarium in addressing strabismus. In most patients, nonsurgical techniques have been employed with suboptimal results prior to surgical intervention. Many of these nonsurgical methods are discussed in Chapters 11.6–11.11. It is important that prior to surgery, reproducible measurements are obtained, that the patient is sufficiently systemically stable to be able to tolerate the procedure and the accompanying anesthetic/analgesia, and that the patient (or parent) understands the goals and limitations of the planned surgery. In addition, careful preoperative testing to evaluate for postoperative diplopia is imperative to ensure patient satisfaction.

Except in unusual cases, the following are goals of all strabismus surgery:

- Attaining peripheral fusion with fusional vergence amplitudes sufficient to maintain alignment of the eyes.
- Achieving comfortable single binocular vision (horizontal, vertical and torsional) to enable the patient to perform visual tasks without asthenopia.
- Minimizing anomalous head positions to maintain single binocular vision.
- Restoring appearance as close to normal as possible.

## HISTORICAL REVIEW

The first eye muscle procedure (horizontal rectus muscle tenotomy) was probably performed in the middle of the eighteenth century by Chevalier John Taylor.<sup>1</sup> The first successful operation for strabismus with the use of horizontal rectus tenotomy was performed on a living patient (a 7-year-old boy with esotropia) in 1839 by Johann Dieffenbach.<sup>2</sup> Von Graefe<sup>3</sup> performed partial tenotomy in 1851 and advancement of a rectus muscle in 1857. By the late nineteenth century, sutures were being used to shorten a muscle, and measured resections and recessions followed soon afterward. More recent contributions include the use of adjustable sutures and techniques for operation on the oblique and vertical rectus muscles.

In modern times, advances have been made in magnification techniques, improved overhead and loupe mounted lighting, instrument technology, suture development, injectable strabismus treatments, and imaging. Contemporary sutures for strabismus surgery often are absorbable and swaged to needles. The needles are typically spatulated with cutting edges directed away from the center of the globe. The cutting edges are on the sides of a spatulated needle making cutting through a tissue plane easier while not cutting above or below the needle, thus decreasing the risk of scleral perforation.

## BOX 11.13.1 Strabismus Surgery: Preoperative Evaluation and Testing

Sensory testing is performed in all patients whenever permitted by age and ability to cooperate.

Testing should, at minimum, include tests for type of fusional ability and quantity of stereoscopic appreciation.

Measurement of visual axis deviation. Prism adaptation therapy may be helpful in quantifying a target angle of strabismus.

In cooperative children and adults: cover tests, including tests for detection and quantitation of phorias and tropias, tests for binocular single vision and corrected deviation induced diplopia.

In very young children: the Krimsky or cover/uncover tests to quantitate tropias.

Exhaustion of nonsurgical treatment methods including, when appropriate, glasses, patching, fusional amplitude enhancement and prisms.

## PREOPERATIVE EVALUATION AND DIAGNOSTIC APPROACH

Ideal preoperative evaluation of the strabismus surgical patient includes quantification of the misalignment in primary positions at distance and at near, in the nine diagnostic gaze positions, and in right and left head tilt (Box 11.13.1). In most patients, the maximal deviation under conditions of complete dissociation of the visual axes is the deviation for which surgery is to be designed. This is altered in cases of anomalous sensory adaptation (see Chapter 11.4). Patients with diplopia are assessed with prisms in free space to determine the amount of horizontal and/or vertical correction needed to fuse in both the primary position and at near. Patients with sensory adaptations, such as suppression, are evaluated to determine if they have the potential to fuse and are tested for postoperative diplopia. Finally, duction and version testing and, when appropriate, forced duction and force generation testing are performed. These topics are discussed in greater detail in Chapter 11.3.

## ANESTHESIA

The choice of anesthetic technique is individualized and depends on the circumstances of the procedure chosen, age, comorbidities, ability of the patient to tolerate discomfort, and patient's choice. Strabismus surgery on children younger than age 16 years usually requires general anesthesia. Many adult patients are uncomfortable with the operating room setting and/or the concept of eye muscle surgery and request general anesthesia. The benefit of general anesthesia is an immobile, insensate patient. The disadvantages include the attendant risks of general anesthesia and increased recovery time. In cases where local anesthesia is used, conversion to general anesthesia may be necessary occasionally.

When planning a retrobulbar injection, preinjection of intravenous dissociative agents or narcotics is often helpful, and lid block is usually not required. Retrobulbar injection may provide sufficient akinesia and anesthesia for cooperative older teenagers and adults to enable them to tolerate strabismus surgery. The benefits of retrobulbar injection include obviation of general anesthesia risks, briefer recovery room time, and more rapid return to normal routine. The disadvantages include risks of globe or nerve perforation,<sup>4</sup> rare cases of presumed brainstem anesthesia with respiratory suppression,<sup>5</sup> inability to immobilize the superior oblique muscle, inability to operate on both eyes in one session unless another technique is used for the second eye, and injection into a muscle belly with resultant damage.

Particular caution must be exercised in those who have large globes or encumbered orbits (patients who have dysthyroid orbitopathy and enlarged extraocular muscles) because of the increased risk of globe perforation, intramuscular injection, or vascular compromise.

Many cooperative older patients can tolerate epibulbar injection of anesthetic agent around the appropriate muscle(s). Generally, the patient who tolerates forced duction testing in the office is a candidate for epibulbar injection or even topical anesthesia. The advantages of epibulbar injection are similar to those of retrobulbar injection; the disadvantages include somewhat greater discomfort (especially when the muscle is hooked) and rare cases of globe perforation. Reoperations dissecting through scar tissue may not be tolerated with local anesthesia modalities. The advent of the delayed adjustable suture technique allowing adjustment much later in the postoperative period eliminates the need to choose the type of anesthesia according to the desired time to perform an adjustment.

Newer anesthetic agents may decrease postoperative nausea and vomiting. Anesthesiologists need to be prepared to medically support bradycardia secondary to the oculocardiac reflex.

## GENERAL TECHNIQUES

Strabismus surgery demands meticulous planning. Surgical findings of muscle configuration and forced ductions often alter the decision-making process. It is helpful to keep a description of the prior eye/strabismus surgeries, sensorimotor examination and proposed surgical plan for ready reference before and during surgery.<sup>6</sup>

The main types of strabismus surgeries are outlined in [Box 11.13.2](#). The exact location and number of conjunctival incisions depend on the muscles to be operated, pre-existing scarring, and the patient's previous surgical history. Limbal incisions more easily permit accurate surgery without the presence of a trained assistant, may expedite surgery in patients who have experienced multiple procedures on a given muscle, may minimize conjunctival shredding in older patients who have limited Tenon's capsule and inelastic conjunctiva, and permit conjunctival recessions if the tissue is contracted.<sup>7</sup> Patients, however, experience increased discomfort because of corneal proximity; the incisions may compromise the conjunctival contribution to the anterior segment circulation; and the incisions heal more slowly than when other options are used.

Forniceal incisions permit rapid access to the muscles, stimulate less discomfort than limbal incisions, preserve conjunctival vascular supply, and may not require suture or diathermic closure.<sup>8</sup> However, they do require the presence of a more skilled assistant, a better knowledge of muscle anatomy to avoid surgery on the wrong muscle, and relatively elastic conjunctiva. It is important not to incise conjunctiva more than 8 mm posterior to the limbus to avoid the risk of invading orbital fat.

Incisions at the anterior border of the muscle tendon (Swan's approach)<sup>9</sup> have fallen from favor because of the tendency for significant postoperative subconjunctival scarring between the limbus and the muscle insertion.

Absorbable sutures generally are utilized when vascular healing of tissues occurs, as in typical recession and resection techniques. Small-caliber 8-0 conjunctival sutures generally absorb within 7–10 days if covered with conjunctiva, slightly longer if exposed. As opposed to the 6-0 Polyglactin 910 (Vicryl, Ethicon) muscle sutures that typically absorb within 56–70 days. Some advocate permanent sutures if avascular tissue, such

as the superior oblique tendon, is harnessed, as in the superior oblique muscle tuck or silicone (Silastic) band-lengthening procedure. Many also use permanent sutures on the inferior rectus muscle to avoid late overcorrections and elongated scarring.

## SPECIFIC TECHNIQUES

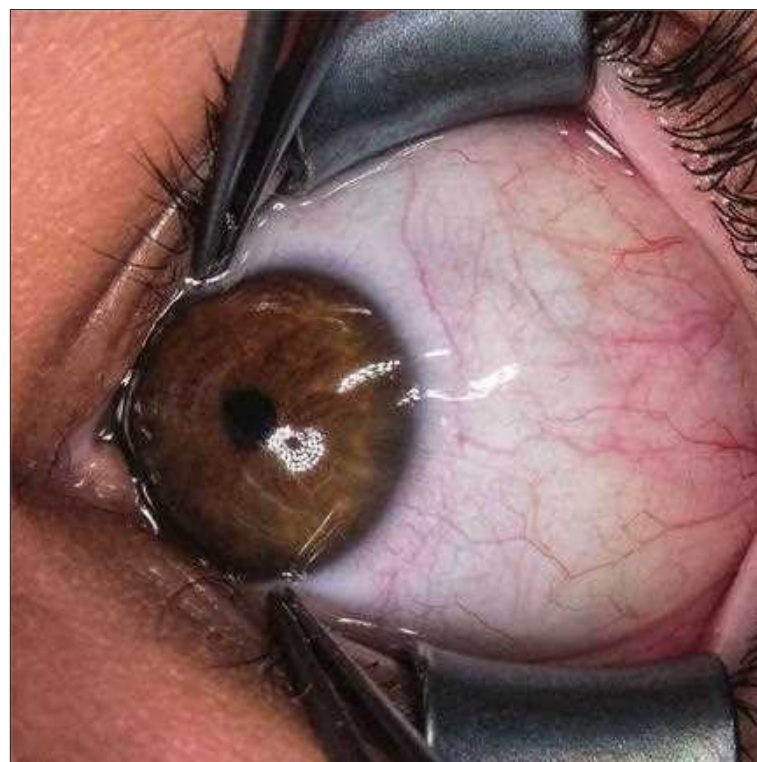
### Recession of a Rectus Muscle

#### Lateral Rectus

There are many variations of strabismus surgery technique and instrumentation. The following is a description of common techniques employed by the author at the University of California San Diego. Forced duction (FD) testing should be considered to obtain information on the tension of the muscles and other causes of restriction in all surgical cases, especially with incomitance and limited clinical ductions. FDs are accomplished by grasping the conjunctiva at the limbus 180° apart and proptosing the globe while pushing away from the muscle in question, thus allowing the recti to be on stretch ([Fig. 11.13.1](#)). This can be repeated for all four recti. Thorpes forceps reduce conjunctival trauma with a 3:2 tooth configuration. The globe is then retropulsed and tortored to put the oblique muscles on stretch to demonstrate restriction or laxity ([Fig. 11.13.2](#)). Exaggerated FD testing can be very helpful in cases of superior oblique muscle pathology.<sup>10</sup>

To perform a lateral rectus muscle recession, the assistant grasps the eye at the conjunctiva–Tenon's capsule junction with a 0.3-mm locking forceps and rotates the eye into elevation and adduction. When an assistant is not present, a traction suture can be placed. The surgeon then elevates the conjunctiva at the base of the fornix and incises the conjunctiva approximately 8 mm from the limbus ([Fig. 11.13.3](#)). The Tenon's capsule is grasped within the conjunctival incision, applying gentle pressure away from the sclera and elevating it from the globe. Tenon's capsule is then incised to expose bare sclera. Visualization of the bare sclera is maintained by leaving the posterior forceps in place.

A Stevens hook is passed to isolate the inferior lateral rectus fibers by keeping the hook tip on sclera ([Fig. 11.13.4](#)). Topical analgesia mixed with epinephrine can be used at any time during the procedure for perioperative analgesia and hemostasis. A Greene self-retaining muscle hook is then passed behind the Stevens hook with the flat edge of the tip on sclera, isolating the full lateral rectus muscle. It is important that no posterior movement of the hook is used so that the inferior oblique fibers are not mistaken for part of the lateral rectus ([Fig. 11.13.5](#)). A second Greene hook is placed posterior to the original Greene hook with a slight turn toward



**Fig. 11.13.1 Forced Duction Testing of Horizontal Rectus Muscles.** The limbal conjunctiva is grasped and the globe is proptosed to place the recti on stretch. Movements of restriction or laxity can then be identified. (All photography in this chapter by Peter Durdaller.)

### BOX 11.13.2 Strabismus Surgery Techniques

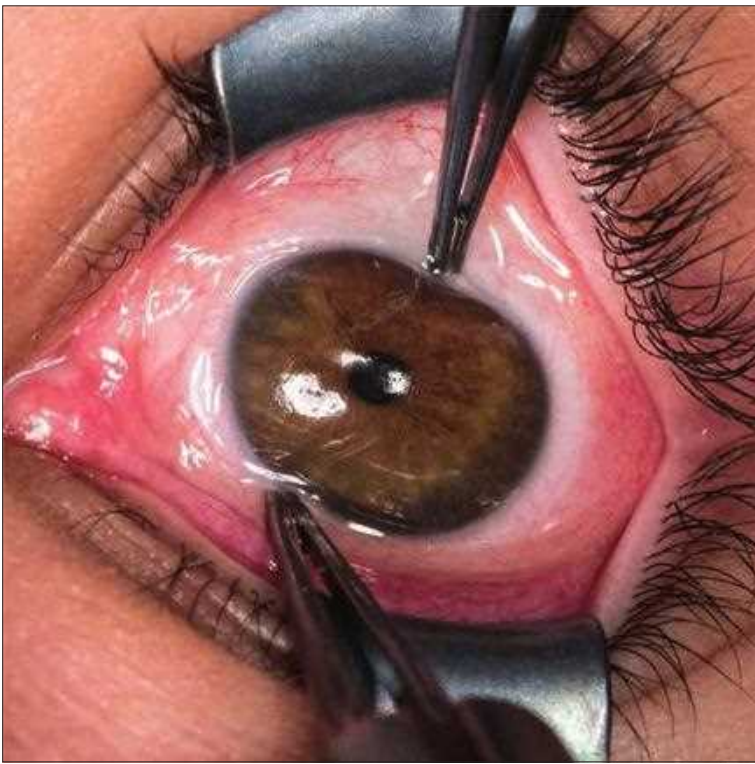
#### Weakening Procedures

Recession:	Moving posteriorly
Lengthening:	Myotomy—cutting part of muscle
Tenotomy:	Cutting part of tendon
Spacer:	Suturing inert foreign body
Myectomy:	Excising part or completely detaching from eye
Posterior Faden:	Decreasing mechanical advantage in field of action
Extirpation/Denervation:	Removing nerve stimulation
Chemically induced:	Using botulinum toxin

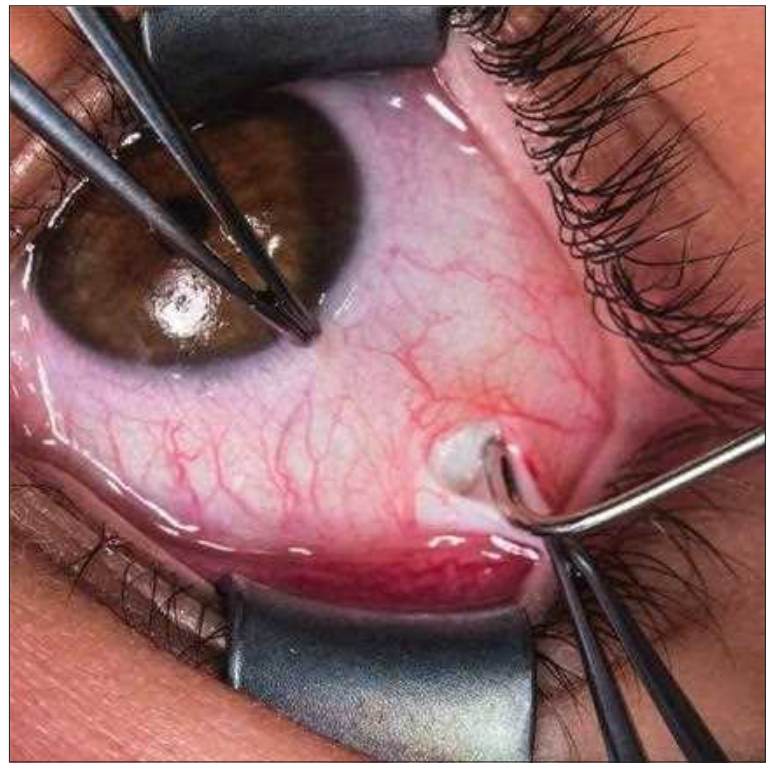
#### Strengthening Procedures

Shortening:	Resection—removing piece without changing insertion location
	Tuck/Plication—creating fold in muscle via suture
	Advancement—moving anteriorly
Chemically Induced:	Using lidocaine
Redirecting Force of Action:	Transposition—moving insertion to new axis

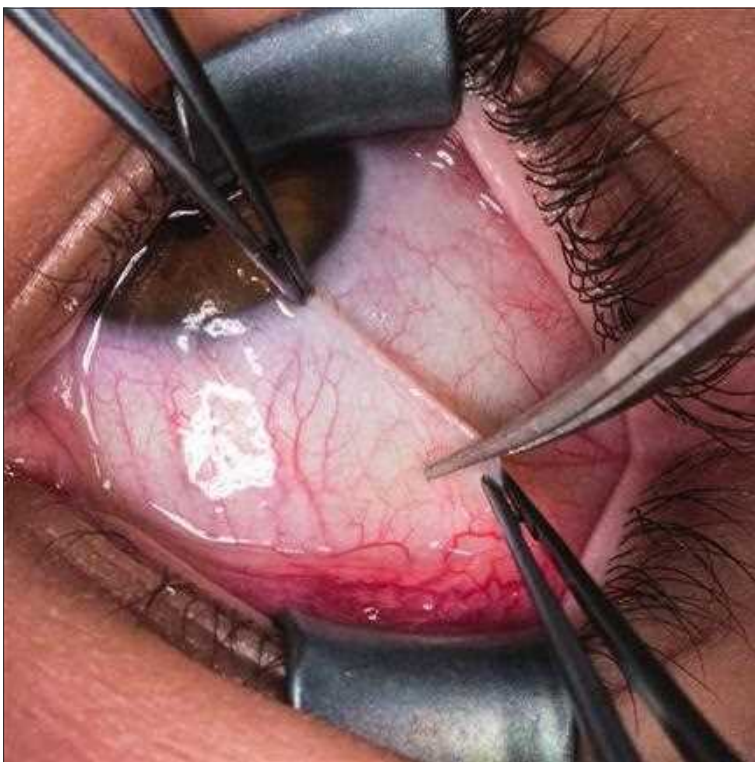




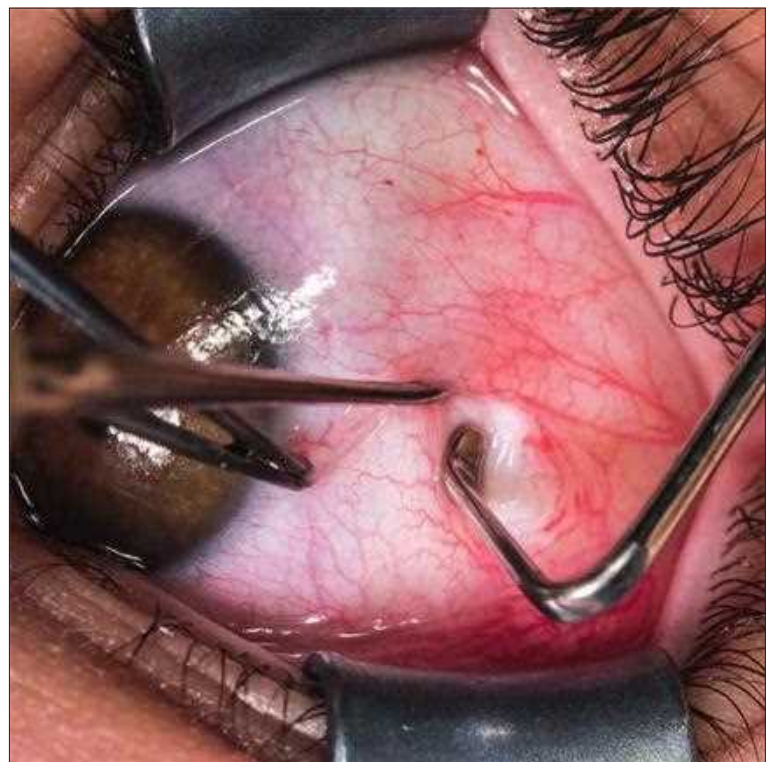
**Fig. 11.13.2 Forced Duction Testing of the Oblique Muscles.** The limbal conjunctiva is grasped and the globe is retro-pulsed to place the oblique muscles on stretch. Movements of restriction or laxity can then be identified.



**Fig. 11.13.4** The Stevens hook is used to isolate the inferior fibers of the muscle by maintaining the tip on sclera. This creates a clear path for a larger hook.



**Fig. 11.13.3 Recession of Lateral Rectus Muscle.** Figs. 11.13.3 through 11.13.19 demonstrate recession of the left lateral rectus muscle. A locking forceps is placed at the 5 o'clock position and used to elevate and adduct the eye. A Thorpe's forceps is used to elevate the conjunctiva about 8 mm posterior to the limbus augmenting the conjunctival incision.

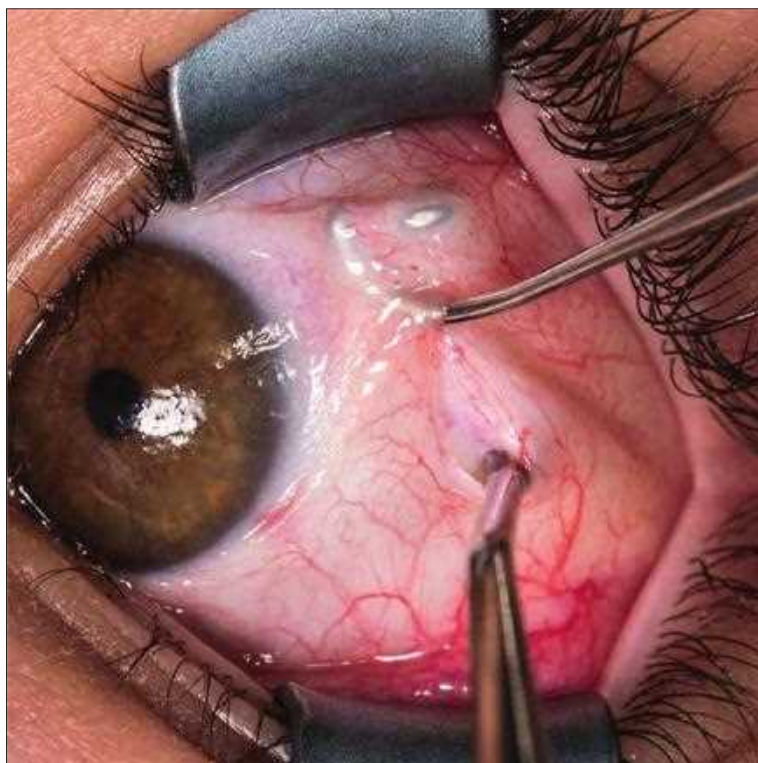


**Fig. 11.13.5** A Greene or Jameson muscle hook is inserted posterior to the Stevens hook under the tendon of the lateral rectus muscle. The toe of the hook is kept flat against the sclera at all times.

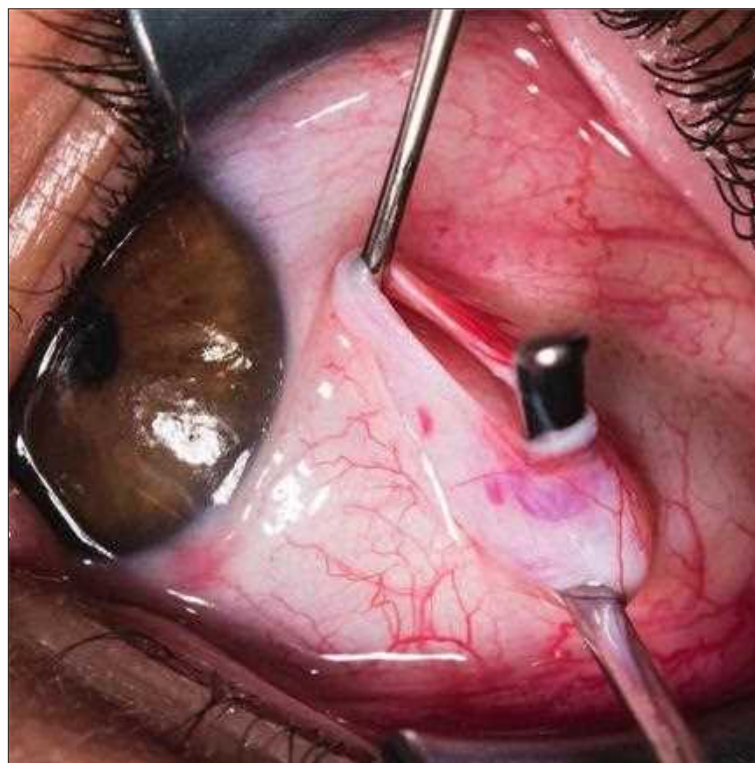
the limbus after there is a tactile sense of isolating all muscle fibers. This ensures the distal fibers will remain on the hook while degloving the conjunctiva and the Tenon's capsule with a Stevens hook. Some surgeons prefer to use a Jameson hook. Once the muscle is degloved (Fig. 11.13.6), scissors are used to incise the superior aspect of Tenon's fascia (Fig. 11.13.7). Through this opening, a Stevens hook is placed, with the tip on the sclera. A pole test ensuring that no splitting of the muscle fibers is accomplished by leaving the Stevens tip on the sclera while arcing toward the limbus

(Fig. 11.13.8). If there are split fibers, the hook tip will meet with resistance. Using direct visualization with the assistance of a variety of hooks is advised if there is any resistance. The presence of heme at this step is often a sign of split muscle, requiring further investigation. With the use of two Stevens hooks, the anterior connective tissue is placed on stretch and cut with scissors (Fig. 11.13.9). The connective tissue adhered to the muscle tendon at the insertion can be further cleared with an Afrin-soaked cotton tip applicator using a posterior motion. Two Stevens or Von Graefe hooks are passed posteriorly along the tendon edges, against bare sclera,

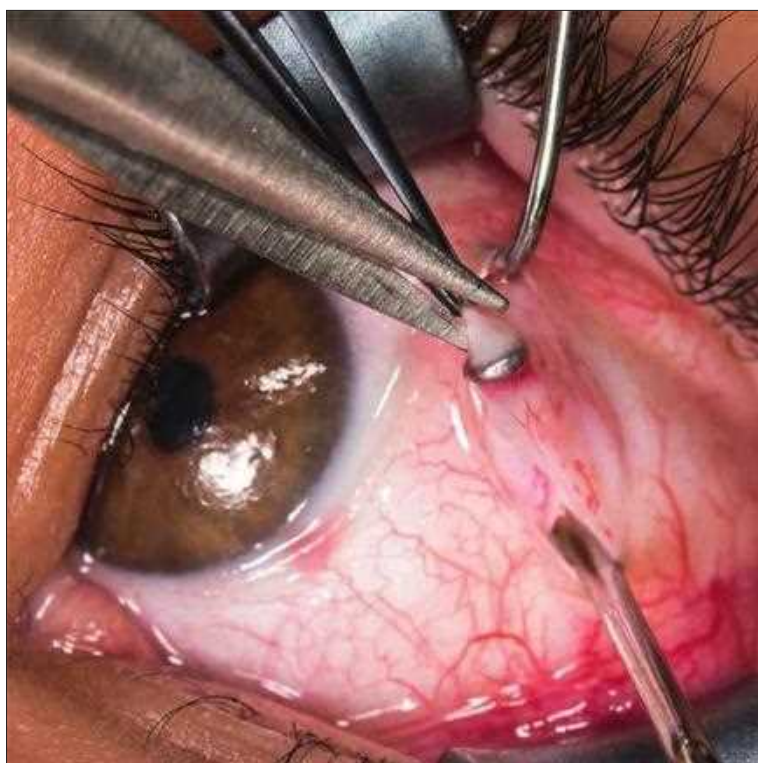




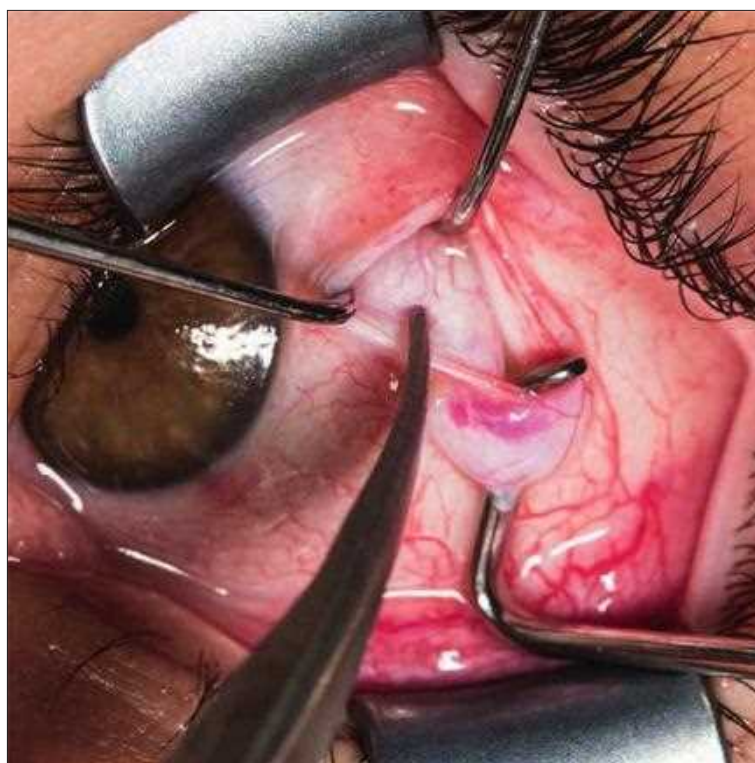
**Fig. 11.13.6** The small Stevens hook is moved forward and backward over the tendon and under the conjunctiva. This separates conjunctiva from the underlying Tenon's capsule and tendon degloving it.



**Fig. 11.13.8** A Stevens muscle hook is placed perpendicular to the sclera through the incision. It is swept around the superior pole of the tendon to ensure that the entire tendon is captured on the muscle hook, the pole test.



**Fig. 11.13.7** A scissors is used to incise the Tenon's fascia at the superior pole of the tendon.



**Fig. 11.13.9** Two Stevens hooks are used to stretch the anterior connective tissue from the insertion in preparation for dissection with scissors.

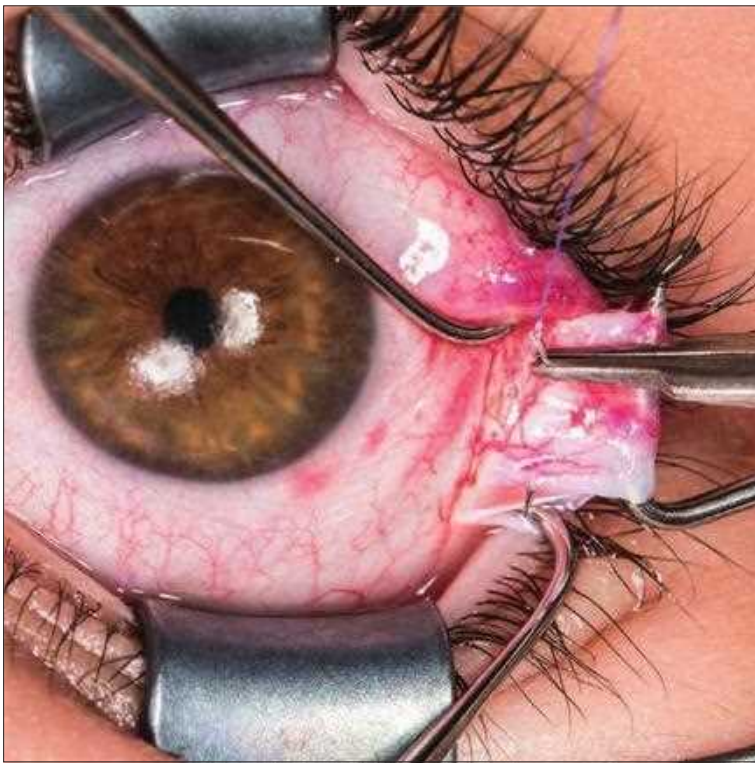
and elevated to expose the intermuscular fascia for dissection close to the muscle belly. The common fascial attachments between the lateral rectus and inferior oblique muscles are removed to avoid undesired effects on oblique muscle functions.

The muscle is sewn 1 mm posterior to the insertion with a 6-0 suture. The author's preference is a double-armed, Polyglactin 910 (Vicryl, Ethicon) on S-29 needle. The needle is passed partial thickness from the middle to the inferior edge of the tendon (Fig. 11.13.10). A full-thickness, locking whipstitch is placed at the edge of the tendon (Fig. 11.13.11). The same technique is used with the opposite suture end to the superior muscle

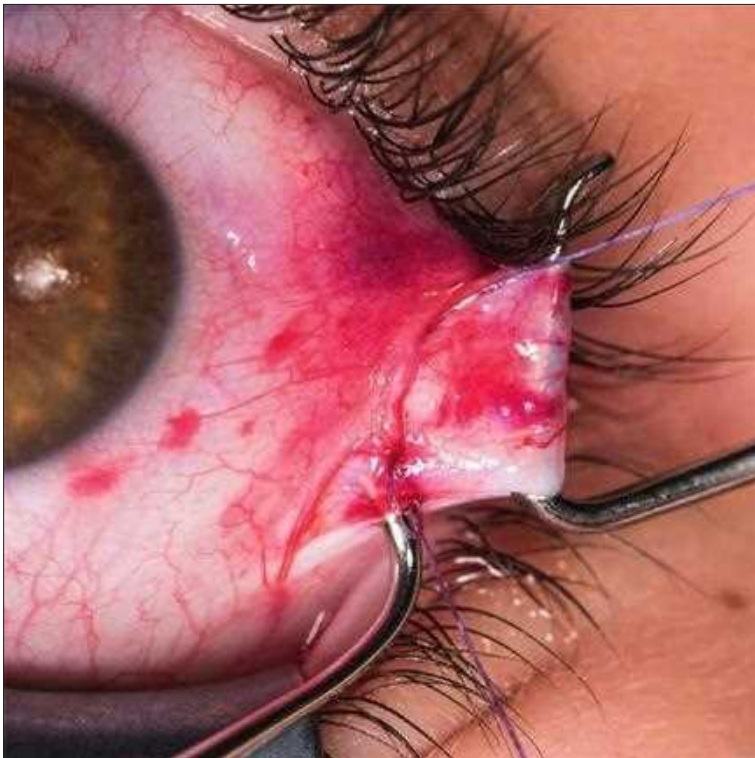
pole (Fig. 11.13.12). A tight muscle can be sewn with the use of a beveled hook, which protects the sclera during this step. The muscle is disinserted using Manson-Aebli scissors in several cuts with the anterior blade being slightly elevated (Fig. 11.13.13). After the first snip, a 0.5-mm Castroviejo locking forceps are placed on the first muscle pole stump disinserted to allow control of the globe, followed by the second forceps at the remaining muscle stump.

The caliper is positioned at the end of the original insertion (Fig. 11.13.14) to the target recession distance posteriorly. This creates an indentation used as a base for the scleral pass, where the needle is laid flat with





**Fig. 11.13.10** The muscle is sewn partial thickness from the center to the inferior pole.

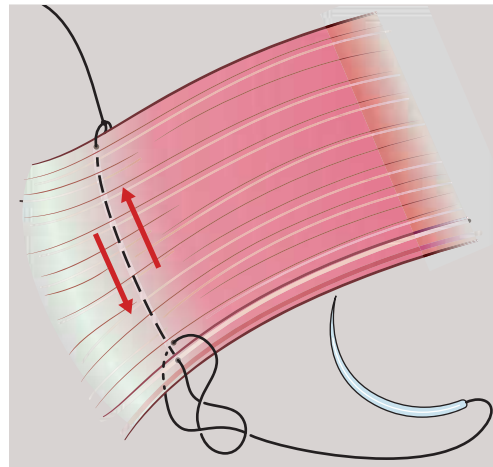


**Fig. 11.13.11** A full-thickness whipstitch is placed at the tendon edge.

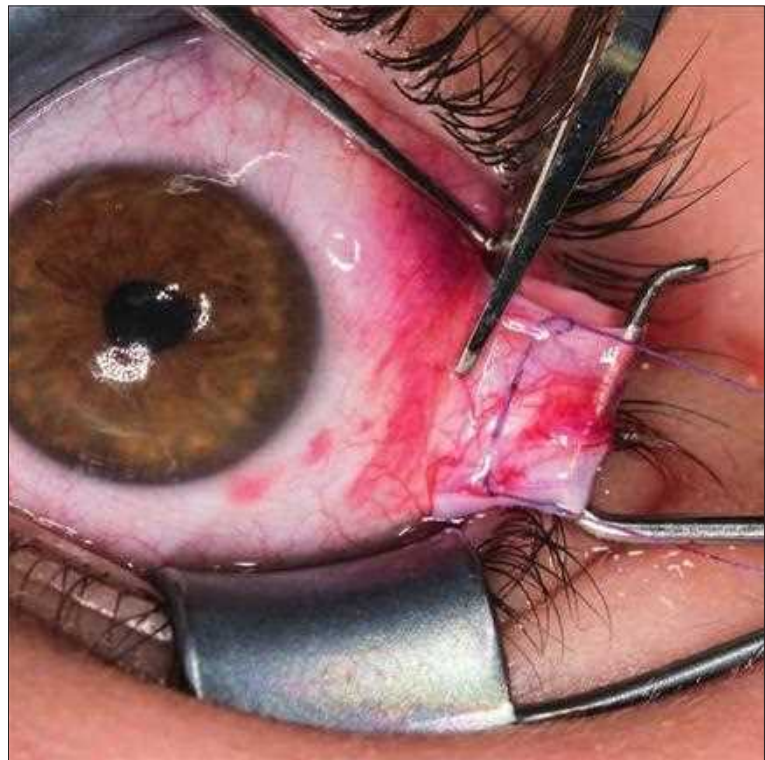
the tip engaging the edge of the scleral depression (**Fig. 11.13.15**). In most cases, it is important to maintain a wide insertion to avoid central sagging of the muscle. An ideal scleral pass can be conceptualized as a mole burrowing a tunnel, whereby the overlying sclera will appear elevated. A common style of scleral pass is the crossed swords, popularized by Marshall Parks, which is thought to increase stability of the new muscle insertion (**Fig. 11.13.16**).<sup>11</sup>

The sutures are then pulled in the direction in which they were passed to avoid ripping the sutures out of the sclera and then tied (**Fig. 11.13.17**). Care must be taken to pull both needles out of the sclera prior to pulling the majority of the suture through; thus, decreasing the likelihood of shredding suture from the opposite needle. Some surgeons close the Tenon's

#### PARTIAL THICKNESS DOUBLE ARMED SUTURING WITH LOCKING SIDE BITES



**Fig. 11.13.12** Partial-thickness double-armed suturing with locking side bites is performed.



**Fig. 11.13.13** The tendon is disinserted from the globe.

capsule separately, although most do not. The overlying conjunctiva is closed with buried 8.0 Polyglactin 910 (Vicryl, Ethicon) or other suture of choice (**Figs. 11.13.18 and 11.13.19**). Sub-Tenon's analgesia is applied.

#### Medial Rectus and Vertical Recti

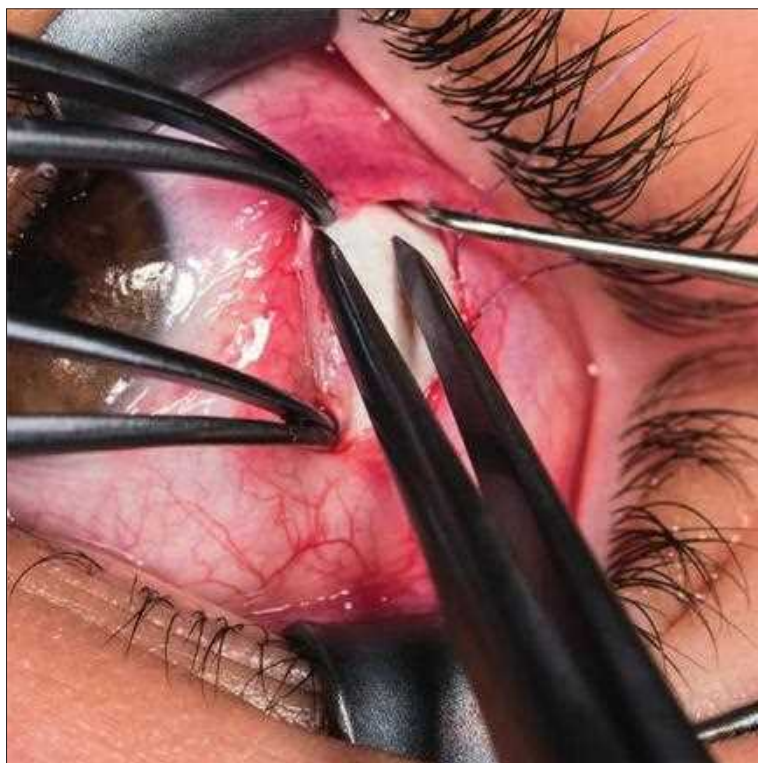
The principles of recession are the same as described previously for the lateral rectus muscle. Recession of the vertical recti, however, includes visualization and preservation of the neighboring oblique muscles before the procedure is performed. The frenulum between the superior rectus and superior oblique muscles is visualized and incised. The lower eyelid retractor muscles must be carefully dissected from the inferior rectus muscle to avoid lower lid ptosis. This is best performed close to the rectus muscle to avoid fat pad violation.

#### Resection of a Rectus Muscle

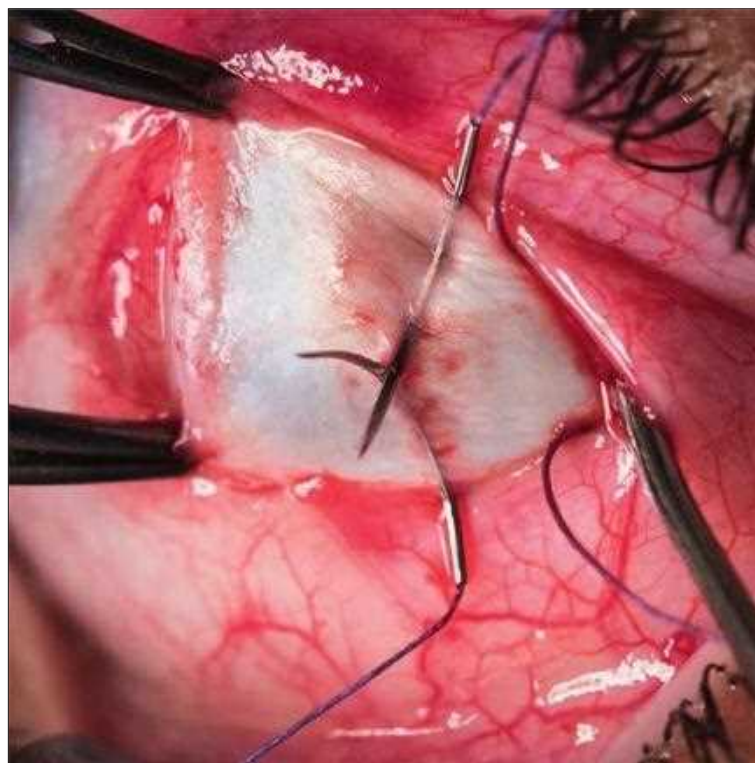
##### Lateral Rectus

The muscle is isolated, cleaned, and dissected posteriorly, employing the same technique as the above recession. A second Greene muscle hook is passed beneath the tendon, and traction is applied between the two muscle hooks which are kept parallel to the insertion. A caliper is used

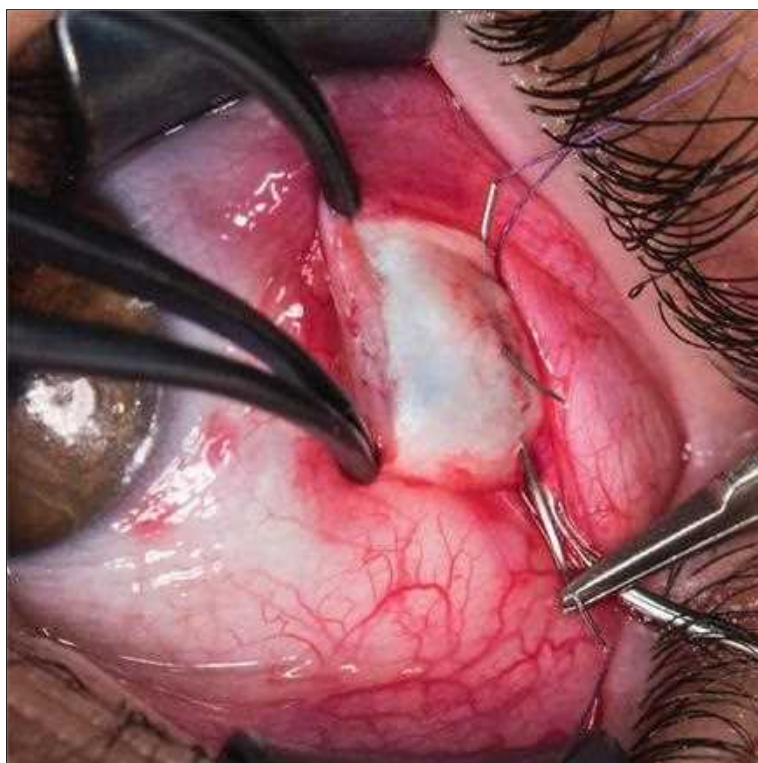




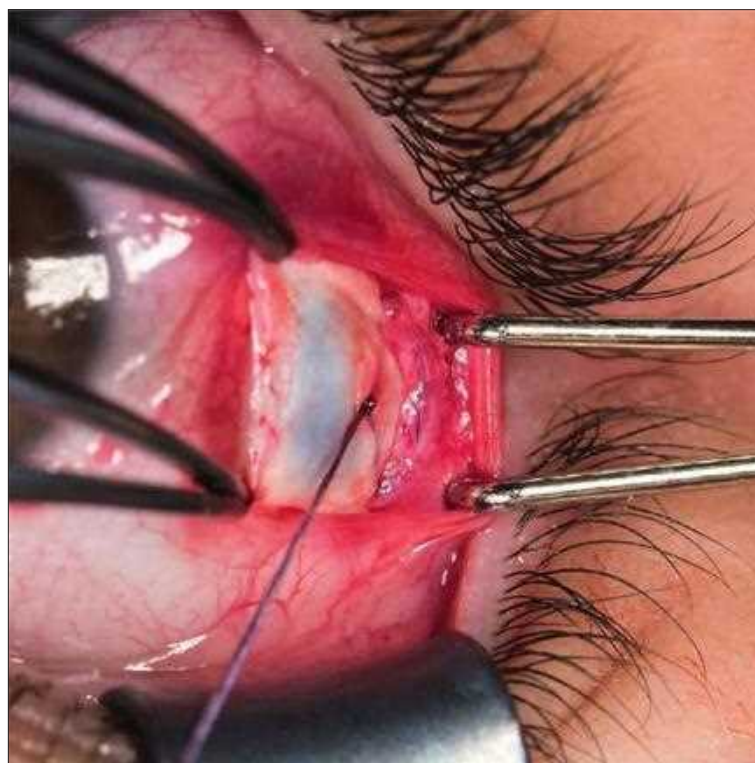
**Fig. 11.13.14** The appropriate position for muscle reattachment is measured from the original insertion.



**Fig. 11.13.16** The second needle of the double-armed suture is placed in similar fashion to the first with overlap of the exit sites creating the "crossed swords" technique.



**Fig 11.13.15** The indentation left by the caliper is used as a base of the needle approach through partial thickness sclera.



**Fig. 11.13.17** The muscle sutures are pulled through sclera in the direction they were placed and secured.

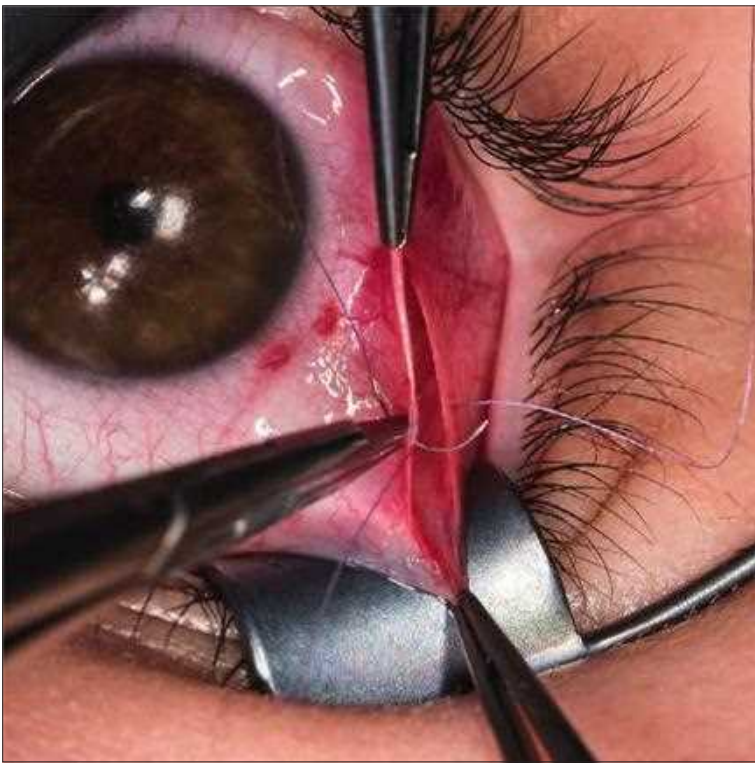
to measure the amount of desired resection. Observing anatomic landmarks (i.e., vascular details) can assist with "seeing" the target point. A central full-thickness bite is taken with a 6.0 double armed Polyglactin 910 (Vicryl, Ethicon) suture on S-29 needle and tied in a square knot ([Fig. 11.13.20](#)). The arms are then passed partial thickness to the edge of the muscle with two locking whipstitch bites at the muscle poles ([Figs. 11.13.21](#) and [11.13.22](#)).

A straight Jakes hemostat is placed across the tendon just anterior to the suture line. The tendon is disinserted in the same manner as the recession ([Fig. 11.13.23](#)). The muscle stump from the cut edge to the hemostat

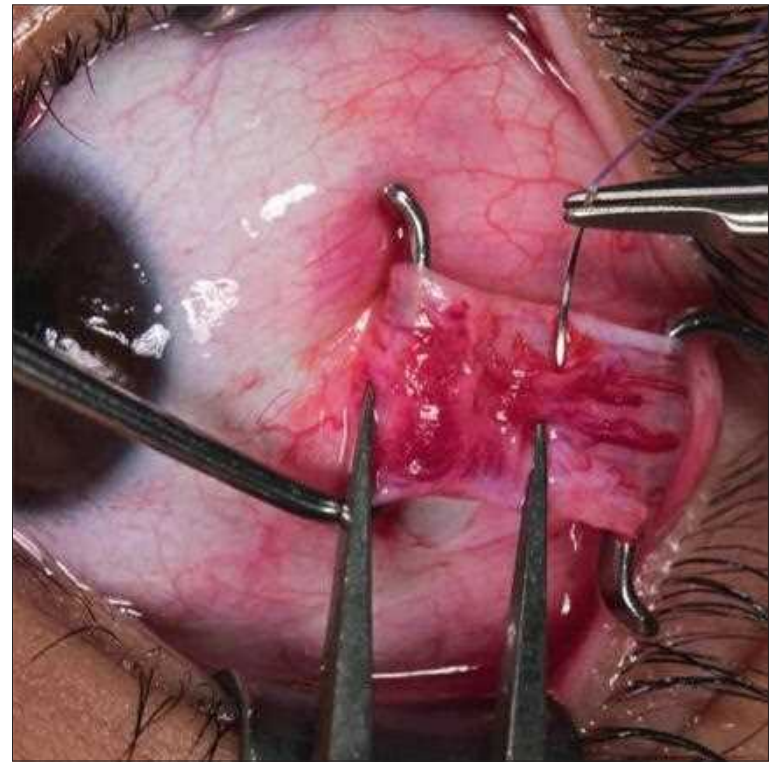
is excised with scissors ([Fig. 11.13.24](#)). Cautery is applied to the fibers at the hemostat followed by balanced salt solution (BSS) prior to removing the hemostat.

The 6.0 S-29 needles are then passed at the original insertion from the posterior to the anterior side ([Fig. 11.13.25](#)). It is necessary to remember that the scleral thickness is at its minimum just posterior to the insertion. At no time should the needle be pointed toward the globe. Calipers can be used instead to compress the scleral layers and serve as a base for the needle to approach the tissue almost parallel. An alternate technique is to pass the needle through the tendon scleral shelf junction, as shown in [Fig.](#)

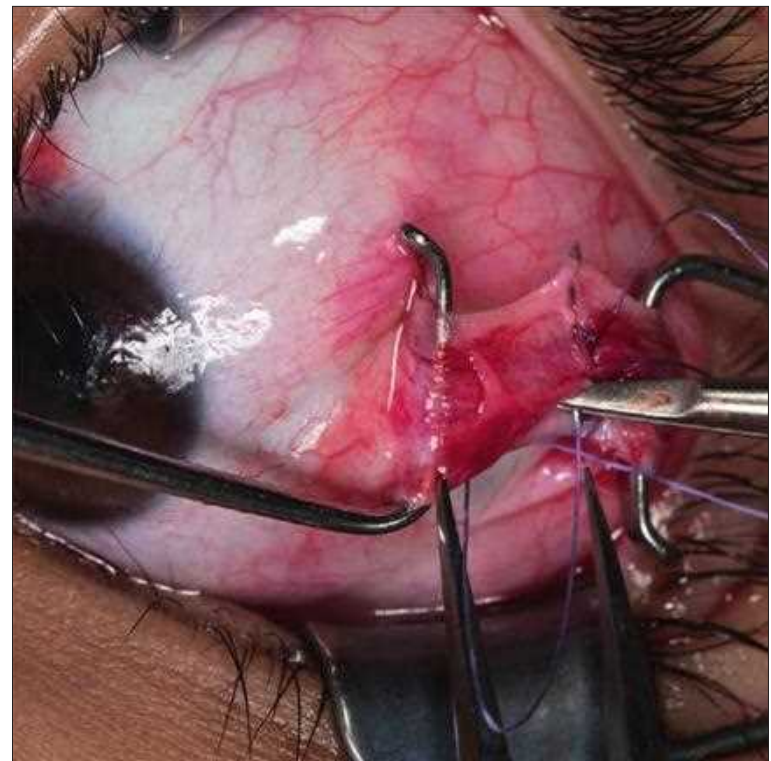




**Figs. 11.13.18, 11.13.19** The incision is reapproximated with interrupted buried suture.



**Fig. 11.13.20** Resection of a Rectus Muscle. **Figs. 11.13.20 through 11.13.30** demonstrate a resection of the left lateral rectus muscle. The same steps as described in "Recession surgery" are used to isolate the rectus muscle. The muscle is put on stretch, and a caliper-measured central full-thickness bite is secured by using a double-armed suture.



**Fig. 11.13.21** A partial-thickness pass from the center to edge is placed.

**11.13.26.** Crossed swords can be used, and this facilitates maintenance of the tendon width and close proximity for tying (**Fig. 11.13.27**).

The resected muscle often has some posterior tension. The globe is mildly abducted, and pressure can be placed on the external portion of the resected muscle by the assistant's hook to minimize the suture tension required to complete the knot. The muscle should be inspected to ensure no hangback has occurred (**Fig. 11.13.28**). The overlying conjunctiva is closed with 8.0 Polyglactin 910 (Vicryl, Ethicon) in a buried fashion (**Figs. 11.13.29 and 11.13.30**). Some use a remaining piece of the 6-0 muscle suture, although this can create more postoperative discomfort. Sub-Tenon's analgesia is applied.

### **Medial Rectus and Vertical Recti**

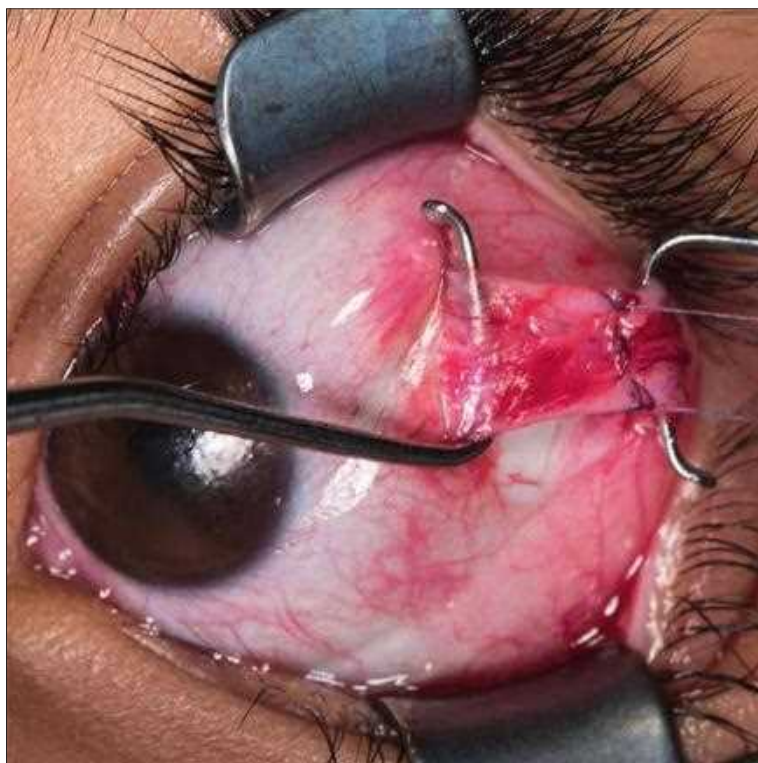
The principles of resection are the same as described previously for the lateral rectus. Resections of the vertical recti include visualization and

preservation of the neighboring oblique muscles before the procedure is performed as described above.

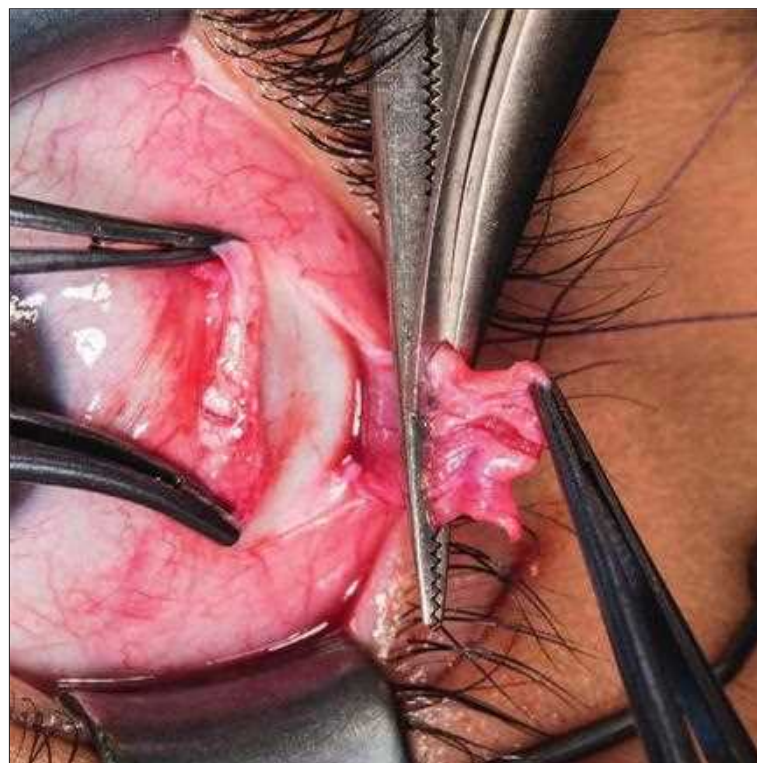
### **Other Surgical Techniques**

Readers interested in surgical approaches to the plication, superior oblique tendon and inferior oblique muscle, adjustable suture technique, and posterior fixation suture are referred to the following references: Wright and Strube,<sup>12</sup> Chaudhuri and Demer,<sup>13</sup> Lingua,<sup>14</sup> Parks,<sup>15</sup> Romano and Roholt,<sup>16</sup> Fierson et al.,<sup>17</sup> Robbins et al.,<sup>18</sup> and Guyton.<sup>19</sup>

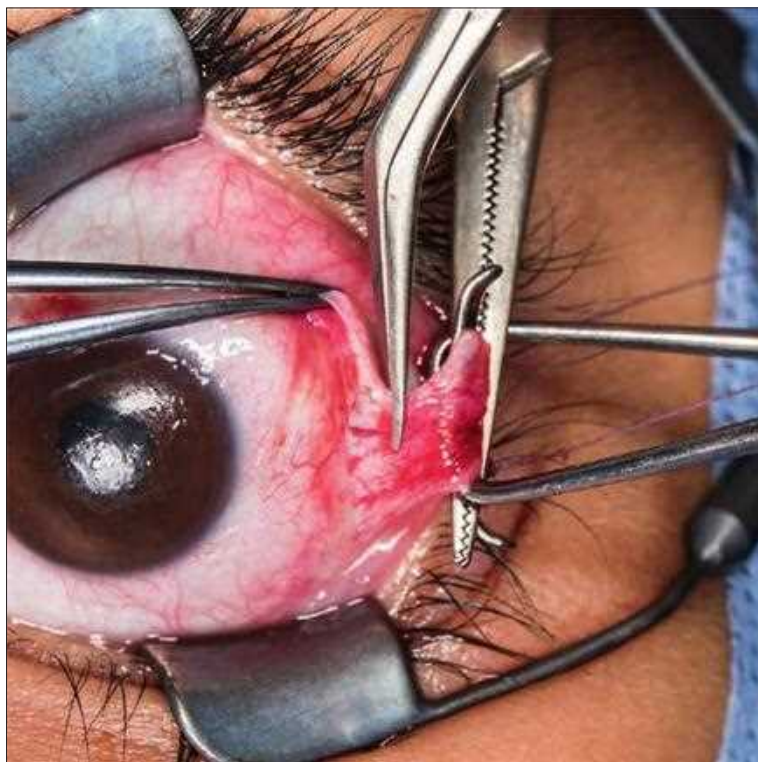




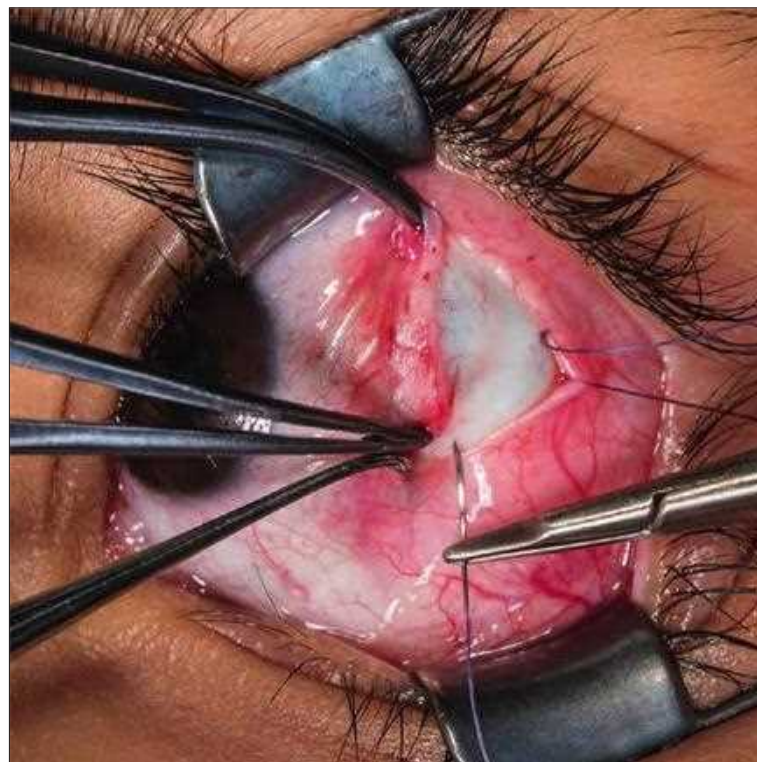
**Fig. 11.13.22** Suturing of opposing partial-thickness passes with two side-locking bites is completed.



**Fig. 11.13.24** The resected tissue is excised from the clamp.



**Fig. 11.13.23** The tendon is disinserted.



**Fig. 11.13.25** The muscle is sewn through partial thickness sclera at the insertion.

## COMPLICATIONS

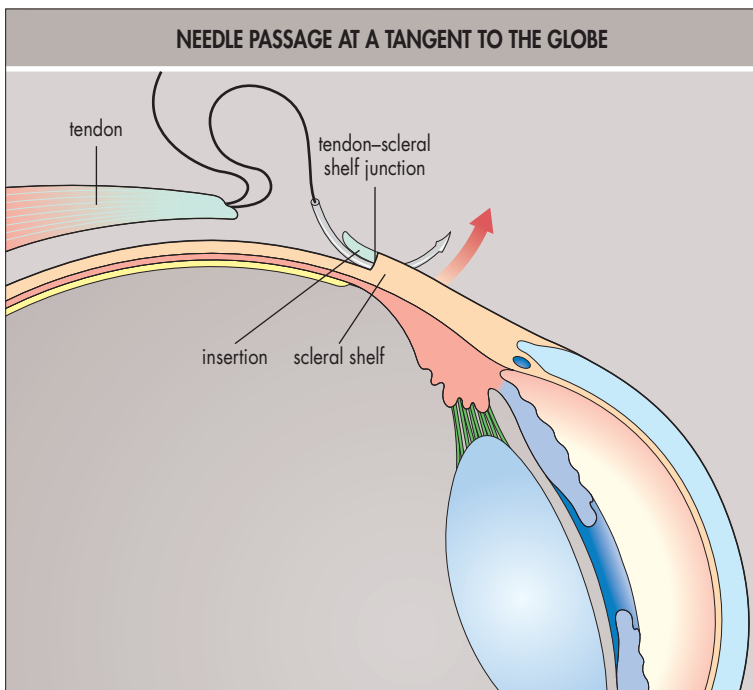
Significant strabismus surgery complications are uncommon ([Box 11.13.3](#)). Optimizing surgical technique assists in minimizing complications; underlying physiological tendencies, however, play a large role. Hemostasis is required at each step in the procedure, whichever conjunctival approach to the muscle is used. Attention to the corneal surface prevents inadvertent drying or instrument-derived abrasion. Particular caution is required with patients who have thin sclera (e.g., those with severe myopia), have a history of scleritis, or have undergone previous scleral procedures, especially when disinsertion is performed or the muscle is reattached to the

globe. The surgeon must be aware of the location of vortex veins during oblique muscle surgery.

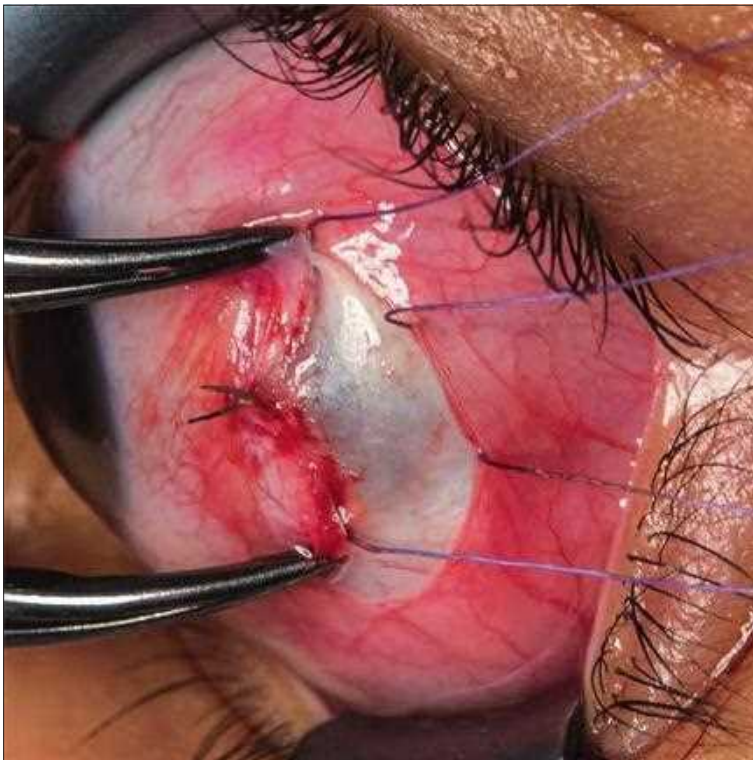
## Violation of the Posterior Tenon's Capsule/Fat Adherence

Violation of the posterior Tenon's capsule permits release of orbital fat into the space contiguous to the globe, allowing fibrofatty proliferations that involve sclera and nearby extraocular muscles.<sup>20</sup> This usually occurs after surgery on the inferior oblique muscle but may occur after surgery on any





**Fig 11.13.26** Needle passage at a tangent to the globe. If this angle is used when the needle is returned through the insertional step of the sclera, the needle tip does not have to be directed toward the globe.

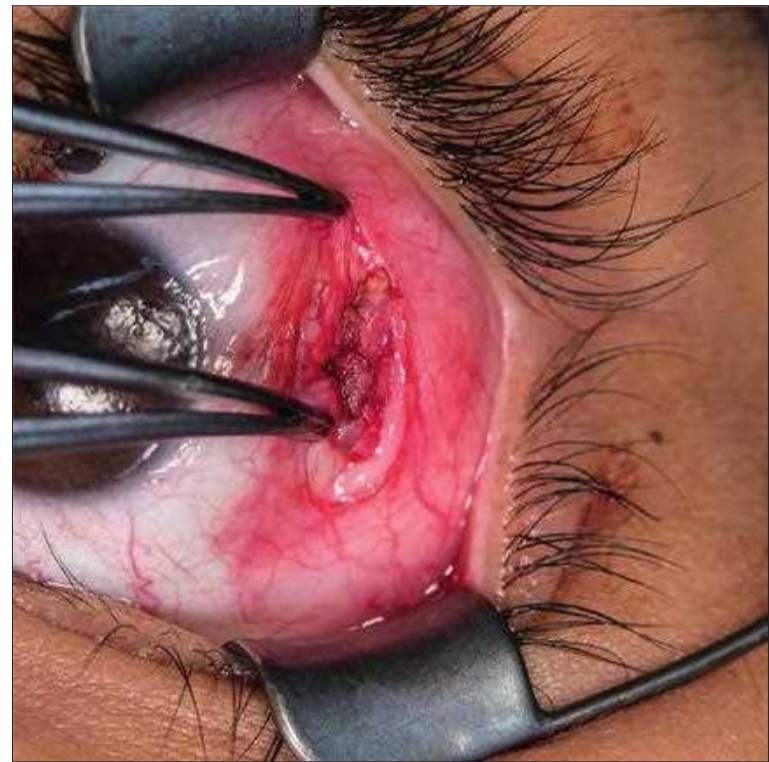


**Fig. 11.13.27** The needles can be placed in "crossed swords" fashion. This maintains normal tendon width.

muscle; the best prevention is to perform all incisions under direct visualization. If a Tenon's capsule perforation is recognized, an attempt can be made to repair the defect with absorbable sutures. In the case of inferior oblique muscle surgery, the patient often presents with a progressive hypotropia, esotropia, and exocycloptropia in the involved eye because of tightening of the tissues around the inferior rectus muscle. Surgical treatment in these cases is difficult and can be unpredictable.

### Anterior Segment Ischemia

Anterior segment ischemia with chemosis, corneal edema, uveitis, hypotony, iris sector paresis or cataract, a rare complication, appears to occur after strabismus surgery, mainly in older patients who have systemic vascular disease<sup>21</sup> or immunocompromising conditions. Surgeons



**Fig. 11.13.28** The resected muscle has been returned to the original insertion with no hangback.

#### BOX 11.13.3 Possible Complications of Strabismus Surgery

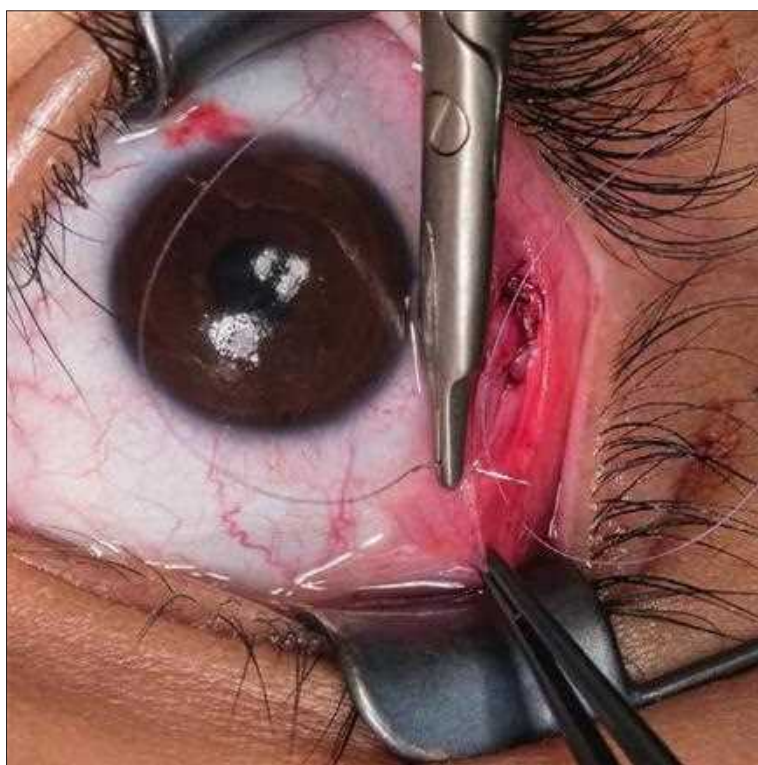
- Allergic reaction
- Anesthesia-related complications
- Anterior ischemic syndrome
- Conjunctival cyst, granuloma, and scarring
- Dellen
- Diplopia
- Eyelid retraction or ptosis
- Fat adherence
- Infection/Endophthalmitis
- Orbital inclusion cyst
- Over- or underresponse
- Refractive changes
- Scleral perforation
- Slipped, lost or ruptured muscle
- Stretch scar

traditionally avoid removal of more than three rectus muscles in one eye simultaneously or within 6 months of previous rectus muscle detachment. Hummelsheim or Jensen transpositions are favored over the Knapp transposition when ischemia is a consideration. Plications versus resections are thought to preserve more blood flow, and complex procedures, such as the California Hummelsheim procedure,<sup>22</sup> have been proposed for this reason. Anterior segment ischemia, however, has been described in rare cases when less surgery was performed, or the rectus muscles were not detached from the globe but rather were split and joined to others (Jensen procedure); it is thus difficult to provide exact guidelines. Most surgeons recommend caution in operations on patients who have systemic vascular disease or are immunocompromised, especially if vertical rectus muscle surgery is planned, because these muscles appear to contribute more significantly to anterior segment circulation. Preoperative iris angiography can be helpful in identifying patients potentially at risk. Evidence suggests that the avoidance of limbal conjunctival incisions preserves the conjunctivally transmitted oxygen contribution. Most patients who have postoperative anterior segment ischemia escape permanent visual sequelae if treated with frequent topical and/or systemic corticosteroids.

### Epithelial Cysts/Suture Granulomas

Epithelial inclusion cysts may form if the conjunctiva folds under itself at any incision site. Careful reapposition of the conjunctival incisions is





**Figs. 11.13.29, 11.13.30** Tenon's Capsule and Conjunctiva Are Replaced in Their Original Position. The incision is closed with interrupted buried sutures.

warranted. Occasionally, cysts or suture granuloma excision is required if anti-inflammatories and time do not suffice.

### Corneal Dellen

The contours of the postoperative conjunctiva lead to uneven tear distribution on the cornea. Corneal thinning occurs in the peripheral cornea adjacent to an area of conjunctival inflammation. Dellen occur more commonly in adults. If left untreated, corneal perforation is possible. With adequate treatment of frequent hydration they typically heal in days to weeks but are associated with temporary decreased visual acuity and pain.

### Globe Perforation

The most ominous adverse occurrence during strabismus surgery is globe perforation. If the needle passes in the suprachoroidal space, which is more likely in cases of thinned sclera (in those with high myopia, reoperations, etc.), it usually is seen as a small mound of brown material at the needle exit site. Treatment is controversial, with some suggesting use of barrier laser around the white linear area seen on dilated retinal examination and others advocating observation. If the retina is perforated, vitreous may appear at the needle entrance or exit site. This should be trimmed and the retina examined; any retinal detachment must be addressed promptly. Usually, the retina appears attached and the perforation site is surrounded by retinal hemorrhage. Appropriate immediate treatment in these cases also is controversial; some investigators recommend performing immediate laser photocoagulation or cryotherapy, others advocate observation only. Children have formed vitreous, and retinal detachment after perforation is rare. When retinal detachment occurs, however, the prognosis is guarded because of a typical delay in treatment.<sup>23</sup> If the depth of a scleral pass is questionable, the conservative approach of performing a dilated peripheral retinal examination is prudent. Rare cases of endophthalmitis associated with scleral perforations have been reported, making it important to consider the use of antibiotics in these cases.

### Underresponse or Overresponse

The most common "complication" after strabismus surgery is under- or overresponse. After a suitable period of observation—depending on the individual clinical situation—and a trial of nonsurgical treatment, reoperation may be necessary. When possible and appropriate, non-operated muscles can be approached, using the prior surgical response to inform surgical dosage planning.

### Lost or Slipped Muscles/Stretch Scar

Only the medial rectus muscle lacks a fascial connection to an oblique muscle, and thus it is the one most at risk of being "lost" should its sutural attachment to the globe slip. The medial rectus muscle retracts within the posterior Tenon's capsule against the medial orbital wall. Excellent illumination, exposure via an assistant or with traction sutures, and meticulous technique may enable the surgeon to reacquire the muscle. Particular care must be devoted to preservation of the Tenon's capsule and prevention of adherence syndrome. The striated muscle may "slip" within its capsule, which results in underaction but not paresis of the muscle<sup>24</sup>; careful examination of the site demonstrates capsule alone attached to sclera. The muscle itself is advanced to its intended position. Immediate reoperation is required as soon as the condition is suspected. If some time has elapsed, the rectus muscle contracts. The reattachment site is determined after consideration of the amount of strabismus and the amount of contracture. If the muscle cannot be identified, often a transposition procedure using the adjacent rectus muscle must be performed and the antagonist muscle crippled. Similarly, the muscle scar may stretch and therefore lose function. The stretch scar is excised and the tendon advanced to the intended position.<sup>25</sup>

### MUSCLE RUPTURE OR PULLED IN TWO SYNDROME (PITS)

Any extraocular muscle, but particularly the inferior and medial rectus muscles, can completely rupture during surgery. The largest reported series suggests this occurs at the tendon muscle junction and often in cases of prior trauma or thyroid induced strabismus.<sup>26</sup> The distal end often can be retrieved and primarily repaired with satisfactory results. Alternatively, a transposition can be considered, or, in the case of the inferior rectus muscle, the inferior oblique muscle can be harnessed to augment infraduction.

### OUTCOMES

Sensorimotor adaptation plays a large role in the stability of postoperative alignment. The effect of a muscle surgery can change over time. Surgical success rates are dependent on many variables, some of which are unique to a given clinical situation. Surgical results are described in the chapters on individual forms of strabismus.

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# Clinical Anatomy of the Eyelids

Jonathan J. Dutton

## 12.1

**Definition:** The eyelids are mobile, flexible, multilamellar structures that cover the globe anteriorly.

### Key Features

- The eyelids provide protection from desiccation and airborne foreign matter.
- The eyelids anatomically contain both superficial musculo-cutaneous elements anteriorly and orbital components posteriorly.

## INTRODUCTION

The eyelids serve a vital function by protecting the globe. They provide fundamental elements of the precorneal tear film and help distribute tears evenly over the surface of the eye. The eyelids collect tears and propel them to the medial canthus, where they enter the lacrimal drainage system. The eyelashes sweep airborne particles from the front of the eye. Constant voluntary and reflex movements of the eyelids protect the cornea from injury and glare. Any aesthetic or reconstructive surgery on the eyelids requires a thorough knowledge of eyelid anatomy.<sup>1,2</sup>

## ANATOMY OF THE EYELIDS

The eyelids undergo a complex embryonic and fetal morphogenesis involving a succession of strictly regulated episodes of proliferation, fusion, and separation that results in functional eyelids at birth.<sup>3</sup> In young adults the interpalpebral fissure measures 10–11 mm vertically. With advancing age this decreases to only about 8–10 mm. The horizontal length of the fissure is 30–31 mm. The upper and lower eyelids meet at an angle of approximately 60° medially and laterally. In primary position, the upper eyelid margin lies at the superior corneal limbus in children and 1.5–2 mm below it in adults. The lower eyelid margin rests at the inferior corneal limbus.

The margin is covered by cutaneous epithelium and eyelashes anteriorly and conjunctiva with meibomian gland openings posteriorly.

### Orbicularis Muscle

The orbicularis oculi is a complex striated muscle sheet that lies just below the skin. It is divided anatomically into three contiguous parts (Fig. 12.1.1): orbital, preseptal, and pretarsal.<sup>4,5</sup>

The orbital portion overlies the bony orbital rims. It arises from insertions on the frontal process of the maxillary bone, the orbital process of the frontal bone, and the common medial canthal tendon. Its fibers pass around the orbital rim to form a continuous ellipse.

The palpebral portion of the orbicularis muscle overlies the mobile eyelid from the orbital rims to the eyelid margins. The muscle fibers sweep circumferentially around each eyelid as a half ellipse fixed medially and laterally at the canthal tendons. It is further divided topographically into the preseptal and pretarsal orbicularis.

The preseptal portion of the muscle is positioned over the orbital septum in both upper and lower eyelids. Its fibers originate perpendicularly along the upper and lower borders of the medial canthal tendon. Fibers arc around the eyelids and insert along the lateral horizontal raphe. The pretarsal portion of the muscle overlies the tarsal plates. Contraction of these fibers aids in the lacrimal pump mechanism.<sup>6</sup> Medially, the deep heads of the pretarsal fibers fuse to form a prominent bundle of fibers, Horner's muscle, that runs behind the posterior limb of the canthal

tendon. It inserts onto the posterior lacrimal crest. Horner's muscle helps maintain the posterior position of the canthal angle and may aid in the lacrimal pump mechanism.<sup>7</sup>

### Orbital Septum

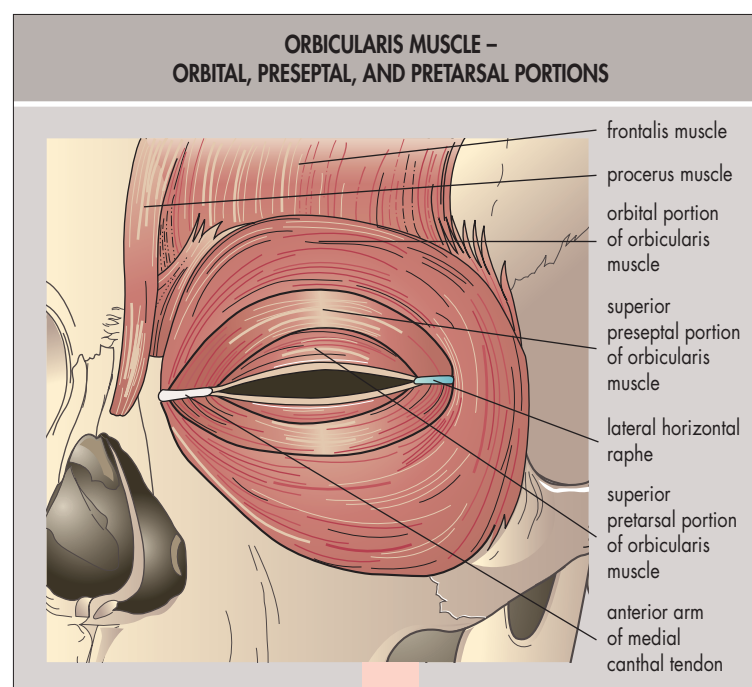
The orbital septum is a thin, fibrous, multilayered membrane that begins anatomically at the arcus marginalis along the orbital rim. Distal fibers merge into the anterior surface of the levator aponeurosis (Fig. 12.1.2).<sup>8</sup> The point of insertion usually is about 3–5 mm above the tarsal plate, but it may be as much as 10–15 mm above it.<sup>9</sup> In the lower eyelid the septum fuses with the capsulopalpebral fascia several millimeters below the tarsus, and the common fascial sheet inserts onto the inferior tarsal edge.<sup>10,11</sup>

### Preaponeurotic Fat Pockets

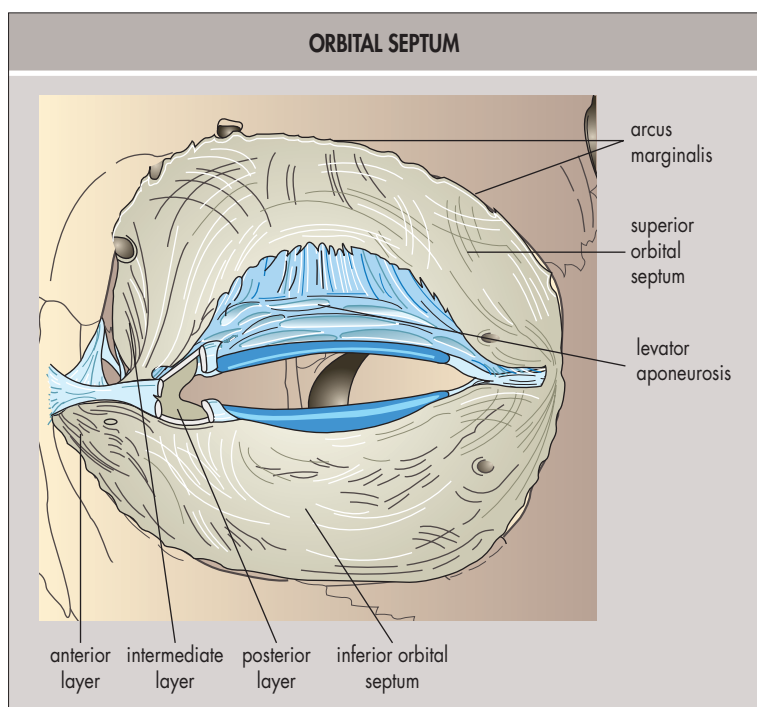
The preaponeurotic fat pockets in the upper eyelid and the precapsulopalpebral fat pockets in the lower eyelid are anterior extensions of extraconal orbital fat. These are surgically important landmarks and help identify a plane immediately behind the orbital septum and anterior to the major eyelid retractors. In the upper eyelid, two fat pockets typically occur: a medial pocket and a central one.<sup>12</sup> In the lower eyelid, three pockets occur: medial, central, and lateral.<sup>13</sup>

### Major Eyelid Retractors

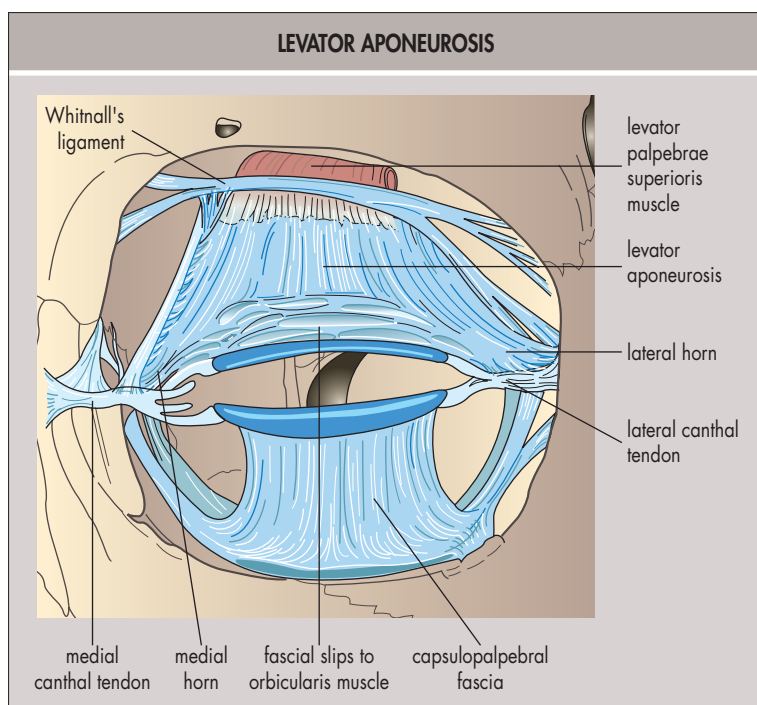
The retractors of the upper eyelid consist of the levator palpebrae and Müller's muscles.<sup>14,15</sup> The levator palpebrae superioris arises from the lesser sphenoid wing and runs forward just above the superior rectus muscle. Near the superior orbital rim, a condensation along the muscle sheath attaches medially and laterally to the orbital walls. This is the



**Fig. 12.1.1 Orbicularis and Frontalis Muscles.** (Adapted with permission from Dutton JJ. Atlas of clinical and surgical orbital anatomy. 2nd ed. London: Elsevier Saunders; 2011. p. 153.)



**Fig. 12.1.2 Orbital Septum.** (Adapted with permission from Dutton JJ. *Atlas of clinical and surgical orbital anatomy*. 2nd ed. London: Elsevier Saunders; 2011. p. 149.)



**Fig. 12.1.3 Levator Aponeurosis and Medial and Lateral Canthal Tendons.** (Adapted with permission from Dutton JJ. *Atlas of clinical and surgical orbital anatomy*. 2nd ed. London: Elsevier Saunders; 2011. p. 149.)

superior transverse orbital ligament of Whitnall. It provides some support for the fascial system that maintains spatial relationships between a variety of anatomical structures in the superior orbit.

From Whitnall's ligament the muscle passes into its aponeurosis (Fig. 12.1.3). This sheet continues downward 14–20 mm to its insertion near the marginal tarsal border. The aponeurotic fibers are most firmly attached at about 3–4 mm above the eyelid margin.<sup>15,16</sup> The aponeurosis also sends numerous delicate interconnecting slips forward and downward to insert onto the interfascicular septa of the pretarsal orbicularis muscle and subcutaneous tissue. These slips maintain the close approximation of the skin, muscle, aponeurosis, and tarsal lamellae and integrate the distal eyelid as a single functional unit. This relationship defines the upper eyelid crease in both white and black people.

As the levator aponeurosis passes into the eyelid from Whitnall's ligament, it broadens to form the medial and lateral “horns.” The lateral horn

forms a prominent fibrous sheet that indents the posterior aspect of the lacrimal gland and so defines its orbital and palpebral lobes. The medial horn is not as well developed. Together, the two horns serve to distribute the forces of the levator muscle along the aponeurosis and the tarsal plate.

In the lower eyelid, the capsulopalpebral fascia is a fibrous sheet that arises from Lockwood's ligament and the sheaths around the inferior rectus and inferior oblique muscles.<sup>17</sup> It passes upward and generally fuses with fibers of the orbital septum about 4–5 mm below the tarsal plate. From this junction, a common fascial sheet continues upward and inserts onto the lower border of the tarsus.

## Sympathetic Accessory Retractors

Smooth muscles innervated by the sympathetic nervous system are present in both the upper and lower eyelids and serve as accessory retractors.<sup>18</sup> In the upper eyelid, the supratarsal muscle of Müller originates abruptly from the undersurface of the levator muscle just anterior to Whitnall's ligament.<sup>19</sup> It runs downward, posterior to the levator aponeurosis and inserts onto the anterior edge of the superior tarsal border. In the lower eyelid, the sympathetic muscle is not as well defined. Fibers run behind the capsulopalpebral fascia to insert 2–5 mm below the tarsus.<sup>20</sup>

## Tarsal Plates

The tarsal plates consist of dense, fibrous tissue 1–1.5 mm thick that imparts structural integrity to the eyelids. Each plate measures about 25 mm horizontally and is curved gently to conform to the contour of the anterior globe; the central height of the tarsal plates is 8–12 mm in the upper eyelid and 3.5–4 mm in the lower. Medially and laterally they taper to 2 mm in height as they pass into the canthal tendons. Within each tarsus are the meibomian glands, numbering about 25 in the upper lid and 20 in the lower lid. These are holocrine-secreting sebaceous glands that are not associated with lash follicles. They produce the lipid layer of the precorneal tear film.

## Canthal Tendons

The medial canthus provides a number of important support structures that maintain alignment and orientation of the medial eyelids and allow for stability of the medial rectus muscle.<sup>21</sup> Medially, the tarsal plates pass into fibrous bands that form the crura of the medial canthal tendon. These lie between the orbicularis muscle anteriorly and the conjunctiva posteriorly. The superior and inferior crura fuse to form a stout common tendon that inserts via three limbs (see Fig. 12.1.3). The anterior limb inserts onto the orbital process of the maxillary bone in front of and above the anterior lacrimal crest. It provides the major support for the medial canthal angle. The posterior limb arises from the common tendon near the junction of the superior and inferior crura and passes between the canaliculi. It inserts onto the posterior lacrimal crest just in front of Horner's muscle and directs the vector forces backward to maintain close approximation with the globe. The superior limb of the medial canthal tendon arises as a broad arc of fibers from both the anterior and posterior limbs. It passes upward to insert onto the orbital process of the frontal bone. The posterior head of the preseptal orbicularis muscle inserts onto this limb, and the unit forms the soft tissue roof of the lacrimal sac fossa. This extension provides vertical support to the canthal angle<sup>22</sup> and appears to play a role in the lacrimal pump mechanism.

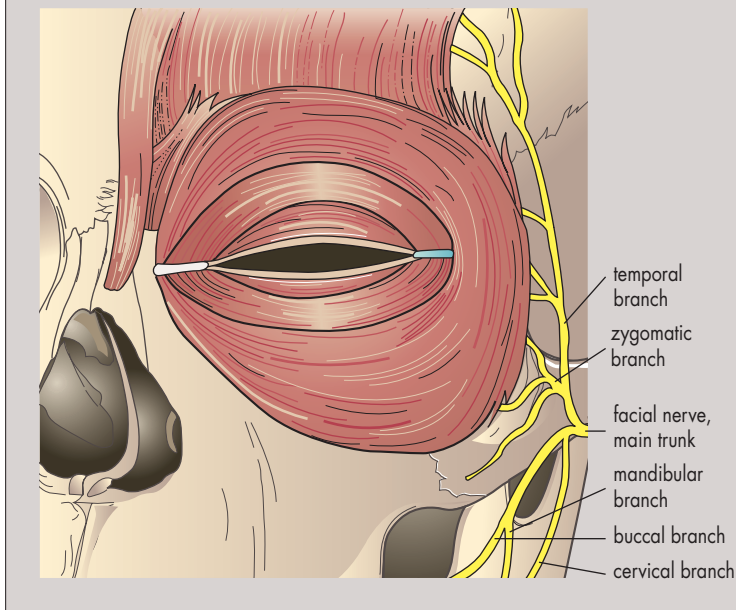
Lateral canthal anatomy is somewhat analogous to that of the medial canthus, but in general its support structures are less defined and less complex.<sup>23</sup> Laterally, the tarsal plates pass into not very well-developed fibrous strands that become the crura of the lateral canthal tendon. This is a distinct entity separate from the orbicularis muscle; it measures about 1 mm in thickness, 3 mm in width, and approximately 5–7 mm in length.<sup>24</sup> The insertion of these fibrous strands extends posteriorly along the lateral orbital wall, where it blends with strands of the lateral check ligament from the sheath of the lateral rectus muscle.

## Conjunctiva

The conjunctiva is a mucous membrane that covers the posterior surface of the eyelids and the anterior pericorneal surface of the globe. The palpebral portion is applied closely to the posterior surface of the tarsal plate and the sympathetic tarsal muscle of Müller. It is continuous around the fornices above and below, where it joins the bulbar conjunctiva. Small accessory lacrimal glands are located within the submucosal connective tissue.



## MOTOR NERVES



**Fig. 12.1.4 Motor Nerve Supply to the Eyelids: The Facial Nerve.** (Adapted with permission from Dutton JJ. Atlas of clinical and surgical orbital anatomy. 2nd ed. London: Elsevier Saunders; 2011. p. 155.)

A small mound of tissue, the caruncle, is at the medial canthal angle. The caruncle consists of modified skin that contains fine hairs, sebaceous glands, and sweat glands. Just lateral to the caruncle is a vertical fold of conjunctiva, the plica semilunaris.

## Nerves to the Eyelids

The facial nerve (seventh cranial nerve) is a unique structure that provides motor innervation to the muscle of facial expression and also contains special and general visceral efferent and special and general somatic afferent fibers. It has a complex anatomical relationship to the parotid gland.<sup>25</sup> The motor nerves to the periorbital muscles originate in the temporal and zygomatic branches (Fig. 12.1.4). These branches innervate the frontalis and orbicularis muscles, respectively. The buccal, mandibular, and cervical branches innervate muscles of the lower face and neck.<sup>26</sup>

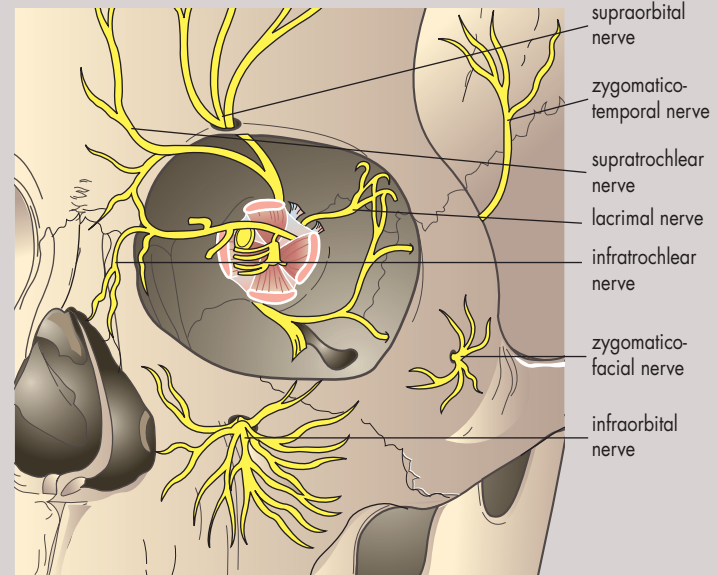
The sensory nerves to the eyelids derive from the ophthalmic and maxillary divisions of the trigeminal nerve (Fig. 12.1.5). Sensory input from the upper lid passes to the ophthalmic division primarily through its main terminal branches, the supraorbital, supratrochlear, and lacrimal nerves. The infratrochlear nerve receives sensory information from the extreme medial portion of both upper and lower eyelids. The lower eyelid sends sensory impulses to the infraorbital nerve. The zygomaticofacial branch from the maxillary nerve innervates the lateral portion of the lower lid, and part of the infratrochlear branch receives input from the medial lower lid.

## Vascular Supply of the Eyelids

Vascular supply to the eyelids is extensive. The posterior eyelid lamellae receive blood through the vascular arcades. In the upper eyelid, a marginal arcade runs about 2 mm from the eyelid margin, and a peripheral arcade extends along the upper border of the tarsus between the levator aponeurosis and Müller's muscle (Fig. 12.1.6). These arcades are supplied medially by the superior medial palpebral vessels from the terminal ophthalmic artery and laterally by the superior lateral palpebral vessel from the lacrimal artery. The lower lid arcade receives blood from the medial and lateral inferior palpebral vessels.

The venous drainage system is not as well defined as the arterial system. Drainage is mainly into several large vessels of the facial system (see Fig. 12.1.6). Lymphatic drainage from the eyelids is restricted to the region anterior to the orbital septum. Traditional teaching is that lymphatic flow from the lateral two-thirds of the upper eyelid and the lateral one-third of the lower eyelid drain laterally into the deep and superficial parotid nodes, and flow from the medial one-third of the upper eyelid and the medial two-thirds of the lower eyelid drains inferiorly into the submandibular

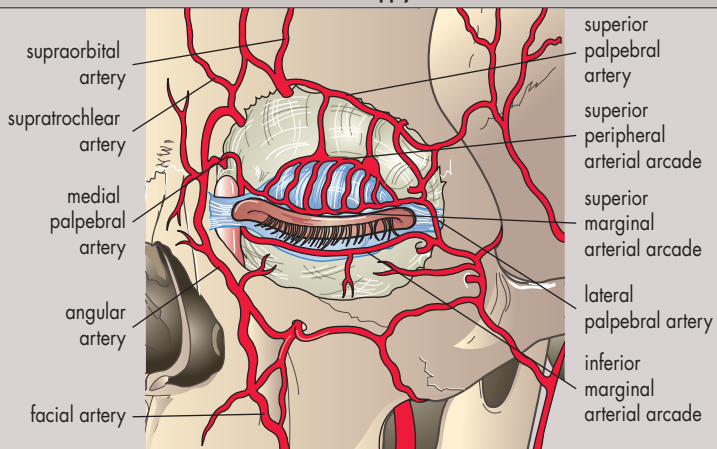
## SENSORY NERVES



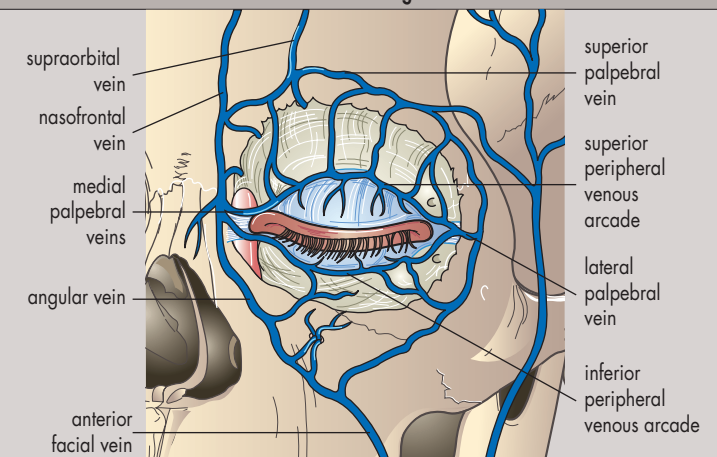
**Fig. 12.1.5 Sensory Nerve Supply From the Eyelids.** (Adapted with permission from Dutton JJ. Atlas of clinical and surgical orbital anatomy. 2nd ed. London: Elsevier Saunders; 2011. p. 155.)

## ARTERIAL SUPPLY AND VENOUS DRAINAGE

## Arterial supply



## Venous drainage



**Fig. 12.1.6 Arterial Supply to and Venous Drainage From the Eyelids.** (Adapted with permission from Dutton JJ. Atlas of clinical and surgical orbital anatomy. 2nd ed. London: Elsevier Saunders; 2011. p. 156.)

and anterior cervical nodes. However, recent studies have shown a more diffuse drainage from all areas of the eyelids into the parotid nodes.<sup>27</sup>

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# Clinical Anatomy of the Orbit

Jonathan J. Dutton

## 12.2

**Definition:** The orbit is the anatomical space bounded by the orbital bones and enclosed within the multilamellar periorbita.

### Key Features

- Anteriorly the orbit is limited by the orbital septum, which represents the anteriormost layer of the orbital septal system and separates the orbit from the eyelids.
- The orbit contains the eye and extraocular muscles, along with the nerves, vascular elements, and connective tissue support systems that subserve the visual system.

### INTRODUCTION

An understanding of orbital disease demands a clear concept of normal orbital anatomy and physiological function.<sup>1</sup> Only with this foundation can the clinician identify and characterize pathological states. In addition, the development of better surgical techniques requires a comprehensive knowledge of the structural relationships among the numerous anatomical systems that are crowded into the small space available.<sup>2</sup>

### GENERAL ORGANIZATION

The human orbit is a small cavity that has the approximate shape of a pear. Within this space is a complex array of closely packed structures, most of which subserve visual function.<sup>3,4</sup> Lobules of orbital fat surrounded by connective tissue fascia completely fill the spaces between the muscles, nerves, and vascular elements. The entire anatomical region is bound together into a functional unit, the complexity and precision of which are unmatched elsewhere in the vertebrate body.

### OSTEOLOGY OF THE ORBIT

Orbital bones arise from a complex series of primary or secondary ossifications around the evolving optic cup and stalk. Initially, the optic vesicles are positioned 170°–180° apart on opposite sides of the forebrain. Later these begin to rotate anteriorly as the primordial orbital bones are laid down around them.<sup>5</sup>

In adults, the bony orbit encloses a volume of about 30 cm<sup>3</sup>. It is composed of seven bones (Box 12.2.1). Except for a series of canals, fissures, and foramina that communicate with extraorbital compartments, the orbit is a closed compartment with a broad opening anteriorly (Fig. 12.2.1).

### Orbital Roof

The orbital roof is composed of the orbital plate of the frontal bone with a small contribution from the lesser wing of the sphenoid bone at the apex. This bone is a thin lamina that separates the orbit from the frontal sinus

anteriorly and from the anterior cranial fossa posteriorly. The roof slopes backward and downward from the orbital rim toward the apex and the optic canal. The optic canal measures 5–6 mm in diameter and 8–12 mm in length; it is oriented posteromedially about 35° to the midsagittal plane and upward about 38° to the horizontal plane.

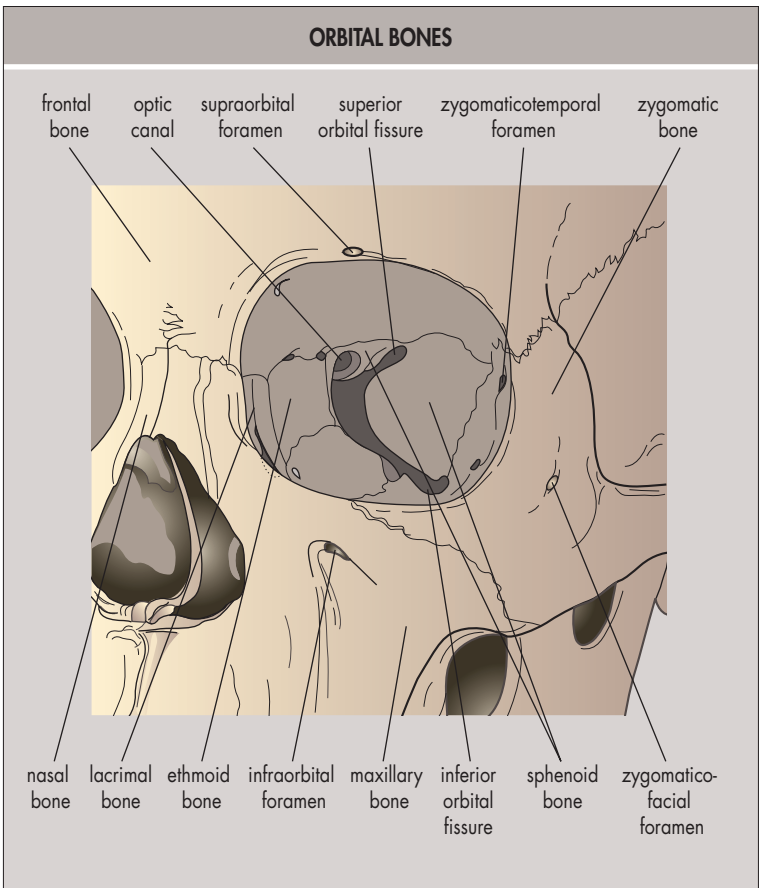
### Lateral Orbital Wall

The lateral wall is formed by the greater wing of the sphenoid bone posteriorly and by the zygomatic process of the frontal bone and the orbital process of the zygomatic bone anteriorly.<sup>6</sup> It lies at a nearly 45° angle to the midsagittal plane. The lateral wall is bounded below by the inferior orbital fissure and medially by the superior orbital fissure. The convoluted frontozygomatic suture line runs approximately horizontally and crosses the superotemporal rim near the lacrimal gland fossa.

The lateral wall contains two areas of thickened bone, the posterolateral trigone in the sphenoid bone and the inferolateral basin in the zygomatic bone. Thinning of these regions has become an important component of balanced medial–lateral wall decompression surgery.<sup>7</sup>

### Orbital Floor

The floor is the shortest of the orbital walls; it extends back only 35–40 mm from the inferior rim. The orbital floor is composed primarily of the



**Fig. 12.2.1 Bony Anatomy of the Orbit in Frontal View.** (Redrawn with permission from Dutton JJ. Atlas of clinical and surgical orbital anatomy. 2nd ed. London: Elsevier Saunders; 2011. p. 22.)

#### BOX 12.2.1 Bones of the Orbit

- |                |                |
|----------------|----------------|
| Ethmoid bone   | Palatine bone  |
| Frontal bone   | Sphenoid bone  |
| Lacrimal bone  | Zygomatic bone |
| Maxillary bone |                |

maxillary bone; the zygomatic bone forms the anterolateral portion, and the palatine bone lies at the posterior extent of the floor. The orbital floor is thinnest just medial to the infraorbital canal, which is the most common site for blowout fractures. The orbital floor shows the greatest degree of deformation when external force is applied,<sup>8</sup> which explains the high rate of floor fractures associated with even minor degrees of blunt trauma.

The infraorbital groove begins at the inferior orbital fissure and runs forward in the maxillary bone. Within this canal runs the maxillary division of the trigeminal nerve and the maxillary artery. These exit just below the central orbital rim at the infraorbital foramen.

The floor is separated from the lateral orbital wall by the inferior orbital fissure, which is approximately 20 mm in length and runs in an anterolateral to posteromedial direction. The inferior fissure transmits structures into the orbit from the pterygopalatine fossa posteriorly and from the infratemporal fossa anteriorly.

## Medial Orbital Wall

The medial walls of the orbits are approximately parallel to each other and to the midsagittal plane. The medial wall is composed largely of the thin lamina papyracea of the ethmoid bone. This plate is exceptionally fragile, measuring only 0.2–0.4 mm in thickness. The lamina papyracea offers little resistance to expanding ethmoid sinus mucocoeles and commonly transmits inflammatory and infectious processes from sinusitis into the orbit.

Posterior to the ethmoid bone, the body of the sphenoid bone completes the medial wall to the apex.<sup>6</sup> The medial wall ends at the optic foramen, where the sphenoid forms the medial wall of the optic canal.

Within the frontoethmoid suture line in the superomedial orbit are the anterior and posterior ethmoidal foramina. The former usually lies 20–25 mm behind the anterior lacrimal crest and the latter about 32–35 mm behind the anterior crest and 5–10 mm anterior to the optic canal.<sup>9,10</sup> These foramina transmit branches of the ophthalmic artery and nasociliary nerve into the ethmoid sinus and nose. These vessels frequently are injured in orbital trauma and are the major sources of subperiosteal hematomas. These openings mark the approximate level of the roof of the ethmoid labyrinth and the floor of the anterior cranial fossa. The cribriform plate may lie up to 10 mm below this level, just medial to the root of the middle turbinate, and can be fractured during medial wall surgery.

Anterior to the ethmoid is the lacrimal bone, a thin plate that contains the posterior lacrimal crest and forms the posterior half of the lacrimal sac fossa. A summary of the orbital bones is given in [Box 12.2.2](#).

## CONNECTIVE TISSUE SYSTEM

In the human, an extensive system of connective tissue forms a framework for compartmentalization and support of all orbital structures.<sup>10,11</sup> It is essential to maintain the appropriate anatomical relationships between structural components.<sup>12–16</sup> Some connective tissue septa are aligned with directions of force that resist displacement of extraocular muscles during contraction. Others suspend and support delicate orbital vascular and neural elements. The essential components of this system include the periorbita, the orbital septal systems, and Tenon's capsule.<sup>17,18</sup>

### BOX 12.2.2 Orbital Bones Contributing to Each Wall

#### Roof

- Frontal bone
- Lesser wing of the sphenoid bone

#### Medial Wall

- Frontal process of the maxillary bone
- Lacrimal bone
- Ethmoid bone
- Body of the sphenoid bone

#### Floor

- Maxillary bone
- Zygomatic bone
- Palatine bone

#### Lateral Wall

- Zygomatic bone
- Greater wing of the sphenoid bone

## Periorbita

The orbit is lined with periosteum that is loosely adherent to the underlying orbital bones. Applied to the inner surface of the periosteum are multiple layers of orbital connective tissue that are continuous with the transorbital septal systems. Together this complex layer is known as the periorbita.

Within the orbit, the periorbita serves to support the extensive septal systems and to stabilize anatomical structures. At the orbital rim the inner layers of the connective tissue system separate from periosteum at the arcus marginalis and extend into the eyelids as the orbital septum. Thus the septum represents the anteriormost boundary of the orbital compartment.

## Orbital Septal System

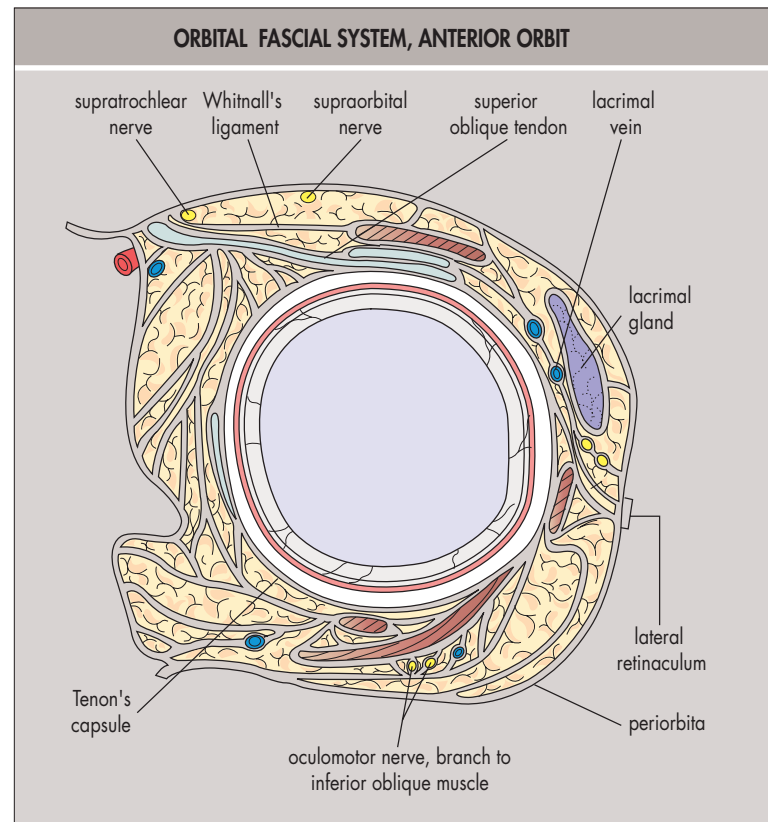
Suspended from the periorbita to form a complex radial and circumferential web of interconnecting slings are connective tissue septa.<sup>12–15</sup> These septa form fine capsules around fat lobules and also surround the extraocular muscles, optic nerve, and neurovascular elements. The fascial slings provide support and maintain constant spatial relationships between these structures during ocular movements.<sup>19</sup> These septa are responsible for the transmission of restrictive forces from incarcerated extraocular muscles after trauma even in the absence of true muscle entrapment.

The anterior fascial system of the orbit primarily supports the globe, anterior orbital structures (such as the lacrimal gland and superior oblique tendon), and the eyelids. It consists of a number of well-developed condensations and ligaments. These structures include Lockwood's inferior ligament, Whitnall's superior suspensory ligament, the lacrimal ligaments, and the intermuscular septum. They coordinate movements between the globe and eyelids and suspend the globe so that gaze movements occur around stable axes of rotation ([Fig. 12.2.2](#)).

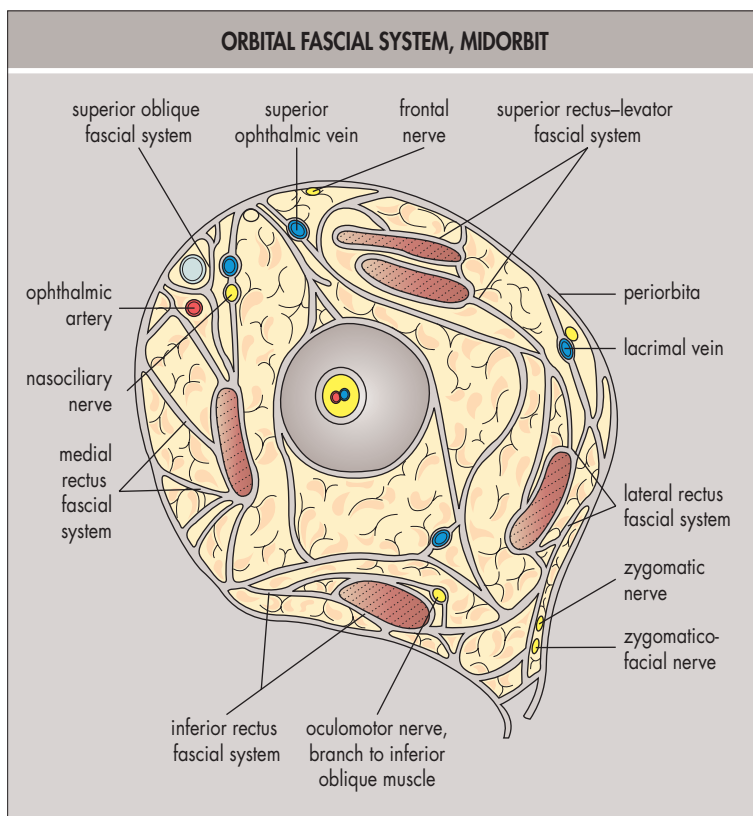
The connective tissue system is best developed in the midorbit. Here it forms well-defined fascial slings and suspensory complexes associated with each of the extraocular muscles ([Fig. 12.2.3](#)).

## Tenon's Capsule

Tenon's capsule is a dense, elastic, and vascular connective tissue layer that surrounds the globe, except over the cornea, and invests the anterior



**Fig. 12.2.2 The Connective Tissue System in Cross-Sectional Frontal View Through the Anterior Orbit at the Level of Whitnall's Ligament.** (Adapted with permission from Dutton JJ. *Atlas of clinical and surgical orbital anatomy*. 2nd ed. London: Elsevier Saunders; 2011. p. 122.)



**Fig. 12.2.3 The Connective Tissue System in Cross-Sectional Frontal View Through the Midorbit.** (Adapted with permission from Dutton JJ. Atlas of clinical and surgical orbital anatomy. 2nd ed. London: Elsevier Saunders; 2011. p. 121.)

portions of the extraocular muscles. This structure begins at the perilimbal sclera anteriorly and extends around the globe to the optic nerve, where it blends with fibers of the dural sheath and sclera.

En route from the orbital apex to the globe, the extraocular muscles must penetrate Tenon's capsule. The four rectus muscles pierce this structure posterior to the equator of the eye. As they proceed forward, the muscles and their thin, fibrous sheaths become invested by sleeve-like extensions of Tenon's capsule, which run with them to their insertions.

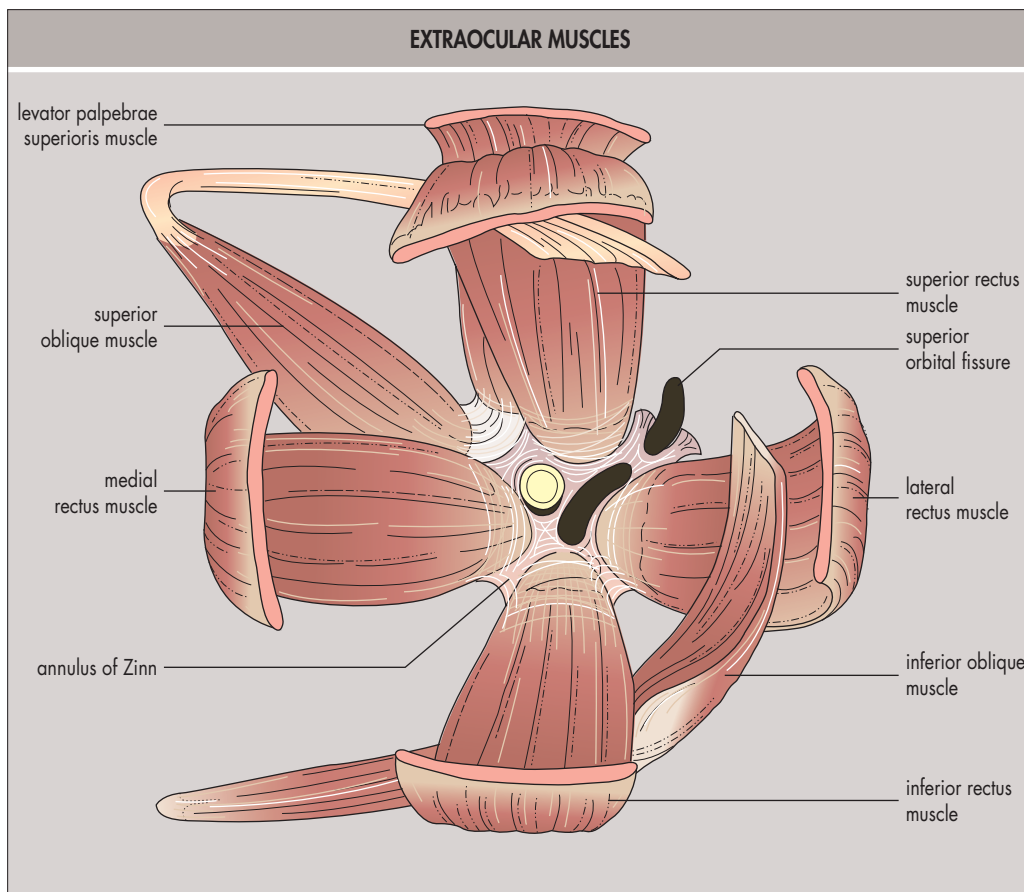
## MUSCLES OF OCULAR MOTILITY

Six striated extraocular muscles are attached to the eye and provide for ocular movement.<sup>20</sup> The four rectus muscles arise posteriorly from the annulus of Zinn, a fibrous band that is continuous with the periorbita and dura at the optic foramen.<sup>21</sup> The muscles run forward from the annulus of Zinn, surrounded by a sheath continuous with the orbital fascial systems. These fascial systems help keep the muscles in proper alignment and minimize the vector shifts that would otherwise be associated with ocular movement (Fig. 12.2.4).<sup>22-23</sup>

The superior oblique muscle arises above the annulus of Zinn just superior and medial to the optic foramen. It runs forward along the superomedial orbital wall to the cartilaginous trochlea, through which its tendon slides before it turns sharply laterally to insert on the superoposterior aspect of the globe.<sup>24</sup>

The inferior oblique muscle arises anteriorly from a small depression just below and lateral to the lacrimal sac fossa. It passes laterally and slightly backward to insert on the inferoposterior surface of the globe near the macula. Along its course, the sheath of the inferior oblique muscle joins that of the inferior rectus muscle and Tenon's capsule just behind the orbital rim to form Lockwood's inferior suspensory ligament. The capsulopalpebral fascia extends anteriorly from this ligament to the inferior tarsal plate.

The levator palpebrae superioris muscle originates from the annulus of Zinn and lesser sphenoid wing. It runs forward along the orbital roof in close approximation to the superior rectus muscle. Near the orbital rim a horizontal condensation is seen within the muscle sheath to form the prominent transverse ligament of Whitnall. The latter fuses to the orbital



**Fig. 12.2.4 Extraocular Muscles.** Orbital muscles of ocular motility as seen in the coronal plane. (Adapted with permission from Dutton JJ. Atlas of clinical and surgical orbital anatomy. 2nd ed. London: Elsevier Saunders; 2011. p. 39.)



wall near the trochlea and around the lacrimal gland. Whitnall's ligament is an important suspensory structure for the superior orbit and eyelid and should not be cut. Anterior to Whitnall's ligament, the levator muscle passes into a thin, fibrous aponeurosis that turns inferiorly and fans out into the eyelid. It inserts onto the inferior two-thirds of the anterior tarsal face.

## MOTOR NERVES OF THE ORBIT

The extraocular muscles are innervated by the third, fourth, and sixth cranial nerves.<sup>25</sup> The oculomotor nerve (third cranial nerve) enters the orbit via two branches. The superior branch innervates the superior rectus and levator muscles. The inferior branch sends fibers to the inferior rectus, medial rectus, and inferior oblique muscles. With the inferior division of the oculomotor nerve run parasympathetic fibers that arise from the Edinger–Westphal subnucleus. These synapse in the ciliary ganglion just lateral and inferior to the optic nerve at 1.5–2 cm behind the globe.<sup>26</sup> They progress via the short ciliary nerves to the ciliary body and iris sphincter. Little redundancy occurs to these nerves, so they may be injured easily during orbital dissection. This results in disturbances of pupillary function and accommodation.

The trochlear nerve (fourth cranial nerve) enters the extraconal space of the superior orbit through the superior orbital fissure above the annulus of Zinn. Here it crosses over the superior rectus and levator muscle complex and runs along the external surface of the superior oblique muscle before penetrating its substance in the posterior third of the orbit. In this position against the orbital roof, the trochlear nerve is damaged easily during blunt trauma.

The abducent nerve (sixth cranial nerve) enters the intraconal space of the orbit through the superior orbital fissure and annulus of Zinn. The nerve runs laterally to supply the lateral rectus muscle.

Sympathetic nerves enter the orbit via a number of different pathways to innervate the vascular muscular walls, the iris, and the accessory eyelid retractor muscles of Müller (Fig. 12.2.5).<sup>27</sup>

## SENSORY NERVES OF THE ORBIT

The optic nerve is technically not a sensory nerve but a central nervous system tract that arises from the retinal ganglion cells. The orbital portion

of the nerve is redundant to allow for ocular movement. It measures about 3 cm in length and takes a sinusoidal path from the globe to the optic canal. In close approximation to the nerve are the ophthalmic artery near the orbital apex and the superior ophthalmic vein in the midorbit. Both these vessels lie superior to the nerve in most individuals. The central retinal artery runs along the inferolateral side of the nerve to enter the dura about 1 cm behind the globe. The short and long posterior ciliary arteries lie close to the nerve for much of its length and are highly convoluted and redundant near the globe.

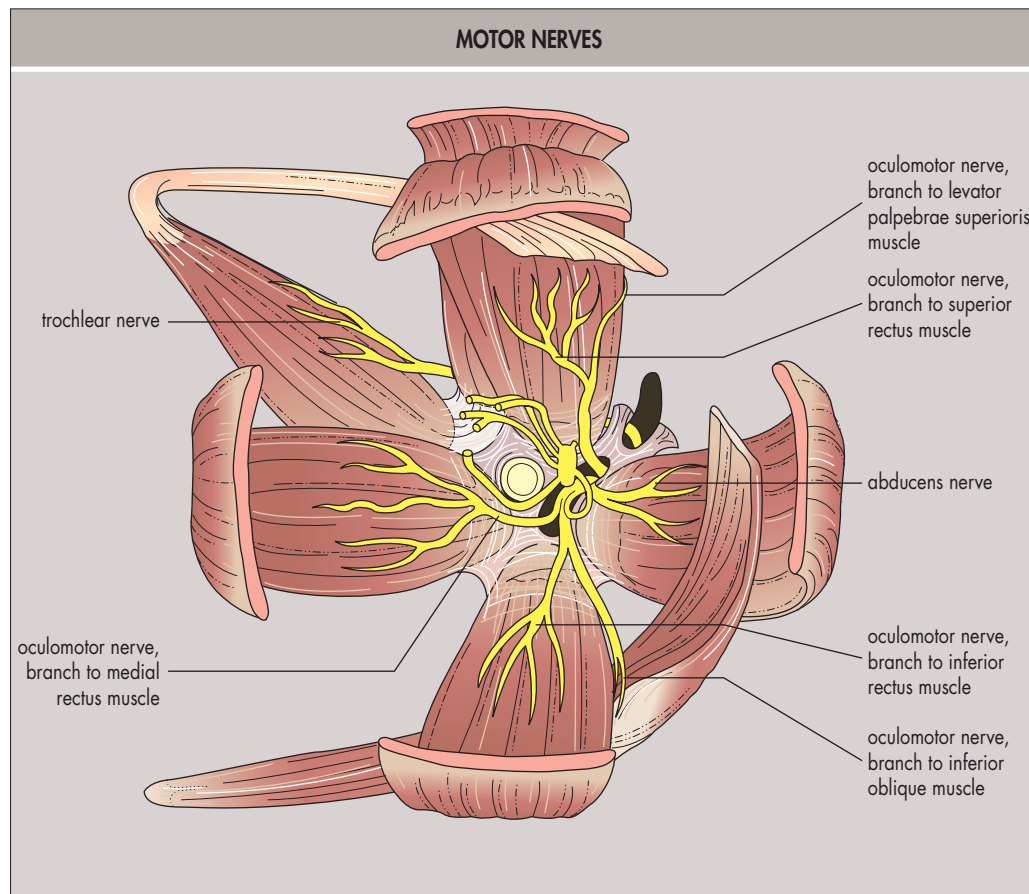
Sensory innervation to the orbit is primarily from the ophthalmic division of the trigeminal nerve (fifth cranial nerve) (Fig. 12.2.6). The maxillary division supplies portions of the inferior orbit. The ophthalmic division divides into branches in the cavernous sinus just as it passes into the superior orbital fissure.<sup>28</sup> The lacrimal nerve enters above the annulus of Zinn and proceeds along the superolateral orbit to the lacrimal gland and upper eyelid. The frontal nerve runs forward between the levator muscle and the orbital roof and exits the orbit at the supraorbital notch. At about the level of the posterior globe, it gives rise to the supratrochlear nerve, which exits the orbit at the superomedial rim.

The nasociliary nerve is a branch of the ophthalmic division that enters the orbit through the superior orbital fissure and annulus of Zinn. It crosses from lateral to medial over the optic nerve after sending small sensory branches that pass through the ciliary ganglion without synapse and continue to the globe with the short ciliary nerves. As it passes to the medial side of the optic nerve, the nasociliary nerve gives off the long posterior ciliary nerves, which extend to the posterior globe. The nasociliary nerve continues forward and exits at the superomedial rim as the infratrochlear nerve.

Recent studies have shown complex neural connections between the trigeminal nerve and motor nerves to the extraocular muscles in the cavernous sinus and in the posterior orbit. It is not clear whether these are all sensory, or some combination of sensory and sympathetic nerves.<sup>29</sup>

## ARTERIAL SUPPLY TO THE ORBIT

The arterial supply to the orbit arises from the internal carotid system through the ophthalmic artery, with anastomotic connections to the external carotid system through the superficial facial vessels.<sup>30</sup> The ophthalmic artery enters the orbit through the optic canal inferotemporal to the optic



**Fig. 12.2.5 Motor Nerves of the Orbit That Serve the Muscles of Ocular Motility, in Coronal View.** (Adapted with permission from Dutton JJ. *Atlas of clinical and surgical orbital anatomy*. 2nd ed. London: Elsevier Saunders; 2011. p. 67.)

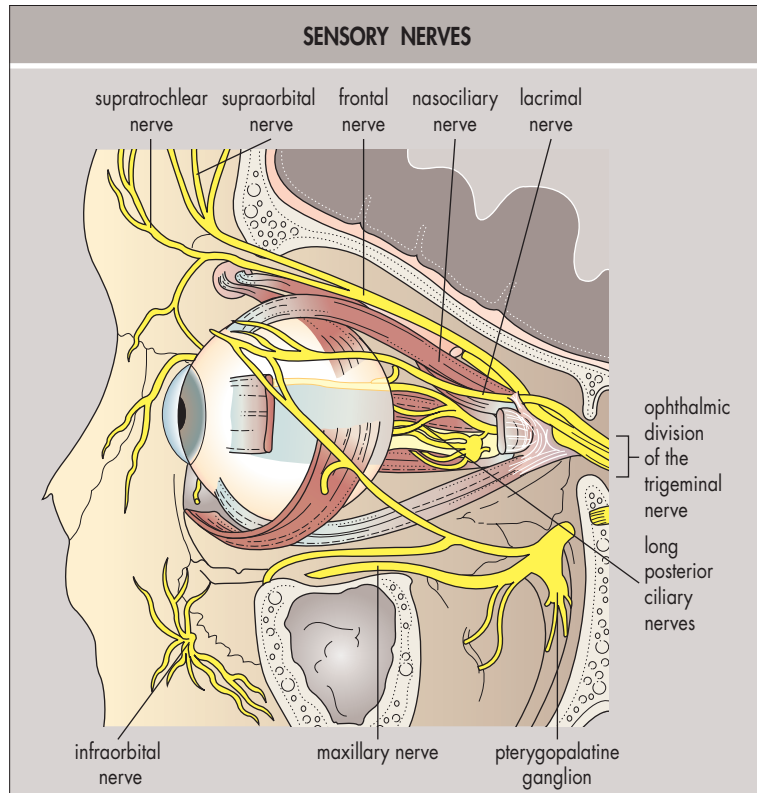
nerve (Fig. 12.2.7). In about 83% of individuals, the vessel crosses over the nerve to the medial side of the orbit; in the remaining 17%, it crosses below the nerve.<sup>31</sup> Shortly after it enters the orbit, the ophthalmic artery gives off a number of branches, with some variability in the sequence between individuals. The central retinal artery is usually the first branch. It runs along the inferior aspect of the optic nerve to penetrate the dura anywhere from

8–15 mm behind the globe. The lacrimal artery generally arises next and gives rise to the zygomaticotemporal artery, which penetrates the lateral wall at about the midorbit, and to the zygomaticofacial artery, which runs inferolaterally to exit through a small foramen in the zygomatic bone. The lacrimal artery terminates in the lids as the lateral inferior and superior palpebral arteries.

As the ophthalmic artery passes toward the medial orbit, the supraorbital branch is given off. This passes through the intermuscular septum medial to the levator muscle and runs forward with the frontal nerve to the supraorbital notch. In the medial orbit, the ophthalmic artery gives rise to the posterior and anterior ethmoidal arteries, which enter the ethmoidal foramina.<sup>32,33</sup> The ophthalmic artery then continues forward to exit just above the medial canthus as the dorsal nasal artery. Here, it gives off the inferior and superior medial palpebral arteries. The branching order is summarized in Box 12.2.3.

## VENOUS DRAINAGE FROM THE ORBIT

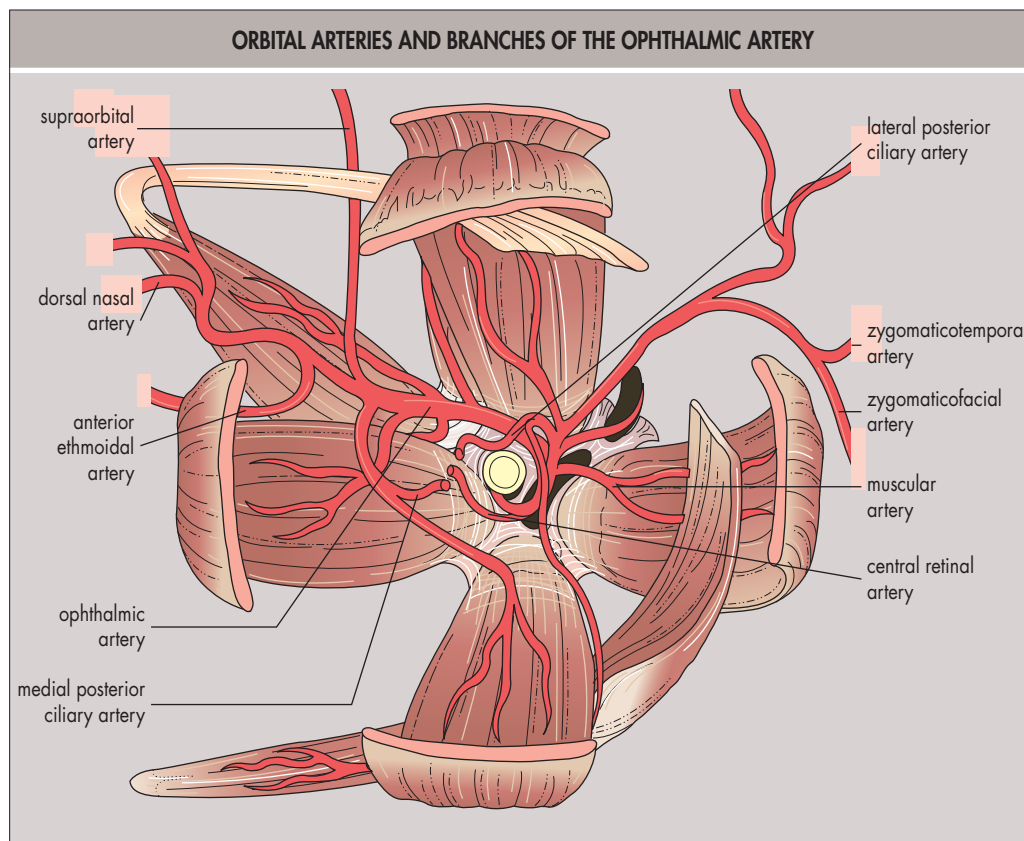
Venous drainage from the orbit is primarily through the superior and inferior ophthalmic veins (Fig. 12.2.8).<sup>34–36</sup> The superior ophthalmic vein



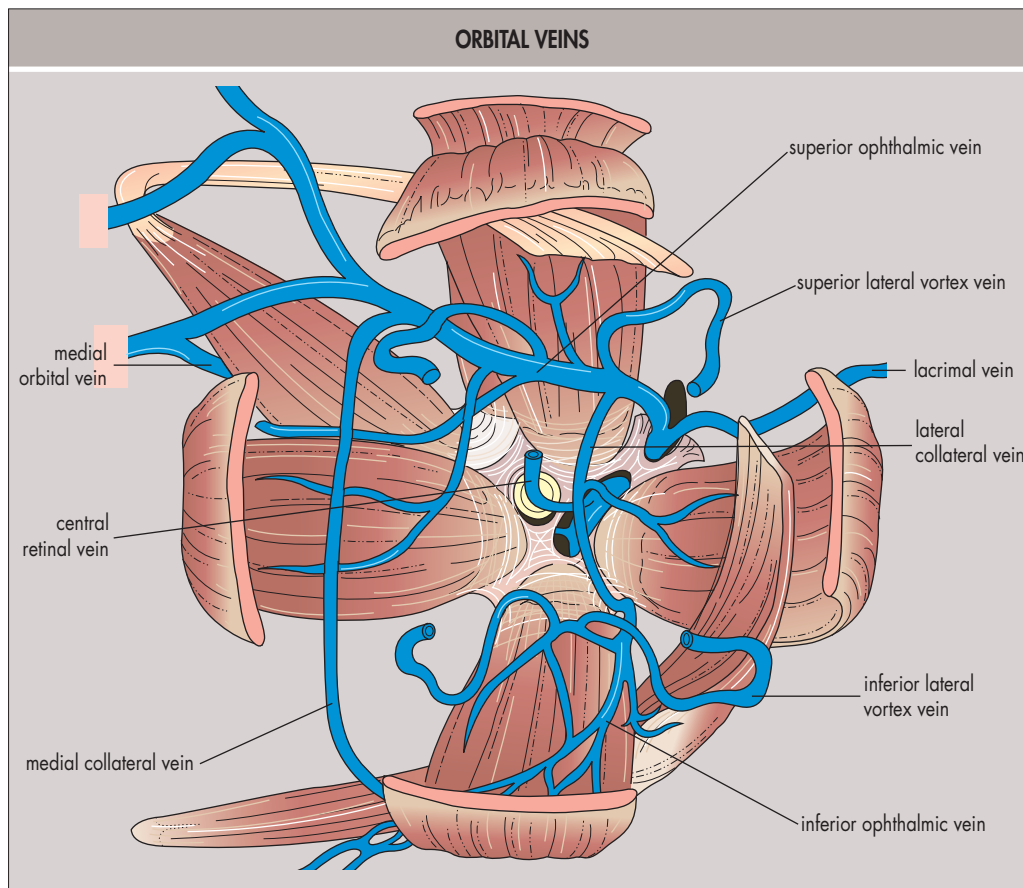
**Fig. 12.2.6 Sensory Nerves of the Orbit, in Lateral View.** (Adapted with permission from Dutton JJ. *Atlas of clinical and surgical orbital anatomy*. 2nd ed. London: Elsevier Saunders; 2011. p. 73.)

### BOX 12.2.3 Most Common Branching Order of the Ophthalmic Artery

1. Central retinal artery
2. Lateral posterior ciliary artery
3. Lacrimal artery
4. Muscular branch to superior rectus and levator muscles
5. Posterior ethmoidal and supraorbital arteries
6. Medial posterior ciliary artery
7. Muscular branch to medial rectus muscle
8. Muscular branch to superior oblique muscle
9. Branch to connective tissue
10. Anterior ethmoidal artery
11. Inferior medial palpebral artery
12. Superior medial palpebral artery
- T1. Dorsal nasal artery
- T2. Supratrochlear artery



**Fig. 12.2.7 Arterial Supply to the Orbit, in Coronal View.** (Adapted with permission from Dutton JJ. *Atlas of clinical and surgical orbital anatomy*. 2nd ed. London: Elsevier Saunders; 2011. p. 93.)



**Fig. 12.2.8 Orbital Veins.** Venous drainage from the orbit, in coronal view. (Adapted with permission from Dutton JJ. *Atlas of clinical and surgical orbital anatomy*. 2nd ed. London: Elsevier Saunders; 2011. p. 103.)

originates at the superomedial orbital rim from branches of the angular, supratrochlear, and supraorbital veins.<sup>37,38</sup> As it passes backward along the medial orbit, it is joined by branches draining the medial and superior rectus muscles and the levator muscle and by the superior vortex veins, the anterior ethmoidal vein, and collateral branches from the inferior ophthalmic vein.<sup>39</sup> At about the midorbit it crosses to the lateral orbit just below the superior rectus muscle. Here it is joined by the lacrimal vein and continues posteriorly to enter the cavernous sinus through the superior orbital fissure.<sup>40</sup>

The inferior ophthalmic vein has an indistinct origin in a plexus of small vessels in the inferior orbit. It passes backward along the inferior rectus muscle and is joined by branches draining the inferior rectus and inferior oblique muscles, the inferior vortex veins, and the lateral rectus muscle.

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# Orbital Imaging

Jonathan J. Dutton

## 12.3

### Definitions:

- Computed tomography: An imaging technique where contrast differences are based on tissue density based on the passage of x-rays through tissues.
- Magnetic resonance imaging: An imaging technique where density differences are based on tissue proton density and their resonance characteristics based on biochemical relationships within the atomic lattice.
- Orbital pathological processes often have characteristic features that can help narrow the diagnostic possibilities when considered in combination with the clinical findings.

### Key Features

- Orbital CT is the imaging procedure of choice for evaluation of bony detail.
- Magnetic resonance imaging has become the most important technique for most orbital lesions, for the optic nerve, and for the orbital apex, where it can distinguish tissues based on their biochemical differences.

## INTRODUCTION

Orbital pathology often presents a challenge in making an accurate diagnosis. Radiographic examination is an essential step in the evaluation of all patients who have suspected orbital disease, and it can help narrow the differential diagnosis. Although imaging can contribute significant information, pertinent clinical input is necessary for adequate radiographic interpretation.<sup>1</sup> Imaging patterns and features can often point to specific diagnostic possibilities compared with expected normal anatomy.<sup>2</sup> Orbital imaging can also may help the physician plan the most appropriate medical therapy or surgical approach.<sup>3-6</sup> Computed tomography (CT) and magnetic resonance imaging (MRI) have largely replaced older techniques (Fig. 12.3.1). MRI in particular has proven valuable in delineating orbital strictures including blood vessels, nerves, and connective tissue septae.<sup>7-9</sup>

## NORMAL ORBITAL ANATOMY IN THE AXIAL PLANE

### Axial Section Through the Lowermost Orbit

The axial plane is horizontal through the orbit, perpendicular to the cephalocaudal axis of the body. The orbital floor appears as a thin, oblique density that runs from anteromedial to posterolateral, separating the orbit from the maxillary sinus.<sup>10,11</sup> Because the floor gradually slopes backward and upward, successively higher cross-sections are cut in axial scan sequences. The orbital cavity is bounded medially by the anterior lacrimal crest and laterally by the lateral rim of the zygomatic bone. Posterior to the orbit is the cranial base.<sup>12</sup> A thin line arches across the orbital opening from the medial to the lateral bony rims; this represents the lower eyelid and orbital septum.<sup>3</sup>

Depending on the level of the cut, the orbital cavity may appear empty (because it contains only orbital fat) or it may contain a rounded density that represents the sclera cut tangentially. Occasionally the inferior oblique muscle is seen as an oblique band of medium-density tissue, and in slightly higher sections, the inferior rectus muscle may appear as a density adjacent to the globe posteriorly.

### Axial Section Through the Inferior Orbit

In low axial sections through the inferior orbit, the floor again appears as a thin density that separates the orbital cavity from the maxillary sinus. In the posterolateral corner of the orbit, where the floor approaches the lateral wall, a channel separates the body of the sphenoid bone from the greater wing. This is the inferior orbital fissure. Posteriorly, behind the inferior rectus muscle, this fissure communicates between the orbital space and the pterygopalatine fossa. In the anteromedial corner of the orbit, the lacrimal sac fossa is seen as a depression in the orbital process of the maxillary bone.

Within the orbital space, a central, rounded density represents the globe. Because the vitreous is primarily aqueous, it appears empty (black) on CT. On MRI scans, the vitreous appears dark on T1-weighted sequences and bright on T2-weighted sequences. Just posterior to the globe is a rounded density that lies on the midportion of the orbital floor and is discontinuous with the globe. This is the inferior rectus muscle cut in cross-section.

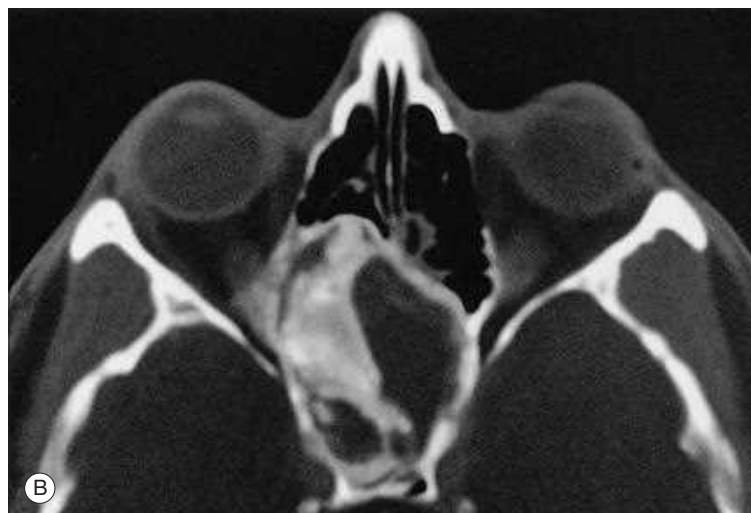
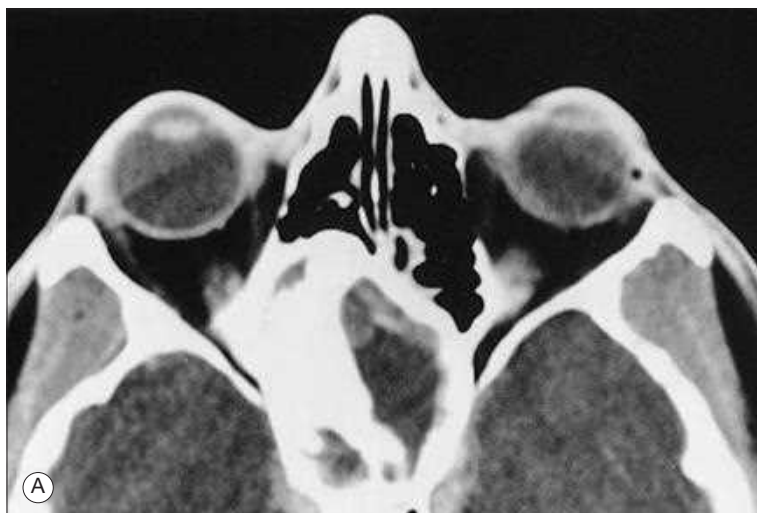


Fig. 12.3.1 Axial Computed Tomography of the Orbits. (A) Tissue density window. (B) Bone density window.

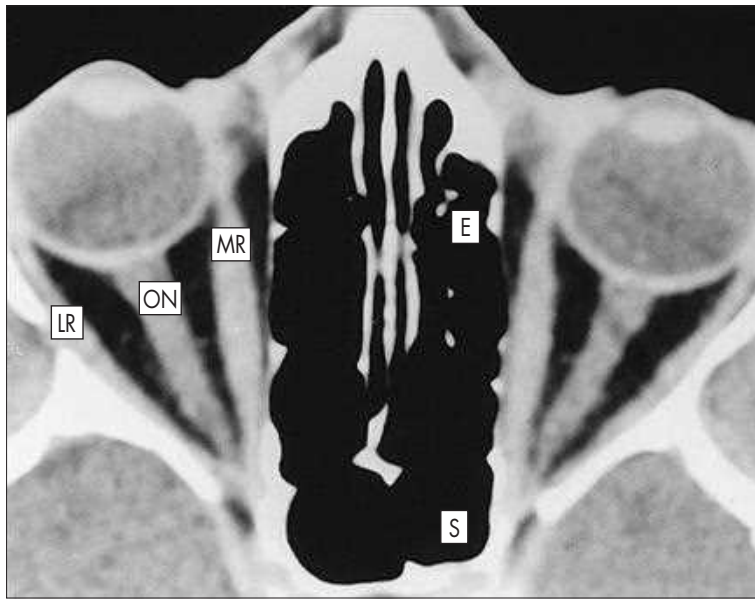
## Axial Section Through the Midorbit

On axial scans through the midorbit, the globe is seen in equatorial section (Figs. 12.3.2 and 12.3.3). Anteriorly, the lens is seen as an oval density. On MRI sections, the ciliary body can be distinguished on either side of the lens.<sup>3</sup> Behind the globe, the optic nerve is seen to emerge from the posterior sclera and run toward the orbital apex.<sup>13,14</sup>

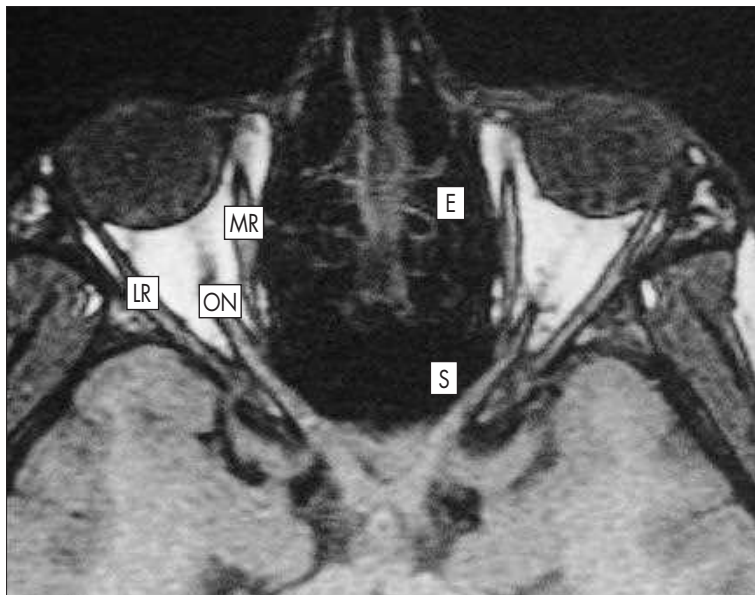
In the midorbit, a gently curved enhancing line crosses the orbit from lateral to medial. This is the superior ophthalmic vein.<sup>15</sup> Near the orbital apex, a small enhancing vessel is seen to cross over the optic nerve from lateral to medial. This is the second portion of the ophthalmic artery. Along the orbital walls are the lateral and medial rectus muscles. At slightly higher levels, both the medial rectus and superior oblique muscles are often seen together. On either side of the midline are the ethmoid sinuses, with the thin lamina papyracea that forms the medial orbital wall. Just medial to the laminae are the ethmoid air cells.

## Axial Section Through the Superior Orbit

At this level, the orbital contour is narrower and terminates posteriorly in a rounded angle above the level of the optic canals. Within the orbital outline,



**Fig. 12.3.2 Axial CT Scan Through the Midorbit.** The globe and optic nerve are seen in the axial plane, along with the medial and lateral rectus muscles. E, Ethmoid sinus; LR, lateral rectus; MR, medial rectus; ON, optic nerve; S, sphenoid sinus.



**Fig. 12.3.3 Axial MRI Scan Through the Midorbit.** The section is slightly higher than in Fig. 12.3.2. The optic nerves are seen passing back to the optic chiasm. E, Ethmoid sinus; LR, lateral rectus; MR, medial rectus; ON, optic nerve; S, sphenoid sinus.

the globe is represented in cross-section above the level of the lens. Along the medial wall is the superior oblique muscle that passes through the trochlea anteromedially. Near the orbital apex, the superior rectus muscle appears as a broad band of tissue directed toward the globe. The superior ophthalmic vein is seen as a curvilinear enhancing structure that crosses from anteromedial to posterolateral just below the muscle. Anterolaterally, near the lateral orbital rim, the lacrimal gland appears as an oval density seen between the zygomatic bone and the globe.

## Axial Section Through the Orbital Roof

In axial sections above the level of the globe, the orbit appears as a rounded contour posteriorly. Because the roof lies in a plane oblique to the tissue slice, in each higher section the roof lies progressively more anteriorly as it approaches the orbital rim. The levator muscle is seen as a broad band that extends from the superior orbital rim backward along the roof. Anteromedially, the trochlea is seen clearly, and at appropriate levels the superior oblique tendon can be visualized as it fans out over the superior globe below the superior rectus muscle insertion.

## NORMAL ORBITAL ANATOMY IN THE CORONAL PLANE

### Coronal Section Through the Antermost Orbit

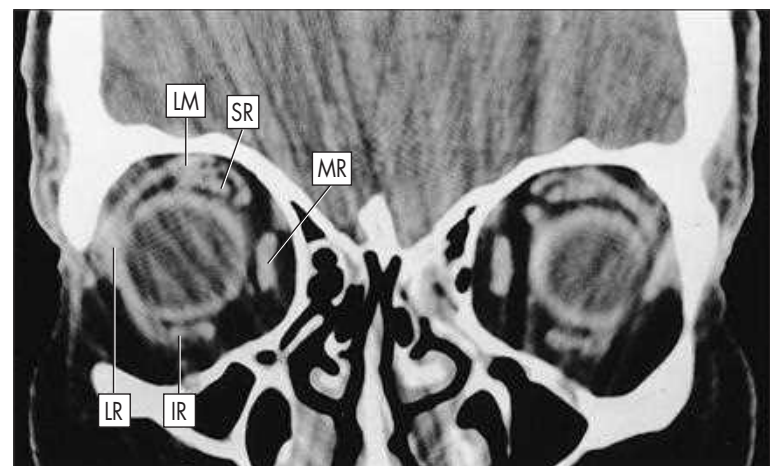
The coronal plane is vertical, passing through the orbit parallel to the left-right axis. The sagittal plane is vertical but in an anterior-posterior direction. In coronal sections through the anteriormost orbit, the globe is cut through the level of the eyelids. The frontal sinus is in the midline of the orbital roof, below the frontal lobes of the brain. The anterior segment of the globe may appear as several concentric densities that represent the cornea, lens, and anterior sclera. In the superior medial corner of the orbit are the trochlea and tendon of the superior oblique muscle. Inferiorly, the inferior oblique muscle can be seen as a linear shadow that runs from the inferomedial orbital wall toward the lateral orbit.

### Coronal Section Through the Anterior Orbit

Sections that cut through the anterior midorbit pass through the globe near its equator. At this level, the orbital roof is seen as a thin, curved plate of bone with an upper surface that undulates against the overlying frontal lobes. In the midline is the crista galli, and on either side are the cribriform plate and roof of the ethmoid sinus.

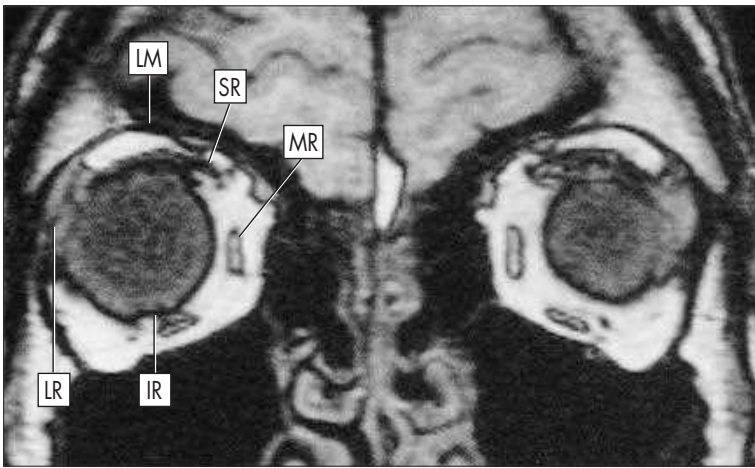
The orbital floor is a thin plate of bone that extends from the lowermost extent of the lamina papyracea and slopes downward and laterally to the inferolateral orbital wall. Immediately below the floor is the triangular maxillary sinus.

Centrally, the globe is seen to fill most of the orbital space (Figs. 12.3.4 and 12.3.5). Superiorly, the thin superior rectus muscle lies adjacent to the globe, and above it is the levator muscle. Medially, the flattened medial rectus muscle lies within the orbital fat between the lamina papyracea and

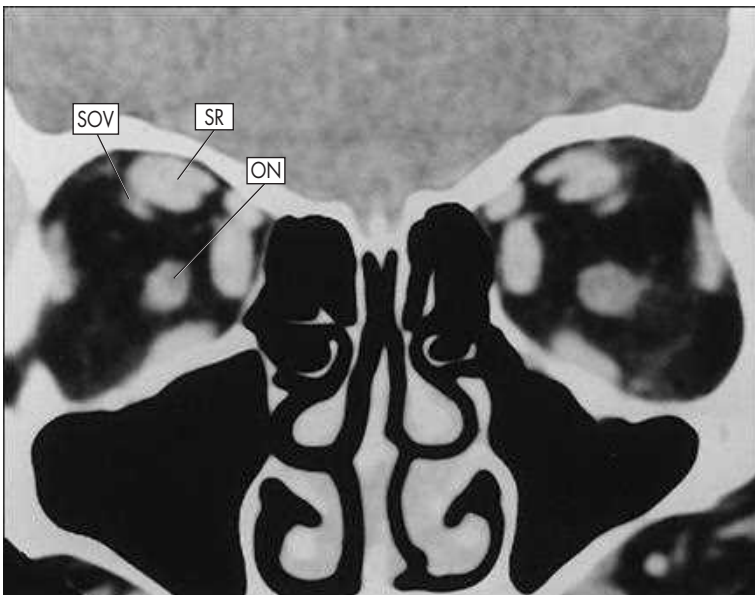


**Fig. 12.3.4 Coronal CT Scan Through the Anterior Portion of the Orbit.** The globes are cut in cross-section, and the rectus muscles are seen as flattened densities near the sclera. IR, Inferior rectus; LM, levator muscle; LR, lateral rectus; MR, medial rectus; SR, superior rectus.





**Fig. 12.3.5 Coronal MRI Scan Through the Anterior Portion of the Orbit.** The cut is similar to that seen in Fig. 12.3.4. IR, Inferior rectus; LM, levator muscle; LR, lateral rectus; MR, medial rectus; SR, superior rectus.



**Fig. 12.3.6 Coronal CT Scan Through the Midorbit.** The optic nerve lies centrally, surrounded by the rectus muscles. Just below the lateral edge of the superior rectus is the superior ophthalmic vein. ON, Optic nerve; SOV, superior ophthalmic vein; SR, superior rectus muscle.

the globe. Just below the eye is the inferior rectus muscle, and laterally is the lateral rectus muscle. In the superomedial corner, a small, round shadow is the superior oblique muscle. At the medial edge of the superior rectus–levator muscle complex is a round enhancing structure, the superior ophthalmic vein.

### Coronal Section Through the Central Orbit

In coronal sections behind the globe, the orbital walls appear as in more anterior sections. Within the central space of the orbit lies the round optic nerve cut in cross-section (Figs. 12.3.6 and 12.3.7). On MRI scans, the central nerve can easily be distinguished from the nerve sheaths; the two are separated by the clear subarachnoid space. The four rectus muscles are seen against their respective orbital walls cut across their midbellies. The levator muscle appears as a separate thin strap just above and medial to the superior rectus. Above the medial rectus muscle, along the superomedial corner of the orbit, is the superior oblique muscle. The superior ophthalmic vein is a small, enhancing circular density between the optic nerve and the superior rectus muscle en route to the lateral orbit.

### Coronal Section Through the Anterior Orbital Apex

Toward the apex, the bony orbit narrows to a triangular section. Inferolaterally, the contour opens into the inferior orbital fissure that communicates



**Fig. 12.3.7 Coronal MRI Scan Through the Midorbit.** Structures are similar to those observed in Fig. 12.3.6. LR, Lateral rectus muscle; MR, medial rectus muscle; ON, optic nerve; SR, superior rectus muscle.

with the infratemporal fossa. Within the orbit, the optic nerve, the superior oblique muscle, and all four rectus muscles can still be identified as separate structures. The superior ophthalmic vein is found more laterally, to the lateral edge of the superior rectus muscle. The ophthalmic artery is seen just above the optic nerve as it crosses over the nerve from lateral to medial.

### Coronal Section Through the Posterior Orbital Apex

At this level, the orbit is reduced to a small, rounded space, open inferiorly to the pterygopalatine fossa. It is bounded laterally by the greater wing of the sphenoid and medially by the body of the sphenoid adjacent to the sphenoid sinus. Superolaterally, the orbit opens into the middle cranial fossa through the superior orbital fissure.

## Computed Tomographic Imaging Features of Some Orbital Pathologies<sup>1</sup>

### Cavernous Hemangioma

These vascular tumors appear as a well-defined, oval to round, homogeneous mass with a density somewhat greater than muscle. It is typically located in the intraconal space, but when large they can extend extraconally. Long-standing larger lesions can cause bone remodeling, and small foci of calcium can sometimes be seen. Enhancement is usually mild to moderate because of its generally low vascular blood flow.

### Dermoid Cyst

Usually located at the superotemporal orbital rim, dermoid cysts are typically round to oval well-defined cystic lesions. The internal signal is low when the fat content is high, and a fat-fluid level may be seen. Dense foci within the cyst represent flecks of keratin and sebum. The cyst is surrounded by a denser enhancing wall that may be partially calcified. The adjacent orbital rim may show remodeling or the cyst may be embedded within the bone.

### Thyroid Eye Disease

The CT scan reflects some of the key clinical findings of this disease, proptosis and increased orbital fat. Multiple extraocular muscles in one or both orbits are enlarged with sparing of the muscle insertions. The inferior and medial rectus muscles are most commonly involved. The superior ophthalmic vein may be enlarged from orbital congestion, and the optic nerve is rarely compressed by enlarged muscle at the apex.

### Optic Nerve Sheath Meningioma

With this tumor of the nerve sheath the optic nerve typically shows a smooth tubular enlargement, but rarely may be exophytic when it breaks

through the dura. In 20%–50% of cases there may be foci of calcification. With contrast there is marked enhancement of the tumor with a central zone of low attenuation representing the optic nerve. This is the so-called tram-track sign. With more posterior lesions the optic canal can be enlarged.

### **Myositis**

One or sometimes several extraocular muscles show a somewhat diffuse enlargement that may have irregular and shaggy borders. Density is usually greater than normal muscle and unlike thyroid orbitopathy the tendon of insertion is frequently also enlarged.

### **Optic Nerve Glioma**

In the orbit gliomas typically appear as a well-outlined fusiform enlargement of the optic nerve, but they may be globular in some cases. The nerve may show tortuosity or kinking and is usually heterogeneous in density. Low-density cystic spaces correspond to areas of mucinous degeneration. Enhancement varies from imperceptible to moderate. The tumor may extend back to the optic chiasm and occasionally along the optic radiations.

### **Adenoid Cystic Carcinoma**

CT shows a heterogeneous mass centered in the lacrimal gland fossa. It can be irregular and poorly demarcated or round and well outlined. It can extend along the lateral rectus muscle and the lateral orbital wall to the orbital apex. Destruction of adjacent bone is common, especially

with larger tumors. With contrast there are often areas of marked focal enhancement.

### **Orbital Mucocele**

There is usually opacification of one or more sinuses with extension of a sharply defined, rounded cystic mass into the adjacent orbit. The intervening bone may be destroyed or remodeled as a thin shell around the cyst. When large, orbital structures such as optic nerve and muscles are displaced laterally. The cyst contents are usually homogeneous and of low density when filled with mucoid material but can sometimes image as dense as muscle when more viscid. There is no enhancement with contrast.

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# Blepharoptosis

Caroline W. Vargason, Jeffrey A. Nerad

## 12.4

**Definition:** Ptosis is defined as the upper eyelid resting in a droopy, abnormally low position while the eye is in primary gaze.

### Key Features

- Blepharoptosis (ptosis) is caused by a weakness in one or both of the eyelid retractors, the levator muscle, and Müller's muscle, which position the upper eyelid.
- Ptosis can be broadly categorized into common and unusual types. Common types are acquired involutional ptosis and simple congenital ptosis.
- Ptosis presents with various symptoms, including decreased vision, brow ache, headache, difficulty reading, and neck ache.
- Surgery is considered in symptomatic patients or patients who are displeased with their droopy eyelid appearance.
- Ptosis repair surgery aims to elevate the eyelid position without causing excessive lagophthalmos.

### INTRODUCTION

Ptosis repair surgery has a storied history of trial and error. Surgical approaches date back to the ancient Arabians and have attempted to modify each anatomical component of the upper eyelid and brow, including superior rectus transposition to the eyelid.<sup>1</sup>

Modern surgical approaches are directed by levator function. Poor levator function requires correction by frontalis suspension. Dransart (1880) first described frontalis suspension with nonabsorbable sutures, and Wright (1922) popularized the fascia lata sling.<sup>1</sup> Good levator function allows correction by levator or Müller's muscle resection. Bowman (1957) described the first transconjunctival levator-Müller's muscle complex resection, and Jones et al. (1975) introduced the levator aponeurosis advancement operation performed today.<sup>1,2</sup> The posterior approach Fasanella-Servat Müller tarsectomy (1961) and Putterman's Müllerectomy (1975) are also used in patients with good levator function.<sup>3-5</sup>

### FOUNDATION: A SIMPLIFIED CLASSIFICATION OF PTOSIS

This simplified classification of ptosis has two main categories, *common ptosis* and *unusual ptosis*. A solid understanding of the two most common types of ptosis, acquired involutional ptosis and simple congenital ptosis, will allow you to recognize easily the uncommon types. [Box 12.4.1](#) lists the differential diagnosis for ptosis.

### Anatomy and Function

To understand ptosis, it is important to first appreciate normal anatomy. The normal upper eyelid rests at the upper limbus. The upper eyelid is opened by retractors, which are the levator, Müller's, and frontalis muscles. Because the levator muscle is the primary upper eyelid retractor, abnormalities in the levator complex are the cause of most ptosis. The levator muscles are innervated by the superior division of the oculomotor nerve and follow Hering's law of equal and simultaneous innervation.<sup>6,7</sup> Thus if ptosis is asymmetrical, and the more ptotic eyelid is lifted, any "extra" innervation to the less ptotic eyelid will disappear, causing that eyelid to drop.

Eyelid health can be assessed by measuring the three *eyelid vital signs*.<sup>8</sup>

- Margin reflex distance 1 (MRD<sub>1</sub>) is the measured distance from the central light reflex to the upper eyelid margin. A normal MRD<sub>1</sub> is 4–5 mm. A low MRD<sub>1</sub> defines ptosis.
- Levator function, which indicates the strength of the levator muscle, is the measured excursion of the upper eyelid margin from downgaze to upgaze with the brow immobilized. A normal levator function is at least 15 mm.
- The lid crease height and strength provide additional information about levator strength. *Levator pulling on the skin creates the skin crease*. Thus a weaker levator has less skin pull, creating a weaker or less distinct crease.

### Classification Based on Levator Function

*Levator function is the basis for classification and treatment of ptosis.* Adults with involutional ptosis will have normal or near-normal levator function and are treated with levator aponeurosis advancement surgery. Children with simple congenital ptosis will have reduced levator function and are treated with frontalis sling surgery. If your patient with ptosis does not fit into these categories—meaning an adult with much decreased levator function or a child with normal levator function—then you must consider other *unusual* diagnoses (see [Box 12.4.1](#)).

### Common Ptosis

Most older adults will have acquired involutional ptosis, and most children will have simple congenital ptosis. Although an oversimplification, this classification is a practical and helpful approach to assessing your ptosis patients.

### Acquired Involutional Ptosis

Most adults with acquired ptosis have involutional changes in the levator muscle and aponeurosis. The ptosis can be unilateral or bilateral ([Fig. 12.4.1](#)). Classically, the pathophysiology of involutional ptosis was described as aponeurotic dehiscence or disinsertion from the superior tarsus.<sup>2,9</sup> It was later found that most patients have an attached aponeurosis with

#### BOX 12.4.1 Differential Diagnosis of Upper Eyelid Ptosis<sup>8</sup>

##### Common Ptosis

- Acquired involutional ptosis—normal levator function
- Simple congenital ptosis—reduced levator function

##### Unusual Ptosis

###### Congenital

- Blepharophimosis
- Marcus Gunn jaw-winking

###### Acquired

- Neurogenic
  - Myasthenia gravis
  - Third cranial nerve palsy
  - Horner's syndrome
- Myogenic
  - Oculopharyngeal dystrophy
  - Myogenic dystrophy
  - Chronic progressive external ophthalmoplegia
- Posttraumatic



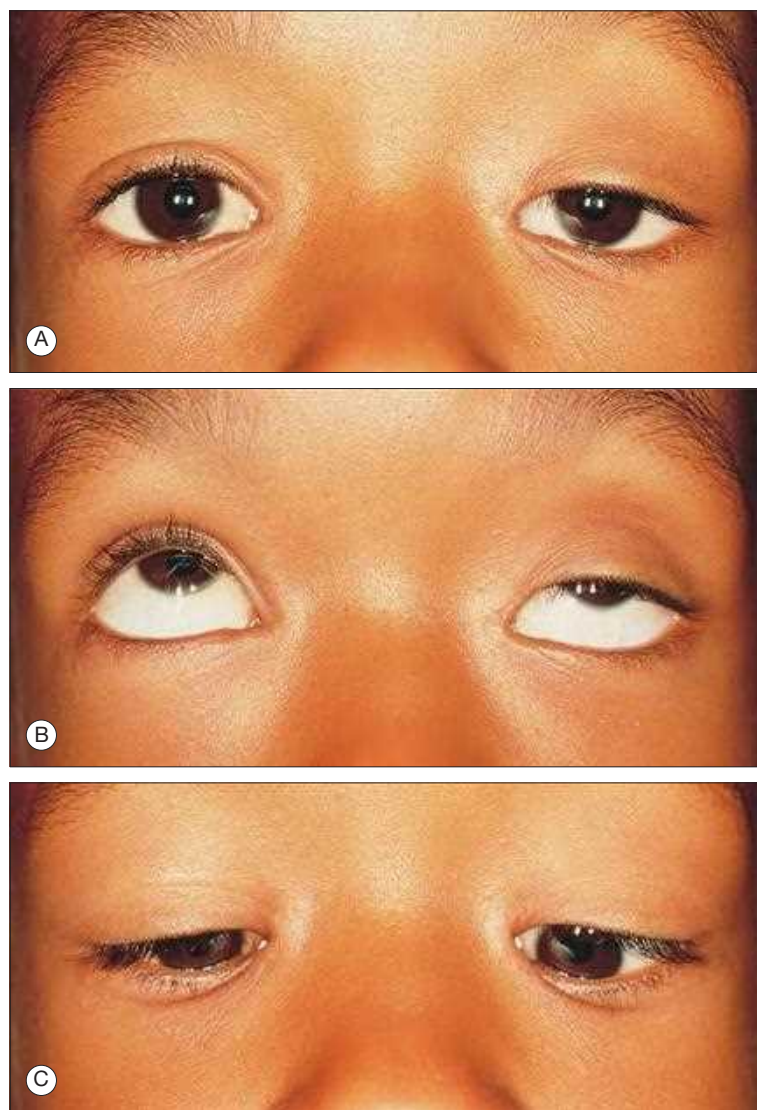
**Fig. 12.4.1 Acquired Involuntional Ptosis.** (A) Bilateral ptosis with a weak, high lid crease. (B) Normal levator function. (C) Weak lid crease and ptosis persist in downgaze. (D) Normal lid height after bilateral levator aponeurosis advancement surgery.

aponeurotic thinning or myogenic abnormalities.<sup>10–12</sup> Thus, involuntional ptosis can be aponeurotic, myogenic, or both.

It is helpful to think of the aponeurosis being “stretched” and the muscle having relatively normal function, as the *three key clinical features* conform to this idea. First, levator function measurement will be normal. Second, a high skin crease is present due to aponeurotic stretching and skin–levator muscle fiber attachment being located more superiorly. Third, lid drop on downgaze is present due to aponeurotic stretching resulting in a “longer” eyelid. Levator aponeurosis advancement surgery will correct the ptosis.

### Simple Congenital Ptosis

Most children with ptosis have simple congenital ptosis. It is present from birth and caused by *dystrophy of the levator muscle*, where fatty tissue infiltration weakens the muscle. *Simple* refers to the dystrophic levator muscle being the only ocular problem (except maybe strabismus and amblyopia)



**Fig. 12.4.2 Simple Congenital Ptosis.** (A) Bilateral upper eyelid ptosis with left much greater than right. Very weak left upper eyelid crease, indicating poor levator muscle function. (B) Left ptosis present in upgaze, again indicating poor levator muscle function. (C) Left lid lag, or ptosis reduction in downgaze, due to decreased excursion of the fibrotic levator muscle.

in an otherwise healthy child. The ptosis is usually bilateral and quite asymmetrical (Fig. 12.4.2). At least 65% of cases are reported as “unilateral” even though many of the so-called unilateral cases in reality have mild ptosis of their other eye.<sup>13,14</sup> Strabismus and amblyopia are more common in patients with congenital ptosis compared with the general pediatric population, emphasizing the importance of monitoring visual acuity and ocular motility in all patients with congenital ptosis.<sup>15–19</sup>

On examination patients will have *three typical findings* consistent with a weak, fibrotic levator muscle. First, levator function measurement will be reduced, as the weak muscle does not move well in upgaze. Second, a weak or absent skin crease is present due to the weak muscle pulling less on the skin. Third, lid lag on downgaze results from the weak muscle also not moving well in downgaze.

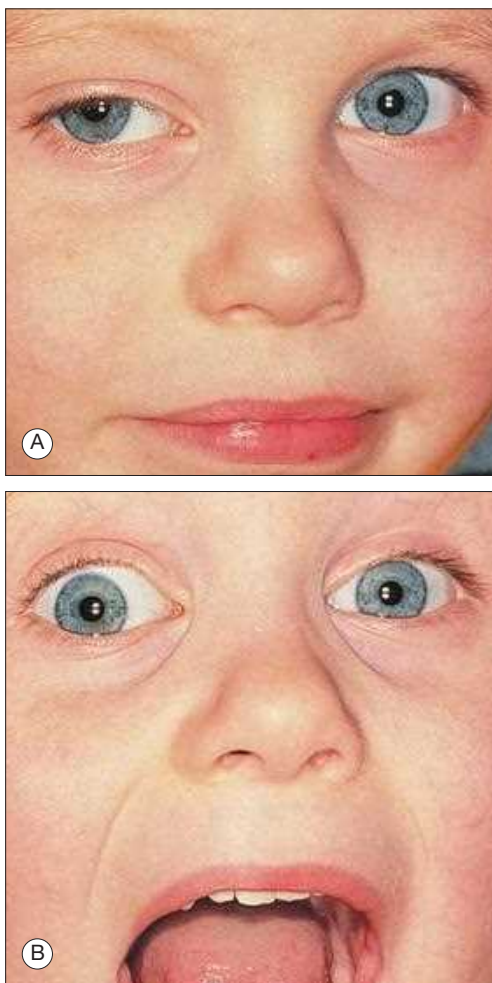
Early surgical intervention is indicated for visual axis obstruction. Surgical treatment is based on levator function. A frontalis sling operation is necessary for severe ptosis with poor levator function of less than 4 mm. For mild to moderate ptosis with at least 4 mm of levator function, tightening the levator with a levator resection operation is appropriate.<sup>20</sup>

## DIFFERENTIAL DIAGNOSIS

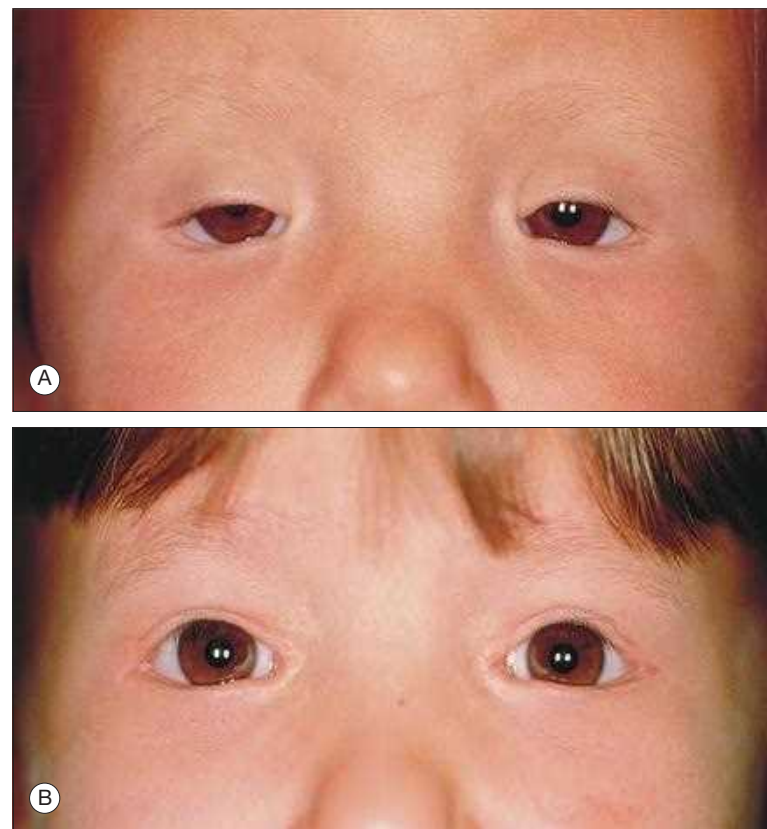
### Common Ptosis

The two most common types of ptosis, *simple congenital ptosis* and *acquired involuntional ptosis*, are reviewed earlier. A complete differential diagnosis is listed in Box 12.4.1. If the patient does not have common ptosis, the history and physical examination will guide you to diagnosis of an unusual type of ptosis.





**Fig. 12.4.3 Marcus Gunn Jaw-Winking Syndrome.** (A) Right upper eyelid ptosis in primary gaze with mouth closed. (B) Right upper eyelid elevates when the jaw is opened.



**Fig. 12.4.4 Blepharophimosis Syndrome.** (A) Symmetrical bilateral ptosis, epicanthus inversus, and telecanthus. (B) Postoperative appearance after bilateral frontalis sling placement and medial canthoplasty.

## Unusual Congenital Ptosis

### Marcus Gunn Jaw-Winking Syndrome

This ptosis results from “miswiring” between the mandibular branch of the fifth cranial nerve, innervating the pterygoid muscle, and the superior branch of the third cranial nerve, innervating the levator muscle. Resulting synkinesis causes the droopy eyelid to elevate when the mouth opens and can be unilateral or bilateral (Fig. 12.4.3).<sup>21</sup> All children with congenital ptosis should be examined for Marcus Gunn jaw-winking by asking them to eat or chew gum.

A broad range of abnormal synkinetic eyelid movement, or winking, occurs. The amount of winking is not necessarily proportional to ptosis or levator function.<sup>22</sup> Moderate 2–4 mm winking is most common, followed by mild, and then severe.<sup>23</sup> Patients with moderate to severe winking, severe ptosis, and poor levator function are treated with levator extirpation to eliminate the abnormal movement and a frontalis sling to elevate the eyelid.<sup>24</sup> Patients with minimal winking, mild ptosis, and good levator function are treated with levator resection. Many children learn to control mouth movements to minimize their winking.

### Blepharophimosis Syndrome

This congenital syndrome is characterized by *ptosis*, *epicanthus inversus*, and *telecanthus* and is inherited in an autosomal dominant pattern. Sporadic cases can also occur. Type I is associated with premature ovarian failure, where 70% have a mutation in the *FOXL2* gene, whereas type II is not.<sup>25,26</sup> Referral to a geneticist is recommended. The ptosis is bilateral and usually severe with poor levator function. Phimosis refers to the horizontal shortening of the lid aperture. Children have characteristic low-set ears and an elfish appearance (Fig. 12.4.4). Coincident amblyopia is more frequent than in simple congenital ptosis and more likely to occur with asymmetrical lid position.<sup>27,28</sup> Severe ptosis is treated with a frontalis sling. Additional reconstructive procedures can correct the epicanthal folds and telecanthus.

## Unusual Acquired Ptosis

Types of unusual acquired ptosis fit into three basic categories. First, neurogenic is a problem with innervation of levator or Müller’s muscle. Second, myogenic is a weakness of the muscle itself. Third, posttraumatic involves scarring of the levator muscle.

## Neurogenic Ptosis

### Myasthenia Gravis

Myasthenia gravis is an autoimmune disease in which antibodies against the neuromuscular junction cause a reduction in acetylcholine receptors, resulting in poor nerve conduction and weak muscles. Ptosis or diplopia are the presenting symptom in up to 85% of patients.<sup>29</sup> Few patients have ocular myasthenia, whereas up to 53% develop generalized myasthenia.<sup>30–32</sup> Most patients have autoantibodies to neuromuscular junction targets.<sup>33</sup>

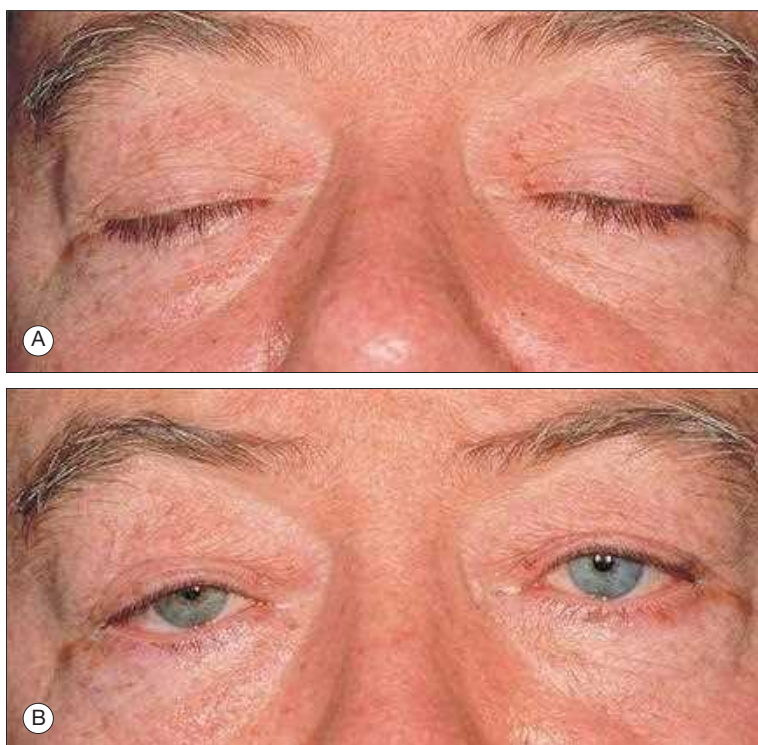
Ptosis is characteristically *variable* and can be unilateral or bilateral. If a patient reports variable ptosis, examine for fatigability and Cogan’s lid twitch on sustained upgaze.<sup>34</sup> Diagnosis is made clinically and is confirmed classically with a Tensilon test (Fig. 12.4.5); this has fallen out of favor due to potential side effects. Ice pack testing, serum autoantibodies, and electromyography are currently used diagnostics.<sup>33,35</sup>

Medical treatment consists of oral cholinesterase inhibitors or immunosuppressive medications.<sup>36</sup> Thymectomy is beneficial in select patients.<sup>37</sup> Ptosis repair surgery is appropriate for patients with vision impairment after maximal medical treatment.<sup>38</sup> Surgical correction options are levator aponeurosis advancement or frontalis suspension, and levator function determines the operation choice.<sup>8</sup>

### Third Cranial Nerve Palsy

The third nerve can be damaged by trauma, ischemia, infection, tumor, or compression, causing ptosis and diplopia.<sup>39</sup> Congenital palsies are rare and usually do not cause diplopia.<sup>40</sup> Acquired palsies have varying degrees of nerve weakness and levator function and can be temporary. *Aberrant regeneration* of the third nerve often develops during recovery, resulting in gaze-evoked lid elevation.<sup>41,42</sup> Diplopia is generally more bothersome to patients than ptosis. After allowance for adequate time (6–12 months) for spontaneous recovery, strabismus surgery is performed before ptosis repair.<sup>39</sup> The ptotic eyelid can be elevated with a frontalis sling or levator aponeurosis advancement.





**Fig. 12.4.5 Myasthenia Gravis.** (A) Severe bilateral ptosis. (B) Improved bilateral ptosis after administration of Tensilon (edrophonium chloride 10 mg/mL).



**Fig. 12.4.6 Horner's Syndrome.** The right side is affected with ipsilateral upper eyelid ptosis and pupillary miosis. Note that the patient is elevating the right brow in attempt to compensate for the ptosis.

### Horner's Syndrome

Horner's syndrome is caused by sympathetic denervation to the face. Patients have ptosis, lower lid elevation, miosis, and ipsilateral facial anhidrosis. Ptosis results from denervation of Müller's muscle and thus is a *mild ptosis with preserved levator function* (Fig. 12.4.6). Heterochromia may be present with congenital Horner's syndrome. The ipsilateral iris is lighter.<sup>43</sup>

Pharmacological testing can diagnose and localize the Horner's lesion. Traditionally cocaine drops were used.<sup>44</sup> They have been replaced largely by apraclonidine, whose  $\alpha_1$  stimulation dilates the Horner's pupil and elevates the ptotic eyelid.<sup>45</sup> Hydroxyamphetamine stimulates norepinephrine release at the neuromuscular junction, reversing the signs of preganglionic Horner's.<sup>46,47</sup> Ptosis repair is indicated for visually significant ptosis or cosmesis. Levator resection and posterior Müllerectomy are both effective.<sup>48</sup>

### Myogenic Ptosis

#### Chronic Progressive External Ophthalmoplegias

Chronic progressive external ophthalmoplegia (CPEO) is a rare progressive myopathy presenting with symmetrical bilateral ptosis in early adulthood (Fig. 12.4.7) and later onset severe ophthalmoplegia.<sup>49</sup> Defects in mitochondrial function are inherited in mitochondrial, autosomal dominant, or autosomal recessive patterns.<sup>50</sup> Systemic involvement variants are termed "CPEO plus" syndromes.<sup>51</sup> Kearns-Sayre syndrome includes pigmentary retinopathy and cardiac conduction defects.<sup>52</sup> All patients with ptosis and



**Fig. 12.4.7 Chronic Progressive External Ophthalmoplegia (CPEO).** Severe bilateral ptosis with extraocular motility deficits. Note that the patient elevates both brow well, making frontalis suspension a possible surgical option.

motility defects should be referred for neurological evaluation. Muscle biopsy can confirm the diagnosis. Ptosis repair by frontalis suspension is appropriate only when vision becomes impaired. Additional surgery to elevate the lower lid is often needed to prevent dryness, as patients often have a weak orbicularis and poor Bell's reflex.<sup>8</sup>

### Oculopharyngeal Dystrophy

Oculopharyngeal dystrophy (OPD) is an autosomal dominant, progressive myopathy, predominantly found in patients of French Canadian ancestry. It presents in the fifth decade with symmetrical bilateral ptosis, dysphagia, and proximal limb weakness.<sup>53</sup> Abnormal filamental internuclear aggregates impair muscle function.<sup>54</sup> Ptosis repair by levator aponeurosis advancement is successful early in the disease course. To prevent a second operation, frontalis sling surgery should be considered earlier than usual for other types of ptosis.<sup>8</sup>

### Myotonic Dystrophy

Myotonic dystrophies are characterized by myotonia, the inability to relax muscles after sustained contraction. Myotonic dystrophy type 1 is an autosomal dominant, progressive myopathy presenting at any age and has increased severity in each successive generation.<sup>55</sup> Most patients present in the second to fourth decade with symmetrical bilateral ptosis, temporal wasting, meibomian gland dysfunction, Christmas tree cataracts, frontal alopecia, and distal limb weakness.<sup>50,55</sup> Abnormal RNA transcripts are toxic to muscle function.<sup>55</sup> Like CPEO, ptosis repair by frontalis sling is helpful early in the disease course. Facial weakness complicates ptosis repair both due to dryness and frontalis weakness limiting sling utility. Surgical ptosis repair may not be feasible in more advanced disease.

### Posttraumatic Ptosis

Levator muscle trauma can cause weakening. Trauma includes eyelid injuries and traction on the levator aponeurosis. Levator muscle injuries should be repaired.<sup>8</sup> Postoperative ptosis after modern anterior segment surgery is thought to be due to stretching of the levator aponeurosis.<sup>56</sup> Repetitive trauma from hard contact lens placement and wear is also associated with aponeurotic ptosis and Müller's muscle fibrosis.<sup>57,58</sup>

## CLINICAL EVALUATION AND PREOPERATIVE CONSIDERATIONS

During history taking and the physical examination, your goal is to discern three key pieces of information: type of ptosis, treatment plan, and factors that modify the treatment plan. For all patients, inquire about the onset and progression of ptosis, measure the *eyelid vital signs*, and take preoperative photographs.

### History and Examination

#### Adults

First determine whether the patient has common *acquired involutional ptosis*. Gradual progression makes it hard to determine the exact onset. Reviewing old photographs is helpful to document progression. Characteristics suggesting *unusual adult ptosis* include sudden onset, family history,

### BOX 12.4.2 Estimating the Amount of Resection for Simple Congenital Ptosis<sup>8</sup>

#### Levator Function Technique

##### Levator Function

2–3 mm (poor)  
4–5 mm (poor)  
6–7 mm (fair)  
8–9 mm (good)  
10–11 mm (good)

##### Intraoperative Lid Height

At upper limbus  
1–2 mm overlap  
2 mm overlap  
3–4 mm overlap  
5 mm overlap

#### MRD<sub>1</sub> Technique

##### Preoperative MRD<sub>1</sub>

3–4 mm (mild ptosis)  
2–3 mm (moderate ptosis)  
1–2 mm (marked ptosis)  
0–1 mm (severe ptosis)

##### Amount of Resection

10–13 mm  
14–17 mm  
18–22 mm  
>23 mm

diplopia, variable lid position, and associated facial movement problems.<sup>8</sup> Document the subjective effect of ptosis on the patient's vision. Visual field testing, with the eyelids relaxed and then taped open, documents vision improvement in the superior visual field.

#### Children

First determine whether the child has *simple congenital ptosis*. The ptosis will have been present since birth and does not progress. Assess for any characteristics of *unusual childhood ptosis*, including family history, developmental delay, or abnormal facies suggesting presence of a syndrome, extreme variation in ptosis throughout the day, and if the lid changes position with chewing or sucking.<sup>8</sup> Determine whether the child has associated ocular problems by measuring visual acuity and motility.

### Formulating a Treatment Plan

#### General Considerations

In all patients, ptosis repair surgery should be avoided if there is an increased risk for postoperative exposure keratopathy. Cautionary factors include poor tear film, corneal epitheliopathy, poor Bell's phenomenon, facial nerve weakness, or prior ptosis repair surgery. The ocular surface should be treated maximally before surgery. If vision is impaired, a limited lid lift can be performed.

The type of ptosis and *levator function* determine the best choice of surgery. Levator muscle shortening is used to correct ptosis with moderate to normal levator function. Ptosis responsive to phenylephrine eye drops can be corrected with a posterior approach Müller's muscle conjunctival resection.<sup>4,48,59</sup> Frontalis suspension procedures are used to correct ptosis with poor levator function and adequate frontalis function. Autologous fascia lata or silicone rod sling material can be used.<sup>60</sup>

The surgical incision should be located at the present or desired lid crease. For unilateral surgery, the lid crease should match the crease height of the nonoperative lid. For weak creases, the crease can be placed at the superior border of the tarsus.

Adults with dermatochalasis or brow ptosis may need additional procedures concurrent with ptosis repair surgery. Children with amblyopia need surgery performed sooner. Otherwise, surgery can be deferred until age 3–5, when more accurate levator function measurement is possible. For *simple congenital* ptosis with levator function of at least 3 mm, the amount of levator resection can be estimated based on levator function or preoperative MRD<sub>1</sub> (Box 12.4.2).<sup>8</sup>

Overall medical health of all patients should be assessed, and your surgical outcome expectations should match the patient or parental expectations.

### SURGICAL CORRECTION OF PTOSIS

#### Anesthesia

Ptosis repair is ideally performed under local anesthesia with light intravenous sedation. A minimal volume (1–1.5 mL per eyelid) of subcutaneous 2% lidocaine with 1:100 000 epinephrine and 0.75% bupivacaine provides adequate anesthesia for most patients. General anesthesia is used for young children and apprehensive adults.

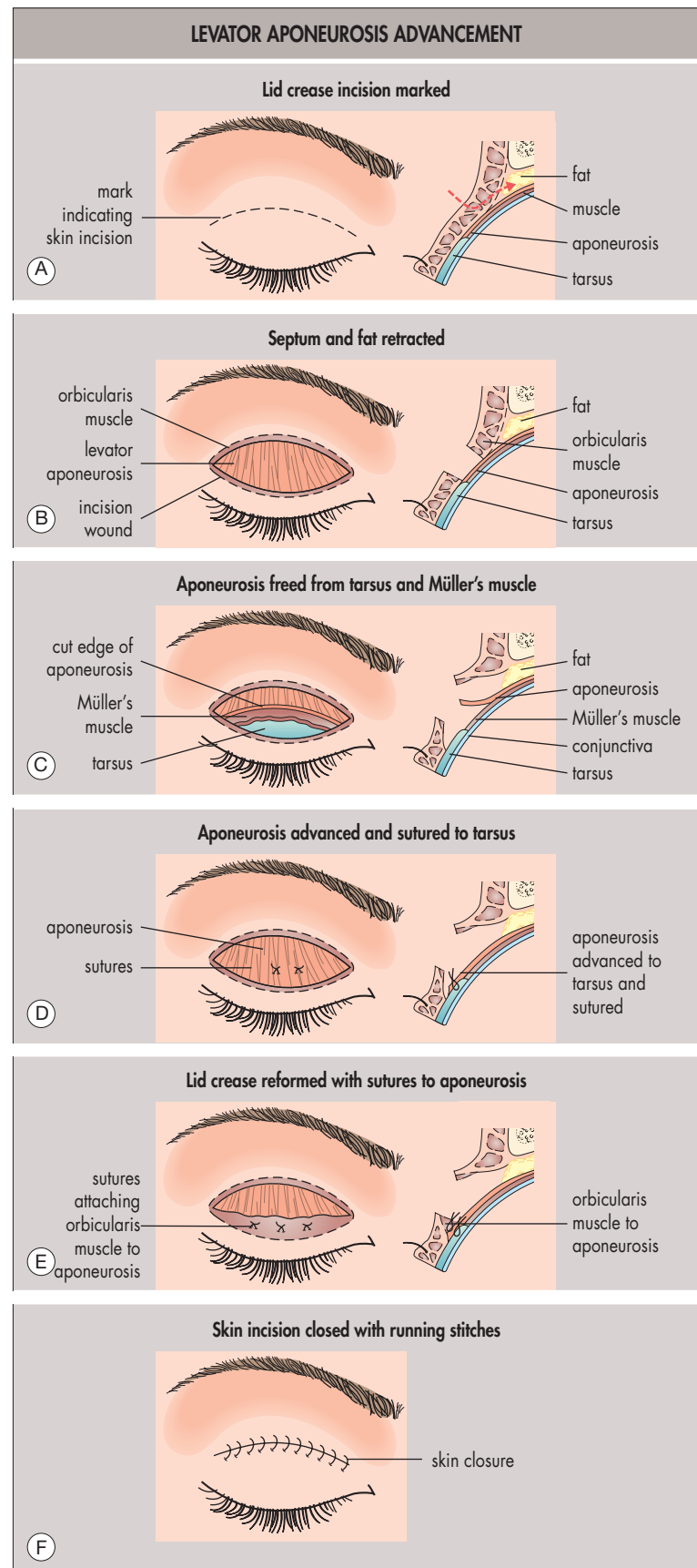


Fig. 12.4.8 Key Steps in the Levator Aponeurosis Advancement Operation.

#### Levator Aponeurosis Advancement

**Patient preparation:** Mark the planned upper eyelid incision (Fig. 12.4.8A), give subcutaneous local anesthetic, and perform a full-face surgical wash.

**Skin incision and identification of the levator aponeurosis:** After making a skin incision at the marked crease, incise and dissect the orbicularis superiorly off the septum. Maintain hemostasis throughout. Open the septum



and dissect preaponeurotic fat from the underlying levator (Fig. 12.4.8B). *Dissection of the levator aponeurosis:* The levator is disinserted from anterior surface of the tarsus and separated from the underlying Müller's muscle by sharp and blunt dissection (Fig. 12.4.8C). *Levator aponeurosis advancement:* Place partial thickness 5–0 Prolene sutures in the central tarsus to attach the levator aponeurosis to the tarsus (Fig. 12.4.8D). *Intraoperative adjustments:* Sit the patient upright to assess lid height, contour, and symmetry between both sides, aiming for 1 mm of overcorrection. Adjust the suture position as necessary.

*Closure:* 6–0 Prolene is used in adults and 6–0 chromic suture is used in children. Reform the lid crease by attaching the skin or orbicularis to the underlying levator aponeurosis (Fig. 12.4.8E). The skin is closed with a running suture (Fig. 12.4.8F).

*Postoperative care:* Ice packs are used for 48 hours postoperatively to decrease bruising and swelling. Topical ophthalmic antibiotic ointment is placed on sutures and in the eyes for 1 week. Prolene sutures are removed 5–7 days after surgery.

## Frontalis Suspension

*Patient preparation:* Children are placed under general anesthesia. Mark the planned lid crease incision (Fig. 12.4.9A). Mark three 4-mm forehead incisions, including at the superior brow slightly medial to the medial limbus and slightly lateral to the lateral limbus and 1 cm above the brow in line with the pupil (Fig. 12.4.9A). For autologous fascia lata grafts, mark a line from the lateral femoral condyle to the anterior iliac crest. Administer local anesthetic and perform a full-face wash and leg wash if necessary. Autologous fascia lata will need to be harvested.<sup>61</sup>

*Skin incisions:* Use a 15 blade to make stab incisions down to the periosteum at the forehead marks (Fig. 12.4.9B). Make an incision at the marked lid crease (Fig. 12.4.9B). Identify the levator and expose the tarsus using the same technique as in the levator advancement surgery. Maintain hemostasis throughout the procedure with bipolar cautery. *Anchoring the implant:* Attach the sling to the tarsus with partial thickness 5–0 Mersilene sutures (Fig. 12.4.9C). *Suspending the lid:* Thread the sling onto a Wright needle. Pass each end of the sling through the skin crease incision, under the orbital septum, superficial to the orbital rim periosteum, and out the brow wounds. Next pass each end of the sling from the brow incision to the central forehead incision (Fig. 12.4.9C and D).

*Lid crease closure:* Form a lid crease by suturing the skin edges to the top of the tarsus with interrupted 7–0 Vicryl sutures, and close the skin with running 6–0 chromic suture (Fig. 12.4.9C and E). *Lid height adjustment:* Adjust tension on the sling ends, placing the lid margin at the limbus with appropriate contour. Join the ends of the sling with 5–0 Mersilene suture for fascia or a silicone Watzke sleeve for silicone rods (Fig. 12.4.9D). *Forehead closure:* Close the skin with 6–0 chromic suture (Fig. 12.4.9E).

*Postoperative care:* Topical ophthalmic antibiotic ointment is placed along the sutures and in the eyes for 1 week. Adults may use ice packs for 48 hours after surgery to decrease bruising and swelling.

## Complications

Careful surgical technique will minimize hemorrhage, infection, and vision loss. Patients should watch for the eyelids being swollen shut, increased pain, or vision loss and should be given an emergency number to call.

Careful intraoperative adjustments will provide the best possible symmetry of lid height, contour, and lid crease position between the two sides. Thorough preoperative evaluation and appropriate patient selection will minimize postoperative ocular surface problems.

### Undercorrection

Persistent ptosis is common with 10%–20% of patients being undercorrected.<sup>62</sup> Lid position should be re-evaluated 3–4 months postoperatively, allowing for adequate healing. Revision surgery is indicated if the ptosis remains visually significant.

### Overcorrection

Mild overcorrection can be improved by performing eyelid stretching exercises. Instruct the patient to close the eye, pull the eyelid down, and try to open the eye. Exposure keratitis can occur due to lagophthalmos, poor blink, or poor Bell's phenomenon. Medical treatments include frequent lubricating eyedrops during the daytime, nightly lubricating ophthalmic ointment, and punctal plug placement. Surgical correction is indicated for persistent overcorrection or keratitis.

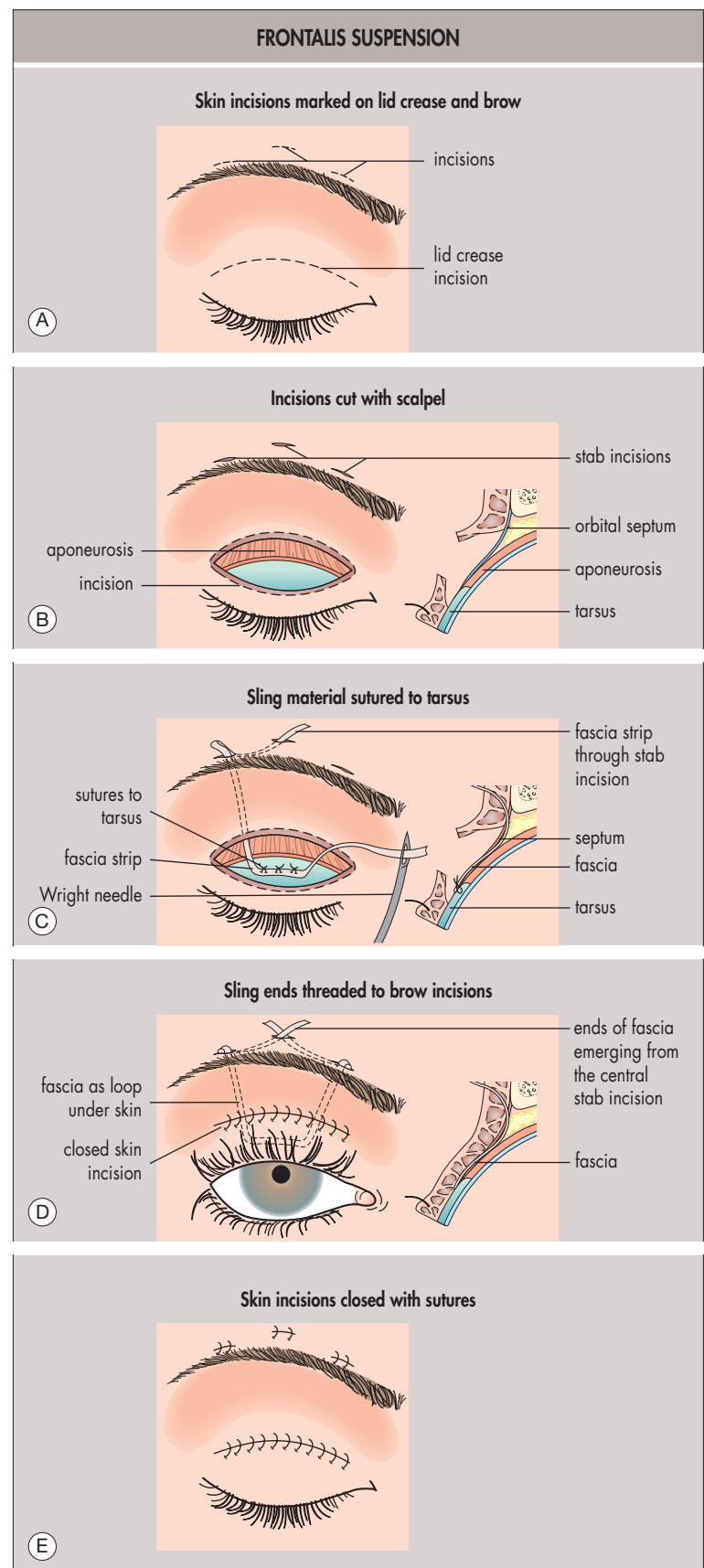


Fig. 12.4.9 Key Steps the Frontalis Suspension Operation.

## Changes in Astigmatism

In general, children do not have significant changes in astigmatism up to 3 years after surgery but must be monitored closely for development of amblyopia.<sup>19,63</sup> Most adult patients have short-term changes in corneal astigmatism for up to 3 months after ptosis repair surgery.<sup>64,65</sup> At 1 year, remaining changes are not subjectively visually significant.<sup>66</sup> It is important to discuss a possible refractive change with patients preoperatively.



## OUTCOME

Rare progressive conditions, such as CPEO and muscular dystrophy, may require reoperation as disease progresses. Most patients with *common ptosis* have improved vision and stable eyelid position after ptosis repair surgery.

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# Entropion

James W. Gigantelli

## 12.5

**Definition:** Entropion: a commonly encountered inward rotation of the tarsus and eyelid margin (Fig. 12.5.1).

### Key Features

- Symptoms and signs include ocular foreign body sensation, secondary blepharospasm, ocular discharge, epiphora, superficial keratopathy, and corneal scarring.
- Natural course is often progressive; early signs and symptoms may be intermittent.
- Numerous corrective techniques for this eyelid malposition are reported; many reflect the failure of earlier practitioners to appreciate this condition's pathophysiology.
- Multifactorial pathogenicity, including tarsotendinous instability, tarsoligamentous laxity, capsulopalpebral fascia dysfunction, preseptal orbicularis muscle override, axial position of the globe, and tarsoconjunctival foreshortening.
- Surgical goals are to normalize eyelid function and appearance by determining the active pathophysiological factors and addressing their direct surgical correction.

### INTRODUCTION

Early procedures to correct entropion can be categorized as vertically shortening the anterior lamella (skin and orbicularis muscle), vertically lengthening the posterior lamella (tarsus and conjunctiva), and/or controlling lamellar rotation. Procedures involving horizontal eyelid tightening were popularized by Fox, Bick, and others. Wies<sup>1a</sup> described a procedure utilizing full-thickness blepharotomy and eyelid margin rotation. Despite the



**Fig. 12.5.1 Right Lower Eyelid Entropion.** Note the inward rotation of the tarsal plate about the horizontal axis and resultant contact between the eyelid mucocutaneous junction and ocular surface. Multiple anatomical defects may be contributing to the eyelid presentation.

nonphysiological basis of this procedure, it gained wide acceptance due to its technical ease.

The mid-twentieth century heralded an anatomical approach to entropion repair. In 1963 DeRoeth<sup>1b</sup> and Jones et al.<sup>2</sup> separately identified the lower eyelid retractor system as pivotal in acquired entropion development. Jones et al.<sup>3</sup> also described surgical correction via lower eyelid retractor repair. Lower eyelid retractor microanatomy and physiology were further refined by Hawes and Dortzbach,<sup>4</sup> Goldberg et al.,<sup>5</sup> and others.<sup>6,7</sup> Orbicularis muscle functions in acquired and congenital entropion were clarified by Dagleish and Smith<sup>6</sup> and Tse et al.,<sup>8</sup> and tarsal plate and canthal ligament physiologies were advanced by Bengner and Musch,<sup>7</sup> Shore,<sup>9</sup> and Liu and Stasior.<sup>10</sup> Finally, the importance of tarsoconjunctival support in entropion was contributed by Shorr et al.<sup>11</sup> and Baylis and Hamako<sup>12</sup> and led to improved posterior lamellar substitutes and grafting techniques by Swamy<sup>13</sup> and others.<sup>14</sup>

### PREOPERATIVE EVALUATION AND DIAGNOSTIC APPROACH

A complete ocular history, including all prior eyelid procedures, and physical examination are essential. The general medical history and physical examination may be critical in uncovering systemic manifestations predisposing to entropion development.

### The Capsulopalpebral Fascia

Capsulopalpebral fascia dysfunction is central to the evaluation of congenital and acquired entropion (see Box 12.5.1 and Chapter 12.1). In cases in which the fascia clinically appears disinserted or dehiscenced from the inferior tarsus, histological observations disclose the capsulopalpebral fascia to sometimes be attenuated or only partially dehiscenced.<sup>15</sup> Clinical observations that identify lower lid retractor dysfunction include a higher eyelid resting position of the lid margin in primary gaze and an increased ability to passively distract the eyelid upward. Although some authors have stated that capsulopalpebral fascia dysfunction can result in a reduced vertical eyelid excursion, Bengner and Musch found normal lower lid excursion similar to the upper eyelid excursion observed in patients with aponeurogenic blepharoptosis.<sup>7</sup>

#### BOX 12.5.1 Preoperative Assessment of Entropion

##### Assessment of Capsulopalpebral Fascia Laxity

- Higher eyelid resting position in primary gaze
- Increased passive vertical eyelid distraction
- Increased depth of inferior conjunctival fornix
- Presence of a white infratarsal band

##### Assessment of Horizontal Eyelid Laxity

- Enhanced distraction of the eyelid from globe

##### Assessment of Relative Enophthalmos

- Exophthalmometry

##### Assessment of Preseptal Orbicularis Muscle Override

##### Assessment of Posterior Lamellar Support

- Vertical height of tarsal plate
- Presence of cicatrizing conjunctival disease

##### Assessment of Marked Orbital Fat Prolapse



In cases of retractor dysfunction, the fornix depth often increases. This can be measured against the contralateral fornix depth in unilateral entropion or against a normal inferior central fornix depth of 11 mm.<sup>16</sup> In some cases, a white band, representing the disinserted edge of the capsulopalpebral fascia, can be observed beneath the palpebral conjunctiva.

## The Tarsus and Canthal Ligament

Some studies suggest that age-related horizontal lower lid laxity occurs especially in patients who have chronic entropion. Histopathological studies of eyelids manifesting entropion demonstrated collagen degradation and loss of elastic fibers affecting multiple eyelid tissues including the tarsus.<sup>17,18</sup> This laxity often results from stretching of the lateral canthal ligament.

## Enophthalmos

Another determinant of the appositional pressure between globe and eyelid is the relative position of the globe. Bick demonstrated that entropion could be temporarily corrected by the intraconal injection of 2–4 mL of saline. Several studies have demonstrated reduced axial globe length as a factor predisposing to the development of involutional entropion.<sup>19,20</sup>

## Orbicularis Muscle

Several investigators have demonstrated a superior migration of the preseptal orbicularis subunit toward inferior tarsal margin.<sup>6,21</sup> It is unclear whether this muscular bunching is a primary phenomenon or an epiblepharon. Clinical evaluation for preseptal orbicularis override is subjective and should be carried out with the eye in primary gaze position, after a spontaneous blink, and following forceful eyelid closure.

## The Posterior Lamella

Entropion can be precipitated by the reduction of tarsoconjunctival vertical height. This can occur in either the presence (cicatricial entropion) or absence of cicatrizing conjunctival disease. Age-related decrease in the vertical dimension of the tarsal plate and a reduced tarsal height associated with involutional entropion have been documented.<sup>6,22</sup>

The majority of cicatricial entropion cases involve trachoma, Stevens–Johnson syndrome, ocular cicatricial pemphigoid, chronic meibomian gland inflammation, chemical and radiation injury, or postoperative fibrosis. Additional diagnostic considerations include sarcoidosis, atopic keratoconjunctivitis, ocular rosacea, toxic epidermal necrolysis, membranous conjunctivitis, herpes zoster ophthalmicus, progressive systemic sclerosis, dysthyroidism, graft versus host disease, prostaglandin associated orbitopathy, and neoplasm. Patients with progressive processes require preoperative and perioperative immunomodulation to suppress their disease activity.<sup>23,24</sup> When the primary process is uncertain, a diagnostic evaluation, including possible conjunctival biopsy, is indicated. Kemp and Collin<sup>25</sup> offered a grading system for cicatricial change. This system focuses on the position of the meibomian gland orifices, conjunctivalization of the eyelid margin, the position and orientation of the cilia, assessment of tarsal plate structure, keratinization of the palpebral conjunctiva, assessment of posterior lamellar scarring, and symblepharon formation.

## Other Factors

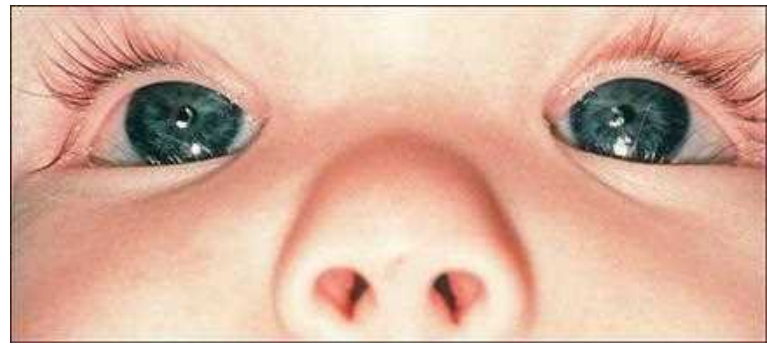
Profoundly prolapsing orbital fat has been suggested as a risk factor for lower eyelid entropion. Bartley et al.<sup>26</sup> reported entropion in pediatric patients manifesting morbid obesity or facial dysmorphism. Carter et al.<sup>27</sup> reported excessive lower eyelid fat prolapse associated with entropion in Asian patients.

## DIFFERENTIAL DIAGNOSIS

Epiblepharon, distichiasis, trichiasis, and eyelid retraction may be confused with entropion. These clinical entities arise from different pathophysiologies, follow a different clinical course, and necessitate different therapies.

## Epiblepharon

In epiblepharon, a horizontal fold of redundant pretarsal skin and orbicularis muscle extends beyond the eyelid margin and compresses the eyelashes against the globe (Fig. 12.5.2). The condition is usually bilateral,



**Fig. 12.5.2 Epiblepharon.** Note the bilaterality, loss of the lower eyelid skin crease, and overriding skin fold. Normal rotational orientation of the tarsal plate distinguishes this condition from entropion.

observed shortly after birth, commonly involves the lower lid, and may be exacerbated in downgaze. Although both epiblepharon and congenital entropion result from lower eyelid retractor defects, their clinical presentation and course contrast sharply.<sup>28</sup> Nearly 80% of children experiencing epiblepharon have no ocular complaints.<sup>29</sup> The condition frequently resolves with normal facial growth. Treatment is reserved for symptomatic cases. Reformation of the lower eyelid crease through the removal of a horizontal skin–orbicularis muscle ellipse with suture fixation to the anterior surface of the capsulopalpebral during wound closure is curative.<sup>28,30</sup>

## Trichiasis

Trichiasis is an acquired condition in which cilia arise from their normal anterior lamellar position but are misdirected toward the ocular surface. This usually results from inflammation-induced scarring of the eyelash follicles. Treatment is usually based on the number, distribution, and severity of the misdirected cilia. Treatment modalities include mechanical epilation, electrolysis, radiofrequency ablation, laser photoablation, cryotherapy to the posterior eyelid lamella, anterior eyelid lamellar recession, and surgical excision of the eyelash bulbs.

## Congenital Entropion

True congenital lower eyelid entropion is rare, and its hypothesized pathophysiology is derived mostly from intraoperative observation.<sup>26,28,30</sup> Congenital lower eyelid entropion is believed to occur when both the anterior and posterior attachments of the capsulopalpebral fascia are dysfunctional. This accounts for the poorly formed lower lid skin crease in addition to the inward tarsal rotation in affected children. Unlike epiblepharon, congenital entropion does not resolve spontaneously and requires prompt surgical intervention.

The horizontal tarsal kink syndrome is a rare form of congenital upper eyelid entropion. In this condition, a right-angled inward rotation of the tarsal margin causes constant apposition of the eyelid margin to the ocular surface and results in early, severe corneal complications. The cause of this variant remains unknown. The potential for severe corneal complications requires early recognition and prompt therapy. Surgical interventions include tarsal eversion sutures, transverse blepharotomy, and resection of the tarsal kink with eversion sutures.<sup>31</sup>

## ALTERNATIVES TO SURGERY

Patients who have entropion should be evaluated as possible surgical candidates. The extent of ocular findings, patient's age, and systemic comorbidities must be considered when devising a treatment plan. Medical therapy is appropriate before surgical intervention and for patients who refuse or are too ill to undergo surgery. Symptoms may be ameliorated through the use of artificial tears, lubricating ointments, or a bandage soft contact lens. Temporary eyelid eversion can sometimes be obtained by repositioning the anterior lamella away from the eyelid margin with tape.

## Quickert–Rathbun Sutures

Eyelid margin rotation and lamellar migration can be corrected with placement of several well-spaced and tightly tied full-thickness sutures.<sup>32</sup> Chromic gut, nylon, and silk sutures create equivalent scarring, but silk and nylon sutures incite epithelial ingrowth along the suture tract.<sup>33</sup> Consensus is that entropion repair by everting sutures lacks permanence with

recurrence rates nearing 50% by 2 years.<sup>32,34</sup> This shortcoming may nevertheless be acceptable in patients who are poor surgical risks or for whom a temporary repair is adequate.

## Botulinum Toxin

Office-based subcutaneous or intramuscular injection of the nasal and temporal lower eyelid with botulinum toxin may provide temporary entropion correction.<sup>35</sup> Chemodenervation is noted within 3–5 days of administration and may last up to 6 months. Injections in the medial lower eyelid may be complicated by temporary medial ectropion, punctal eversion, or inferior oblique muscle paresis.

## ANESTHESIA

Entropion surgery is an outpatient procedure usually performed under local anesthesia. Monitored anesthesia care, which combines intravenous sedation with local analgesia, may be performed instead. Pediatric patients usually require general anesthesia.

A 1:1 dilution of lidocaine (lignocaine) 2% with 1:100 000 epinephrine (adrenaline) and bupivacaine 0.75% combined with hyaluronidase (150 units per 10 mL of injectable anesthetic) provides excellent anesthesia. Hyaluronidase enhances diffusion of the anesthetic solution, thereby reducing tissue distortion and preserving intraoperative tissue anatomy. When coadministered with epinephrine, it does not reduce the anesthetic duration of action.

Sodium bicarbonate (1 mL of 1 mEq/mL [1 mmol/mL] solution per 10 mL of injectable anesthetic) may also be added to local anesthetic solutions to decrease pain on injection.<sup>36</sup> Tissue infiltration or a regional nerve block is best performed with a 27- or 30-gauge hypodermic needle. Epinephrine-induced vasoconstriction requires up to 10 minutes, so tissue infiltration should be performed before the surgical skin preparation and patient draping.

## GENERAL TECHNIQUE

The advances and improved surgical success in entropion management occurred through the appreciation of its pathophysiological and anatomical basis.<sup>37</sup> The surgical procedure as planned entails the correction of each underlying defect. Frequently entropion is multifactorial in origin and requires the correction of a combination of defects. Several authors have demonstrated that a single entropion procedure performed universally provides insufficient short- and long-term results.<sup>38,39</sup> In broad terms, entropion surgery may include:

- Correction of capsulopalpebral fascia dysfunction.
- Reduction of horizontal lower eyelid laxity.
- Debulking of excessive lower lid fat.
- Prevention of preseptal orbicularis muscle shifting.
- Reconstruction of vertically foreshortened eyelid posterior lamellar tissue.

In cases of capsulopalpebral fascia dysfunction, the fascia must be vertically advanced or reattached to the inferior border of tarsus. Transcutaneous and transconjunctival approaches are described for this repair.<sup>38,40</sup> Both approaches can be combined with techniques to correct horizontal laxity, prolapsed orbital fat, and preseptal orbicularis muscle override. The transconjunctival approach readily lends itself to the synchronous placement of a posterior lamellar graft. Except in cases where posterior lamellar foreshortening exists as a causative factor, the surgical management of entropion whether by transcutaneous or transconjunctival approach has a success rate of 97% or greater.<sup>40–43</sup>

The capsulopalpebral fascia can be advanced to the inferior tarsal border with or without its separation from the orbital septum. Separation of the septum from the fascia allows broader fascial exposure and a reduced likelihood of entrapping orbital septum during the advancement.

Surgical correction of horizontal eyelid laxity addresses foreshortening by either resection of the tarsal plate or plication-resection of the lateral canthal ligament. Greater dysfunction appears to reside in the canthal ligament and its attachments rather than in the tarsal plate itself.<sup>9</sup> Reconstruction of the lateral canthal ligament is therefore preferred over purely tarsal resections performed in the central eyelid. This removes the dysfunctional canthal ligament and preserves the integrity of the relatively healthier tarsus. Orbicularis muscle dysfunction is corrected by creation of a fibrous barrier between the orbicularis muscle and deeper eyelid structures at the junction of the muscle's pretarsal and preseptal subunits. This can be

achieved through a cutaneous incision placed at this level, the stimulation of fibrosis through the use of sutures, or the extirpation of a preseptal muscular subunit.<sup>38</sup>

Progressive inflammatory processes such as ocular cicatricial pemphigoid, scleroderma, and sarcoidosis are likely to require local and/or systemic immunomodulators to stabilize the disease course before surgical intervention.<sup>24,44</sup> For certain disease states, manipulation of the eyelid posterior lamella may precipitate a local inflammatory exacerbation.<sup>45</sup> In such situations, deviation from direct correction of the pathophysiological defect may be appropriate. A modest advance of the capsulopalpebral fascia may suffice to correct mild to moderate "cicatricial" entropion and obviate the need for potentially dangerous surgical manipulation of the tarsus and conjunctiva.<sup>44</sup>

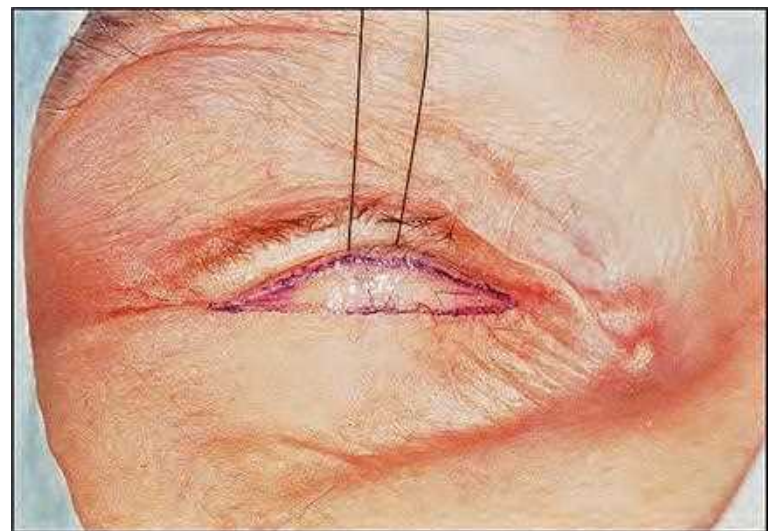
In most cases of tarsoconjunctival foreshortening, once the process is identified and optimal immunosuppression achieved, a posterior lamellar technique is performed. This may take the form of a tarsal out-fracture with marginal rotation or placement of a posterior lamellar graft. The transverse tarsotomy directly addresses those eyelid structures affected by the underlying disease process.<sup>46,47</sup> When manipulation of these layers is limited, the risks of avascular necrosis of the lid, cutaneous scarring, and levator aponeurosis damage are minimized.

The selection of an appropriate donor material is essential when posterior lamellar support is needed. Favored tissue should be autologous, epithelium covered, and semirigid. Materials utilized for tarsoconjunctival reconstruction or replacement have included tarsoconjunctival flaps and grafts, hard palate mucosa, nasal chondromucosa, and nasal mucoperiosteum. Although an autologous tarsoconjunctival composite flap or graft provides the most exact reconstruction, these tissues may be in short supply, especially if the primary disease process is either advanced or bilateral. The hard palate mucosa and nasal mucoperiosteum are the current alternative tissues of choice.<sup>14</sup> They are plentiful, easy to harvest, minimally resorptive, structurally similar to tarsus, and can be harvested repeatedly if necessary. Other materials that may be grafted to lengthen the tarsus include amniotic membrane, periosteum, temporalis fascia, banked sclera, irradiated homologous aorta, porous polyethylene, and polytef.<sup>11,12,48–51</sup>

## SPECIFIC TECHNIQUES

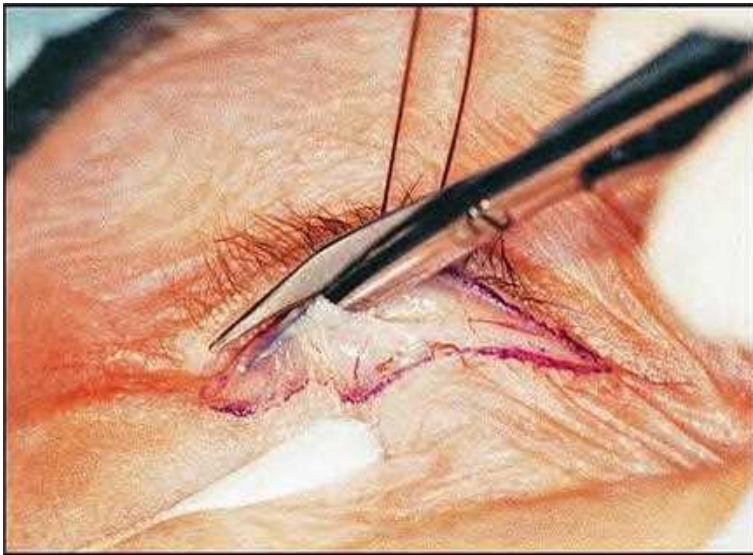
### Retractor Reattachment

In most cases of involutional entropion, retractor plication or reattachment effectively corrects the defect.<sup>52</sup> In patients without posterior lamellar foreshortening, a transcutaneous approach is appropriate. A 4–0 silk traction suture is passed horizontally through the central lower eyelid margin and clamped to the drape overlying the brow (Fig. 12.5.3). A cutaneous incision is made 4 mm inferior to the eyelid margin (or 2.5 mm inferior to the lower lid lashes). This extends from immediately lateral to the lacrimal punctum to beyond the lateral canthal angle. The orbicularis muscle is buttonholed at the junction of the pretarsal and preseptal subunits (see Chapter 12.1) and separated for the full length of the skin incision (Fig. 12.5.4). A myocutaneous flap is developed from the incision to the inferior orbital rim.

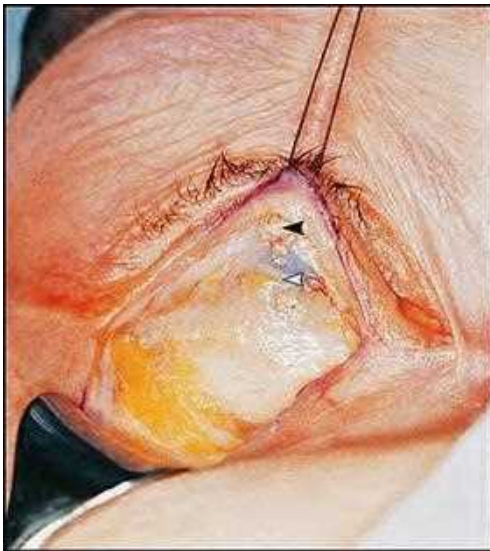


**Fig. 12.5.3** A Subciliary Incision Has Been Made Following the Placement of an Intramarginal 4–0 Silk Traction Suture.





**Fig. 12.5.4** Westcott Scissors Divide the Pretarsal and Preseptal Subunits of the Orbicularis Muscle.



**Fig. 12.5.5** Following Opening of the Orbital Septum, the Lower Eyelid Fat Is Retracted Inferiorly. The capsulopalpebral fascia (open arrow) appears disinserted from the inferior tarsus (closed arrow).

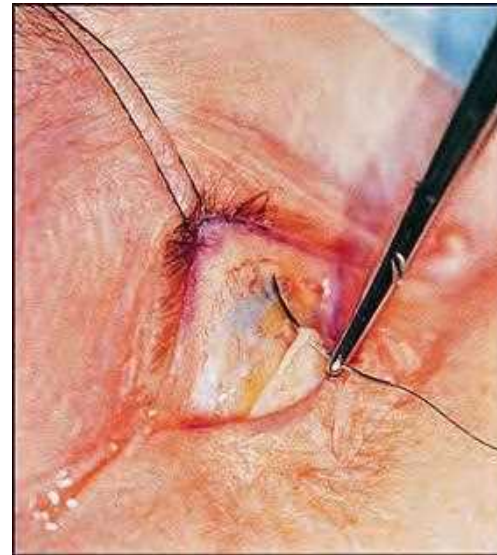
The “free edge” of the capsulopalpebral fascia is often visualized several millimeters inferior to the tarsal border. The orbital septum can be buttonholed 1 mm inferior to its fusion with the capsulopalpebral fascia and opened the horizontal length of the anterior lamellar incision. An important surgical landmark is the lower eyelid fat, which rests between the septum and fascia. The three lower lid fat pads may be dissected from the anterior surface of the capsulopalpebral fascia (Fig. 12.5.5). If necessary, profoundly prolapsed fat may be debulked.

The capsulopalpebral fascia is then advanced upward and reattached to the inferior tarsal border (Figs. 12.5.6–12.5.8). Fascial identification can be confirmed by grasping the tissue in toothed forceps and having the patient gaze inferiorly. When gross disinsertion is present, the fascia is advanced to the inferior tarsal border. In cases in which the fascia is attenuated but not disinserted, the fascia is surgically disinserted by the surgeon, a narrow horizontal strip excised, and the remaining fascia reattached to the inferior tarsal border. Reattachment to the tarsus is performed with several interrupted 6-0 Prolene sutures.<sup>53</sup>

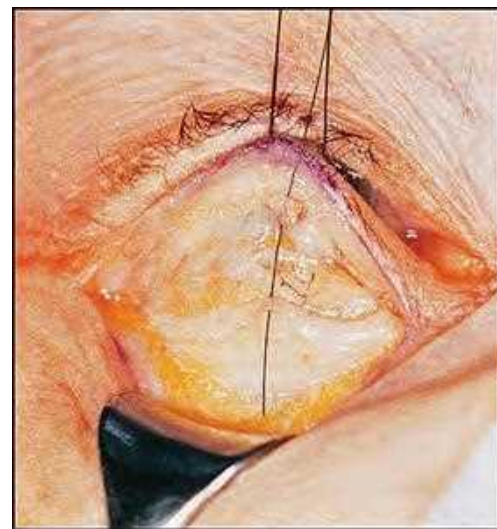
In patients demonstrating preseptal orbicularis muscle override, a 5–8 mm vertically wide horizontal strip of preseptal muscle is extirpated en bloc from the muscle's posterior surface (Fig. 12.5.9). The skin incision can be closed with a running 6-0 mild chromic or nylon suture. Topical antibiotic ointment is sufficient for postoperative infection prophylaxis.

### Lateral Tarsal Strip Procedure

A horizontal tightening of the lower lid may be combined with reattachment of the retractors or be done as a separate procedure (see Chapter



**Fig. 12.5.6** The Free Edge of the Capsulopalpebral Fascia Can Be Elevated Easily From the Underlying Conjunctiva. Vertical fascial advancement and reattachment to tarsus is performed following resuspension of the lateral tarsal strip.



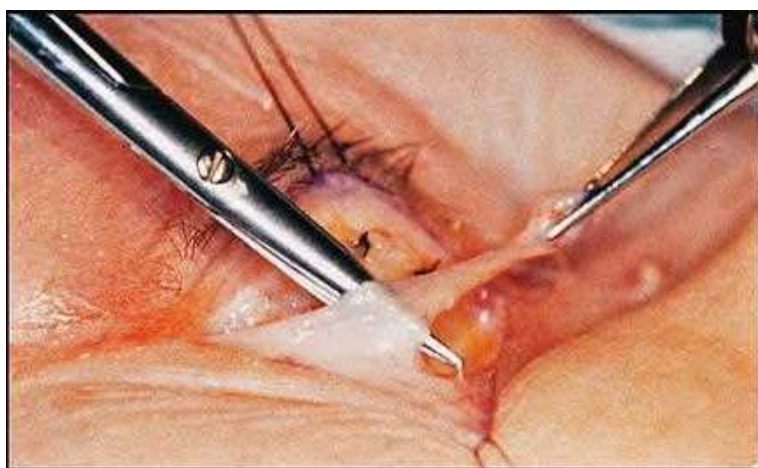
**Fig. 12.5.7** The Capsulopalpebral Fascia Is Advanced and Sutured to the Inferior Border of the Tarsal Plate. Care must be taken to obtain a solid purchase of the inferior tarsus and to avoid advancing the fascia superiorly along the tarsal anterior surface.



**Fig. 12.5.8** The Completed Lower Eyelid Retractor Advancement. Multiple point fixation with nonabsorbable suture ensures permanence.

12.6).<sup>54</sup> The tightening is best performed using a standard lateral tarsal strip technique.<sup>55</sup> A lateral canthotomy and inferior cantholysis of the canthal ligament are performed. Within the temporal eyelid, the anterior and posterior lamellae are separated from one another beginning at the gray line and extending across the anterior surface of the tarsus. The lid margin is then de-epithelized. The palpebral conjunctiva is disinserted from the inferior tarsal border to complete formation of the tarsal strip. The redundant tissues of the strip are determined by drawing the strip to the lateral orbital tubercle. The excess tissue is excised and the new lateral





**Fig. 12.5.9** A Strip of Preseptal Orbicularis Muscle Is Extirpated Using Westcott Scissors. Muscle manipulation predisposes to hemorrhage; complete hemostasis are essential.

border of tarsus is resuspended to periosteum at the lateral orbital tubercle with either two interrupted or a single horizontal mattress 4-0 gauge suture. Use of a small-radius, half-circle (P-2, S-2, or D-2) needle facilitates the periosteal anchor at the lateral orbital tubercle.

Meticulous hemostasis is established before closure. An absorbable 6-0 horizontal mattress canthopexy suture creates an acute canthal angulation and prevents imbrication of the upper lid over the temporal lower lid. To enhance esthetics, a small cutaneous triangle may be excised from the inferior wound margin lateral to the canthal angle. The lateral canthotomy is closed in a layered fashion. In some cases, Quickert-type lid sutures may enhance the marginal rotation.<sup>56-59</sup>

## Transverse Tarsotomy

In moderate cicatricial entropion, a posterior transverse tarsotomy with eyelid margin rotation provides excellent correction. A 4-0 silk traction suture is placed horizontally through the central eyelid margin and the lid everted over a Desmarres retractor. A transverse incision is created through the palpebral conjunctiva and tarsus using a scalpel. The tarsotomy should be made equal to or greater than 3 mm from the eyelid margin to avoid the marginal vascular arcade (Fig. 12.5.10). The marginal rotation is accomplished using double-armed 6-0 sutures at multiple sites along the eyelid. The suture is first passed in a horizontal mattress fashion through the anterior edge of the nonmarginal tarsal plate. Each arm of the suture is then passed through the tissues of the marginal strip between the planes of the tarsus and orbicularis muscle exiting the skin immediately anterior to the cilia. Sutures are then tied under appropriate tension to evert the margin. Prophylactic topical antibiotic ointment for 1 week is sufficient.

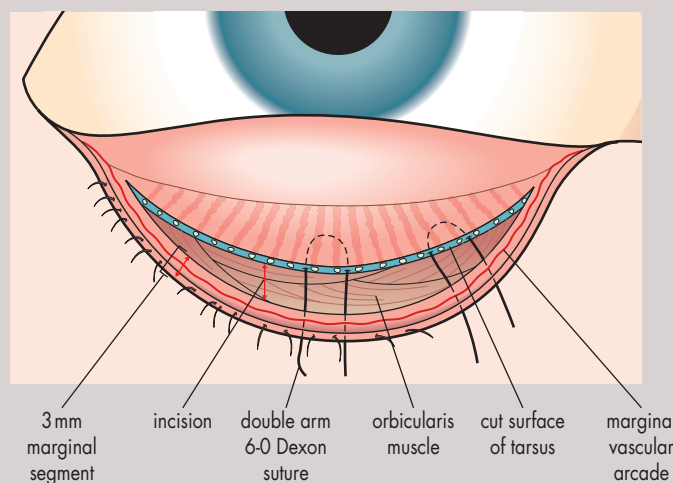
## Hard Palate Mucosal Graft

In severe cicatricial entropion, the posterior eyelid lamella often requires buttressing. After the nonmarginal tarsal plate is everted over a Desmarres retractor and the transverse tarsotomy is performed, a limited dissection is performed in the marginal strip between the planes of the tarsus and orbicularis muscle.

A hard palate graft may be harvested using a local anesthetic block of the greater palatine and nasopalatine nerves followed by diffuse submucosal infiltration. The mucosa is outlined with a marking pen and the palate incised with a scalpel. The graft is undermined with the scalpel or a sharp periosteal elevator. Avoiding the greater palatine foramen and palatine vessels minimizes bleeding. The palatal defect is not closed but may be covered with an acrylic retainer or the patient's upper dentures, if available.

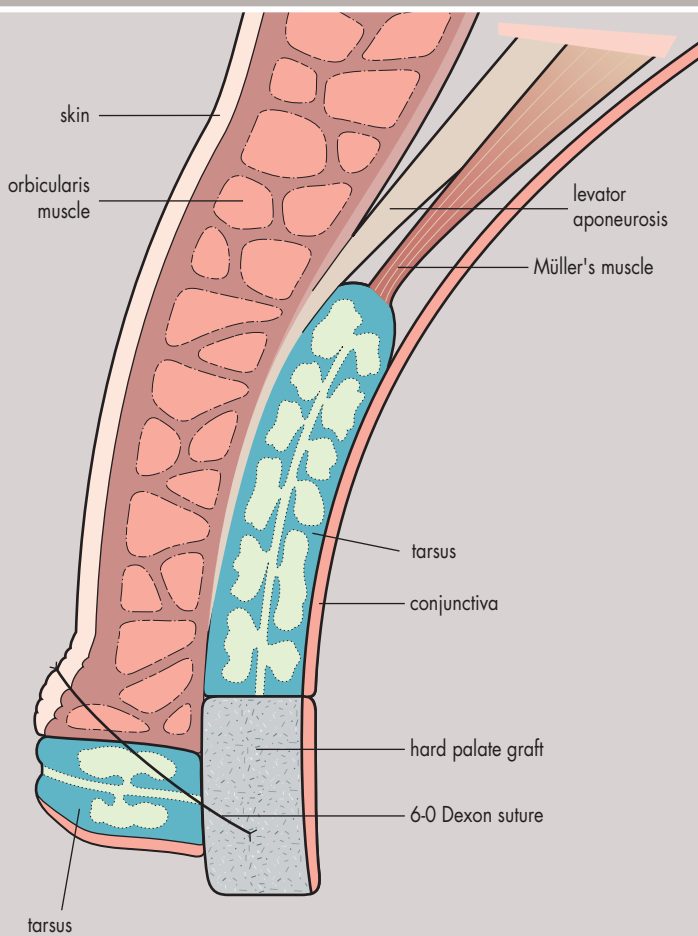
The graft is thinned of fatty tissue on its submucosal surface and secured in the posterior eyelid lamellar defect with 6-0 absorbable sutures along its nonmarginal and lateral borders (Fig. 12.5.11). The rotated marginal strip of the eyelid is then secured to the anterior surface of the graft with three double-armed sutures, as previously described for the transverse tarsotomy procedure. A Frost traction suture and pressure dressing are used for 5-7 days to immobilize the lid in a stretched position. Oral

## TRANSVERSE TARSTOMY OF POSTERIOR LAMELLA



**Fig. 12.5.10** The Transverse Tarsotomy of the Posterior Lamella Allows Rotation of the Marginal Eyelid Segment. Incision placement preserves the integrity of the marginal vascular arcade.

## BUTTRESSING THE POSTERIOR LAMELLA



**Fig. 12.5.11** Posterior Lamella Buttressing Is Accomplished Through a Hard Palate Graft. Graft bed preparation and marginal segment rotation are performed similarly as for posterior tarsotomy.

antibiotics are prescribed until removal of the dressing, after which topical antibiotic ointment is administered.

When hard palate grafts are placed in the upper lid, corneal protection by copious surface lubrication or a bandage contact lens is frequently necessary.

## COMPLICATIONS

Postoperative complications can be reduced through meticulous preoperative planning and intraoperative technique. The best way to prevent recurrent entropion is through the appropriate selection of surgical procedures. When entropion recurs during the early postoperative period, the patient should be re-evaluated for overlooked or undercorrected predisposing factors. Later recurrences may be due to progression of underlying pathophysiology. Recurrences in patients with cicatrizing conjunctival disease may be due to graft failure, graft contracture, or disease progression.

### Overcorrection

Overcorrection of the eyelid margin position may follow excessive advancement of the capsulopalpebral fascia, attachment of the fascia too high on the anterior tarsal surface, undercorrected horizontal eyelid laxity, and incorporation of the orbital septum in the advancement or surgical closure. Postoperative ectropion can also occur following unintended extirpation of the pretarsal orbicularis subunit or excessive vertical skin resection. If the ectropion is mild and tolerated by the patient, conservative management with time, warm compresses, and massage may suffice. When it is severe, transposition of a preseptal orbicularis strip closer to the eyelid margin or full-thickness skin grafting may be necessary.

### Hematoma

The risk of hematoma can be reduced by preoperative discontinuation of medications that impair platelet function and the clotting cascade. Meticulous hemostasis through intraoperative use of electrocautery is essential. Attention should be given to the lateral branches of the palpebral arcades following lateral cantholysis and to areas of extirpation of the preseptal orbicularis muscle. When eyelid hematomas occur, they are usually self-limiting and resolve with periodic warm compresses and observation.

Hemorrhage that occurs at a hard palate donor site usually originates from the greater palatine or nasopalatine artery. It can be controlled with digital pressure, submucosal epinephrine injection, conservative electrocautery, chemical cautery, cellulose or collagen sponge, periodontal putty, or a palatal stent.<sup>60</sup>

### Eyelid Retraction

Postoperative eyelid retraction usually results from excessive horizontal tightening of the tarsus or excessive vertical advancement of the capsulopalpebral fascia. It is also important that the lateral tarsal strip is reattached to Whitnall's lateral orbital tubercle rather than the lateral raphe of the orbicularis complex. An excessively shortened tarsal strip can be resuspended from either the superior crus of the lateral canthal ligament or a periosteal strip elevated from the lateral orbital wall.

### Exposure Keratopathy

Corneal epithelial damage can develop from postoperative lagophthalmos, exposed conjunctival sutures, lagophthalmos, and keratinized hard palate

grafts. This risk is higher following upper lid entropion repair. Postoperative lagophthalmos can result from excessive capsulopalpebral advancement, orbicularis extirpation, or skin excision. Treatment includes ocular surface lubricants, bandage soft contact lens, suture removal, or dermabrasion of the keratinized graft.

### Ptosis

Aponeurogenic ptosis can complicate the repair of cicatricial upper lid entropion. The posterior fibers of the levator aponeurosis attach to the inferior one-third of the tarsal plate's anterior surface. During posterior tarsotomy, it is important to avoid disrupting these fibers.

## OUTCOME

Advances in the understanding of entropion have provided surgeons with improved, more reproducible, and longer-lasting treatment options. A systematic approach to the evaluation and treatment of this condition ensures that patients will benefit from these therapeutic outcomes. Appropriate surgical procedure selection should result in the immediate correction of the eyelid malposition. Most patients report symptomatic relief as early as their first postoperative day. Except in cases of posterior lamellar foreshortening, surgical management of entropion has a success rate of 97% or greater.<sup>40</sup> When tarsoconjunctival contraction is present, surgical success still exceeds 90%. An exception occurs in ocular cicatricial pemphigoid, where lower success is predicted.<sup>25,46</sup>

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# Ectropion

*Robi N. Maamari, Steven M. Couch*

# 12.6

**Definition:** Ectropion is an outward rotation of the eyelid margin from the eye.

## Key Features

- Ectropion may result from progressive age-related eyelid laxity, vertical skin shortening, orbicularis muscle weakness, or mechanical force on the eyelid.
- Lower eyelid ectropion result in epiphora, palpebral and conjunctival surface irritation and keratinization, and corneal exposure with potential corneal ulceration and scarring.
- Surgical correction aims to re-establish proper eyelid margin apposition against the ocular surface.

## Associated Features

- Epiphora.
- Conjunctival erythema.
- Exposure keratopathy.
- Ocular surface pain.

## INTRODUCTION

Ectropion is an outward rotational displacement of the eyelid margin that is frequently encountered in clinical practice. This eyelid malposition most commonly affects the lower eyelid but can also occur in the upper eyelid. Clinically, it is important to identify the etiology of ectropion to properly select a surgical intervention that addresses the underlying anatomical defect.

## PREOPERATIVE EVALUATION AND DIAGNOSTIC APPROACH

A thorough ocular history should be taken before physical examination. The surgeon should specifically ask about a history of facial palsy, previous periocular surgery, and prior facial trauma. Common symptoms reported by patients with ectropion include eye irritation and redness caused by ocular surface exposure and tearing due to punctal malposition or laxity-induced lacrimal pump dysfunction. With long-standing ectropion, the exposed palpebral conjunctiva may become keratinized, leading to symptoms of chronic redness, discharge, and bleeding.

When performing the ophthalmic examination, it is important to carefully assess eyelid laxity, eyelid margin appearance, medial and lateral canthal integrity, orbicularis muscle tone, anterior and posterior lamellar characteristics, and lower eyelid retractor anatomy (Box 12.6.1).

## Eyelid Laxity Evaluation

The lower eyelid naturally apposes the globe when the eye is open and throughout the entire blinking cycle. When pulled downward and released, a normal eyelid quickly recoils back to its normal position against the globe. In the presence of diminished tone or excessive laxity, the eyelid recoils slowly or requires the eye to blink one or more times to return to position. If needed, a measurement of laxity can be taken between the ocular surface and the downward pulled eyelid (lower eyelid distraction

test). Normally, the eyelid cannot be distracted more than 6 mm from the ocular surface (Fig. 12.6.1).

## Medial Canthal Tendon Laxity

Lateral traction is applied to the lower eyelid and the total amount of inferior punctal displacement is measured. A shift in inferior punctal position by more than 1–2 mm with traction indicates medial canthal laxity. Rarely, patients with marked dehiscence may require tendon repair, a procedure that is difficult because of the lacrimal drainage system.

## Lateral Canthal Tendon Laxity

The normal lateral canthal angle maintains an acute confluence that is positioned 1–2 mm medial to the lateral orbital rim. Laxity is present when

### BOX 12.6.1 Preoperative Evaluation of Ectropion

Full ocular history

General ocular examination

Examination of specific eyelid changes

- Eyelid laxity
  - Horizontal eyelid laxity
  - Medial canthal tendon laxity
  - Lateral canthal tendon laxity
- Lacrimal puncta evaluation
- Anterior lamellae inspection
- Orbicularis muscle tone
- Eyelid masses
- Inferior eyelid retractor laxity



**Fig. 12.6.1 Lower Eyelid Distraction Test: The Lower Eyelid Is Pulled From the Globe and the Distance Between the Eyelid Margin and the Globe Can Be Measured.** This is an example of severe lower eyelid laxity.

the lateral canthus demonstrates medial displacement, rounding of the angle, or thinning of the canthal skin. Additionally, laxity is confirmed when medial eyelid traction displaces the canthus nasally by more than 1–2 mm.

### Lacrimal Puncta Evaluation

In the normal eyelid, puncta are not visible on passive external evaluation. Visualization of the puncta before eyelid distraction suggests medial eyelid ectropion. Chronic ectropion with punctal malposition can result in punctal stenosis or obliteration secondary to scarring.

### Anterior Lamellae Inspection

Vertical shortening of the lower eyelid anterior lamella with eversion of the eyelid margin can result from actinic skin damage, facial trauma, chronic eyelid malposition (involutional or paralytic), and prior surgical procedures including blepharoplasty. In mild cases, vertical tension lines in the eyelid skin can be visualized and manual elevation of the cheek skin improves the ectropion by diminishing the downward tension. Limitation of superior migration of the eyelid margin in upgaze and eversion of the margin when opening the mouth widely also indicate a shortage of skin in the anterior lamella.

### Orbicularis Oculi Muscle Tone

The resting orbicularis muscle tone allows the lower eyelid to remain well apposed to the ocular surface. Adequate muscle tone is also required for proper lacrimal pump function. Orbicularis muscle weakness is assessed during forced eyelid closure. Lagophthalmos results from the exaggerated horizontal eyelid laxity caused by orbicularis weakness. Additional signs of facial nerve palsy, including brow ptosis, diminished forehead rhytids, reduced nasolabial folds, and smile asymmetry should be evaluated.

### Eyelid Masses

Eyelid masses, such as neoplasms or cysts, can physically displace the lower eyelid margin as a result of both mass effect and the gravitational force on the mass shifting the eyelid margin down and away from the globe (Fig. 12.6.2). It is important to thoroughly inspect the conjunctival surfaces and fornices in addition to a careful examination of the anterior lamellar tissue for any cicatricial changes caused by local neoplastic infiltration.

### Lower Eyelid Retractor Dehiscence

Inspection of the posterior lower eyelids allows visualization of the relationship between the tarsal plate and the lower eyelid retractors. Laxity of the eyelid retractors may be associated with ectropion, especially in the

setting of severe horizontal laxity. Profound retractor attenuation may lead to excessive conjunctival redundancy and poor definition of the inferior fornix.

## DIFFERENTIAL DIAGNOSIS

### Involutional Ectropion

Involutional changes are the most common cause of ectropion and result from age-related laxity in the supporting structures of the lower eyelid (Fig. 12.6.3). It typically progresses from the medial eyelid and extends laterally based on the degree of lower eyelid retractor dehiscence and horizontal laxity. Initially, patients may only report epiphora due to the lower punctal eversion caused by early medial ectropion. Additional contributing structural changes include elongation of the tarsus, inferior displacement of the pretarsal orbicularis, and increased laxity of the medial and lateral canthal tendons.<sup>1</sup> As a result of the horizontal laxity and diminished pretarsal orbicularis support on the tarsal plate, preseptal orbicularis contraction predominantly acts on the inferior tarsal margin, exacerbating the eyelid eversion.<sup>2</sup> With progression, ocular exposure results in conjunctival inflammation and late-stage keratinization, tarsal thinning, eyelid margin thickening, and lagophthalmos—all of which contribute to worsening of the ectropion.

### Cicatricial Ectropion

Cicatricial ectropion is caused by scarring or vertical shortening of the lower eyelid anterior lamella due to previous trauma, eyelid and facial surgery, or a variety of actinic or infiltrative conditions (Fig. 12.6.4). Occasionally, acute entities causing cicatricial changes such as allergic blepharitis can be reversed with discontinuation of the offending agent or treatment with topical corticosteroids (Fig. 12.6.5). Cutaneous fibrosis and infiltration can be seen with skin malignancies and a wide variety of cicatrizing dermatological conditions. Suspicious lesions should be biopsied before eyelid surgery. Epidermal contraction can also be observed following long-standing involutional or even paralytic ectropion.

### Paralytic Ectropion

Paralytic ectropion is caused by decreased tone and weakened contraction of the orbicularis muscle due to facial nerve palsy (Fig. 12.6.6). The underlying facial palsy can result from Bell's palsy, surgical or traumatic injury, and stroke. Patients with pre-existing horizontal laxity before the facial nerve palsy may develop significant ectropion and lagophthalmos. Epiphora is commonly present due to reflex tearing from exposure keratopathy, punctal eversion, and an ineffective lacrimal pump mechanism due to improper orbicularis contraction. If the palsy is transient and recovery is



**Fig. 12.6.2** Mechanical Ectropion Resulting From a Large Lower Eyelid Mass (Squamous Cell Carcinoma).



**Fig. 12.6.3** Involutional Ectropion With Generalized Eyelid Laxity and Redundancy of the Lateral Canthal Tendon.





**Fig. 12.6.4** Cicatricial Ectropion From Severe Actinic Damage to the Lower Eyelid Skin and Previous Skin Cancer Resection.



**Fig. 12.6.5** Bilateral Cicatricial Ectropion Caused by Severe Allergic Blepharitis.



**Fig. 12.6.6** Paralytic Ectropion Associated With Seventh Nerve Palsy.

expected (i.e., Bell's palsy), use of lubricating ointment is sufficient until the palsy resolves. Surgery is typically required to correct ectropion caused by a permanent facial palsy.

## Mechanical Ectropion

Mechanical ectropion is observed when a mass causes the eyelid margin to shift away from the globe (see Fig. 12.6.2). This can be caused by a tumor or cyst near the eyelid margin pulling the eyelid down and away. Alternatively, periocular edema, conjunctival chemosis, and conjunctival growths and cysts can mechanically push the eyelid margin away from the globe. Treatment should initially address the underlying cause with medical intervention or resection of the causative mass. Although coexisting

involutional or cicatricial ectropion often is present, surgical intervention should be performed only if residual ectropion persists after treatment of the primary mechanical cause.

## Congenital Ectropion

Congenital ectropion is rare but commonly observed with absence or atrophy of the tarsal plate, conjunctival edema after birth trauma, and eyelid malformations with skin shortage and retraction. It is most often seen in association with Down syndrome but can also be associated with the blepharophimosis syndrome. If corneal exposure is mild or expected to resolve, as seen in cases with conjunctival chemosis from birth trauma, treatment with topical lubricants may be adequate. In more severe cases, skin grafting may be required to address the skin shortage and prevent corneal scarring and amblyopia.

## ALTERNATIVES TO SURGERY

Patients with symptomatic ectropion must be evaluated for surgical intervention to prevent corneal decompensation that can progress to ulceration and scarring from exposure. Medical treatment with artificial tears and ointment may be attempted before surgical intervention in patients with mild symptoms and in patients with systemic comorbidities preventing them from undergoing the surgical procedure.

## ANESTHESIA

Surgical repair of ectropion is an outpatient procedure that can be performed using only local infiltrative anesthetic in the physician's office or minor procedure room. A 1:1 solution of 2% lidocaine with 1:100 000 epinephrine and 0.75% bupivacaine provides satisfactory local analgesia. A subcutaneous injection of local anesthetic is often adequate for procedures involving the anterior lamella, but a transconjunctival injection may be required in surgeries involving posterior lamellar structures.

Monitored anesthesia care combines local anesthesia with intravenous sedation with propofol and should always be considered when skin harvesting and grafting is being performed. Finally, general anesthesia should be utilized for all pediatric patients and apprehensive adults.

## GENERAL TECHNIQUES

Numerous techniques have been described to correct ectropion. Early procedures include a lateral canthal shortening procedure described in 1812 by Sir William Adams,<sup>3</sup> an eyelid wedge excision procedure performed by Von Ammon in 1831,<sup>4</sup> and several variations of the traditional Kuhnt-Symanowski procedure.<sup>5,6,7</sup> Modern surgical procedures utilize our increased understanding of eyelid anatomy and physiology to address the specific underlying structural mechanism causing ectropion.

Thorough preoperative evaluation is critical to determine the proper surgical intervention based on presence of horizontal eyelid laxity, vertical redundancy and laxity, anterior lamellar shortening, or a combination of these conditions. When ectropion is caused by horizontal laxity, eyelid shortening is the treatment of choice. Presence of vertical eyelid laxity and conjunctival redundancy requires reattachment of the lower eyelid retractors. When anterior lamellar shortening due to cicatricial changes exist, surgical treatment is guided by the location and degree of cicatricial ectropion. In mild cases of cicatricial ectropion, horizontal tightening of the eyelid may be sufficient. Cases exhibiting more severe cicatricial findings may require skin grafts and skin flaps to adequately lengthen the anterior lamella. Importantly, patients may exhibit ectropion secondary to more than one cause and may require multiple procedures to fully address the condition.

## SPECIFIC TECHNIQUES

### Involutional Ectropion

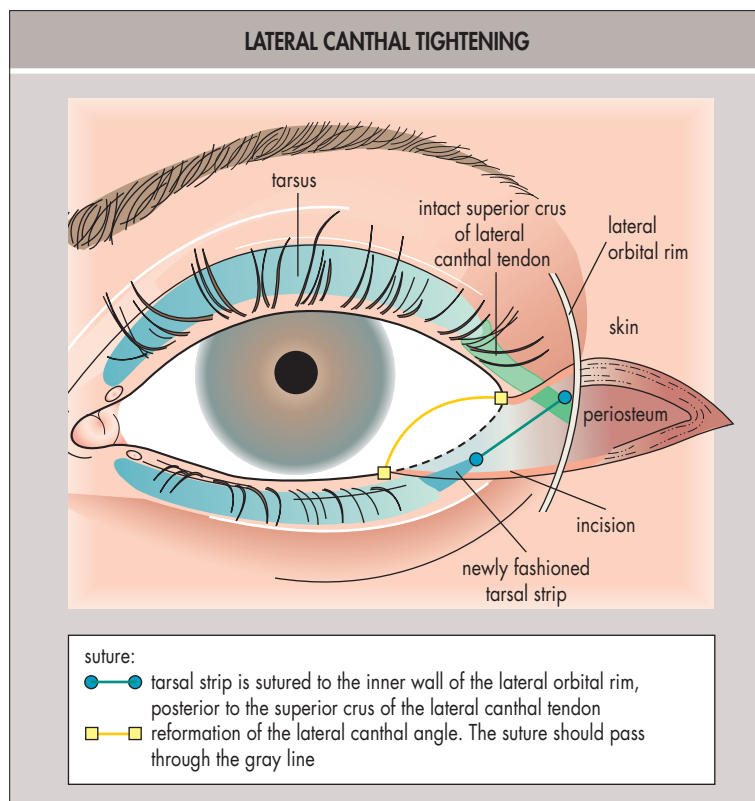
#### Lateral Tarsal Strip Procedure

In 1969, Tenzel described the lateral canthal sling procedure for treatment of lagophthalmos and lower eyelid elasticity, in which the lower arm of the canthal tendon is passed through a buttonhole created in the upper canthal tendon and attached to the temporal periosteum.<sup>8</sup> Subsequently in 1979, Anderson and Gordy described the well-known lateral tarsal strip procedure, which involves shortening and repositioning the inferior crus of the lateral canthus to the periosteum of the lateral orbital rim.<sup>9</sup> The



advantages of this technique over other horizontal eyelid shortening procedures include minimal visible scarring, lower incidence of symptomatic trichiasis, preservation of the tarsal plate, and restoration of lateral canthal fixation. The tarsal strip is constructed by separating the anterior and posterior lamella, releasing the lower eyelid retractors, and removing the eyelash follicles, mucocutaneous junction, and conjunctival epithelium. The size of the lateral tarsal strip is determined by the degree of horizontal laxity of the lower eyelid, and fixation of this strip to the lateral orbital periosteum creates a secure attachment that can be utilized to reform the lateral canthal angle.

A lateral canthotomy is performed to horizontally divide the lateral canthal tendon spanning from the canthal angle to the lateral orbital rim. The inferior crus of the canthal tendon is then visually or mechanically isolated and divided to complete a cantholysis. Successful inferior cantholysis results in a fully mobile lower eyelid margin freed from all lateral attachments. Care is taken to ensure that the upper arm of the canthal tendon remains intact. The required amount of horizontal shortening is determined by pulling the lower eyelid laterally until the desired tension is achieved, and the lower eyelid is marked where it intersects with the lateral canthal angle. A subciliary incision is made and a skin-muscle flap is elevated. Next, the anterior and posterior lamellae of the eyelid are separated at the gray line and the pilosebaceous units (anterior margin and eyelash follicles) are excised to expose the underlying tarsus. The lower eyelid retractors and conjunctiva are then divided at the tarsal base and the palpebral conjunctival mucosa of the tarsal strip is removed. The conjunctiva on the posterior lamella of the tarsal strip can either be scraped with a scalpel or ablated using electrocautery. An excessively long tarsal strip may be slightly shortened by transecting its distal end. The resulting strip is then secured to the periosteum along the inside of the lateral orbital rim (Fig. 12.6.7). Multiple types of sutures have been used to attach the tarsal strip, including permanent Prolene (polypropylene) or Mersilene (polyester) sutures and dissolving sutures such as Vicryl (polyglactin). To ensure proper positioning and contour of the lateral canthus and eyelid margins, care is taken to place the sutures under the upper crus of the canthal tendon so that the medial edge of the tarsal strip sits adjacent to the canthal incision of the upper eyelid without excessively tightening the lower eyelid. If necessary, the tarsal suture is adjusted or replaced if the position and shape of the eyelid or canthal angle are not appropriate. Next, the lateral canthal angle is reformed using a 6-0 Vicryl (polyglactin) suture that joins the upper and lower eyelid margins and orbicularis. Lastly, the overlying skin is rearranged, occasionally trimmed, and sutured with 6-0 gut suture.

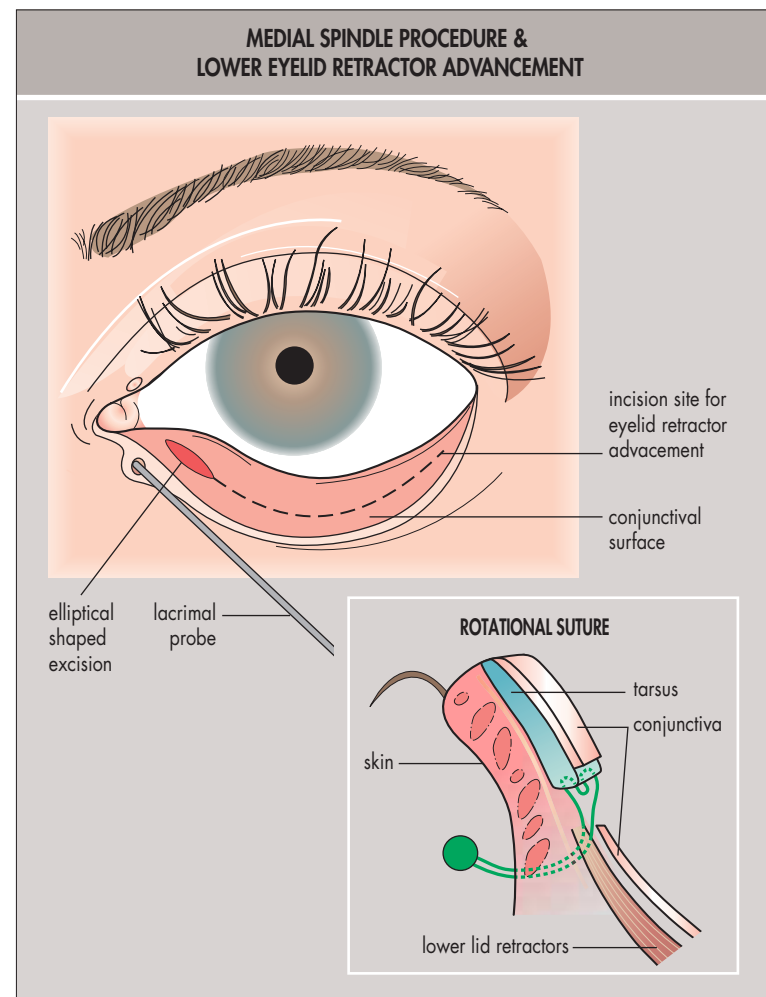


**Fig. 12.6.7** Tightening of the Lateral Canthal Tendon Using the Lateral Tarsal Strip Procedure.

### Medial Spindle Procedure With Rotational Suture

In 1985, Nowinski and Anderson described the medial spindle procedure for involutional medial ectropion.<sup>10</sup> This procedure can be used in conjunction with the lateral tarsal strip procedure if medial ectropion is not fully correctable with horizontal tightening of the eyelid. In this procedure, a defect is created in the posterior lamellae at the medial eyelid and the lower eyelid retractors are advanced to mechanically rotate the eyelid using sutures that are passed through the anterior lamellae. Occasionally this procedure can be performed as a stand-alone treatment for patients with medial ectropion without significant horizontal eyelid laxity and for patients with mild medial cicatricial ectropion due to the vertical anterior lamellar shortening that improves after resection of any redundant medial conjunctiva and medial eyelid retractors.

In the medial palpebral conjunctiva, an elliptical segment of redundant conjunctiva and lower eyelid retractors is resected just below the inferior tarsal border (Fig. 12.6.8). If needed, a canalicular probe is placed in the lower canaliculus to protect the canaliculus and assist in eversion of the lower eyelid for improved exposure of the palpebral conjunctiva. A double-armed 5-0 chromic gut suture is placed in a horizontal mattress fashion for segmental advancement of the retractors to the tarsal border. Each arm of the 5-0 chromic gut suture is placed sequentially through the inferior edge of the tarsus, upper edge of the lower eyelid retractors, and then through the anterior eyelid lamella. The exit point for the rotational sutures must be inferior to the placement of the eyelid retractor suture passes to provide an appropriate rotational effect. The externalized ends of the sutures are then tied at the skin. In more severe cases, multiple sutures are placed or a larger conjunctival area is resected. However, it is important to avoid excessive conjunctival resection during the procedure to avoid cicatricial entropion or shortening of the fornix. If the eyelid does not rotate into normal position, then consider replacement of sutures or further evaluation for cicatricial anterior lamellar changes.



**Fig. 12.6.8** Medial Spindle Procedure Using a Medial Elliptical Excision. Lower eyelid retractor advancement performed by extending the incision laterally (dashed line). Inset shows placement of rotational suture.

### Lower Eyelid Retractor Advancement

Severe involutional ectropion may result from marginal external rotation that initially involves the medial lower eyelid and over time extends laterally to affect the entire eyelid due to progressive lower eyelid retractor dehiscence. Advanced cases may demonstrate tarsal ectropion, where the entire eyelid is completely everted as a consequence of severe retractor laxity, dehiscence, or disinsertion.<sup>11,12</sup> This is corrected by advancing the retractors to re-establish their attachment at the lower tarsus.<sup>13</sup> In patients with coexisting horizontal eyelid laxity, retractor advancement can be combined with a tarsal strip procedure.

A transconjunctival incision is made at the inferior tarsal border along the length of the eyelid (see Fig. 12.6.8). Redundant conjunctiva and attenuated subconjunctival tissue are resected. The lower eyelid retractors are attached along the inferior tarsal edge with use of several internal 6-0 Vicryl (polyglactin) sutures. Alternatively, externalized 5-0 chromic gut rotational sutures, tied similar to the medial spindle procedure, may be utilized if medial or punctal ectropion is present.

### Full-Thickness Pentagonal Block Resection

In patients who demonstrate horizontal eyelid laxity without significant medial or lateral canthal tendon laxity or dehiscence, a pentagonal full-thickness block resection of the eyelid can be performed to correct the laxity.<sup>14</sup> Typically this procedure is preferred in patients with ectropion and isolated eyelid lesions that could also be addressed within the margins of the block resection. In the presence of medial horizontal laxity and punctal ectropion, the pentagonal block resection can be combined with a medial spindle procedure and rotational sutures (lazy-T procedure).<sup>15</sup> Additionally, horizontal laxity with coexisting mild cicatricial ectropion can be addressed using a modified block resection that preserves the eyelid skin so that it may be used as a skin flap to provide additional anterior lamellar tissue.

An initial full-thickness incision is made perpendicular to the eyelid margin and is extended to the inferior border of the tarsus. The medial and lateral edges of the transected eyelid are overlapped to evaluate the dimensions of the eyelid resection required to correct the eyelid laxity. Based on the desired size to be resected, a second incision that is also oriented perpendicular to the eyelid margin is extended to the inferior border of the tarsus. The two eyelid incisions are then angled to meet near the inferior fornix, completing the excision and forming an eyelid defect in the shape of a pentagon. Using two or three absorbable sutures such as 6-0 Vicryl (polyglactin), the two edges of the tarsal plate are carefully aligned with partial thickness sutures (Fig. 12.6.9). The edges of the eyelid retractors and orbicularis inferior to the tarsal plate are aligned and sutured together using 6-0 Vicryl to close the apex of the pentagonal defect. Marginal closure

is completed using absorbable 7-0 chromic gut sutures placed through the gray line or nonabsorbable 6-0 silk sutures with long, tied-over tails. The skin is closed using 6-0 plain gut sutures. A bandage contact lens may be placed for any patient experiencing foreign body sensation caused by the marginal sutures. These marginal sutures may be removed at 7-10 days if the patient continues to experience corneal irritation.

### Cicatricial Ectropion

#### Local Skin Flaps (Z-Plasty)

Localized cicatricial changes with focal areas of traction may occasionally be treated using Z-plasty or other skin flap procedures. The Z-plasty technique is a transposition procedure that corrects localized skin shortening or scarring by rearranging skin laxity to increase the tissue length in the direction of the shortening at the expense of the tissue perpendicular to the focal defect.<sup>16</sup>

After the entire eyelid scar is marked, two additional lines equal in length to the scar line are drawn at the upper and lower borders to form 60° angles on opposing sides of the scar (Fig. 12.6.10). The resulting Z configuration is then cut, the skin flaps and surrounding tissue are undermined to release tension, and the superficial or deep scar tissue is excised. The two triangular skin flaps are transposed so that the apices are positioned at the distal ends of the initial 60° lines and closed using 6-0 sutures.

#### Full-Thickness Skin Graft

When significant skin shortage causes cicatricial ectropion, an increase in both vertical length and the overall area of the anterior lamellar tissue is required. A full-thickness skin graft addresses this diffuse anterior lamellar deficiency and commonly returns the eyelid to a normal position. It is important to consider the color and thickness of the surrounding eyelid tissue when choosing an appropriate skin graft donor site. Potential donor sites include the upper eyelid, retro-auricular area, preauricular area, and inner arm.<sup>17</sup> Commonly, this procedure is combined with a lateral tarsal strip and/or rotational suture placement.

In patients with isolated scarring, a horizontal incision is created at the upper border of the fibrotic tissue. In patients with diffuse skin shortage, a subciliary skin incision is made 2-3 mm below the lashes. Careful sharp dissection is performed along the lower eyelid tissue to release any deep cicatricial bands and still maintain a healthy recipient bed. After the surrounding lower eyelid tissue has been undermined to release all of the cicatrized regions, the lid margin is easily elevated to normal position. The lower eyelid is then maintained in normal anatomical position with the margin apposed to the globe and the residual anterior lamellar defect is

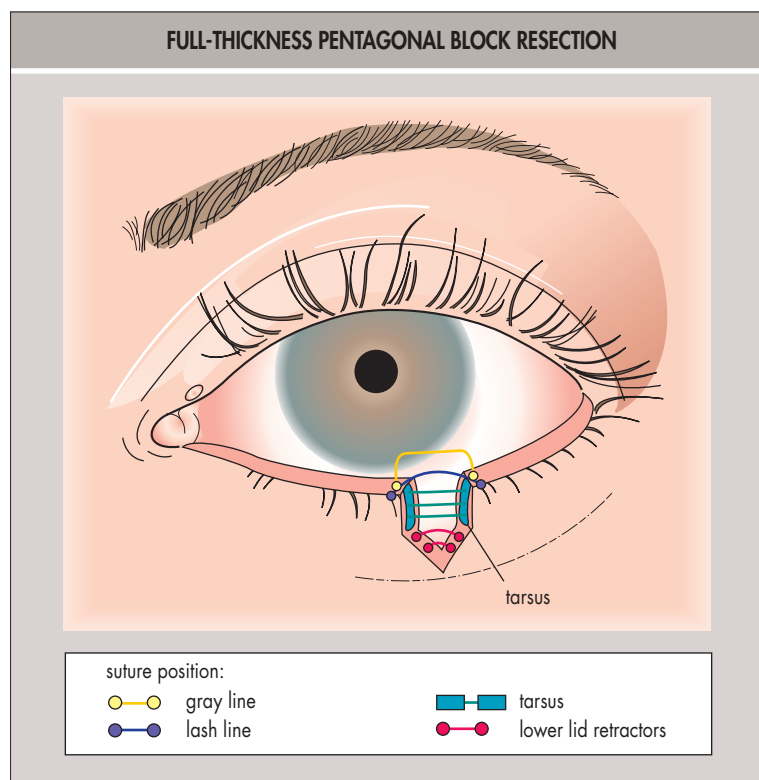


Fig. 12.6.9 Horizontal Lid Shortening With a Full-Thickness Block Resection.

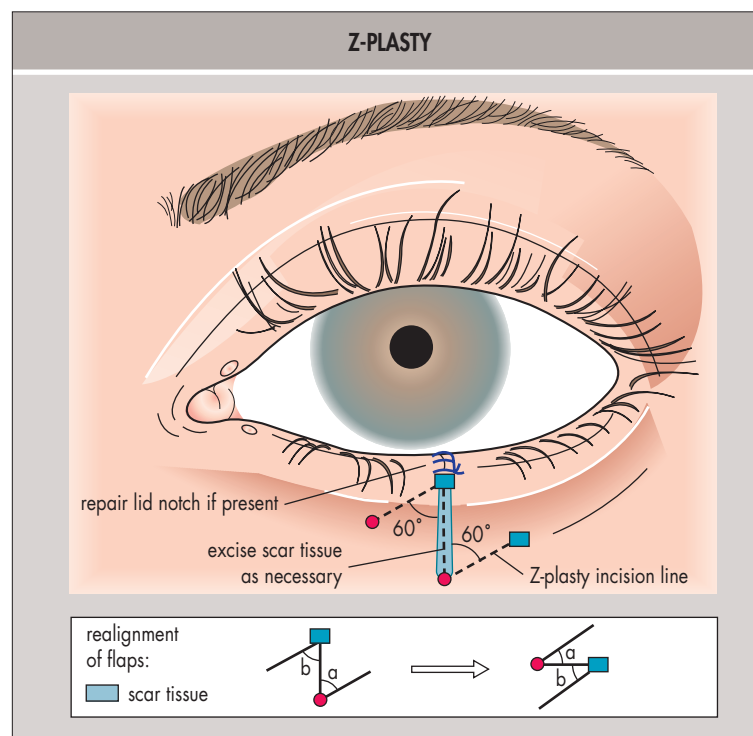
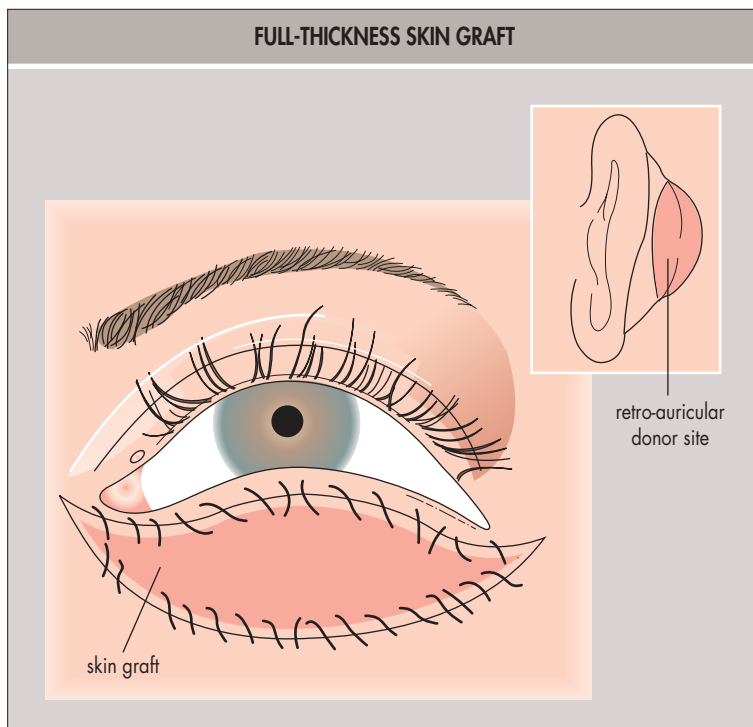


Fig. 12.6.10 Z-Plasty Procedure for Lengthening Focal Cicatricial Scarring. Flaps a and b are transposed to lengthen the scar line.



**Fig. 12.6.11 Full-Thickness Skin Graft for Lower Lid Cicatricial Ectropion.** Inset shows the retro-auricular donor site.

measured. Next, the donor site is marked, and the appropriately sized graft is then harvested from the donor site. The skin graft is then thinned of excess subcutaneous tissue and fat and placed into position at the site of the defect. The skin graft is trimmed to properly match the defect margins and attached using interrupted or running 6–0 gut sutures (Fig. 12.6.11). A bolster composed of nonadherent dressing is then secured over the graft with nonabsorbable sutures to help induce successful graft integration and prevent graft dislocation and fluid collection deep to the graft. The bolster and donor site sutures are removed at the initial follow-up visit 6–8 days after surgery.

## Paralytic Ectropion

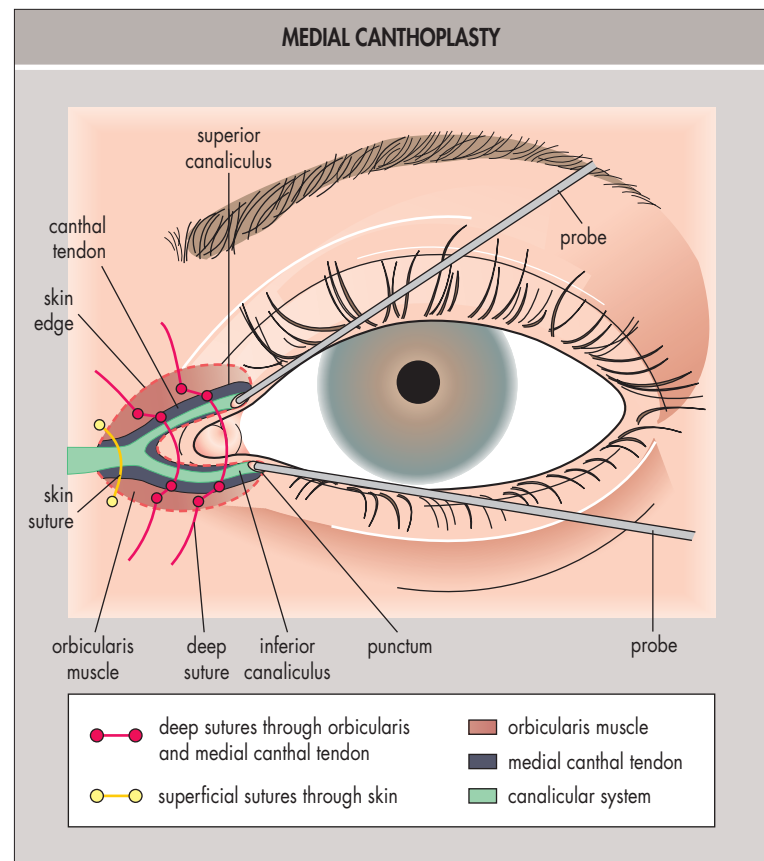
### Medial Canthoplasty

In 1951, Lee described the medial canthoplasty procedure for the treatment of epiphora caused by punctal eversion.<sup>18</sup> Subsequently, this procedure has also been utilized to treat patients with paralytic ectropion due to orbicularis muscle weakness, as commonly observed with facial palsy.<sup>19,20</sup> The medial canthoplasty joins the upper and lower medial canthal tendons to nasally displace the fixation point and provide increased support for the medial lower eyelid. This also reduces the palpebral fissure to improve lagophthalmos and reduce corneal exposure. The procedure may be performed alone in patients with mild paralytic ectropion and punctal eversion or combined with other procedures when horizontal laxity is present.

An incision is made at the upper eyelid mucocutaneous junction starting 1 mm medial to the upper punctum and extended to the medial canthal angle. A second mucocutaneous incision is made medial to the lower punctum and extended to meet the prior incision. A skin flap is then elevated over the upper and lower medial canthal tendons. Canaliculi probes may be used to identify and protect the canaliculi. Next, a thin strip mucosa of the upper and lower eyelids is excised to expose the upper and lower medial canthal tendons. The upper and lower medial canthal tendons are adjoined using two or three interrupted 6–0 or 7–0 Vicryl (polyglactin) sutures (Fig. 12.6.12). These sutures are passed through the upper palpebral portion of the orbicularis oculi, then through the upper and lower medial canthal tendons, and finally through the lower palpebral orbicularis oculi. The skin flaps are closed with interrupted 6–0 gut sutures.

### Lateral Tarsorrhaphy

A lateral tarsorrhaphy horizontally shortens the palpebral fissure by creating an adhesion between the upper and lower eyelid margins. It is commonly performed as a protective measure in patients with lagophthalmos and paralytic ectropion caused by facial palsy to reduce corneal exposure and decrease the risk of corneal ulceration.<sup>21</sup> In cases where horizontal laxity is also present, a lateral tarsorrhaphy can be combined with



**Fig. 12.6.12 Medial Canthoplasty to Improve Medial Lower Eyelid Support and Reduce Corneal Exposure.**

horizontal tightening procedures or performed as a staged procedure to address residual corneal exposure.

After the desired tarsorrhaphy length is marked, an incision is made along the gray line of the upper and lower eyelids at a depth of approximately 2–3 mm. Further undermining is then performed to free the eyelids anterior and posterior lamellae. A 1-mm strip of the posterior lamellar mucocutaneous junction is then excised from the eyelid margins. Next, partial thickness 6–0 Vicryl (polyglactin) sutures are passed through the tarsal tissue to attach the upper and lower posterior lamellar tissue (Fig. 12.6.13). Care must be taken to ensure that these sutures do not incorporate the palpebral conjunctiva to prevent any resultant postoperative irritation. The orbicularis is closed using buried interrupted 6–0 Vicryl sutures, which is followed by closure of the skin edges using interrupted 6–0 gut sutures.

## COMPLICATIONS

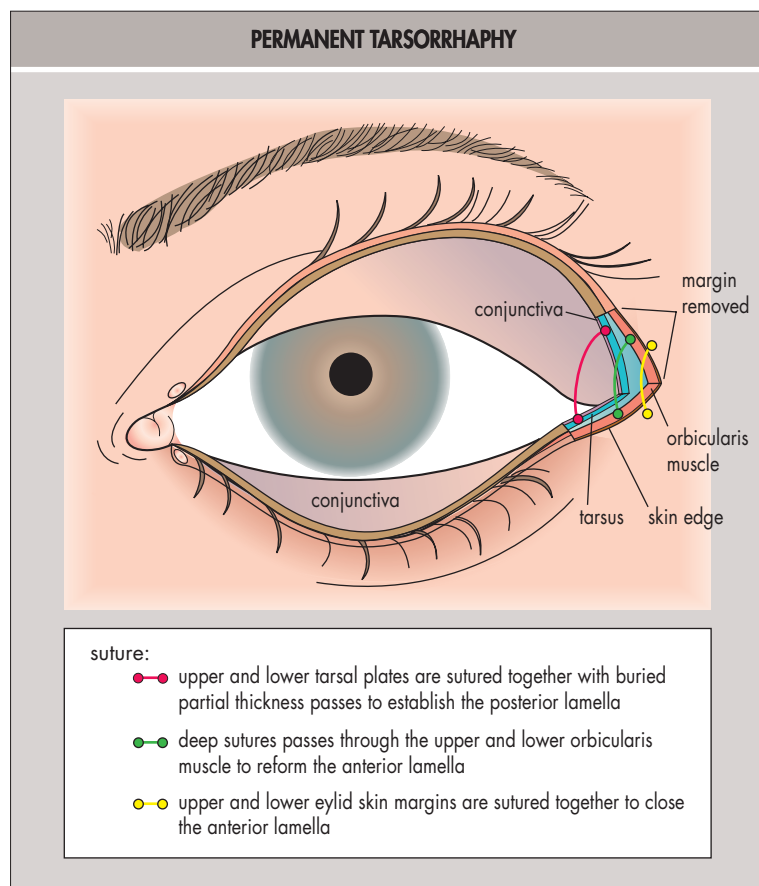
Complications of surgical ectropion repair include:

- Undercorrection (under tightening).
- Overcorrection (over tightening).
- Lateral canthal angle malposition.
- Eyelid margin notching or asymmetry.
- Lacrimal system damage.
- Skin or conjunctival scarring.
- Trichiasis.
- Corneal abrasion.
- Poor cosmesis.

Undercorrection results from insufficient horizontal shortening, graft shrinkage, or suture-related fixation loss, and often requires reoperation to address the undercorrection. Overcorrection is caused by aggressive eyelid shortening, over tightening of the rotational sutures during medial spindle procedures, or excessive resection of posterior lamellar tissue and retractors causing entropion or lower eyelid retraction. Although overcorrection usually improves with time as the tissue stretches, any postoperative entropion that results in trichiasis must be temporarily addressed with epilation or may require permanent treatment with cryotherapy, electrolysis, or surgical correction.

Poor alignment of the lid margins and canthal malposition may result from several procedures, including full-thickness block resection, medial





**Fig. 12.6.13 Permanent Lateral Tarsorrhaphy Procedure to Horizontally Shorten the Palpebral Fissure.**

canthoplasty, and lateral tarsorrhaphy. A full-thickness resection may result in irregular eyelid contour and notching, as well as trichiasis. Surgical repair of the eyelid notching or contour irregularities is typically preferable to improve long-term outcomes.

Damage to the lacrimal drainage system is a potential complication when medial canthal procedures are performed. Insertion of canaliculal probes and meticulous dissection near the medial canthal region are important considerations to reduce the risk of canaliculal injury. If any concern for canaliculal injury arises during the procedure, placement of a silicone stent may prevent canaliculal stenosis and any further complications.

## OUTCOME

Careful preoperative clinical evaluation and proper surgical intervention should restore the lower eyelid margin and punctum to their normal anatomical positions so that they are apposed to the ocular surface. Mild ectropion and medial punctal ectropion are usually fully corrected with a simple procedure. Advanced cases of involutional, cicatricial, or mixed ectropion often require a combination of procedures including horizontal tightening and grafting to address the deficits.

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# Benign Eyelid Lesions

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12.7

**Definition:** Benign eyelid lesions can arise from epithelial or dermal adnexal elements. These include epithelium, hair follicles, apocrine and eccrine glands, blood vessels, and nerves. Some may appear aggressive and must be differentiated from malignancies.

## Key Features

- Three to six times more common than malignant neoplasms.
- Can occur on any skin surface, some occur most often or exclusively on the eyelids.
- May reflect local pathology or be manifestations of systemic disease.
- Many lesions appear similar and present a diagnostic challenge.

## Associated Features

- Solid or cystic.
- Epithelial or subepithelial.
- Often multiple.
- Confused with malignant neoplasms.

## INTRODUCTION

The eyelids may be affected by a wide spectrum of benign lesions. In studies that analyzed all eyelid lesions submitted for histopathological examination, benign lesions were 3–6 times more frequent than malignant neoplasms.<sup>1,2</sup> Many lesions that affect the eyelids may occur on any skin surface, but some occur exclusively or more frequently on the eyelids.

The more common benign eyelid lesions are presented here, classified by origin, with each discussion highlighting the important clinical features, differential diagnosis, pertinent systemic associations, histopathology, and treatment.

## EPITHELIAL TUMORS

A variety of histopathological changes that affect these layers of the epidermis may be observed within lesions affecting the eyelids. Hyperkeratosis, or thickening of the keratin layer, is seen clinically as an adherent scale. Parakeratosis is a form of hyperkeratosis characterized by incomplete keratinization with retention of nuclei within the keratin layer. Dyskeratosis is abnormal keratinization of cells within the squamous layer. Acanthosis, or thickening of the squamous layer, is seen commonly in proliferative epithelial lesions. Acantholysis refers to separation of epithelial cells.

Each type of epithelial tumor may exhibit some variability in its clinical picture and morphological features. In addition, different types of tumors may share similar clinical and morphological features, which results in clinical diagnostic confusion. A definitive diagnosis of these various lesions depends on histopathological examination.<sup>3,4</sup>

## Squamous Papilloma

The most common benign lesion of the eyelid is the squamous papilloma, also known as a *fibroepithelial polyp*, *acrochordon*, or *skin tag*. These lesions may be single or multiple and commonly involve the eyelid margin. Squamous papillomas characteristically are flesh colored and may be sessile or pedunculated (Fig. 12.71). Diagnosis is made by the typical clinical appearance and histological characteristics. The differential diagnosis includes seborrheic keratosis, verruca vulgaris, and intradermal nevus.

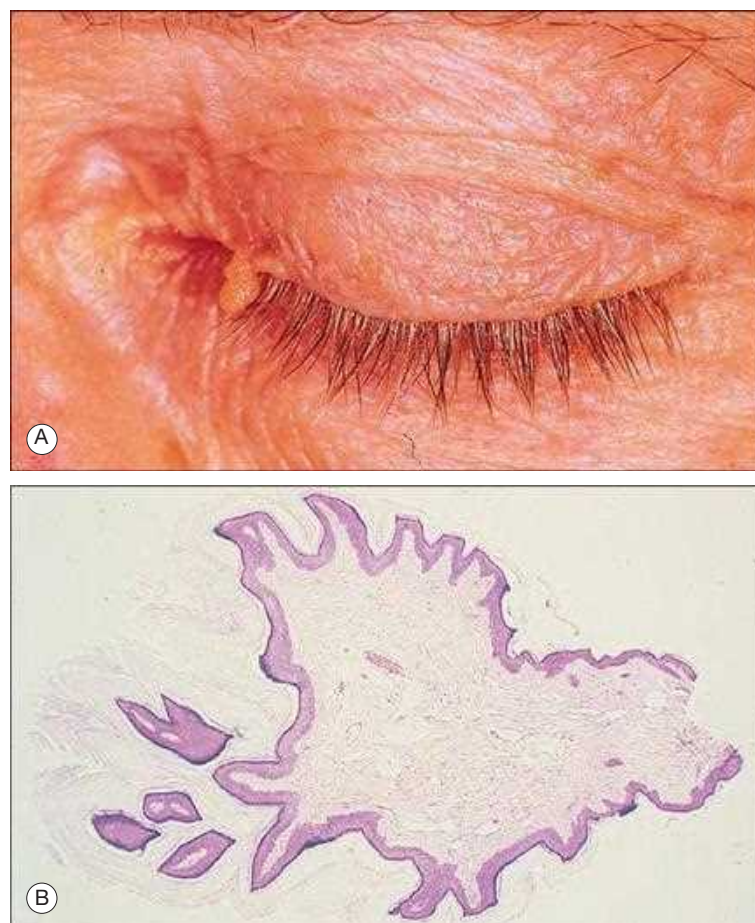
Microscopically, the lesion has finger-like projections (fronds) with a fibrovascular core, and the overlying epidermis demonstrates acanthosis and hyperkeratosis. Treatment is simple excision at the base of the lesion.

## Cutaneous Horn

A cutaneous horn is a projection of packed keratin (Fig. 12.72). This is a clinically descriptive term, not a diagnostic one. Cutaneous horn is not a distinct pathological entity but may develop from a variety of underlying lesions, including seborrheic keratosis, actinic keratosis, inverted follicular keratosis, verruca vulgaris, basal cell carcinoma (BCC), squamous cell carcinoma (SCC), and other epidermal tumors. Because definitive therapy is dependent on the underlying cause, biopsy of the cutaneous horn (including the underlying epidermis) is required to obtain a histological diagnosis.<sup>5</sup>

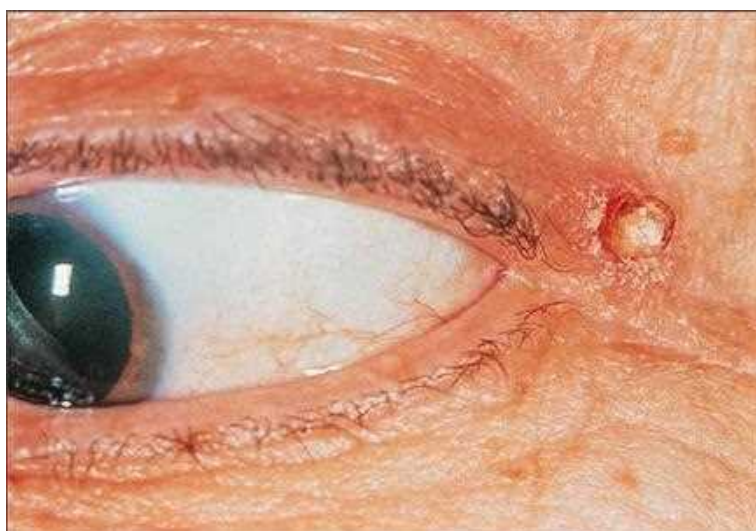
## Seborrheic Keratosis

Seborrheic keratosis, also known as *senile verruca*, is a common benign epithelial neoplasm that may occur on the face, trunk, and extremities. These lesions usually affect middle-aged and older adults, occurring as



**Fig. 12.7.1 Squamous Papilloma.** (A) Typical flesh-colored, pedunculated skin tag involving the left upper eyelid. (B) Fibroepithelial papilloma consists of a narrow-based (to the right) papilloma with fibrovascular core and finger-like projections covered by acanthotic, hyperkeratotic epithelium.





**Fig. 12.7.2 Cutaneous Horn.** Note the projection of packed keratin that arises from the skin in the region of the left lateral canthus.



**Fig. 12.7.3 Seborrheic Keratosis.** Brown, stuck-on plaque, typical of seborrheic keratosis.

single or multiple, greasy, stuck-on plaques (Fig. 12.7.3). Color varies from tan to brown, and the surface is frequently papillomatous. The differential diagnosis includes skin tag, nevus, verruca vulgaris, actinic keratosis, and pigmented BCC. Seborrheic keratoses are not considered premalignant lesions. A systemic association, however, known as the *sign of Leser-Trélat*, denotes a rapid increase in the size and number of seborrheic keratoses, which may occur in patients with occult malignancy.

A variant of seborrheic keratosis, which shares a similar histopathological appearance, is dermatosis papulosa nigra, which occurs primarily in dark-skinned individuals. These lesions usually appear on the cheeks and periorbital region as multiple pigmented papules (Fig. 12.7.4).

Although different histopathological types of seborrheic keratoses exist, all lesions share features of hyperkeratosis, acanthosis, and papillomatosis.<sup>6</sup> Most lesions contain horn cysts, which are keratin-filled inclusions within the acanthotic epidermis, and pseudohorn cysts, which represent invaginations of surface keratin.<sup>7</sup> Simple excision may be performed for biopsy or cosmesis or to prevent irritation.

### Inverted Follicular Keratosis

Inverted follicular keratosis, also known as *basosquamous cell acanthoma*, usually appears as a small, solitary, papillomatous lesion on the face. It is a well-demarcated, keratotic mass that may appear as a cutaneous horn. The lesion may resemble verruca vulgaris and seborrheic keratosis—many consider it an irritated seborrheic keratosis.<sup>8</sup> Histopathology reveals hyperkeratosis and lobular acanthosis. Proliferation of basaloid cells occurs with areas of acantholysis and zones of squamous cells, often arranged



**Fig. 12.7.4 Dermatitis Papulosa Nigra.** Multiple pigmented papules involving the malar region.



**Fig. 12.7.5 Keratoacanthoma.** (A) Lesion shows typical clinical appearance; history was also typical. (B) The lesion that can be seen above the surface epithelium has a cup-shaped configuration and a central keratin core. The base of the acanthotic epithelium is blunted (rather than invasive) at the junction of the dermis.

in whorls called *squamous eddies*. Treatment is complete excision, because recurrence is common after incomplete removal.

### Keratoacanthoma

Keratoacanthoma most commonly appears as a solitary, rapidly growing nodule on sun-exposed areas of middle-aged and older individuals. The nodule is usually umbilicated, with a distinctive central crater filled with a keratin plug (Fig. 12.7.5). The lesion develops rapidly over weeks and typically undergoes spontaneous involution within 6 months to leave an atrophic scar. Lesions that occur on the eyelids may produce mechanical





**Fig. 12.7.6 Epidermal Inclusion Cyst.** This lesion appeared as a slow-growing, cystic lesion in a region of previous penetrating trauma.

abnormalities such as ectropion or ptosis and occasionally may cause destructive changes. The differential diagnosis includes SCC, BCC, verruca vulgaris, and molluscum contagiosum (MC). Patients with Muir–Torre syndrome may develop, in association with internal malignancy, multiple keratoacanthomas and sebaceous neoplasms.

Microscopically, there is cup-shaped elevation of acanthotic squamous epithelium that surrounds a central mass of keratin. Microabscesses, which contain necrotic keratinocytes and neutrophils, may be found within the proliferative epithelium. Cellular atypia may be present, making differentiation from SCC difficult. Many pathologists consider keratoacanthoma a type of low-grade SCC. Complete excision is recommended because an invasive variant exists, with the potential for perineural and intramuscular spread.<sup>9</sup> Additional treatment modalities including intralesional chemotherapy, topical agents, lasers, cryotherapy, and photodynamic therapy have also been described.<sup>10</sup>

## Actinic Keratosis

Actinic keratosis, also known as *solar* or *senile keratosis*, is the most common premalignant skin lesion. The lesions develop on sun-exposed areas and commonly affect the face, hands, and scalp and, less commonly, the eyelid. They usually appear as multiple, flat-topped papules with an adherent white scale. The development of SCC in untreated lesions reportedly ranges as high as 20% (see Chapter 12.10).<sup>11</sup> Microscopically, actinic keratoses display hyperkeratosis, parakeratosis, and dyskeratosis. Atypical keratinocytes in the deep epidermal layers often form buds that extend into the papillary dermis. Management is surgical excision or cryotherapy (following biopsy).

## Epidermal Inclusion Cyst

Epidermal inclusion cysts appear as slow-growing, round, firm lesions of the dermis or subcutaneous tissue. Eyelid lesions are usually solitary, mobile, and less than 1 cm in diameter. These cysts usually arise from traumatic implantation of surface epidermis (Fig. 12.7.6). Cysts may become inflamed with a foreign body granulomatous reaction.

Diagnosis is based on the clinical appearance and histopathology. Differential diagnosis includes dermoid cyst, pilar cyst, and neurofibroma. Microscopically, the cyst is filled with keratin and is lined by a keratinizing, stratified squamous epithelium. Adnexal structures are not present in the cyst wall.<sup>12</sup> Treatment is complete excision, preferably of the entire cyst wall, to prevent recurrence.

## Pilar Cyst

Pilar cysts, formerly known as *sebaceous cysts*, are smooth, round, movable dermal or subcutaneous masses, clinically identical to epidermal inclusion cysts. The differentiation within these cysts is thought to be toward hair keratin.<sup>13</sup> These cysts tend to occur in areas with large numbers of hair follicles and are found most commonly on the scalp. They may occur occasionally in the periocular region, particularly in the brow or along the



**Fig. 12.7.7 Dermoid Cyst.** Cystic, subcutaneous lesion in the right upper lid and brow region, attached to the underlying frontozygomatic suture.

eyelid margin. Histopathology reveals an epithelium-lined cyst, with palisading of the basal layer. The lining lacks a granular layer, unlike that of epidermal cysts. Eosinophilic material within the cyst comprises desquamated cells and keratin and commonly calcifies. Cyst rupture may occur and incite a foreign body granulomatous response. Treatment is complete surgical excision; incomplete excision may result in recurrence.

## Epidermoid and Dermoid Cysts

Although generally considered in discussions of orbital lesions (see Chapter 12.10), epidermoid and dermoid cysts are included here because they may appear as an eyelid mass. These cysts can occur as superficial, subcutaneous, or deep orbital lesions. Both are choristomas (composed of tissue not usually found at the site) that are firm, slowly enlarging, nontender masses, most commonly in the lateral upper eyelid and brow region (Fig. 12.7.7). Superficial lesions usually are recognized during early childhood.<sup>14</sup> These cysts presumably occur secondary to entrapment of skin along embryonic closure lines. Attachment to underlying bony sutures often is present (see Chapter 12.1). Lesions may extend posteriorly into the orbit.

Microscopically, both dermoid and epidermoid cysts are lined by a stratified squamous keratinizing epithelium. Dermoid cysts also contain adnexal elements in the cyst wall, including hair follicles and sebaceous and eccrine glands. Treatment is complete surgical excision. Preoperative orbital imaging is indicated if the entire cyst cannot be palpated or if orbital extension is suspected. Complete excision eliminates the potential for cyst rupture, which can produce secondary foreign body granulomatous inflammation.

## ADNEXAL TUMORS

Lesions of adnexal origin arise from the epidermal appendages, which include the sebaceous glands of Zeis, meibomian glands, pilosebaceous units (consisting of hair follicles and associated sebaceous glands), eccrine sweat glands, and apocrine sweat glands of Moll.

## Benign Lesions of Sebaceous Origin

Sebaceous lesions of the eyelid may arise from several sources: the glands of Zeis, found in association with the eyelashes; the meibomian glands, located within the fibrous tarsal plates; and sebaceous glands, associated with hair follicles of the eyebrows and on the cutaneous surfaces of the eyelids. The sebaceous glands create their secretions by a holocrine mechanism in which the central cells undergo disintegration and subsequent extrusion into a common excretory duct.

### Milia

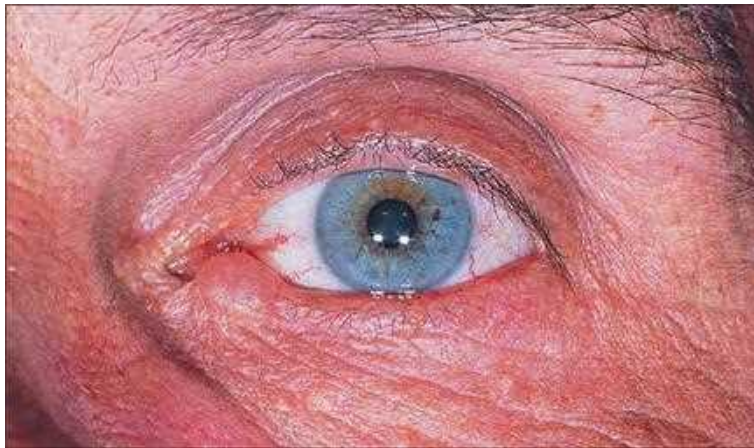
Milia form as multiple firm, white lesions that range between 1 to 4 mm in diameter. They usually appear on the face and commonly affect the eyelids, nose, and malar region (Fig. 12.7.8). Lesions may occur spontaneously or secondarily due to trauma, radiotherapy, skin infection, or bullous diseases. Occlusion of pilosebaceous units with retention of keratin is thought to be the causative mechanism. Histopathology reveals a dilated, keratin-filled hair follicle, with compression and atrophy of the adjacent sebaceous glands. Treatment includes simple incision, electrodesiccation of the surface, or puncture and expression of the contents.

### Sebaceous Adenoma

This uncommon lesion usually appears in the elderly as a solitary, yellow papule, with a predilection for the eyelid and brow. The importance of



**Fig. 12.7.8 Milia.** Multiple small white lesions that affect the upper and lower eyelids.



**Fig. 12.7.9 Eccrine Hidrocystoma.** Cystic lesion involving the left lower eyelid margin. The lesion was filled with translucent fluid.

this and other benign sebaceous neoplasms is the association with internal malignancy, known as the Muir–Torre syndrome. Even a single cutaneous sebaceous neoplasm may be significant, so patients should be evaluated accordingly.<sup>15</sup> Patients with this syndrome also may develop multiple keratoacanthomas. Microscopically, the sebaceous adenoma is a well-circumscribed lesion with lobules containing an outer layer of basal germinal cells that become lipidized centrally. Treatment is complete surgical excision, because incompletely excised lesions commonly recur.

### Benign Lesions of Eccrine Origin

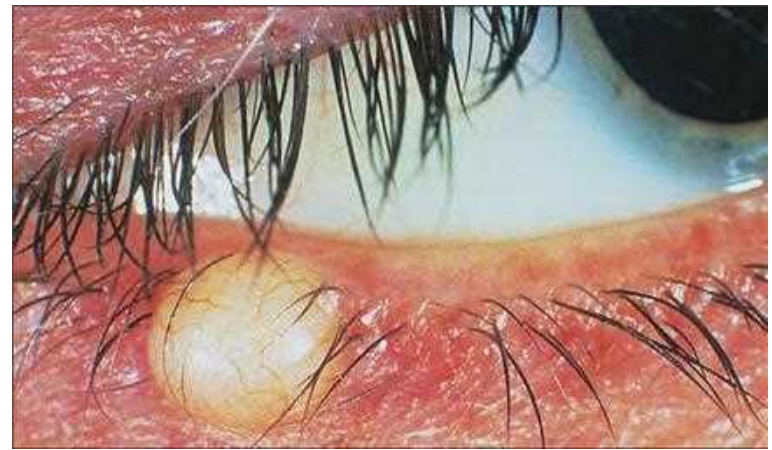
The eccrine sweat glands are found throughout the cutaneous surface of the eyelids. They are composed of three segments, including an intradermal secretory coil, an intradermal duct, and an intraepidermal duct.

#### Eccrine Hidrocystoma

Eccrine hidrocystomas, also known as *sudoriferous* or *sweat gland cysts*, appear as solitary or multiple small nodules on the eyelids. The overlying skin is shiny and smooth, and the cyst usually is translucent and fluid filled (Fig. 12.7.9). Eccrine hidrocystomas are thought to be ductal retention cysts, which tend to increase in size in hot, humid weather. The differential diagnosis includes apocrine hidrocystoma and epidermal inclusion cyst. Histopathology reveals a dermal cyst lined by a double-layered cuboidal epithelium without papillary infoldings. Treatment is complete excision.

#### Syringoma

The syringoma is a common adnexal tumor arising from adenomatous proliferation of the intraepidermal duct of eccrine glands. They occur primarily in young women, occurring as multiple, small (1–3 mm diameter), skin-color to yellowish papules distributed symmetrically on the lower eyelids and cheeks. Microscopically, syringomas contain ducts lined by double-layered cuboidal epithelium embedded in a dense fibrous stroma. The ducts may taper to a solid core of cells to produce a comma-shaped or



**Fig. 12.7.10 Apocrine Hidrocystoma.** Cystic lesion filled with milky fluid, involving the right lower eyelid margin.

“tadpole” configuration.<sup>16</sup> Rarely, syringomas can undergo malignant transformation. Treatment modalities include surgical excision, electrodesiccation, and carbon dioxide laser.<sup>17</sup>

#### Chondroid Syringoma

Chondroid syringoma, also known as a *pleomorphic adenoma* or *mixed tumor of the skin*, most commonly occurs in the head and neck region and, rarely, may involve the eyelid.<sup>18</sup> It appears as a 0.5–3 cm in diameter, asymptomatic, dermal nodule. The lesions are thought to arise from eccrine sweat glands and owe their name to the mixture of sweat gland and cartilaginous elements. Differential diagnosis includes epidermal inclusion cyst, pilar cyst, neurofibroma, and pilomatrixoma. Microscopically, it is identical to pleomorphic adenoma (mixed tumor) of the lacrimal gland. Ducts lined with an inner secretory layer and an outer myoepithelial layer are embedded in a stroma with areas of chondroid metaplasia. Treatment is surgical excision. Malignant variants have been reported.

### Benign Lesions of Apocrine Origin

The apocrine glands of Moll are found along the eyelid margin in association with the eyelash follicles. They are modified sweat glands that contain a secretory coil, an intradermal duct, and an intraepithelial duct. Their secretions are produced by decapitation of the secretory cells.

#### Apocrine Hidrocystoma

Apocrine hidrocystoma, also known as *cystadenoma*, usually appears as a solitary, translucent cyst on the face, sometimes at the eyelid margin. The cyst is usually small (less than 1 cm in diameter) and filled with clear or milky fluid, with shiny, smooth overlying skin (Fig. 12.7.10). Lesions may display a bluish coloration, attributed to the Tyndall effect. Unlike the eccrine variety, these lesions are thought to be proliferative in origin and do not increase in size in hot weather. The differential diagnosis includes eccrine hidrocystoma and cystic BCC. An association has been reported, thought to represent an ectodermal dysplasia, in which patients display multiple apocrine hidrocystomas, hypodontia, palmar–plantar hyperkeratosis, and onychodystrophy.<sup>19</sup>

Histopathology reveals a dermal cyst with papillary infoldings, lined by an inner secretory layer with eosinophilic columnar cells and an outer myoepithelial layer. Treatment is usually by complete excision. Larger or multiple lesions may be treated by chemical ablation with trichloroacetic acid.<sup>20</sup>

#### Cylindroma

Cylindroma, presumably of apocrine origin, may occur on the eyelid or brow. It usually appears as a dome-shaped, skin-colored or pinkish red dermal nodule (Fig. 12.7.11). Solitary lesions usually occur in adulthood in the head and neck region and may appear similar to a pilar or epidermal inclusion cyst. Multiple lesions are inherited in an autosomal dominant fashion and usually appear on the scalp, where extensive involvement is referred to as a *turban tumor*. Multiple lesions have been associated with trichoepitheliomas. Microscopically, the cylindroma consists of islands with large, pale-staining cells centrally and small, cuboidal cells peripherally, surrounded by an eosinophilic basement membrane. Treatment is surgical excision.





**Fig. 12.7.11 Cylindroma.** Multiple, pinkish red dermal nodules involving the eyelids, forehead, nose, and malar region.



**Fig. 12.7.12 Pilomatrixoma.** Reddish nodule arising from the left lower eyelid.

## Benign Lesions of Hair Follicle Origin

Benign lesions of hair follicle origin are rather rare tumors, often confused clinically with BCC, the most common malignant eyelid lesion. Confirmation of diagnosis by incisional biopsy is helpful for suspicious-looking lesions, which allows less extensive resection of lesions confirmed as benign.<sup>21</sup>

### Trichoepithelioma

Trichoepithelioma is a tumor of hair follicle origin with a predilection for the face. The solitary lesion tends to occur in older individuals as an asymptomatic, flesh-colored to yellowish, firm papule that rarely ulcerates.

Multiple lesions, also known as *multiple benign cystic epithelioma* or *Brooke's tumor*, are inherited in an autosomal dominant pattern with variable penetrance. Lesions appear during adolescence as multiple firm nodules involving the face and the scalp, neck, and trunk. They may increase in size and number but rarely ulcerate. Diagnosis is made by the clinical appearance, family history, and histopathology. Differential diagnosis includes basal cell nevus syndrome, in which lesions tend to ulcerate more frequently (see Chapter 12.10).

Histopathology reveals multiple keratin-filled horn cysts surrounded by islands of basaloid cells that display peripheral palisading. The abundant fibrous stroma is well demarcated from the surrounding dermis. Lesions may histologically resemble BCC, and rare reports of transformation to BCC exist.<sup>22</sup> Treatment includes surgical excision of solitary lesions and cryosurgery or laser for multiple lesions.

### Trichofolliculoma

Trichofolliculoma is a fairly well differentiated hamartomatous lesion, usually appearing as an asymptomatic, solitary, flesh-colored nodule during adulthood on the face or scalp. A central umbilication usually is present, which is the opening of a keratin-filled follicle. Small white hairs may protrude from the central pore and are suggestive of the diagnosis. The lesion may be confused clinically with a pilar cyst, nevus, or BCC. Histopathology reveals a dilated follicle, filled with keratin and hair shafts, and lined by stratified squamous epithelium continuous with the epidermis. Surgical excision is curative.

### Trichilemmoma

Trichilemmoma is a tumor that arises from the outer hair sheath. A solitary lesion generally appears during adulthood as an asymptomatic, flesh-colored, nodular, or papillomatous lesion. The nose is the most common site of occurrence, followed by the eyelid and the brow. The lesion may appear as a cutaneous horn or may resemble verruca vulgaris or BCC.

Multiple trichilemmomas are a marker for Cowden's disease, or multiple hamartoma syndrome, a rare genodermatosis inherited in an autosomal dominant fashion. In addition to the facial trichilemmomas, patients may develop acral keratoses and oral papillomas. Patients are at increased risk of developing breast and thyroid carcinoma, as well as multiple hamartomas. The mucocutaneous lesions usually precede the onset of malignancy.

Microscopically, glycogen-rich cells with clear cytoplasm proliferate in lobules, with peripheral palisading and a distinct basement membrane.

Hair follicles may be present. Treatment is surgical excision, cryosurgery, or laser.

### Pilomatrixoma

The pilomatrixoma, also known as the *calcifying epithelioma of Malherbe*, is a benign tumor of hair matrix origin.<sup>23</sup> The lesion tends to occur in children and young adults on the head and upper extremities. Lesions may occur in the periorbital region, particularly the upper eyelid and brow.<sup>24</sup> Usually a solitary lesion, it appears as a solid or cystic, mobile, subcutaneous nodule with normal overlying skin. It is firm, irregular, often reddish blue, and may contain chalky white nodules (Fig. 12.7.12). Histopathology reveals islands of basophilic epithelial cells, which transform into shadow cells located more centrally. Most tumors contain masses of calcified shadow cells, which may incite a giant cell granulomatous response. Rare cases of malignant transformation have been reported. Treatment is surgical excision.

## VASCULAR TUMORS

### Capillary Hemangioma

The capillary hemangioma, also known as a *benign hemangioendothelioma*, is a common vascular lesion of childhood. It occurs in 1%–2% of infants and is the most common orbital tumor found in children. Girls are more commonly affected than boys, with a 3:2 ratio. A periorbital hemangioma may appear as a superficial cutaneous lesion, subcutaneous lesion, deep orbital tumor, or combination of these types. Approximately one-third of lesions are visible at birth, with the remainder manifest by 6 months of age. There is typically an initial rapid growth phase within 6 months of diagnosis, followed by a period of stabilization and subsequent involution over several years. It is estimated that approximately 75% regress to some extent by the time the child reaches 7 years of age.

The classic superficial lesion, the strawberry nevus, appears as a red, raised, nodular mass that blanches with pressure (Fig. 12.7.13). It may first be seen as a flat lesion with telangiectatic surface vessels. A subcutaneous lesion appears as a bluish purple, spongy mass. Deep orbital lesions may cause proptosis and globe displacement with no associated cutaneous findings.

The most common ocular complication is amblyopia, which may result from occlusion of the visual axis, or from anisometropia due to induced astigmatism. Strabismus may occur secondary to the amblyopia or be caused by orbital involvement with restriction of ocular motility.<sup>25</sup>

Lesions that involve the eyelid and anterior orbit usually can be diagnosed by clinical findings. The differential diagnosis of orbital lesions includes rhabdomyosarcoma, neuroblastoma, encephalocele, lymphangioma, and inflammatory masses (see Chapter 12.10). Ultrasonography, computed tomography, and magnetic resonance imaging may aid in diagnosis and in determining the extent of involvement (see Chapter 12.3).

Microscopically, the early proliferative phase of the lesion contains lobules of plump endothelial cells separated by fibrous septa, with frequent mitotic figures and small, irregular vascular lumina. Mature lesions contain more prominent vascular structures and flatter endothelial cells



**Fig. 12.7.13 Capillary Hemangioma.** (A) Superficial, raised, red mass involving the right upper eyelid. (B) High magnification of endothelial cells.

diminished in number. As regression takes place, progressive fibrosis occurs, with thickening of the fibrous septa and replacement of endothelial lobules by adipose tissue. Atrophy of the vascular component of the lesion eventuates.

Because most capillary hemangiomas undergo spontaneous regression to some extent, treatment generally is reserved for patients who have specific ocular, dermatological, or systemic indications for intervention. Various management modalities have been advocated, each with potential significant risks, which are beyond the scope of this discussion. Ocular indications include amblyopia, compressive optic neuropathy, and proptosis with globe exposure. Previous treatment modalities have included intralesional corticosteroid injection,<sup>26</sup> systemic corticosteroids, radiotherapy, laser therapy, systemic interferon, and surgery. More recently, however, systemic propranolol has emerged as the treatment of choice as a relatively safe and effective agent in inducing lesion regression.<sup>27,28</sup> Surgery should be considered for localized, noninfiltrative lesions, or for those that fail to respond medically.<sup>29</sup> Amblyopia should be treated with appropriate patching and spectacle correction, as indicated.

### Lymphangioma

Lymphangiomas may involve the eyelid, conjunctiva, or orbit. Lesions often appear at birth or early in childhood and only occasionally in adulthood. They often are poorly circumscribed, with an infiltrative growth pattern. Eyelid involvement may occur as a superficial lesion with multiple cystlike excrescences or as a complex of channels that cause lid thickening and distortion. Hemorrhage into the lesion may occur to produce a hematoma when the eyelid is involved or proptosis when orbital lesions are present (see Chapter 12.10). Biopsy may be needed for definitive diagnosis. Microscopically, dilated, thin-walled vascular spaces lined by endothelial cells are present. Surgical excision is indicated for cosmesis or eyelid malposition. Large lesions may be difficult to manage due to extensive infiltration. The use of intralesional sclerosing agents, oral sildenafil, and subtotal surgical resection have been recently described as effective treatment modalities.<sup>30</sup>

### Nevus Flammeus

Nevus flammeus, also known as a *port-wine stain*, presents as a flat, purple, vascular lesion, usually unilateral and in the distribution of a branch of the



**Fig. 12.7.14 Nevus Flammeus.** Flat, purple, vascular lesion involving the skin of the face.

trigeminal nerve (Fig. 12.7.14). It is congenital and does not undergo spontaneous regression. If associated with ocular and leptomeningeal vascular hamartomas, it represents Sturge–Weber syndrome. Ocular manifestations of this syndrome include diffuse choroidal hemangioma, ipsilateral glaucoma, and serous retinal detachment. Histopathology of the skin lesion reveals dilated, telangiectatic capillaries within the dermis. Management is primarily with cosmetics. Tunable dye laser therapy also may be used to improve the appearance of the lesion.<sup>31</sup>

### Pyogenic Granuloma

Pyogenic granuloma is the most common acquired vascular lesion to involve the eyelids. It usually occurs after trauma or surgery as a fast-growing, fleshy, red-to-pink mass, which readily bleeds with minor contact (Fig. 12.7.15). Lesions also may develop in association with inflammatory processes, including chalazia. The differential diagnosis includes Kaposi's sarcoma and intravascular papillary endothelial hyperplasia, a rare endothelial proliferation. Microscopically, there is granulation tissue consisting of fibroblasts and blood vessels, with acute and chronic nongranulomatous inflammatory cells. Notably, a pyogenic granuloma is neither pyogenic nor granulomatous. Treatment is by surgical excision at the base of the lesion.

## TUMORS OF NEURAL ORIGIN

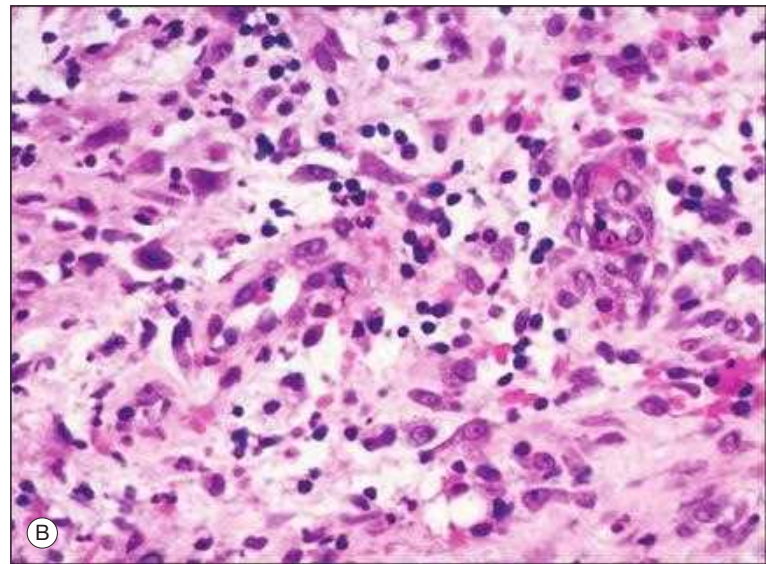
### Neurofibroma

Neurofibromas most commonly are considered in the context of neurofibromatosis, in which patients often develop multiple cutaneous lesions in association with other stigmata of the disease, usually apparent by adolescence.<sup>32</sup> The neurofibromas may occur on any cutaneous surface, including the eyelid, and typically enlarge slowly over many years. They appear as soft, fleshy, often pedunculated masses (Fig. 12.7.16). Isolated cutaneous neurofibromas, often resembling intradermal nevi, may occur in individuals with no other associated abnormality.

The plexiform neurofibroma, characteristic of type 1 neurofibromatosis, often occurs as a diffuse infiltration of the eyelid and orbit. The upper eyelid is usually ptotic, with an S-shaped curvature (Fig. 12.7.17). On palpation, the lesion feels like a “bag of worms.” Histopathology reveals units of proliferating axons, Schwann cells, and fibroblasts, with each unit surrounded by a perineural sheath.

Management depends on the site and extent of disease. Isolated cutaneous lesions, unrelated to neurofibromatosis, may be excised surgically. Surgical debulking may be performed for plexiform neurofibromas that produce mechanical ptosis or cosmetic deformity. However, due to the infiltrative nature of these lesions, complete excision is usually impossible and recurrence is common.





**Fig. 12.7.15 Pyogenic Granuloma.** (A) Red mass arising from the palpebral conjunctiva and protruding over the eyelid margin. This lesion developed in association with a chalazion. (B) Vascularized tissue (granulation tissue) that consists of inflammatory cells (polymorphonuclear lymphocytes and fibroblasts) and the endothelial cells of budding capillaries.



**Fig. 12.7.16 Neurofibroma.** Note the fleshy mass on the eyelid of this patient with disseminated cutaneous neurofibromas.



**Fig. 12.7.17 Plexiform Neurofibroma.** Note the ptosis and typical S-shaped curvature of the upper lid.



**Fig. 12.7.18 Xanthelasma.** Multiple soft, yellow plaques involving the lower eyelid. Lipid-laden foam cells are seen in dermis and tend to cluster around blood vessels.

on the medial aspect of the eyelids (Fig. 12.7.18). The diagnosis often can be made clinically. Hyperlipidemia is reported to occur in approximately 50% of patients with xanthelasma,<sup>33</sup> therefore lipid serum screening is recommended. Type IIa is the most commonly associated hyperlipidemia. The differential diagnosis of atypical lesions includes Erdheim–Chester disease, a systemic xanthogranulomatous disorder that has lesions that typically appear more indurated.

Microscopically, xanthelasmas are composed of foamy, lipid-laden histiocytes (xanthoma cells) clustered around blood vessels and adnexal structures within the superficial dermis. Surrounding fibrosis and inflammation may be observed. Treatment modalities include surgical excision, carbon dioxide laser ablation, and topical trichloroacetic acid. Recurrence is common.

## XANTHOMATOUS LESIONS

Xanthomatous lesions are characterized by the presence of histiocytes that have accumulated lipid, resulting in a foamy appearance of the cytoplasm histologically.

### Xanthelasma

Xanthelasma palpebrarum is the most common cutaneous xanthoma, typically occurring in middle-aged and older adults as soft, yellow plaques

### Juvenile Xanthogranuloma

Juvenile xanthogranuloma (JXG), also known as *nevooxanthoendothelioma*, is a benign histiocytic proliferation that most commonly affects the skin. It occurs mainly in children under 2 years of age and usually appears within the first year of life. The skin lesions mostly appear in the head and neck region as elevated orange, red, or brown nodules. They typically increase in size and number initially, but subsequently regress spontaneously into an atrophic scar over months to years. Lesions that appear in adulthood are more likely to persist and often require treatment to induce regression.



The most common site of extracutaneous involvement is the eye, with a predilection for the iris.<sup>34</sup> The iris may contain localized vascular nodules or diffuse infiltration of tumor. Complications include hyphema, uveitis, and glaucoma, with resulting visual loss and phthisis. Treatment, which includes topical and subconjunctival corticosteroids, is recommended for intraocular lesions<sup>35</sup> because they rarely regress spontaneously and complications are common.

Biopsy of skin lesions helps to confirm the clinical diagnosis in patients who have cutaneous disease alone and in patients who have suspicious eye findings associated with skin lesions. Microscopically, lesions contain an infiltrate of lipid-laden histiocytes, lymphocytes, eosinophils, and Touton giant cells. Fibrosis appears in older lesions. Skin lesions may be treated by excision or corticosteroid injection if necessary.

## PIGMENTED LESIONS OF MELANOCYTIC ORIGIN

Skin lesions of melanocytic origin arise from one of three cell types:

- Epidermal, or dendritic, melanocytes, which lie between the basal cells of the epidermis.
- Nevus cells, or nevocytes, which usually form nests of cells within the epidermis.
- Dermal, or fusiform, melanocytes, which lie in the subepithelial tissues.

Melanocytes are derived from neural crest cells. Epidermal melanocytes produce melanin, which is transferred to surrounding epidermal cells, with tanning and racial pigmentation resulting from this process.

### Freckles

Freckles, also known as *ephelides*, arise from epidermal melanocytes. They appear as small (1–3 mm in diameter), tan-to-brown macules in sun-exposed areas, including the eyelids (Fig. 12.7.19). Freckles occur more commonly in light-complected individuals and darken with sun exposure. These lesions reflect melanocytic overactivity, not proliferation. Microscopically, hyperpigmentation occurs within the basal layer of the epidermis. No treatment is necessary, but sunscreen may help prevent further darkening of lesions.

### Lentigo Simplex

Lentigo simplex is another epidermal melanocytic lesion that may appear on skin and mucous membranes as small, brown macules. They usually appear during childhood and are unaffected by sun exposure. Lesions may be solitary and have an appearance similar to that of junctional nevi. Multiple lesions may be a manifestation of a systemic syndrome, such as Peutz–Jeghers. Patients who have this syndrome develop multiple lesions, often periocular and perioral in distribution, in association with gastrointestinal polyps, which may undergo malignant transformation. Multiple lesions may resemble freckles but do not change in pigmentation with sun exposure as freckles often do. Microscopically, lentigo simplex has hyperpigmentation along the basal layer of the epidermis with an increased

number of melanocytes. Elongation of the rete ridges occurs along with mild lymphocytic infiltration of the superficial dermis. Because these lesions are thought to have no malignant potential, intervention is not required.

### Solar Lentigo

Lesions of solar lentigo, also of epidermal melanocytic origin, are tan-to-brown macules found commonly in sun-exposed areas of older individuals. They are known as *senile lentigines* but may occur in younger individuals after prolonged sun exposure. These lesions are found commonly in patients who have xeroderma pigmentosum, often appearing during the first decade of life. Lesions usually have slightly irregular borders but are evenly pigmented. Initially, lesions are a few millimeters in diameter but slowly increase in size. They may resemble junctional nevi and seborrheic keratoses. Lesions should be differentiated from lentigo maligna, a premalignant condition that usually has variable pigmentation and more prominent border irregularity and notching. Biopsy should be performed on suspicious-looking lesions.

Histologically, solar lentigo lesions display hyperpigmentation of the basal layer of the epidermis with proliferation of melanocytes. More extensive elongation of the rete ridges is found in comparison with lentigo simplex. Treatment is not required unless desired for cosmetic reasons.<sup>36</sup>

### Melanocytic Nevi

Melanocytic nevi, also known as *nevocellular nevi*, are derived from nevocytes. They are extremely common lesions, especially in fair-complected individuals.<sup>36,37</sup> These lesions frequently occur on the eyelid skin and eyelid margin. The clinical appearance often is predictive of the histological type, which may be junctional, compound, or intradermal.

Lesions typically occur during childhood as small, flat, tan macules that gradually increase in size radially. Nests of nevus cells are found within the epidermis, at the dermal–epidermal junction, representing a junctional nevus. As the lesion ceases to increase in diameter in older children and young adults, nests of cells “drop off” into the dermis, forming a compound nevus. Clinically, compound nevi are slightly elevated and pigmented. Lesions further evolve as the remaining epidermal nests migrate into the dermis to produce an intradermal nevus. This lesion, most common in adults, may be dome shaped, pedunculated, or papillomatous and usually is less pigmented or amelanotic (Fig. 12.7.20). Later in life, as the nevus cells induce fibroplasia within the dermis, the cells decrease in number and are replaced by normal dermal tissue.

Diagnosis usually is based on the typical clinical appearance. Malignant transformation may occur rarely, generally in the junctional or compound stages. Thus suspicious-looking lesions that demonstrate irregular growth or appearance should be excised. Otherwise, removal of common nevi is not required unless desired for cosmesis or relief of mechanical irritation.

### Congenital Melanocytic Nevus

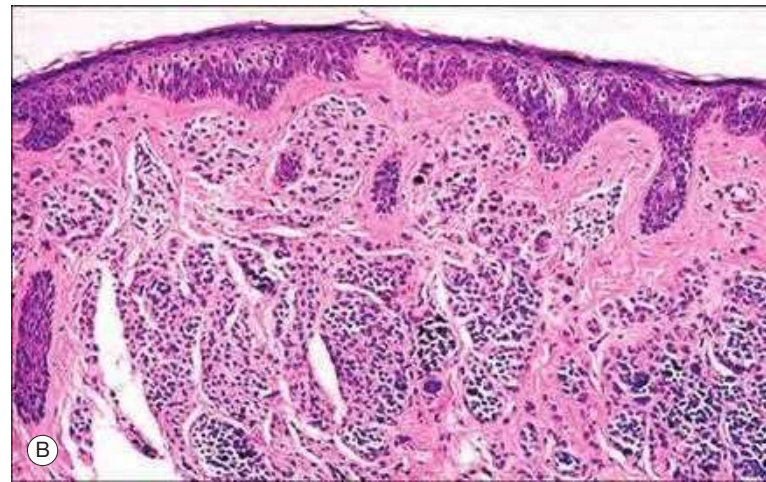
These lesions are derived from nevocytes and occur in approximately 1% of newborns. Lesions may be single or multiple and usually are deeply pigmented. The border often is irregular and the surface may be covered with hair. Congenital nevi that appear in a symmetrical fashion on adjacent portions of the upper and lower eyelids are referred to as *kissing nevi* and are formed as a result of melanocytic migration to the lids before separation of the embryonic eyelids (Fig. 12.7.21).

The size of congenital nevi is critical in management, because large lesions are associated with a higher risk of malignant transformation. There is controversy regarding the definition of “large” and “small” congenital nevi. Large lesions in the head and neck region commonly are defined as those greater than or equal to the area of the patient’s palm. The risk of malignant transformation is estimated at 5%.

Histologically, congenital nevi display a variety of patterns. Many lesions contain features of compound nevi, with nevus cells in the dermis and the dermal–epidermal junction. Nevus cells often extend into the deep dermis and subcutaneous tissue. Malignant melanoma usually develops within the deep dermis, which makes early diagnosis difficult. Thus any suspicious-looking lesion should be sampled for biopsy. Large lesions should be excised, but complete excision is impossible in some patients due to the size and extent of the lesion. The management of small lesions is controversial—some advocate excision of all congenital nevi.<sup>38</sup>



**Fig. 12.7.19 Freckles.** Multiple, tan-brown, small macules, involving the skin of sun-exposed areas.



**Fig. 12.7.20 Intradermal Nevus.** (A) Elevated, papillomatous lesion, amelanotic in color, involving the eyelid margin. (B) Nests of nevus cells fill the dermis except for a narrow area just under the epithelium. The nuclei of the nevus cells become smaller, thinner or spindle shaped, and darker as they go deeper into the dermis (i.e., they show normal polarity).



**Fig. 12.7.21 Kissing Nevus.** Congenital melanocytic nevus in a symmetrical fashion on adjacent portions of the upper and lower eyelids.

## Nevus of Ota

Nevus of Ota, or oculodermal melanocytosis, arises from dermal melanocytes. The lesion appears as a blue-to-purple, mottled discoloration of the skin in the distribution of the ophthalmic and maxillary divisions of the trigeminal nerve. It is usually congenital and unilateral and frequently is associated with ipsilateral ocular melanocytosis involving the conjunctiva, sclera, and uveal tract. Diagnosis is based on the typical clinical appearance.<sup>39</sup> Histopathology reveals pigmented, dendritic melanocytes throughout the dermis. Malignant degeneration may occur, particularly in white people, with the choroid the most common site of involvement.<sup>40</sup> Thus periodic dilated fundus examination is recommended.

## Blue Nevus

The blue nevus appears as a solitary blue nodule, usually less than 1 cm in diameter. The differential diagnosis includes melanoma, pigmented BCC, and vascular lesions. Microscopically, the lesion is composed of pigmented dendritic melanocytes and melanophages scattered throughout the dermis, often with fibrosis of adjacent tissue.

The cellular blue nevus is a lesion that also arises from dermal melanocytes. It is less common and usually larger than the blue nevus and appears as a solitary blue papule. Histologically, the lesion contains pigmented dendritic melanocytes interspersed with pale spindle cells. This lesion occasionally may become malignant and metastasize to regional lymph nodes.

Excision of these lesions may be performed for definitive diagnosis or cosmesis.

## INFLAMMATORY LESIONS

### Chalazion

A chalazion is a focal inflammatory lesion of the eyelid that results from the obstruction of a sebaceous gland, either meibomian or Zeis. Extravasated lipid material produces a surrounding, chronic, lipogranulomatous

inflammation. A chalazion may occur acutely with eyelid edema and erythema and evolve into a nodule, which may point anteriorly to the skin surface or, more commonly, toward the posterior surface of the lid. The lesion may drain spontaneously or persist as a chronic nodule, usually a few millimeters from the eyelid margin. Lesions also may appear insidiously as firm, painless nodules (Fig. 12.7.22). Chalazia often occur in patients with blepharitis and rosacea. These lesions may be mistaken for other more serious lesions such as malignancies.<sup>41</sup>

Diagnosis is based on the typical clinical features. Acute lesions appear similar to hordeola in appearance—differentiation is nearly impossible to make clinically. In recurrent or atypical lesions, a sebaceous gland carcinoma needs to be excluded, thus histopathological examination is important. Histopathology reveals lipogranulomatous inflammation, with clear spaces corresponding to lipid, surrounded by foreign body giant cells, epithelioid cells, neutrophils, lymphocytes, plasma cells, and eosinophils. A fibrous pseudocapsule may form around a lesion.

Treatment varies according to the stage of a lesion. Acute lesions are treated with hot compresses to encourage localization and drainage. Chronic chalazia may be treated using intralesional corticosteroid injection or surgical drainage. Vertical transconjunctival incisions allow adequate exposure of lesions and limit damage to surrounding meibomian glands. Small chalazia, which may resolve spontaneously, can be removed with incision and curettage.

### Hordeolum

A hordeolum is an acute purulent inflammation of the eyelid. An external hordeolum, or sty, results from inflammation of the follicle of a cilium and the adjacent glands of Zeis or Moll. The lesion typically causes pain, edema, and erythema of the eyelid, which becomes localized and often drains anteriorly through the skin near the lash line (see Fig. 12.7.22). An internal hordeolum occurs due to obstruction and infection of a meibomian gland. Initially, a painful edema and erythema localizes as an inflammatory abscess on the posterior conjunctival surface of the tarsus. In both external and internal lesions, cellulitis of the surrounding soft tissue may develop. Diagnosis is based on the clinical appearance and culture, with *Staphylococcus aureus* most frequently isolated. Hordeola frequently occur in association with blepharitis. Histopathology reveals an abscess or a focal collection of polymorphonuclear leukocytes and necrotic tissue.

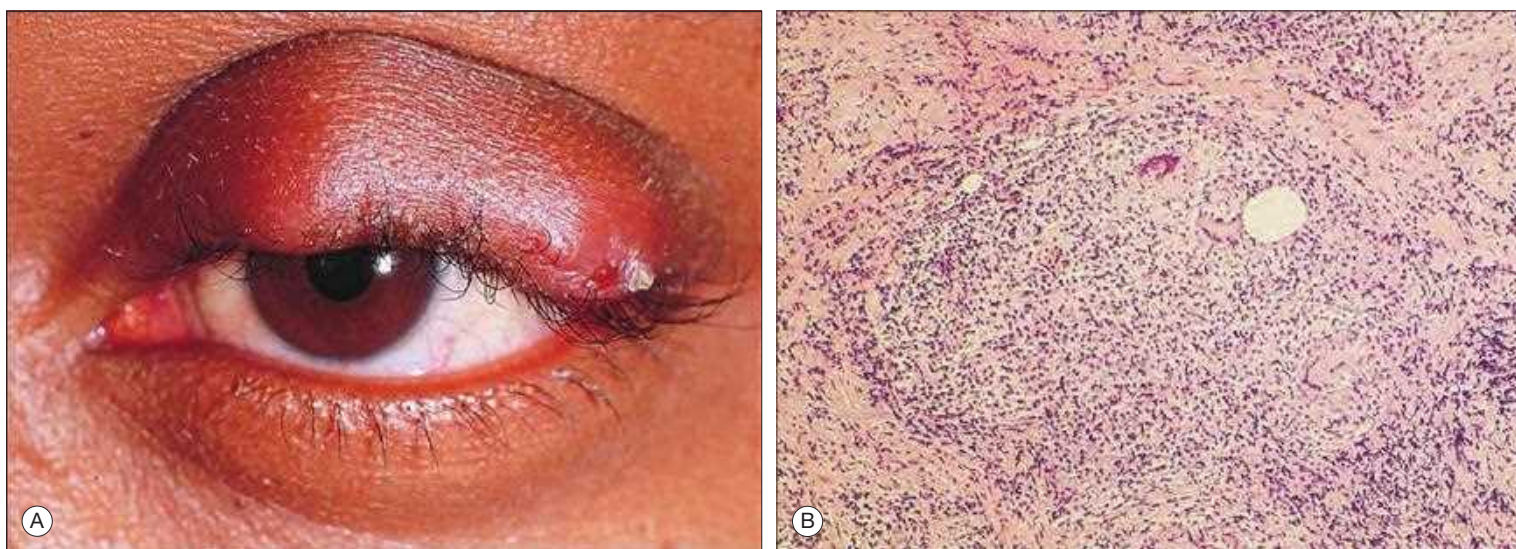
Although the inflammatory process usually is self-limited, with drainage and resolution occurring within 5–7 days, hot compresses and topical antibiotics help confine the spread of the lesion. Rarely, incision and drainage are necessary. Systemic antibiotics are used only if significant cellulitis exists. Treatment of accompanying blepharitis is helpful to prevent the formation of new lesions.

## INFECTIOUS LESIONS

### Molluscum Contagiosum

A common viral skin disease, molluscum contagiosum (MC) is caused by a large DNA pox virus. Infection usually arises from direct contact or fomites in children and by a sexually transmitted route in adults. The





**Fig. 12.7.22 Chalazion and External Hordeolum.** (A) The medial lesion of the upper eyelid appeared as a firm, painless nodule consistent with a chalazion. The lateral lesion caused pain and eyelid erythema, subsequently becoming more localized with drainage of purulent material through the skin surface. (B) A clear, circular area surrounded by epithelioid cells and multinucleated giant cells can be seen. In processing the tissue, lipid is dissolved out, leaving a clear space.



**Fig. 12.7.23 Molluscum Contagiosum.** (A) Multiple flesh-colored nodules affecting the lower eyelid. (B) Small intracytoplasmic, eosinophilic molluscum bodies occur in the deep layers of epidermis. The bodies become enormous and basophilic near the surface. The bodies may be shed into the tear film, where they cause a secondary irritative, follicular conjunctivitis.

typical lesion appears as a raised, shiny, white-to-pink nodule with a central umbilication filled with cheesy material. Lesions may be single or multiple, but usually fewer than 20 are present. Eyelid margin lesions may produce a secondary follicular conjunctival reaction. Other ocular manifestations include epithelial keratitis, pannus formation, conjunctival scarring, and punctal occlusion. Primary conjunctival or limbal lesions occur rarely.

Diagnosis of MC usually is based on the clinical appearance of the lesion. Biopsy rarely is required in an otherwise healthy individual. The differential diagnosis includes keratoacanthoma, verruca vulgaris, squamous papilloma, milia, and SCC or BCC (see Chapter 12.8).

Patients who have acquired immunodeficiency syndrome (AIDS) often have an atypical clinical picture of MC. Disseminated disease may be present and lesions often are more confluent. Patients may have 30 to 40 lesions on each eyelid, or a confluent mass (Fig. 12.7.23). Secondary keratoconjunctivitis develops less frequently.

Histopathology of MC shows invasive acanthosis, with lobules of epithelial hyperplasia invaginating into the dermis. The epithelium at the surface degenerates and sloughs into a central cavity that opens through a pore to the epidermal surface. Intracytoplasmic inclusions containing virions, referred to as *molluscum bodies*, are round and eosinophilic in the lower layers of the epidermis. These inclusions increase in size and are more basophilic in the granular and horny layers.

Usually, MC spontaneously resolves within 3 to 12 months, but the patient may be treated to prevent corneal complications, reduce transmission, and speed recovery. Various treatment options exist, including simple incision or excision, incision and curettage, cryosurgery, and electrodesiccation. Management is more difficult in patients with AIDS because of extensive involvement and recurrences. Hyperfocal cryotherapy has been effective in these patients.<sup>42</sup>

## Verruca Vulgaris

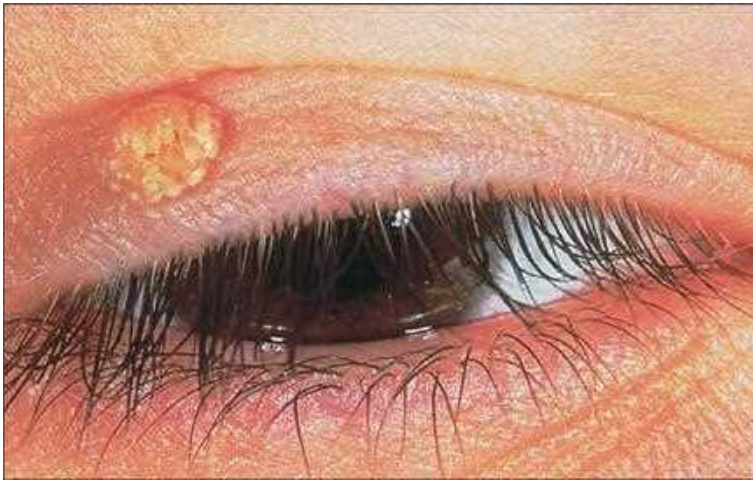
Verruca vulgaris, or the common cutaneous wart, is caused by epidermal infection with the human papillomavirus, which is spread by direct contact and fomites. Verruca vulgaris is more common in children and young adults and may occur anywhere on the skin, occasionally on the eyelid. Lesions appear elevated with an irregular, hyperkeratotic, papillomatous surface (Fig. 12.7.24). Lesions along the lid margin may induce mild papillary conjunctivitis due to shedding of virus particles into the tear film. Patients also may develop a superficial punctate keratitis and may have pannus formation. Primary conjunctival lesions also may occur.<sup>43</sup>

Diagnosis is based on the typical appearance and is confirmed by biopsy. Histologically, papillomatosis is present, with hyperkeratosis, acanthosis, and parakeratosis. Large, vacuolated keratinocytes are seen, with deeply basophilic nuclei surrounded by a clear halo. Observation is recommended if no ocular complications occur, because most lesions are self-limiting. Treatment, if necessary, is either cryotherapy or complete surgical excision. Incomplete excision may cause multiple recurrences.

## CONCLUSION

The eyelids may be affected by a variety of benign lesions, some indicative of local pathology, others associated with or resulting from systemic pathology. Some lesions may be identified readily by the clinical appearance and behavior, but many pose a diagnostic challenge.





**Fig. 12.7.24 Verruca Vulgaris.** Skin-colored, irregular lesion with a papillomatous surface appearing on the upper eyelid.

Most important is the differentiation of benign from malignant lesions, because management often differs. Biopsy with ocular pathology consultation is, thus, warranted for any suspicious-looking lesion.<sup>3</sup> Epithelial lesions that display painless growth, irregular or pearly borders, ulceration, induration, or telangiectasis should raise concern for malignancy. Signs that herald malignant change in pigmented lesions include irregular borders, asymmetrical shape, color change or presence of multiple colors, recent changes, or diameter greater than 5 mm.

In general, biopsy should precede all extensive tumor resections, even if the clinical diagnosis seems apparent. An incisional biopsy should be

performed for the diagnosis of large lesions before definitive therapy. Small lesions may be excised for both diagnosis and treatment.

## OUTCOMES

Most benign eyelid lesions have an excellent prognosis. The treatment varies according to site, diagnosis, concurrent systemic involvement, and other factors.

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# Eyelid Malignancies

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# 12.8

**Definition:** Cutaneous cancers that arise from the epidermis, dermis, or adnexal structures of the eyelid. Rarely, they may be metastatic from distant sites. They include a number of histologically distinct tumors from diverse skin cell types.

## Key Features

- Flat, eroded, or elevated lesion on the eyelid margin, eyelid skin, or brow.
- Nodular and well-circumscribed or irregular with indistinct borders.
- Ulcerated with a central crater or benign in appearance with some telangiectatic vessels.
- Slow, generally painless, growth.

## Associated Features

- Dilated blood vessels.
- Ectropion from skin contracture.
- Firm induration.
- Loss of eyelashes.
- Palpable preauricular nodes.
- Proptosis.
- Ptosis.
- Restricted ocular motility.
- Thickened eyelid margin.

## INTRODUCTION

Malignant lesions are common around the eyes, partly because many are induced by sun exposure or develop from sun-related benign lesions. Typically, most of these are small and grow slowly, which results in minimal concern for the patient and a low index of suspicion for the physician. Although the most common malignancies rarely metastasize, they can all be very destructive locally. Any periocular lesion that shows some growth, especially when associated with chronic irritation or bleeding, should undergo a diagnostic biopsy. Confirmation of histopathology is also mandatory before the patient is committed to a major resection or reconstructive procedure.

## BASAL CELL CARCINOMA

Basal cell carcinoma (BCC) is a malignant tumor derived from cells of the basal layer of the epidermis. The etiology is linked to excessive ultraviolet light exposure in fair-skinned individuals. Other predisposing factors include ionizing radiation, arsenic exposure, and scars. Although metastases are rare, local invasion is common and can be very destructive.

## EPIDEMIOLOGY AND PATHOGENESIS

BCC is the most common malignant tumor of the eyelids and constitutes 85%–90% of all malignant epithelial eyelid tumors at this site.<sup>1,2</sup> Over 99% of BCCs occur in white people; about 95% of these lesions occur between the ages of 40 and 79 years, with an average age at diagnosis of 60 years.<sup>3</sup> Rarely, they also may be seen in children.<sup>4</sup> BCC arises from a pluripotent stem cell in the epidermis that proliferates, amplifies, and eventually terminally differentiates.<sup>5</sup> Proposed mechanisms for BCC invasion include

enhanced tumor cell motility and collagenase content.<sup>1</sup> Having had one BCC is a prognostic factor for the development of additional lesions.

## OCULAR MANIFESTATIONS

Up to 50%–60% of BCCs affect the lower eyelid. The medial canthus is involved 25%–30% of the time. The upper eyelid is involved nearly 15% of the time, and the lateral canthus is only rarely involved (5%). On the basis of their histopathological presentation, BCCs may be classified into five basic types:

- Nodular-ulcerative.
- Pigmented.
- Morphea or sclerosing.
- Superficial.
- Fibroepithelioma.

Two additional, although very rare, types are the linear basal cell nevus and generalized follicular basal cell nevus.<sup>6</sup>

The nodular type of BCC, the most common lesion, has the classical appearance of a pink or pearly papule or nodule with overlying telangiectatic vessels. As the nodule grows in size, central ulceration may occur surrounded by a rolled border (Fig. 12.8.1). This appearance is often described as a “rodent ulcer.”

The pigmented BCC is similar to the noduloulcerative type in morphology but with brown or black pigmentation. These lesions represent the most common pigmented malignancy on the eyelids and may resemble malignant melanoma.

The morphea or sclerosing type of BCC appears as a flat, indurated, yellow–pink plaque with ill-defined borders. It may simulate a blepharitis or dermatitis. As it has a flat appearance, it may not be as clinically noticeable as others. However, this form of BCC is aggressive and may invade the dermis deeply. It characteristically occurs in the medial canthal region and may invade into the paranasal sinuses and orbit.

Superficial BCC appears as an erythematous, scaling patch with a raised pearly border. Fibroepithelioma BCC presents as a pedunculated or sessile smooth, pink nodule. Both the superficial and fibroepithelioma types typically arise on the trunk rather than the eyelid.<sup>7</sup>



**Fig. 12.8.1 Nodular Basal Cell Carcinoma of the Eyelid.** A firm, pink-colored left upper eyelid BCC is seen with raised border, superficial telangiectatic vessels, and characteristic central ulceration. These lesions are more commonly seen on the lower eyelid. (Courtesy Dr Morton Smith.)



TABLE 12.8.1 Differential Diagnosis of Periocular Malignancies

Simulating Lesion	BCC	SCC	SGC	MM
Basal cell carcinoma		X	X	
Malignant melanoma	X			
Sebaceous cell carcinoma	X	X		
Squamous cell carcinoma	X		X	
Squamous cell carcinoma in situ	X	X		
Actinic keratosis	X	X		
Radiation dermatitis	X			
Keratoacanthoma	X	X		
Cavernous hemangioma				X
Cutaneous horns	X			
Dermoid and sebaceous cysts	X			
Eccrine and apocrine cysts	X			
Inverted follicular keratosis		X		
Nevus cell and nevocellular nevi, pigmented lesions of epidermal and dermal melanocyte origin				X
Papillomatous lesions	X	X	X	
Pseudoepitheliomatous hyperplasia		X		
Seborrheic keratosis nevus	X	X		
Trichilemmoma		X		
Blepharitis	X		X	
Chalazion	X		X	
Eczema	X			
Fungal infections		X		
Hordeolum	X			
Psoriasis	X			
Seborrheic dermatitis	X			
Superior limbic keratoconjunctivitis			X	
Verruca vulgaris		X		
Conjunctival hemorrhage				X

BCC, Basal cell carcinoma; MM, malignant melanoma; SCC, squamous cell carcinoma; SGC, sebaceous gland carcinoma.

DIAGNOSIS

The diagnosis of BCC is initially made from its clinical appearance, especially with the noduloulcerative type with its raised pearly borders and central ulcerated crater. Definitive diagnosis, however, can be made only on histopathological examination of biopsy specimens.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of BCC and of other periocular malignant lesions may be divided into several categories: other malignant lesions, premalignant lesions, benign adnexal tumors and cysts, and inflammatory and infectious conditions (Table 12.8.1; see Chapter 12.7).<sup>8</sup> In many cases the diagnosis depends on histopathology.

SYSTEMIC ASSOCIATIONS

Basal cell nevus syndrome (Gorlin–Goltz syndrome) is inherited as an autosomal dominant disorder with high penetrance and variable expressivity. Basal cell nevus syndrome is rare, occurring in less than 1% of individuals with BCC.<sup>9</sup> The group of clinical findings described in 1960 as a syndrome by Gorlin and Goltz<sup>10</sup> includes:

- Multiple BCCs affecting the face, trunk, and extremities.
- Cysts of the jaw (odontogenic keratocysts).
- Skeletal abnormalities (e.g., bifid ribs).
- Neurological abnormalities (e.g., mental retardation, ectopic calcification, cerebellar medulloblastoma).
- Endocrine disorders (e.g., ovarian cysts and testicular disorders).<sup>7</sup>

Palmar and plantar pits also develop in young adulthood. The BCCs in this syndrome typically develop at puberty and have a predilection for the periorbital region and face.<sup>3</sup> Multiple lesions occur with a high rate of recurrence. Other rare BCC syndromes include Bazex syndrome, linear unilateral basal cell nevus, and Rombo syndrome.

Also, BCC may be associated with albinism, xeroderma pigmentosum, and nevus sebaceus.

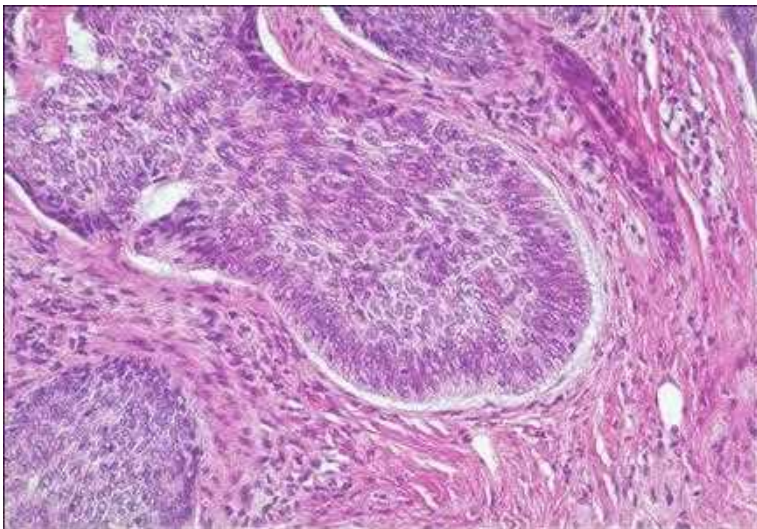


Fig. 12.8.2 Nodular Basal Cell Carcinoma of the Eyelid. Basophilic nests of proliferating epithelial tumor cells are shown with characteristic peripheral, palisading nuclei and stromal reaction. (Courtesy Dr Morton Smith.)

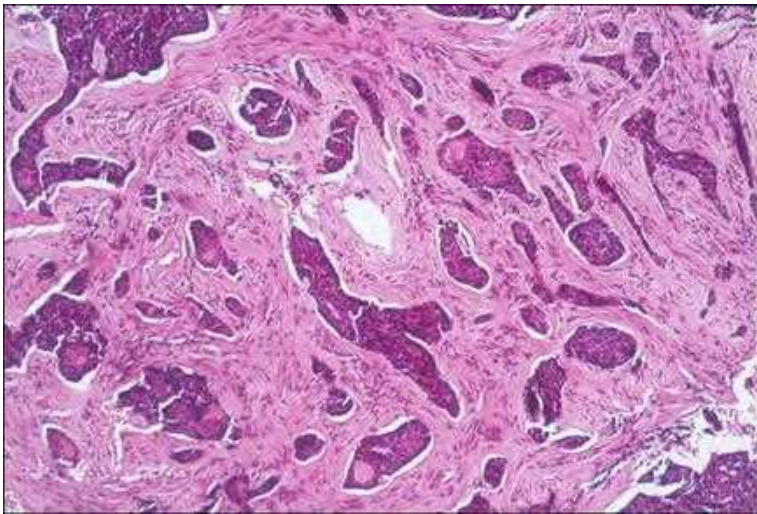


Fig. 12.8.3 Morphea or Sclerosing Type of Basal Cell Carcinoma of the Eyelid. Strands and islands of basaloid cells are shown within a dense connective tissue matrix. (Courtesy Dr Morton Smith.)

PATHOLOGY

The BCCs may be grouped as either undifferentiated or differentiated by their histopathological appearance.<sup>6</sup> The typical histopathology of an undifferentiated BCC consists of nests, lobules, and cords of tumor cells with peripheral palisading of cells and stromal retraction (Fig. 12.8.2). Undifferentiated BCCs include the solid noduloulcerative, morphea or sclerosing, pigmented, superficial, and fibroepithelioma forms. The morphea or sclerosing form is characterized by strands of proliferating, malignant basal cells in a fibrous stroma (Fig. 12.8.3).

The adenoid and metatypical or basosquamous are the most common differentiated forms. These tumors differentiate toward glandular structures with mucinous stroma. They exhibit morphological features between those of basal cell and squamous cell carcinoma. The metatypical BCCs are more aggressive and invasive with a higher recurrence rate and potential for metastasis.<sup>11</sup>

TREATMENT

The goal of therapy is the complete removal of tumor cells with preservation of unaffected eyelid and periorbital tissues. Although nonsurgical treatments such as cryotherapy, electrodesiccation, and laser ablation are advocated by some,<sup>12</sup> surgical therapy is the generally accepted treatment of choice for removal of BCCs.<sup>13</sup> Some BCCs, especially the morphea and multicentric types, may extend far beyond the area that is apparent clinically. Recurrences are generally more aggressive, infiltrative, and destructive than the primary tumor.<sup>2</sup> Therefore, histological monitoring of tumor margins is essential. Mohs’ micrographic surgery and excisional biopsy

with frozen section control are the two basic techniques available. An incisional biopsy may be performed before definitive treatment to confirm the clinical suspicion of BCC.<sup>14</sup>

## Surgery

Mohs' micrographic surgery provides the highest cure rate with the most effective preservation of normal tissue.<sup>15,16</sup> Tissue is excised in layers that provide a three-dimensional mapping of the excised tumor. These layers are processed as frozen sections and viewed under the microscope. Any areas of residual tumor are identified, and the map is used to direct additional tumor excision.<sup>17,18</sup> This technique is particularly useful for morphea and multicentric-type BCCs in the medial canthal region, which may exhibit subclinical extension to orbital bone or sinuses. Mohs' micrographic surgery technique is somewhat limited if the tumor has extended to the plane of orbital fat. In addition, it requires the collaboration of a Mohs' surgeon trained in both the surgical technique and interpretation of the dermatopathology.

Excisional biopsy with frozen section control is also an effective way to remove BCCs and can be performed by the ophthalmologist. Several studies have reported no recurrences after excision of BCCs with frozen section monitoring.<sup>19,20</sup> However, following simple excisional biopsy without frozen section control, recurrence rates up to 50% have been reported.<sup>21</sup>

Eyelid reconstruction should be performed within 2–3 days after tumor excision. Various reconstructive surgical techniques may be used, depending on the location and size of the residual defect.

## Radiation Therapy

Radiation therapy is generally not recommended in the initial treatment of periocular BCCs.<sup>22</sup> However, it may be useful in the treatment of advanced or recurrent lesions in the medial canthal region or elsewhere. Doses are in the range 4000–7000 cGy.<sup>23</sup> Radiation therapy is less effective in treating morphea BCCs, with the likelihood of BCC recurrence following radiotherapy being higher than that for previously described surgical techniques. A recurrence rate of 12% was noted in one series following radiation therapy.<sup>24</sup> Surgical management is very difficult after radiation treatment of an affected area. Radiotherapy complications include skin atrophy and necrosis, madarosis, cicatricial entropion and ectropion, dry eye syndrome, cataract, and corneal ulceration.<sup>25</sup> Radiation therapy is contraindicated in basal cell nevus syndrome and is associated with significant complications in patients who have scleroderma or acquired immunodeficiency syndrome (AIDS).

## Cryotherapy

Cryotherapy is often used to treat BCCs outside the periorbital area but has also been shown to be effective for eyelid tumors with less than a 1% recurrence rate.<sup>26</sup> Around the eyelids it may result in eyelid notching and malpositions, symblepharon formation with fornix foreshortening, and pigmentary changes. It is associated with a higher recurrence rate than the surgical approaches. Cryotherapy is contraindicated in lesions greater than 1 cm in diameter, medial canthal lesions, morphea-like lesions, and recurrent BCC.<sup>27</sup>

## Chemotherapy and Photodynamic Therapy

Topical, intralesional, and systemic chemotherapeutic agents—including topical 5% imiquimod, 5 fluorouracil, cisplatin, doxorubicin, bleomycin, and interferon—have been used to treat BCCs.<sup>28</sup> In a more recent nonrandomized trial, imiquimod resulted in a histological clearance rate of 39.5% at 40 months.<sup>29</sup>

Photodynamic therapy may be considered as an alternative treatment for large numbers of cutaneous BCCs (e.g., basal cell nevus syndrome). It has been shown to be effective for noninvasive low-risk tumors and results in excellent cosmetic outcomes.<sup>30</sup> Recurrence rates of 9% at 12 months have been seen, but improved outcomes were achieved with pretreatment and repeat cycles.<sup>31–32</sup>

## COURSE AND OUTCOME

Complete surgical excision of BCCs is almost always curative, because these lesions rarely metastasize. Incomplete primary resection is the main risk factor for recurrence of tumor and is especially more common with

a medial canthal location or morpheaform histology.<sup>30</sup> The incidence of metastasis ranges from 0.028% to 0.55%.<sup>7</sup> Tumor-related death is exceedingly rare, but when it does occur, it is usually caused by direct orbital and intracranial extension.

Orbital invasion is rare and management can be difficult. Risk factors for orbital invasion include medial canthal location, previous recurrence, large tumor size, more aggressive histological subtype, and perineural spread. Management requires a multidisciplinary approach. Although orbital exenteration is the treatment of choice in most cases, globe-sparing techniques may be used for selected patients with adjuvant radiotherapy and chemotherapy.<sup>33</sup>

## SQUAMOUS CELL CARCINOMA

Squamous cell carcinoma (SCC) is a malignant tumor of the squamous layer of cells of the epidermis. It is much less common than BCC on the eyelids and carries a greater potential for metastatic spread.<sup>34,35</sup>

## EPIDEMIOLOGY AND PATHOGENESIS

Typically, SCC affects elderly, fair-skinned individuals. In the region of the eye it is usually found on the lower eyelid. Although SCC is 40 times less common than BCC of the eyelid, it is more common than BCC on the upper eyelid and lateral canthus.<sup>31</sup>

The exact mechanism of the pathogenesis of SCC is not known. However, environmental and intrinsic stimuli initiate a process in which cell growth and regulation are lost. Most periorbital SCCs arise from actinic lesions, but they may also arise de novo. Environmental factors may contribute to the development of SCC, including cumulative ultraviolet radiation (sun exposure), ionizing radiation, arsenic ingestion, psoralen plus ultraviolet A (PUVA) therapy for psoriasis, and the human papilloma virus.<sup>32</sup>

Intrinsic factors that contribute to the development of SCC include the autosomal recessive conditions xeroderma pigmentosum and oculocutaneous albinism. Chronic skin dermatoses, ulceration, and scarring are also associated with the development of this tumor. In fact, scarring of the skin is the most common intrinsic factor leading to SCC in black patients.<sup>33</sup>

## OCULAR MANIFESTATIONS

Typically, SCC presents as an erythematous, indurated, hyperkeratotic plaque or nodule with irregular margins. These lesions have a high tendency toward ulceration and tend to affect the eyelid margin and medial canthus. Lymphatic spread and perineural invasion are possible.

## DIAGNOSIS

The diagnosis of SCC is often suspected from the clinical appearance. However, because so many other malignant and benign processes can be confused with SCC, the diagnosis requires biopsy for histological confirmation.

## PATHOLOGY

Well-differentiated SCC exhibits polygonal cells with abundant eosinophilic cytoplasm and hyperchromatic nuclei (Fig. 12.8.4). Dyskeratosis, keratin pearls, intercellular bridges, and abnormal mitotic figures are prominent. Poorly differentiated lesions show little keratinization and fewer intercellular bridges.<sup>7</sup>

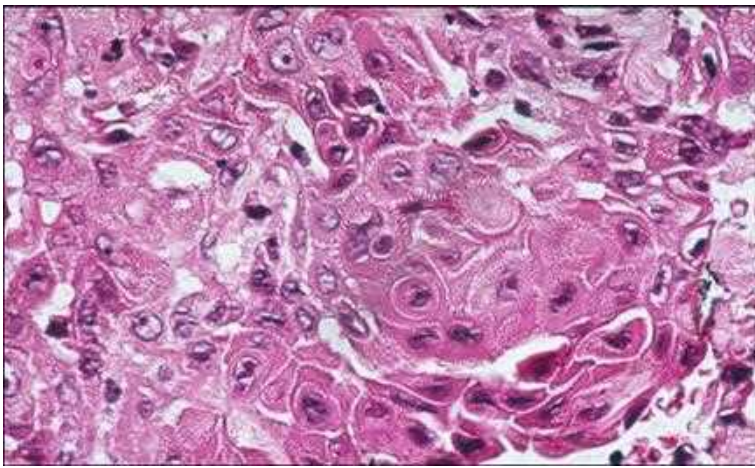
## TREATMENT

Before any therapy is planned, the clinical diagnosis of SCC should be confirmed by incisional biopsy.<sup>36</sup> Compared with BCC, SCC is a more aggressive and invasive tumor, but early SCC lesions of the eyelid rarely metastasize. Surgery, irradiation, and cryotherapy management options are similar to those described previously for BCC.

## COURSE AND OUTCOME

Wide local surgical excision, either with the Mohs' technique or under frozen section control, is usually curative. Advanced cases may be associated with metastasis to the preauricular and submandibular lymph nodes, which heralds a more guarded prognosis. Invasion of the deep orbital





**Fig. 12.8.4 Squamous Cell Carcinoma of the Eyelid.** Anaplastic squamous cells with hyperchromatic nuclei, abundant eosinophilic cytoplasm, and intercellular bridges. (Courtesy Dr Morton Smith.)



**Fig. 12.8.5 Sebaceous Cell Carcinoma of the Eyelid.** A large, firm, irregular nodule with yellowish coloration of the left upper eyelid is shown. Associated inflammation, telangiectatic vessels, and loss of cilia are observed. (Courtesy Dr Morton Smith.)

tissues may sometimes be seen and frequently requires orbital exenteration for cure.

## SEBACEOUS GLAND CARCINOMA

Sebaceous gland carcinoma (SGC) is a highly malignant neoplasm that arises from the meibomian glands, the glands of Zeis, and the sebaceous glands of the caruncle and eyebrow. It is an aggressive tumor with a high recurrence rate, a significant metastatic potential, and a notable mortality rate.<sup>34,35,37</sup>

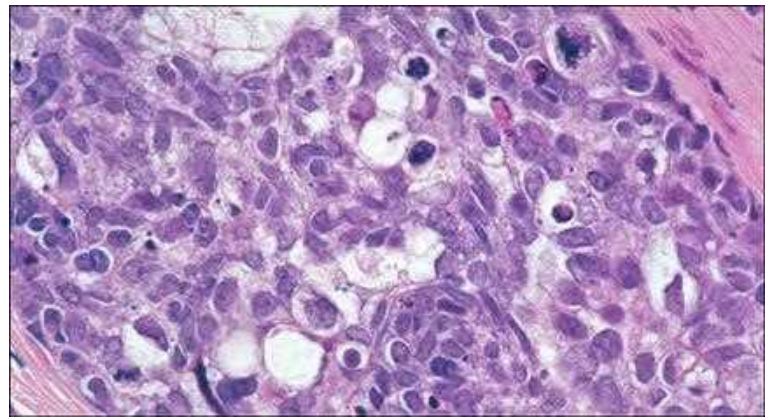
## EPIDEMIOLOGY AND PATHOGENESIS

Although it is relatively rare, SGC is the third most common eyelid malignancy, accounting for 1%–5.5% of all eyelid cancers. It affects all races, occurs in women more often than men, and usually presents in the sixth to seventh decades, but cases in younger patients have been reported.<sup>38</sup>

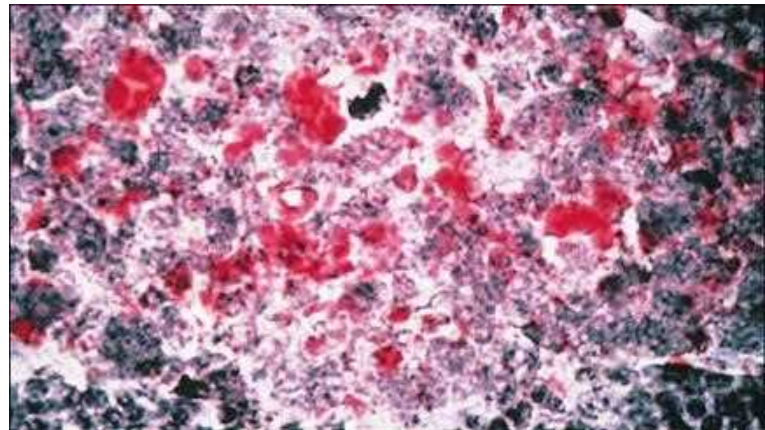
The cause of SGC is unclear. However, there are reported associations that link SGC with prior radiation therapy<sup>39</sup> and with the production of nitrosamines and photosensitization from prior diuretic use.<sup>40</sup>

## OCULAR MANIFESTATIONS

The upper eyelid is the site of origin in about two-thirds of all cases, but SGC may arise from any of the periocular structures previously mentioned<sup>7</sup> and may have a variety of clinical appearances. It often presents as a firm, yellow nodule that resembles a chalazion. It may present as a plaque-like thickening of the tarsal plate with destruction of meibomian gland orifices and tumor invasion of eyelash follicles leading to madarosis or loss of lashes (Fig. 12.8.5). Also, SGC may mimic a chronic blepharoconjunctivitis,



**Fig. 12.8.6 Sebaceous Cell Carcinoma of the Eyelid.** Large, hyperchromatic neoplastic cells with vacuolated (frothy), basophilic cytoplasm are observed. (Courtesy Dr Morton Smith.)



**Fig. 12.8.7 Lipid Stain (Oil Red O) of Sebaceous Gland Carcinoma.** Tumor cells stain strongly positive (red) for lipid. (Courtesy Dr Morton Smith.)

meibomianitis, or chalazion that does not respond to standard therapies, thus the term “masquerade syndrome.”

SGC tends to invade overlying epithelium, which may form nests of malignant cells (pagetoid spread), or may result in diffuse spread that replaces the entire thickness of the conjunctiva (intraepithelial carcinoma). The carcinoma may exhibit multicentric spread to the other eyelid, conjunctiva, or corneal epithelium.<sup>7</sup> This neoplasm may spread through the canaliculus to the lacrimal excretory system and even to the nasal cavity.<sup>40</sup>

## DIAGNOSIS

The clinical appearance of SGC must be confirmed by a full-thickness wedge biopsy of the affected eyelid. Because of potential multicentric spread, multiple biopsy specimens should also be taken from the adjacent bulbar and palpebral conjunctiva and the other ipsilateral eyelid. The pathologist should be alerted to the clinical suspicion of SGC, and fresh tissue should be submitted to pathology so that special lipid stains may be performed on the specimen to confirm the diagnosis.<sup>41</sup>

## PATHOLOGY

Dysplasia and anaplasia of the sebaceous lobules in the meibomian glands are exhibited by SGC, with associated destruction of tarsal and adnexal tissues. Intraepithelial (pagetoid) spread to conjunctiva distant from the primary tumor may be observed. The intraepithelial spread may resemble SCC in situ.

Typically, SGC shows highly pleomorphic cells arranged in lobules or nests with hyperchromatic nuclei and vacuolated (foamy or frothy) cytoplasm due to a high lipid content (Fig. 12.8.6). Histologically, SGC may resemble the appearance of SCC. However, the cytoplasm in SGC tends to be more basophilic compared with the eosinophilic appearance of SCC. Also, SCC cells tend not to exhibit a regular, lobular arrangement. Four histological patterns have been described: lobular, comedocarcinoma, papillary, and mixed. Special stains for lipid (e.g., oil red O) on fresh tissue may assist in the histopathological diagnosis of SGC (Fig. 12.8.7).<sup>7</sup>



Periocular sebaceous carcinoma can be challenging to diagnose using histomorphology alone and can have overlapping features with both BCC and SCC. Immunohistochemistry can help differentiate these entities, especially epithelial membrane antigen, Ber-Ep4, androgen receptor, and adipophilin.<sup>42</sup>

## TREATMENT

Successful treatment of SGC depends largely on heightened clinical suspicion and awareness of the possible masquerade syndrome followed by early confirmatory biopsy. Wide surgical excision with microscopical monitoring of the margins is the procedure of choice.<sup>43</sup> Mohs' micrographic surgical excision may be used, but it may not be as successful as in BCC or SCC because of the possibility of multicentric and pagetoid spread. If the tumor is very large or recurrent with demonstrated spread to bulbar conjunctiva, to the other eyelid, or to orbital tissues, a subtotal or complete exenteration may be necessary.<sup>3,40</sup> If evidence of spread to regional lymph nodes is present, the patient should be referred to a head and neck surgeon for possible lymph node or radical neck dissection.

Radiation therapy may be considered as an adjunct to local surgery. However, primary treatment of the tumor with irradiation alone is inadequate. Few studies are available, but a 5-year survival of 80% with a progression-free rate of 93% has been reported following doses of 50–66.6 Gy.<sup>44</sup>

## COURSE AND OUTCOME

An invasive, potentially lethal tumor, SGC may cause extensive local destruction of eyelid tissues. It carries a risk of metastasis to preauricular and submandibular lymph nodes or may spread hematogenously to distant sites. It may invade locally into the globe, the orbit, the sinuses, or the brain. In a recent review of 60 cases mostly treated with surgical excision and cryotherapy, 88% were alive and well after a mean follow-up of 41 months. Orbital exenteration was necessary in 13%, local recurrence developed in 18%, and distant metastasis occurred in 8%.<sup>45</sup>

## MALIGNANT MELANOMA

Cutaneous malignant melanoma is an invasive proliferation of malignant melanocytes. Melanoma may also arise from the conjunctiva, where it constitutes a distinct entity (see Chapter 4.8). Cutaneous malignant melanoma may be classified into four different types<sup>7</sup>:

- Lentigo maligna melanoma (5%).
- Superficial spreading melanoma (70%).
- Nodular melanoma (16%).
- "Other," including acral lentiginous melanoma (9%).

Nodular melanoma is the most common type to affect the eyelids.<sup>46</sup>

## EPIDEMIOLOGY AND PATHOGENESIS

Cutaneous malignant melanoma of the eyelid accounts for about 1% of all eyelid malignancies.<sup>47</sup> The incidence of malignant melanoma has been increasing and causes about two-thirds of all tumor-related deaths from cutaneous cancers. The incidence increases with age but remains relatively stable from the fifth to the seventh decades.<sup>48</sup>

Risk factors for the development of malignant melanoma include congenital and dysplastic nevi, changing cutaneous moles, excessive sun exposure and sun sensitivity, family history (genetic factors), age greater than 20 years, and white race. Malignant melanoma is 12 times more common in white people than in black people and 7 times more common in white people than in Hispanic people. In contrast to BCC, a history of severe sunburns rather than cumulative actinic exposure is thought to be a major risk factor for developing malignant melanoma.<sup>48</sup>

Cutaneous malignant melanoma arises from the neoplastic transformation of intraepidermal melanocytes derived from the neural crest. Initially, a noninvasive horizontal growth phase occurs, which is followed by an invasive vertical growth phase.

## OCULAR MANIFESTATIONS

Lentigo maligna melanoma and its precursor lentigo maligna (melanotic freckle of Hutchinson) present as a flat macule with irregular borders and variable pigmentation. It may have a long in situ (horizontal growth) phase



**Fig. 12.8.8 Lentigo Maligna Melanoma (Hutchinson Freckle).** Clinical appearance of acquired pigmented lesion of the left lower lid.

in which the pigmentation extends for up to several centimeters in diameter and lasts many years. This phase is associated with variable growth and spontaneous regression of the lesion with alteration in pigmentation. It typically occurs in sun-exposed areas and commonly involves the lower eyelid and canthi (Fig. 12.8.8). Superficial spreading melanoma is typically a smaller pigmented lesion with mild elevation and irregular borders. It tends to have a more rapid progression to the invasive phase, characterized by development of nodules and induration. Nodular melanoma may present as a markedly pigmented or amelanotic nodule that rapidly increases in size with associated ulceration and bleeding. Acral lentiginous melanoma occurs on the palms, soles, and distal phalanges as well as on the mucous membranes.<sup>7,48</sup>

## DIAGNOSIS

The diagnosis of cutaneous malignant melanoma is made by clinical suspicion and confirmed with excisional biopsy and histopathological examination.

## SYSTEMIC ASSOCIATIONS

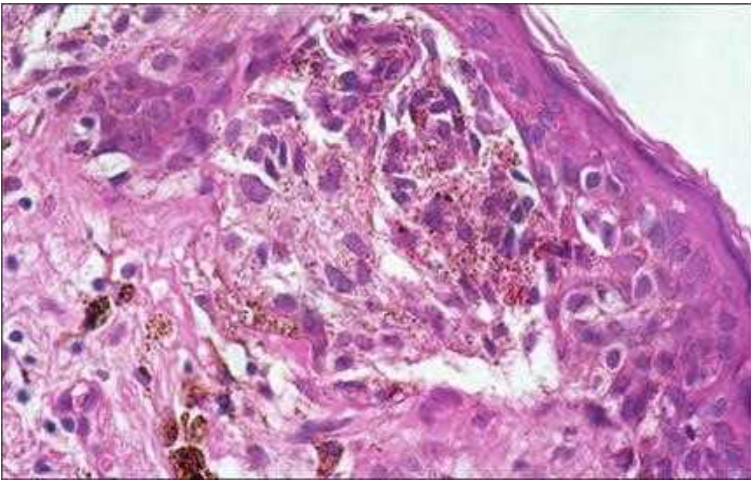
The dysplastic nevus syndrome (also known as B-K mole syndrome) is an autosomal dominantly inherited condition characterized by multiple large, atypical cutaneous nevi.<sup>49</sup> The moles appear in childhood and continue to grow through adulthood. Patients with this syndrome have a high risk of developing malignant melanoma.<sup>50</sup>

## PATHOLOGY

Lentigo maligna is hyperpigmentation in the epidermis characterized by a diffuse hyperplasia of atypical melanocytes throughout the basal cell layer. The entity is regarded as lentigo malignant melanoma when dermal invasion occurs during the transition to the vertical growth phase (Fig. 12.8.9). Superficial spreading melanoma is typified by atypical melanocytes that occur in nests or singly throughout all levels of the epidermis. Pagetoid spread into the epidermis is characteristic. A mixture of epithelioid, spindle, and nevus-like cells may be present. In nodular melanoma, dermal invasion is always present; it exhibits large, anaplastic epithelioid cells.

## TREATMENT

Wide surgical excision, with 1 cm of skin margins (when possible) confirmed by histological monitoring, is the procedure of choice for treatment of cutaneous malignant melanoma of the eyelid. Sentinel lymph node biopsy should be performed for tumors 1 mm thick or more, those with more than 1 mitotic figures per high-power field, and/or those with histological ulceration.<sup>51</sup> A metastatic evaluation is also recommended for patients who have such tumors. Cryotherapy may be useful in treating some conjunctival malignant melanomas, but it is not an effective treatment option for cutaneous malignant melanoma of the eyelid.<sup>45</sup> More



**Fig. 12.8.9 Malignant Melanoma.** Subepithelial pigmented, spindle-shaped melanoma cells invade the dermis. (Courtesy Dr Morton Smith.)

recently, topical 5% imiquimod has shown some encouraging results for periocular lentigo maligna.<sup>52</sup>

## COURSE AND OUTCOME

Prognosis and metastatic potential are linked to the depth of invasion and thickness of the tumor. Clark and associates<sup>53–54</sup> correlated prognosis with depth of invasion, characterized at five levels:

- Level 1: tumor confined to the epidermis with an intact basement membrane.
- Level 2: tumor extension beyond the basement membrane with early invasion of the papillary dermis.
- Level 3: tumor fills the papillary dermis and reaches the interface between the papillary and reticular dermis.
- Level 4: tumor penetrates the reticular dermis.
- Level 5: tumor invasion of the subcutaneous tissues.

For lentigo maligna melanoma in levels 1 and 2 there is a 100% survival rate after therapy, whereas for nodular melanoma extending to level 4 there is a 65% survival rate following treatment. The survival drops dramatically to only 15% with extension of any type to level 5.<sup>55</sup>

Breslow<sup>56</sup> related prognosis to tumor thickness—malignant melanomas less than 0.76 mm thick are associated with a 100% 5-year survival rate after excision; tumors greater than 1.5 mm in thickness are associated with a less than 50% 5-year survival rate. Therefore nodular melanoma has the worst prognosis, and lentigo maligna melanoma has the most favorable prognosis of all tumor types. The Clark and Breslow systems may be used in conjunction to predict the prognosis for patients with malignant melanoma.

In a review by Tahery et al.,<sup>57</sup> malignant melanoma involving the eyelid margin was found to have a poorer prognosis than eyelid malignant melanoma that did not affect the margin. This worse prognosis was attributed to conjunctival involvement in the eyelid margin tumors.

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# Evaluation and Management of Periorbital Soft Tissue Trauma

12.9

*Ivan Vrcek, Marie Somogyi, Vikram D. Durairaj*

**Definition:** Injuries varying from simple skin abrasions to more complex cases with extensive tissue loss and underlying fractures of the facial skeleton caused by blunt or penetrating facial trauma.

## Key Features

- Partial-thickness eyelid injury.
- Eyelid margin lacerations.
- Eyelid injuries with tissue loss.
- Full-thickness eyelid injury.

## INTRODUCTION

Periorbital soft tissue injuries, including blunt and penetrating trauma to the eyelids and lacrimal apparatus, are common presentations to emergency departments and outpatient ophthalmology clinics.<sup>1-3</sup> These injuries can vary from simple skin abrasions to more complex wounds that involve de-gloving facial injury with damage to the lacrimal apparatus, globe, and underlying periorbital bony anatomy. Following a thorough assessment of the patient's vital signs and overall medical stability, a thorough examination that includes a complete ophthalmic examination is required. Treatment of these injuries requires careful identification of the anatomical structures involved and a repair that focuses primarily on restoring normal function and preserving globe integrity.

Secondarily the repair should strive to recreate normal anatomy in a way that respects the aesthetic facial subunits to maximize the patient's long-term cosmesis. Postoperative care of these patients can be complex, including revision surgery to restore lacrimal function, interventions to optimize scar management, and surgical correction of chronic eyelid malposition. In this chapter, we discuss these injuries in detail with an emphasis on the diagnosis, treatment, and postoperative care of these often challenging patients.

## PREOPERATIVE EVALUATION AND DIAGNOSTIC APPROACH

### Systemic Stabilization

The evaluation and treatment of periorbital injuries begins after the patient has been stabilized and life-threatening injuries addressed. A complete and thorough assessment is required to assure that life- and limb-threatening injuries have been adequately assessed and managed before the periorbital area is addressed.

### Medical History

A complete history is obtained, with an emphasis on the time course and circumstances of the injury. In children and the elderly, consideration must be given to the possibility of nonaccidental trauma. A history consistent with injuries from high-speed projectile particles typically requires the appropriate imaging studies to determine the presence of intraocular

or intraorbital foreign bodies. Animal and human bites deserve particular attention and are managed accordingly with the administration of appropriate antibiotics.

## Examination

Once the patient is medically stable, a comprehensive ophthalmic and adnexal assessment is required. We advocate a methodical and stepwise approach to this examination. The periorbital region is first assessed, beginning with the skin envelope. Attention is directed to the presence, location, and depth of skin and subcutaneous injury. Particular emphasis is placed on a thorough examination of the eyelid margin and the medial and canthal regions because lacerations in these areas can be difficult to immediately identify. Injuries to the skin and soft tissue must be carefully documented and their dimensions recorded. Photography is often helpful for documentation in these situations. Lacerations of the eyelid margin should be carefully examined for the presence of full-thickness margin-involving lacerations. The medial canthal area must be examined for the presence of injuries to the lacrimal system and medial canthal tendon because such injuries can have long-lasting sequelae. Lateralization of the punctum is a sign that a canalicular laceration and/or damage to the medial canthal tendon is likely. Similarly, poor apposition of the eyelid to the globe medially also suggests damage to the medial canthal tendon.<sup>3,4</sup> If an injury to the lacrimal system is suspected, lacrimal probing with or without irrigation can be performed. In many cases, a knowledge of medial canthal anatomy makes probing and irrigation unnecessary. For example, if there is a full-thickness laceration medial to the punctum and the eyelid is lateralized, the likelihood of canalicular injury is extremely high.<sup>3,4</sup> The lateral canthal tendon integrity must also be assessed and repaired if indicated.

In analyzing the extent of soft tissue injury to the eyelids, it is helpful to conceptualize the eyelid in terms of anterior, middle, and posterior lamella. The anterior lamella is composed of the skin and orbicularis. The middle lamella is composed of the tarsus, lower eyelid retractions, Müller's muscle, levator muscle, and septum. The palpebral conjunctiva constitutes the posterior lamella. Immediately recognizing the lamellae involved can aid the surgeon in identifying the particular anatomical structures that must be addressed. In addition, reconstructive maneuvers often treat these lamella as functional subunits in the eyelid.

A detailed understanding of neurovascular anatomy is also required, and care must be directed to injuries that may involve branches of the facial nerve and critical periorbital vasculature.

Following assessment of the skin envelope and adnexa, the periorbital bony anatomy is assessed. This can be accomplished by carefully and methodically palpating the lateral, superior, and inferior orbital rims. The nasal sidewall is also assessed for step-offs and deformities. A low threshold for obtaining radiographic studies should be maintained as bony orbital trauma may not be immediately obvious.

The cranial nerves are examined sequentially with particular focus on the frontal and zygomatic branches of the facial nerve and cranial nerves III, IV, and VI. It is important to assess sensation in the territories of the first and second divisions of the fifth cranial nerve. Attention is then directed toward the ophthalmic portion of the examination.

The ophthalmic examination should proceed in a similar methodical stepwise fashion. Visual acuity, pupil examination, intraocular pressure testing, extraocular motility, and confrontation visual field testing are the cornerstones of a complete ophthalmic examination and should be performed in every patient where possible. Next, a complete ophthalmic examination is performed. We find it helpful to proceed methodically from

anterior to posterior. The conjunctiva and sclera are examined first with an emphasis on detecting lacerations. Examiners should be aware that large amounts of subconjunctival hemorrhage may obscure a scleral laceration, and if indications exist, a low threshold should be maintained for operative globe exploration. The cornea is examined next. Fluorescein staining is a useful adjunct, both for detection of abrasions and for exploring Seidel positivity. The anterior chamber is examined next with care taken to ascertain depth as well as the presence of foreign material, cell and flare, and synechiae. The lens is examined next. A sectoral cataract or dislocation may indicate penetrating injury. A full dilated examination is then performed to examine the vitreous and retina.

In situations where globe injury is suspected, a shield is placed over the eye in question without pressure on the eye. It is important to perform a full and comprehensive examination of the fellow eye.

Ancillary Testing

In most emergency department settings, basic laboratory studies typically have been performed. If the injury is chronic and purulent, a culture is warranted to guide antibiotic therapy. In many scenarios, radiographic testing, typically computed tomography (CT), is indicated as the test of choice. There should be a low threshold to obtain a CT scan, as bony trauma in the orbit can often go undetected.<sup>5</sup> Additionally, imaging is often very helpful in the event that retained foreign material is present in the soft tissue or the globe itself. Caution must be used if magnetic resonance imaging (MRI) is planned, as there may be retained metallic foreign material.

Documentation

All injuries are documented precisely and completely with a detailed description in the patient's charts. Photographic documentation is advised in all cases. Bullets and other projectiles must be retained and marked so that no break occurs in the chain of evidence. The medicolegal implications can be significant, so every effort must be made to complete the preoperative documentation of every injury.<sup>6</sup>

Infection Prophylaxis

Depending on the mechanism of injury, preventing infection is of the utmost concern. Although the role of antibiotic prophylaxis has been controversial,<sup>7–12</sup> we advocate thoughtful use of appropriate antibiotic prophylaxis. In the case of obviously contaminated wounds with extensive injury, thorough washout should be performed with a low threshold for the use of systemic antibiotic prophylaxis. Less extensive injuries and superficial abrasions may not require systemic antibiotics, but topical antibiotic ointment should be used. The patient should be queried regarding their tetanus immunization history and provided a tetanus vaccine if the patient is not up to date or unaware of their last vaccination (Table 12.9.1).<sup>6</sup> In the case of an animal bite, all information about the animal's history, the owner of the animal, and site of injury must be recorded and the local animal care department notified. In these situations, the standard rabies protocol must also be followed.<sup>6–8</sup>

The role of antibiotic prophylaxis in cases of animal bites has been controversial.<sup>8–12</sup> Cat bites carry a high risk for infection, mainly with *Pasteurella multocida*. The mechanism of injury, typically a deep puncture wound, increases the risk of contamination and subsequent infection. Infection

prophylaxis should be initiated with either amoxicillin/clavulanate or penicillin VK 500 mg a day for 5–7 days.<sup>8</sup> In penicillin-allergic patients, tetracycline can be used as an alternative. A more detailed discussion on dog bites can be found later, but these injuries also carry risk of infection. Thorough washout is required, and antibiotic prophylaxis should be strongly considered in all wounds that are surgically closed and in high risk injuries. Amoxicillin/clavulanate is the antibiotic of choice.<sup>8–11</sup>

Human bite injuries also carry a high risk for infection due to the large amount of bacteria present. As a result, it is necessary to provide appropriate broad-spectrum antibiotic coverage such as penicillin, amoxicillin/clavulanic acid, cephalexin, or ciprofloxacin.<sup>8–11</sup>

Almost universally following a traumatic injury, it is prudent to copiously irrigate all injured tissue with antibiotic irrigation solution. Any remaining foreign material should also be removed to prevent future infection.

Timing of Repair

The timing of surgical repair is dependent on many factors. Ideally, all injuries would be repaired almost immediately following the initial injury. First and foremost, the patient must be systemically evaluated for any signs of more life-threatening injuries. Once the patient has been cleared and thoroughly examined, every effort should be made to arrange for prompt surgical repair. The timing for anesthesia may also be dependent on the patient's last intake of food. Depending on the nature of the patient's injuries, there may be multiple specialists involved, which also takes coordination and may result in a delay. The best chance for successful restoration of function and cosmesis exists in the first surgery, so it is in both the surgeon and the patient's best interest to arrange for the personnel needed.

In some cases, the patient has more pressing systemic issues that have to be addressed first. In these circumstances, waiting 24–48 hours does not typically negatively affect the patient, but it is recommended to initiate an antibiotic regimen to prevent secondary infection of the open wound. The wound should also be kept moist with saline-soaked gauze and topical ophthalmic lubrication to prevent exposure keratopathy.

ANESTHESIA

There are many factors that influence the choice of anesthetic. First and foremost, the patient's age often dictates the type of anesthesia, with general anesthesia being the treatment of choice in pediatric patients, whereas adults may tolerate intravenous sedation with local anesthetic. Many adult injuries can even be repaired using only local anesthetic or regional anesthetic. Irrespective of the patient's age, extensive soft tissue injuries and bony fractures are often best performed under general anesthetic.

Regardless of the type of systemic anesthesia, it is always recommended to provide local infiltrative or regional anesthetic for both analgesia and hemostasis. Typically, 1%–2% lidocaine with 1:100 000 epinephrine in combination with 0.5%–0.75% bupivacaine is used to provide both immediate and long-term anesthetic, taking advantage of lidocaine's short onset of action and bupivacaine's longer duration of action. Furthermore, the addition of hyaluronidase will facilitate local infiltration of tissues with less distortion of tissue planes. Nerve blocks are an excellent adjunct to local anesthetic to provide regional coverage without excessive tissue distortion. In the periorbital region, this is successfully accomplished through supra-orbital (V<sub>1</sub>) and infraorbital (V<sub>2</sub>) nerve blocks.<sup>13</sup>

TREATMENT

General Concepts

In patients with eyelid trauma, the first step in planning reconstruction is to identify which anatomical structure(s) are violated.<sup>14</sup> In this way, one first defines the problem before developing a plan for repair. Guiding principles in reconstruction include recreating normal anatomy, restoring functional units, and secondarily, respecting aesthetic facial subunits to produce the most cosmetically acceptable result possible.<sup>15</sup> The primary function of the eyelids, for example, is protection of the globe. Depending on the degree of disruption to this protective mechanism, severe injury to the globe can result over a period of hours to days due to desiccation, ulceration, and infection.<sup>6</sup>

Conceptualizing the eyelids in terms of lamellae, as described earlier, can be helpful in devising a reconstructive plan. By identifying the lamellar deficiencies, one can identify the anatomical problem created by the injury. The reconstruction then focuses on recreating the necessary lamellae.

TABLE 12.9.1 Guidelines for Tetanus Prophylaxis in Wound Treatment

Immunization History	Clean, Minor Wound	Other Type of Wound
Uncertain history	Tetanus and diphtheria toxoids <sup>a</sup>	Tetanus and diphtheria toxoids + tetanus immune globulin
None or one previous dose	Tetanus and diphtheria toxoids <sup>a</sup>	Tetanus and diphtheria toxoids + tetanus immune globulin
Two previous doses	Tetanus and diphtheria toxoids <sup>a</sup>	Tetanus and diphtheria toxoids <sup>b</sup>
More than three previous doses	None unless the last dose is more than 10 years previously	None unless the last dose is more than 10 years previously

<sup>a</sup>Adult type; for children less than 7 years of age, DTP (diphtheria, tetanus, pertussis).

<sup>b</sup>For wounds more than 24 hours old, add tetanus immune globulin.

Adapted from Mustarde JC. Eyelid reconstruction. Orbit 1983;1:33–43.

Reconstructive surgery requires an expert knowledge of the local anatomy. In particular, understanding the blood supply to the eyelids is critical to the success of reconstructive maneuvers. Fortunately, the eyelids are exceptionally well-vascularized tissues, but preserving the integrity of the peripheral and marginal arcades must be carefully considered.

Finally, it is recommended to take advantage of the many successful, well-established techniques in eyelid reconstruction that have been utilized following tumor excision, including advancement and rotational flaps, tarsoconjunctival flaps, and periosteal flaps.<sup>6,16,17</sup>

## COMMON PATTERNS OF EYELID INJURY

### Partial-Thickness Eyelid Injuries and Abrasions

Not all periorbital injuries require surgical intervention. In some cases, wounds may be allowed to heal by second intention with close observation over time.<sup>18,19</sup> Small partial-thickness lacerations that do not involve the eyelid margin may fall in this category. Similarly, abrasions to the eyelid skin do not always require surgical intervention. Indeed, if there is epidermal tissue loss and one attempts to approximate intact epidermis, eyelid malposition and distortion may result by the alteration of normal eyelid architecture.<sup>18,19</sup>

In these situations, appropriate wound care is required to obtain an optimal result. Lubrication with ophthalmic antibiotic ointment is the mainstay of encouraging wound healing over the ensuing days. If the wound is dirty or is suspected of being contaminated, a thorough washout is recommended. Hydrogen peroxide can be used to keep the wound sterile. Excessive use of hydrogen peroxide, however, will impede wound healing.

On the other hand, sutured closure is an appropriate course of action if a superficial partial-thickness laceration exists that involves the epidermis and can be reapproximated without distorting normal architecture. In most cases, the orbicularis muscle does not require a separate layer of closure; indeed, doing so may result in architecture disruption in some situations. Typically, 6-0 gauge suture represents a suitable choice to impart the necessary strength to maintain adequate closure. The suture material to be used is dependent on a variety of variables, including the location of the laceration, the reliability and age of the patient, and surgeon preference. In our practice, lacerations that will be concealed in the eyelid crease are well suited to the use of absorbable sutures. Similarly, children and patients who may have difficulty with follow-up are good candidates for absorbable sutures. Lacerations that will not conceal well in the eyelid crease in patients who will reliably follow up may be closed with nylon or polypropylene sutures to be removed in 6-7 days. In all cases, patients are instructed to lubricate the wound with ophthalmic antibiotic ointment for at least 1 week following repair.

Wounds that violate the orbital septum should be treated as deep partial-thickness lacerations, discussed in the next section.

### Deep Partial-Thickness and Full-Thickness Eyelid Lacerations

Lacerations that penetrate the orbital septum or represent true full-thickness nonmarginal lacerations typically require timely surgical repair. These lacerations often demonstrate significant anatomical injury and infection risk. Thus we recommend repair in a sterile setting with copious washout using antibiotic solution and careful closure.

Thoughtful closure should respect anatomical planes and consider the future healing process. Each layer of the eyelid should be inspected for integrity. The conjunctiva and Müller's muscle may be approximated with buried sutures, but in many cases these layers can be carefully reapproximated without sutured closure. Although a surgeon can attempt to isolate and repair injuries to the levator, extreme care should be taken not to incorporate other layers, particularly the septum, into this closure. Incorporation of the septum can lead to severe eyelid retraction with cicatricial lagophthalmos that can lead to corneal decompensation and serious morbidity. As a general rule, the septum should be left unsutured in the repair of eyelid lacerations. In many cases it is advisable to not repair levator injuries primarily. Secondary ptosis repair is often a safer alternative.<sup>20,21</sup>

The tarsus typically extends 10 mm from the eyelid margin in the upper eyelid and 4 mm from the eyelid margin in the lower eyelid. Knowledge of this anatomy can aid the surgeon in identifying tarsus-involving lacerations. If the tarsus is involved in the laceration, the tarsus should be carefully trimmed to establish regular squared-off edges to facilitate repair without postoperative kinking or step offs.<sup>22</sup> Repair then proceeds

with partial-thickness sutures to avoid any suture contact with the ocular surface. We advocate the use of braided suture such as a 6-0 polyglactin on a spatulated needle. This needle choice minimizes trauma to this critical layer of the eyelid, and the braided suture and gauge maximize the tensile strength of the closure of this critical layer.

In most cases, orbital fat should be repositioned below the septum gently and the overlying skin should be carefully closed without incorporation of other layers. Orbicularis closure is also typically not required, as reapproximation of the overlying skin will often bring lacerated edges of the orbicularis into close proximity for future healing.<sup>20,21</sup>

### Eyelid Margin Lacerations

The repair of lacerations that involve the margin requires meticulous attention to each layer of the eyelid. Without careful closure, notching, trichiasis, and tarsal irregularities with subsequent ocular surface complications can occur. We advocate the stepwise reapproximation of these injuries in the following fashion. First, a vertical mattress 6-0 polyglactin suture is passed through the eyelid margin at the level of the tarsus. A useful landmark for identifying the tarsal plane at the eyelid margin is the space immediately posterior to the lash line and anterior to the gray line. This suture can be left temporarily untied, but the appropriate apposition should be carefully evaluated because this is the critical suture for lid margin apposition and proper wound eversion. Leaving this knot temporarily untied allows ease of access to the remainder of the tarsus. Next, partial-thickness bites through the tarsus with 6-0 or 7-0 polyglactin on a spatulated needle should be used to reapproximate the entire length of the tarsus. The next step is closure of the overlying orbicularis, which can be accomplished with single interrupted sutures. The margin suture is then tied securely, providing suitable eversion of the eyelid margin. When tying these sutures, care should be taken to trim the knots short to avoid the knots to potentially irritate the ocular surface during the healing phase. The skin is then closed according to surgeon preference (Fig. 12.9.1).<sup>6,20-22</sup>

### Eyelid Injuries With Tissue Loss

Eyelid injuries with tissue loss can pose a significant reconstructive challenge. The entire armamentarium of the reconstructive surgeon must come to bear on these injuries, including the use of rotational flaps, advancement flaps, skin grafts, periosteal flaps, and canthal release. Particular consideration should be given to the possibility of postoperative eyelid retraction, and placement of a Frost or reverse Frost suture tarsorrhaphy should be considered in these cases.

#### Tissue Loss of 0% to 25%

In most cases, full-thickness injuries with this degree of tissue loss can be closed primarily as described previously. In some situations, careful trimming of necrotic tissues or irregularities in the tarsus may be required to allow for appropriate reapproximation. These maneuvers should be performed with the intent of maximal preservation of viable anatomical tissue to facilitate repair.<sup>20-22</sup>

#### Tissue Loss of 25% to 60%

These injuries may preclude direct closure and may require advancement of surrounding tissues. As a general rule, the surgeon should focus on taking advantage of intact native anatomy. In particular, the medial and lateral canthal tendons and periosteum offer robust anchor points for advancement and rotational flaps.

When necessary, lateral canthal tendon release can facilitate the advancement of lateral eyelid tissues and even tissues lateral to the lateral canthus, such as in a Tenzel flap (Fig. 12.9.2).<sup>6,23</sup>

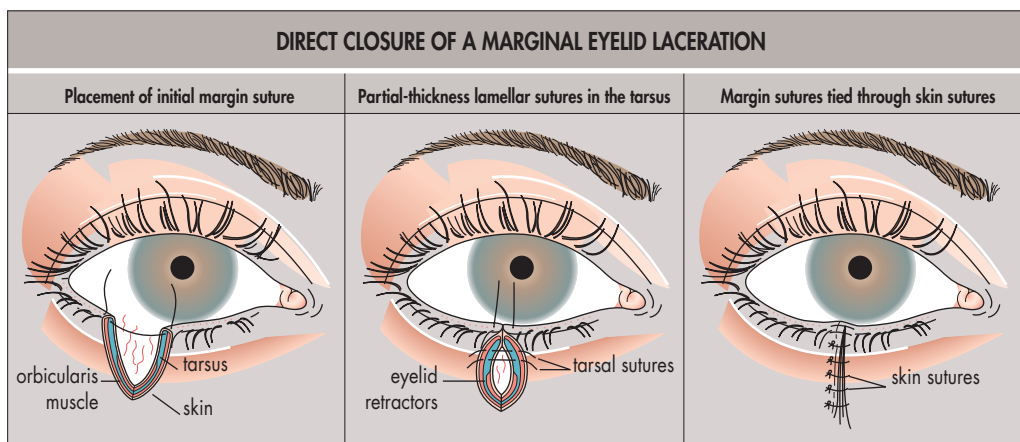
Periosteal flaps are also very useful in the recreation of normal anatomy in these types of injuries. Periosteal flaps have the advantage of providing robust support for the lower eyelid and the correct vector to facilitate the eyelid maintaining apposition with the globe (Fig. 12.9.3).<sup>6,24</sup>

### Full-Thickness Eyelid Injuries With Greater Than 60% Tissue Loss

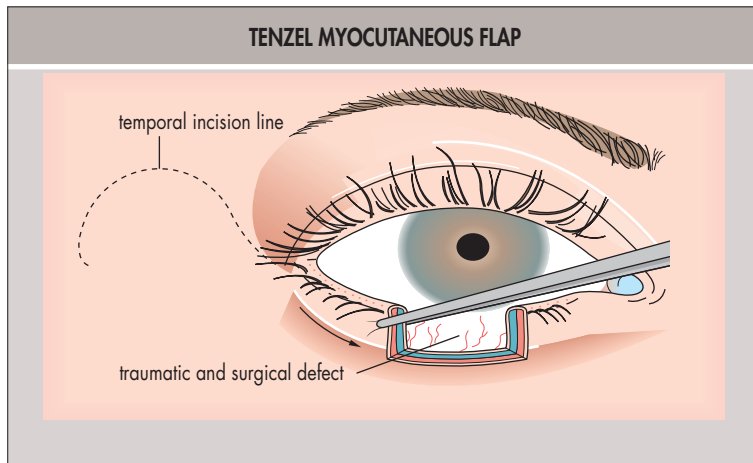
#### Lower Eyelid

Lower eyelid defects of this type may be attempted to be repaired with advancement, rotational, or periosteal flaps, but such methods may be unsuccessful in large defects. General principles of closure in these situations are similar to those involved in reconstructive surgery following

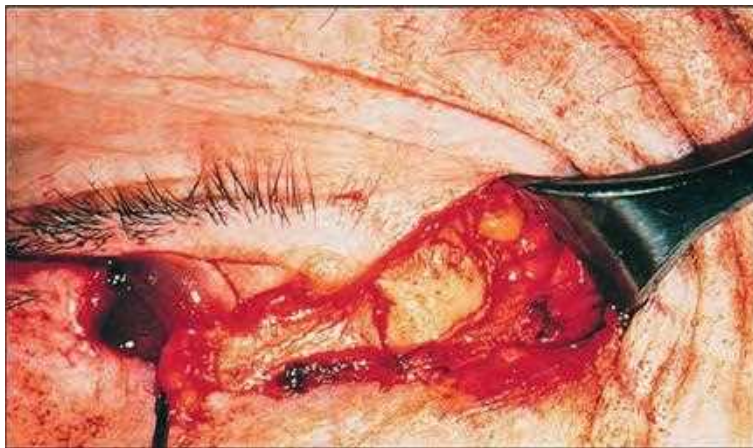




**Fig. 12.9.1 Direct Closure of a Marginal Eyelid Laceration.** The suture is placed precisely in the plane of the meibomian glands at the eyelid margin, approximately 2 mm from the wound edges and 2 mm deep. This placement should provide adequate margin eversion. Partial-thickness lamellar sutures are placed across the tarsus and tied anteriorly. The anterior skin and muscle lamella is closed with fine sutures, and these are tied over the long marginal sutures to prevent corneal touch.



**Fig. 12.9.2 Repair of a Lower Eyelid Defect With the Tenzel Myocutaneous Flap.**



**Fig. 12.9.3 A Periosteal Flap Can Be Rotated to Supplement the Lateral Posterior Lamella in Eyelid Reconstruction.** (Courtesy Regents of the University of California, 1997; reprinted with permission.)

eyelid skin cancer resection. In particular, the Hughes tarsoconjunctival flap is a two-stage procedure that is very well suited to centrally located full-thickness lower eyelid defects.<sup>25</sup> In most cases, a full-thickness skin graft is required to supply the anterior lamella and can be harvested from the contralateral eyelid or pre- or postauricular skin (Fig. 12.9.4).<sup>6</sup>

Alternatively, free tarsoconjunctival flaps or transposition tarsoconjunctival flaps have been shown to be very effective in these types of reconstructions.<sup>26</sup> These flaps may require advancement of skin for anterior lamellar closure.

For very large defects, a cervicofacial advancement flap such as that described by Mustarde may be required (Fig. 12.9.5).<sup>6,27</sup>

### Upper Eyelid

Large injuries of the upper eyelid with tissue loss pose perhaps the highest degree of difficulty in repair. There are numerous considerations in the repair of these injuries including the status of the levator

muscle, potential septal scarring and retraction, and globe protection. It has been said that one can live without a lower eyelid, but the globe cannot survive without an upper eyelid.<sup>28</sup> Repair of these defects follows the general principles outlined earlier—the recreation of normal anatomy with an emphasis on globe protection. Careful consideration of both vertical and horizontal tension is required to avoid retraction and ptosis respectively.

In some cases, a large lateral or horizontal advancement of an upper eyelid tarsoconjunctival flap can be used to recreate the posterior lamella. A laterally based periosteal flap may supply lateral support and horizontal length in these situations. A full-thickness skin graft can be used to supply the anterior lamella.<sup>28</sup>

The Cutler–Beard flap has been used to repair very large defects in the upper lid when other maneuvers are not possible.<sup>29</sup> This two-stage procedure uses the full thickness of the distal lower eyelid to repair the proximal upper eyelid. The flap is passed under a bridge of intact lower eyelid margin. The second stage is used to divide the flap and open the palpebral aperture (Fig. 12.9.6).<sup>6</sup> This technique is limited by the fact that the tarsus is typically 4 mm in vertical dimension in the lower lid. The procedure must maintain a portion of this tarsus in the lower eyelid to preserve lower eyelid integrity, thus the upper eyelid is left with deficient tarsus and therefore structural instability. This frequently leads to chronic postoperative sequelae in the reconstructed upper eyelid, but the procedure does allow for globe protection.

### Postoperative Care

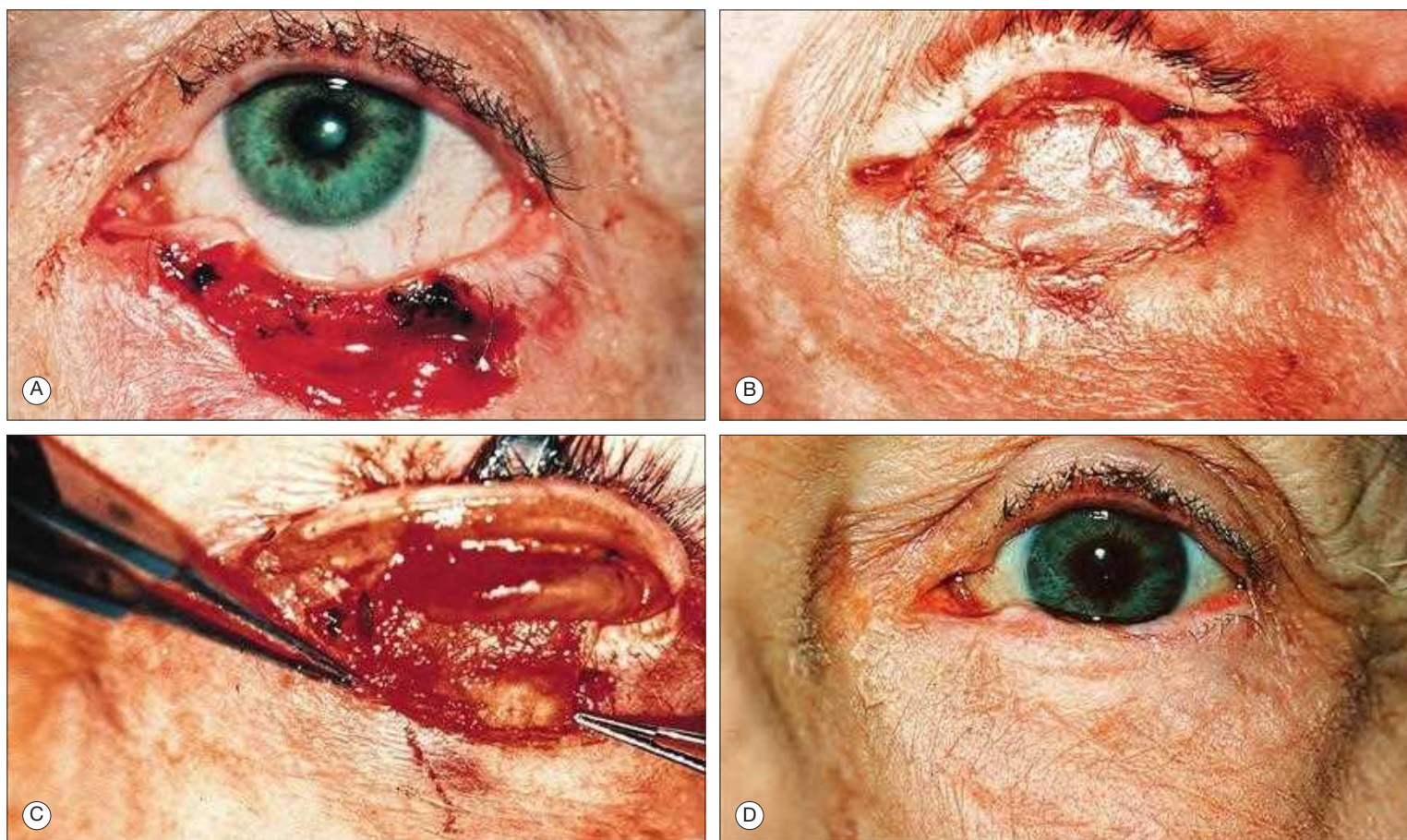
As with most facial trauma, patients with eyelid injuries often require frequent early postoperative evaluation. In the early phase, evaluation should focus on wound integrity and any signs or symptoms of infection. Antibiotic prophylaxis has been a point of controversy, but we advocate a low threshold for the use of prophylactic systemic antibiotic use in contaminated wounds. In addition, lubrication with antibiotic ointment is typically indicated. Antibiotic ointment functions not only as a lubricant and disinfectant but also speeds re-epithelialization in areas that are left to heal by second intention.

As stated earlier, we advocate the use of Frost and reverse Frost suture tarsorrhaphies in complex eyelid reconstruction to aid in minimizing postoperative eyelid retraction. We typically remove such tarsorrhaphies at 7–10 days postoperatively.

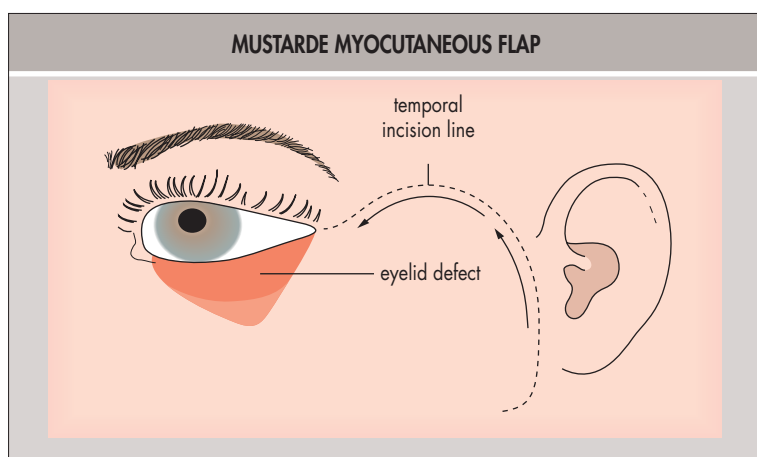
After the early postoperative phase, patients with eyelid trauma should be followed for the development of potential complications such as lacrimal dysfunction, cicatricial eyelid retraction, and hypertrophic scarring. All patients should be counseled on sun avoidance and sunscreen use to minimize scarring. In the event of future eyelid malposition or lacrimal dysfunction, these issues can be addressed if clinically indicated.

During the cicatricial phase of healing (commonly 3–4 weeks following repair), it may be beneficial to advocate massage or other scar-modulating therapies such as off-label injection of Kenalog or 5 fluorouracil (5-FU). The use of these interventions must be individualized and advocated with care with appropriate informed consent. The biochemical underpinning of these maneuvers exists through their disruption of fibroblast activity. During the cicatricial phase of healing, fibroblasts are depositing cartilage in a linear, nonmeshlike fashion. Downregulating fibroblast activity, either mechanically through stretch or chemically, can be helpful in reducing this robust collagen deposition that is a feature of the cicatricial phase of healing.<sup>30</sup>





**Fig. 12.9.4 The Hughes Tarsalconjunctival Flap Procedure.** (A) The lower eyelid defect is examined to estimate the width of the flap. (B) The flap is dissected from the posterior lamella of the upper eyelid. At least 4 mm of tarsus must remain along the upper eyelid margin to enable stabilization. (C) A skin graft can provide adequate anterior lamella of the lower eyelid. (D) After 4–6 weeks the flap is divided to restore the eyelid margins. (Courtesy Regents of the University of California, 1997; reprinted with permission.)



**Fig. 12.9.5 Repair of Large, Full-Thickness Lower Eyelid Defects With the Mustarde Myocutaneous Flap.**

We typically defer further reconstructive surgery until after the cicatricial phase of healing is complete—typically a minimum of 3 months after initial repair. Exceptions to this practice include situations in which the ocular surface is at risk of decompensation, severe desiccation, ulceration, or scarring. Deferring surgery until after the wounds are mature allows for a higher chance of future success and more facile dissection planes.<sup>30</sup>

### Late Repair of Eyelid Injuries

Late repair of eyelid injury is often plagued by cicatricial processes that involve cicatricial elements of eyelid anatomy. In the upper eyelid, levator scarring is common, resulting in tethered ptosis or cicatricial lagophthalmos. The medial and lateral canthal attachments may require repair. If eyelid margin trauma is neglected, notching is a frequent occurrence.



**Fig. 12.9.6 The Cutler-Beard Bridge Flap.** A full-thickness flap of lower eyelid tissue is advanced beneath a marginal bridge into the upper eyelid defect. After 3–4 weeks the flap is cut at the appropriate level and the lower lid is repaired. (Courtesy Regents of the University of California, 1997; reprinted with permission.)

The evaluation of these patients should proceed as described earlier with a systematic evaluation of the eyelids and adnexal tissues followed by evaluation of the globe.

In situations where late repair is required, the standard guidelines remain unchanged: The focus is on restoring function by recreating normal anatomy. The secondary goal is to optimize cosmesis.

Areas of eyelid margin notching can often be excised and repaired as a full-thickness margin-involving laceration as described earlier. Extensive cicatricial processes surrounding the levator complex may require extensive debridement to recreate normal functioning anatomy. Addressing lower eyelid retraction may require lateral canthal support, release of cicatrix, medial canthal support, and midfacial advancement and support. Skin grafting may even be necessary in some cases.

The surgical plan should begin with identifying the anatomical problem(s) and then proceeding to the design of a stepwise surgical plan that addresses each issue.

## Dog Bites

Dog-bite injuries occur at a rate of more than 750,000 incidences per year in the US resulting in significant morbidity, with 4%–8% of these injuries resulting in periocular trauma.<sup>5,31–35</sup> Children are at particular risk and demonstrate a disproportionately higher incidence of dog-related eyelid trauma compared with adults. It has been estimated that the likelihood of a child sustaining a dog bite in their lifetime is around 50%, and approximately 80% of severe dog bites in children involve the head and neck.<sup>5,31–35</sup>

When evaluating patients who have suffered dog-related injuries, it is critical to ascertain information regarding the dog's health and rabies vaccination status. In the majority of dog-related trauma cases, the dog is known to the victim. If rabies is suspected, the local health department should be notified and rabies prophylaxis should be strongly considered because rabies infection can result in devastating sequelae.

Although globe injuries are uncommon in dog-related trauma,<sup>31–33</sup> a full and complete ophthalmic examination should be performed. Dog-related injuries do commonly result in canalicular injury, and the lacrimal system should be thoroughly evaluated in all cases.<sup>35</sup>

The repair of dog bite injuries follows the general principles of the techniques described earlier: The priority is to recreate normal function through re-establishing normal anatomical architecture. The secondary goal is to optimize cosmesis. As contamination is a common occurrence, copious irrigation with antibiotic irrigant is required. Antibiotic prophylaxis has been controversial, but because injuries are known to harbor a high rate of microbial contamination, we recommend prophylaxis with broad-spectrum antibiotics. *Pasteurella multocida* is the most common isolate in dog bite injuries, but a number of pathogens have been described in these instances, and surgeons should maintain a low threshold for obtaining culture and adjusting antibiotic coverage when indicated.<sup>8,11</sup>

## Lacrimal Injury

Medial upper and lower eyelid injuries often can result in trauma to the lacrimal system. Indeed, 16% of all eyelid lacerations from either penetrating or blunt trauma result in canalicular injury.<sup>3,4</sup> Lacerations that involve tissue medial to the punctum should be treated as canalicular involving until proven otherwise. Testing at the bedside with lacrimal irrigation or canalicular probing is possible, but we advocate testing the integrity of the lacrimal system in a controlled environment, such as in the operating room, when possible. We also advocate for the repair of all canalicular injuries, including monocanicular injuries with temporary stenting. There has been some controversy regarding this topic in the literature because some canalicular lacerations that are not repaired do not result in epiphora.<sup>3,4,36</sup> Because there is no predictive test to separate those injuries that will result in epiphora from those that will not, we defer to the wisdom of Hawes and Dortzbach, who state, “The only way to avoid symptomatic patients is to repair all canalicular lacerations.”<sup>37</sup>

The surgical steps of canalicular injury repair follow the general principles of those outlined earlier: The primary goal is to recreate the normal functioning anatomy with a secondary goal of optimizing cosmesis. We recommend copious but gentle cleaning of the lacerated tissues with antibiotic irrigant followed by gentle exploration of the medial tissues to identify the distal cut end of the canaliculus. Once the distal cut end is identified, we advocate placement of either a monocanicular or bicanicular stenting system to remain in place for approximately 4 weeks.

When difficulty arises in identifying the distal cut end, irrigation of the intact limb of the system with fluorescein dyed saline or viscoelastic can be used for identification. With patience, the distal cut end should be possible to identify in most cases.

A recent analysis of outcomes following repair of canalicular injury by Murchison and Bilyk revealed that repair of canalicular lacerations is more successful when performed in the operating room under general anesthesia under the direct supervision of an experienced oculoplastic surgeon. The authors found no significant difference in success between monocanicular and bicanicular stenting systems when controlling for other variables.<sup>4</sup>

Multiple studies have reinforced the fact that canalicular lacerations can be repaired several days after the initial injury without compromising the

success of the surgery, but we advocate for repair of these injuries as early as possible.<sup>4,37,38</sup> Our experience is that after 24–48 hours, an increased degree of difficulty exists in finding the distal cut end of the canaliculus.

In cases where the lacrimal system cannot be repaired, further lacrimal surgery, such as dacryocystorhinostomy, or more commonly conjunctivodacryocystorhinostomy can be explored, but these interventions should be deferred until full healing of the lacerated tissues has taken place.

## Eyelid Burns

Whether via thermal or chemical injury, burns can have devastating effects that can result in considerable ophthalmic morbidity. Severe burn injuries frequently involve the face, with the incidence of eyelid involvement being 20%–30%.<sup>39</sup> Fortunately, the presence of the eyelids, blink reflexes, Bell's phenomenon, and shielding of the eyes with arms and hands often prevent ocular surface injury.<sup>40–42</sup>

In the acute phase, attention is directed to protecting the globe and ocular surface from exposure and desiccation. Frequent lubrication is nearly universally required. Other measures such as moisture chambers and temporary tarsorrhaphy are commonly employed in these cases.<sup>40–42</sup>

In the majority of cases, first-degree burns behave similarly to eyelid abrasions and superficial lacerations and may be treated as such. Many of these injuries heal well by second intention. Frequent ocular surface lubrication and lubrication of the skin with moist gauze and ophthalmic ointment can aid in the re-epithelization of these injuries.<sup>40–42</sup>

Second- and third-degree burns typically demonstrate considerable tissue destruction and can develop early eyelid retraction or cicatricial ectropion. In these injuries, emergent temporizing measures such as suture tarsorrhaphy placement may be required to protect the ocular surface. Early surgical intervention is indicated in cases of ocular surface decompensation. Fortunately, permanent visual impairment is rare in cases where appropriate early surgical intervention is employed.<sup>40–42</sup>

When the cicatricial phase of healing is complete, burn injuries can be treated using the principles outlined earlier. In most cases, the anterior lamella requires the majority of the reconstructive effort. Eyelid retraction and/or ptosis may also require intervention. In severe cases, mucous membrane grafting may be required to restore the posterior lamella to avoid a keratinized surface contacting the ocular surface.<sup>43</sup>

## CONCLUSIONS

Periorbital injury and eyelid trauma demonstrate a wide spectrum of presentations from superficial abrasions to globe-threatening injury. The evaluation of these patients requires stepwise and methodical examination with a focus on anatomical architecture of the periorbital structures. When injuries are identified, the treatment plan should be developed thoughtfully, with an emphasis on first identifying the anatomical problems and then devising solutions. The primary goal of reconstruction is preservation of vision and protection of the globe. To achieve this goal, one must recreate the injured anatomy with a focus on the functional subunits. Secondly, the surgeon must consider the long-term cosmesis of the patient. Fortunately, achieving this secondary goal often follows from the restoration of normal functional anatomy.

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Orbital Diseases

Jonathan J. Dutton

12.10

**Definition:** The orbit is the bony cavity that contains the eye, eye muscles, lacrimal gland, and neural and vascular structures that serve eye function. Numerous diseases involving any of these structures occur in the orbit and can affect visual function.

Key Features

- A mass lesion of the orbit may cause proptosis or displacement of the eye.
- Orbital lesions may be the presenting sign of systemic diseases such as metastatic cancer.
- Demographics such as age, sex, time course of presentation, and location within the orbit may be helpful in making a specific diagnosis.
- Treatment of orbital lesions may be medical, such as the use of corticosteroids or radiotherapy for inflammatory disease, and does not always require surgery.

INTRODUCTION

The orbit and ocular adnexa are important sites for primary and secondary diseases. Various tissue types, such as osseous, vascular, neural, muscular, fibrous, adipose, and glandular, may be involved with specific pathologies.<sup>1–5</sup> Tumors or inflammations can secondarily invade the orbit from periorbital regions including the paranasal sinuses, eyelids, and intracranial compartment.

CLINICAL EVALUATION

The initial step in the evaluation of orbital disease is a complete ophthalmic examination.<sup>5</sup> A careful medical and ophthalmic history, including time course of the disease, past trauma, ocular surgery, and systemic illnesses, must be obtained. A complete clinical examination includes assessment of visual acuity and visual fields, anterior and posterior segment evaluation, optic nerve function, and external and periorbital inspection. The use of modern imaging techniques is almost always indicated—the choice depends on the disease processes suspected.

In this chapter, the most common orbital lesions are categorized by diagnostic criteria to enable the reader to evaluate patients more easily and establish a meaningful differential diagnosis (Tables 12.10.1–12.10.3).<sup>5,6</sup> In addition, the key points and diagnostic criteria for each lesion are given.

METASTATIC TUMORS

INTRODUCTION

Metastatic tumors represent 2%–3% of all orbital tumors.<sup>6</sup> In 30%–60% of patients, orbital metastases develop before the diagnosis of the primary tumor (Table 12.10.4). Metastases reach the orbit via hematogenous spread and occur less commonly than do uveal metastases. In adults, metastases are usually carcinomas. In children, metastases are more likely to be sarcomas and embryonal tumors of neural origin. Only 4% of orbital metastases are bilateral. Clinical symptoms include proptosis, axial displacement of the globe, ptosis, diplopia, pain, and chemosis<sup>7</sup> (Fig. 12.10.1).

METASTATIC CARCINOMA

Key Points

The most common primary sites of metastatic carcinoma to the orbit are the breast, lung, prostate, gastrointestinal tract, and kidney.<sup>8–10</sup> Key features are:

- For breast carcinoma, the interval from primary diagnosis to orbital metastasis is 3–5 years.

TABLE 12.10.1 Frequency of Orbital Lesions by Major Diagnostic Group

Diagnostic Group	Frequency (%)
Thyroid orbitopathy	50
Inflammatory lesions	11
Cystic lesions	10
Lymphoproliferative lesions	5
Other and unclassified	5
Vascular neoplasms	4
Secondary tumors	4
Mesenchymal lesions	4
Optic nerve tumors	3
Lacrimal gland lesions	2
Metastatic tumors	2
Vascular, structural	1

Data from Rootman JL. Diseases of the orbit. A multidisciplinary approach. Philadelphia, PA: JB Lippincott; 1988. p. 119–39; and Shields JA, editor. Diagnosis and management of orbital tumors. Philadelphia, PA: WB Saunders; 1989. p. 291–315.

TABLE 12.10.2 Age Distribution of Common Orbital Diseases

Diagnostic Group	Frequency (%)		
	Childhood and Adolescence (0–20 years)	Middle Age (21–60 years)	Later Adult Life (61+ years)
Adenoid cystic carcinoma of lacrimal gland	18	73	9
Capillary hemangioma	100	0	0
Cavernous hemangioma	10	75	15
Cystic lesions	77	3	4
Fibrous histiocytoma	25	50	25
Infectious processes	35	3	3
Inflammatory lesions	12	5	9
Lymphangiomas	6	1	0
Lymphoproliferative diseases	1	3	12
Optic nerve glioma	5	1	1
Optic nerve meningioma	4	88	8
Pleomorphic adenoma of lacrimal gland	0	89	11
Rhabdomyosarcoma	98	2	0
Secondary and metastatic malignancies	1	2	9
Thyroid orbitopathy	4	59	40
Trauma	7	4	2

Data rounded to the nearest percentage point.  
Modified from Rootman JL. Diseases of the orbit. A multidisciplinary approach. Philadelphia, PA: JB Lippincott; 1988. p. 119–39.



**Fig. 12.10.1** Metastatic Breast Carcinoma to the Right Orbit With Ptosis, Proptosis, and Downward Displacement of the Globe.

**TABLE 12.10.3** Temporal Onset of Common Orbital Diseases

Hours	Days	Weeks	Months	Years
Traumatic	Inflammatory	Inflammatory	Neoplastic	Neoplastic
Hemorrhagic	Infectious	Neoplastic	Lymphoid	Degenerative
Infectious	Traumatic	Traumatic	Vascular	Lymphoid
	Hemorrhagic	Lymphoid	Inflammatory	Vascular
	Vascular	Vascular	Degenerative	Inflammatory

Modified from Rootman JL. Diseases of the orbit. A multidisciplinary approach. Philadelphia, PA: JB Lippincott; 1988. p. 119–39.

**TABLE 12.10.4** Primary Origins of Metastatic Tumors of the Orbit

Origin	Percent
Breast	53
Prostate	11
Gastrointestinal	11
Lung	4
Sarcomas and other	21

Modified from Rootman JL. Diseases of the orbit. A multidisciplinary approach. Philadelphia, PA: JB Lippincott; 1988. p. 119–39; and Shields JA, editor. Diagnosis and management of orbital tumors. Philadelphia, PA: WB Saunders; 1989. p. 291–315.

- In scirrhous cell breast carcinoma and gastric carcinoma, enophthalmos may result from orbital fibrosis.
- Metastatic lung cancer is seen most commonly in males aged 45–60 years who smoke and may present before the primary is discovered.
- Prostatic metastases occur most commonly in elderly men, and pain is common because of bony involvement.
- Metastases are characterized by a rapid onset of orbital symptoms, which include exophthalmos and globe displacement.

## Orbital Imaging

Metastatic carcinomas usually are poorly defined, nonencapsulated, diffuse masses that are somewhat infiltrative (Fig. 12.10.2). Extraocular muscles are often involved. Osteoblastic changes may be seen with prostatic carcinoma. On magnetic resonance imaging (MRI), the T1-weighted image is usually isointense and the T2-weighted image hyperintense to muscle.

## Treatment and Prognosis

Treatment requires chemotherapy combined with local radiotherapy. Orchiectomy may be indicated for prostate carcinoma and hormonal therapy for breast carcinoma.

Orbital metastases from carcinoma reflect more widespread systemic disease, so the prognosis for survival is generally poor.



**Fig. 12.10.2** CT Scan of a Metastatic Breast Carcinoma With an Irregular Mass in the Right Retrobulbar Orbit.

### BOX 12.10.1 Causes of Abaxial Globe Displacement

#### Downward Displacement

- Fibrous dysplasia
- Frontal mucocele
- Lymphoma
- Neuroblastoma
- Neurofibroma
- Schwannoma
- Subperiosteal hematoma
- Thyroid orbitopathy

#### Upward Displacement

- Lacrimal sac tumors
- Lymphoma
- Maxillary sinus tumor
- Metastatic tumors

#### Lateral Displacement

- Ethmoid mucocele
- Lacrimal sac tumors
- Lethal midline granuloma
- Metastatic tumors
- Nasopharyngeal tumors
- Rhabdomyosarcoma

#### Medial Displacement

- Lacrimal fossa tumors
- Sphenoid wing meningioma

The direction of ocular displacement may be helpful in narrowing the differential diagnosis.

## LACRIMAL GLAND LESIONS

### INTRODUCTION

Lesions of the lacrimal gland include infiltrative processes such as inflammatory diseases and lymphoma,<sup>11</sup> structural disorders (such as cysts), and epithelial neoplasms.<sup>12–16</sup> Epithelial tumors represent 20%–25% of all lacrimal gland lesions. The appropriate management of lacrimal fossa lesions requires a thorough evaluation and determination of the cause. Almost all lacrimal gland lesions result in a mass effect, with swelling of the lateral eyelid and often with a downward and medial displacement of the globe (Box 12.10.1). Inflammatory processes are more commonly associated with pain, eyelid edema, and conjunctival chemosis and injection.



## PLEOMORPHIC ADENOMA (BENIGN MIXED CELL TUMOR)

### Key Points

Pleomorphic adenomas occur mainly in the orbital lobe and rarely in the palpebral lobe of the lacrimal gland.<sup>17–20</sup> They are composed of epithelial and mesenchymal elements (thus the term benign “mixed” cell tumor), but both elements are derived from epithelium. Key features are:

- They represent 3%–5% of all orbital tumors, 25% of lacrimal mass lesions, and 50% of epithelial lacrimal gland tumors.
- They occur most commonly in the second to fifth decades of life (mean age, 39 years).
- The male to female ratio is 1.5:1.

Orbital symptoms are painless proptosis, downward displacement of the globe, diplopia, retinal striae, fullness of the upper eyelid, and a palpable eyelid mass. These tumors are slowly progressive over 12 or more months.

### Orbital Imaging

Well-circumscribed, round-to-oval, encapsulated lesions are typical. Remodeling of the bone may be seen with long-standing tumors, but no bone destruction occurs. The tumors may be cystic and may contain areas of calcification. On MRI the T1-weighted image is hypointense and the T2-weighted image hyperintense to muscle.

### Pathology

Pleomorphic adenomas are encapsulated tumors that demonstrate ducts, cords, and squamous pearls, with myxoid and chondroid tissue (Fig. 12.10.3).



**Fig. 12.10.3 Benign Mixed Tumor.** (A) The patient had proptosis of the left eye for quite some time. It had gradually increased in severity. (B) The characteristic diphasic pattern is shown. It consists of a pale background that has a myxomatous stroma and a relatively amorphous appearance, contiguous with quite cellular areas that contain mainly epithelial cells. C, Cellular epithelial areas; M, myxomatous stroma; S, surface of tumor. (Reproduced with permission from Yanoff M, Fine BS. Ocular pathology. 5th ed. St Louis, MO: Mosby; 2002.)

### Treatment and Prognosis

These adenomas must be excised completely with an intact capsule; biopsy or incomplete removal may result in recurrence associated with infiltration. Malignant degeneration occurs at a rate of 10% in 10 years.

The prognosis generally is very good despite the small possibility of malignant transformation.

## ADENOID CYSTIC CARCINOMA

### Key Points

Adenoid cystic carcinoma accounts for 23% of all epithelial tumors of the lacrimal gland and is the most common epithelial malignancy of the lacrimal gland (Table 12.10.5).<sup>21</sup> Key features are:

- It occurs most commonly in the fourth decade of life but may be seen at any age.
- It is slightly more common in women.
- The duration of symptoms is generally short—often less than 6 months, and usually less than 12 months.

Orbital symptoms include proptosis, downward globe displacement, ptosis, and diplopia. Orbital pain as a result of perineural spread is common, seen in 10%–40% of cases.

### Orbital Imaging

Computed tomography (CT) and MRI usually show a poorly demarcated, irregular lesion that may extend along the lateral wall to the orbital apex. Bone destruction is common, and foci of calcification are seen frequently. On MRI the T1- and T2-weighted images are hyperintense to muscle, and the signal is heterogeneous.

### Pathology

Solid cords of malignant epithelial cells are seen, with cystic spaces (“Swiss cheese” appearance) or hyalinization of cylinders of connective tissue (Fig. 12.10.4).

### Treatment and Prognosis

Treatment consists of radical en bloc excision or exenteration, with wide margins including bone. A recent histological study<sup>22</sup> showed that 80% of these lesions involved adjacent bone. Adjunctive radiotherapy for incompletely excised lesions may be necessary. The prognosis is often poor, with relentless recurrences. The mortality rate is high.

## MESENCHYMAL TUMORS

### INTRODUCTION

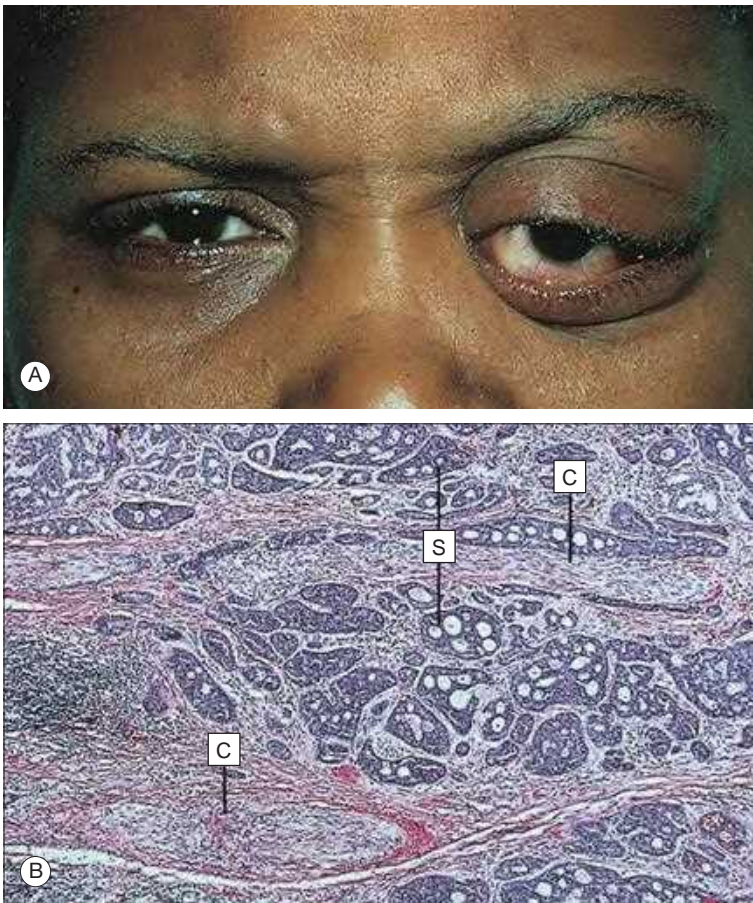
Nonosseous mesenchymal tumors arise from fibroblasts, myoblasts, and lipoblasts. Classification of such lesions is difficult, as their features overlap, so the terminology is confusing. Together these orbital lesions form an important group that accounts for about 8% of all orbital lesions.<sup>23–33</sup>

**TABLE 12.10.5 Frequency of Lacrimal Fossa Lesions**

Lesion	Frequency (%)
Dacryoadenitis	51
Pleomorphic adenoma	18
Reactive lymphoid hyperplasia	9
Adenoid cystic carcinoma	7
Dacryops (epithelial cyst)	5
Lymphoma	4
Mucoepidermoid carcinoma	3
Pleomorphic adenocarcinoma	2
Plasmacytoid lesions	1

Modified from Rootman JL. Diseases of the orbit. A multidisciplinary approach. Philadelphia, PA: JB Lippincott; 1988. p. 119–39; and Shields JA, editor. Diagnosis and management of orbital tumors. Philadelphia, PA: WB Saunders; 1989. p. 291–315.





**Fig. 12.10.4 Adenoid Cystic Carcinoma.** (A) The patient had a rapidly progressing proptosis of the left eye. (B) The characteristic “Swiss cheese” pattern (S) of adenoid cystic carcinoma is shown. The “Swiss cheese” tumor is also present in the perineural sheath around the ciliary nerve (C). Adenoid cystic carcinoma is noted for its rapid invasion of ciliary nerves. (Reproduced with permission from Yanoff M, Fine BS. *Ocular pathology*. 5th ed. St Louis, MO: Mosby; 2002.)

## FIBROUS HISTIOCYTOMA

### Key Points

Fibrous histiocytoma is a benign or malignant mesenchymal tumor that arises from fascia, muscle, or other soft tissues.<sup>34,35</sup> In children, it may result from early orbital radiotherapy. In adults, it is the most common mesenchymal orbital tumor, usually seen in middle-aged patients (40–60 years).

The upper nasal quadrant is the most common orbital site. Symptoms are proptosis, decreased vision, ptosis, motility restriction, and epiphora. The lesions may be circumscribed or infiltrative and can be locally aggressive.

### Orbital Imaging

Usually a well-defined, rounded mass is seen, as in other benign lesions, but the tumor can be more infiltrative. On MRI the signal is heterogeneous, with isointense T1 and variable T2 signals with respect to muscle. Enhancement with gadolinium is moderate.

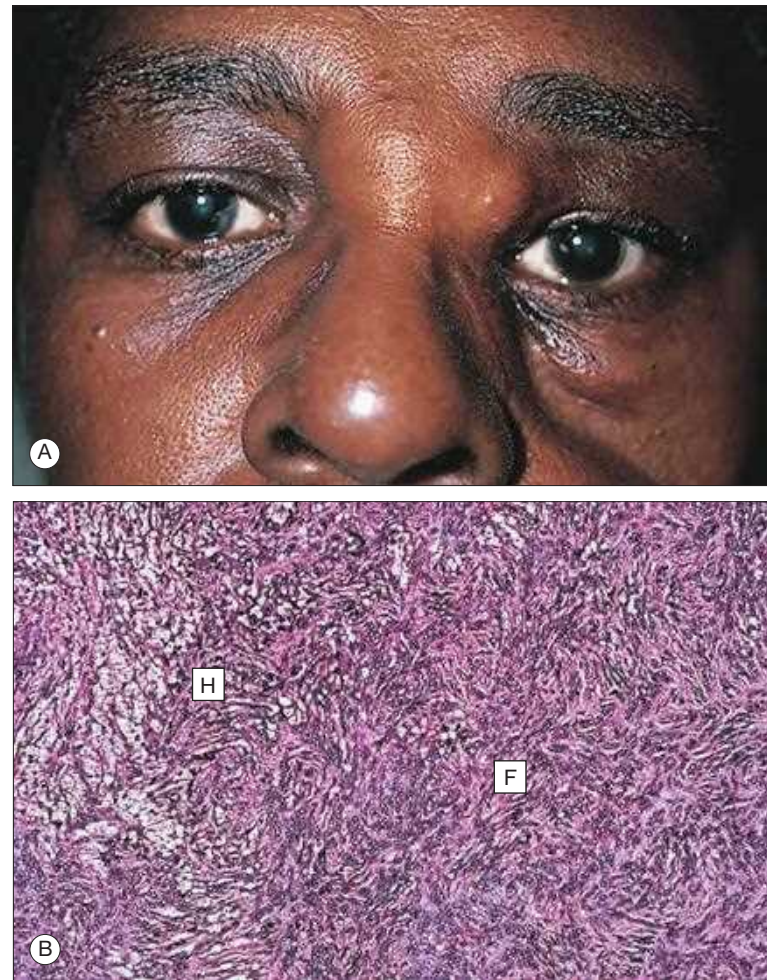
### Pathology

The tumor is a mixture of spindle-shaped fibroblasts and histiocytes arranged in a storiform pattern twisted about a central focus (Fig. 12.10.5). The benign form (63% incidence) is a well-circumscribed, slow-growing lesion with a fine capsule. A small potential exists for malignant degeneration.

The malignant form (37% incidence) is more infiltrative and rapidly growing and is often associated with pain and necrosis.

### Treatment and Prognosis

Local surgical excision for benign or orbital exenteration for malignant lesions is required, with recurrences being common (in up to 30% of



**Fig. 12.10.5 Fibrous Histiocytoma.** (A) This is the fourth recurrence of an orbital tumor that was first excised 10 years previously. The histology of the primary lesion and of the four recurrences appear identical. (B) A histological section shows the diphasic pattern consisting of a histiocytic component (H), mainly on the far left, and a fibrous component (F). (Reproduced with permission from Yanoff M, Fine BS. *Ocular pathology*. 5th ed. St Louis, MO: Mosby; 2002.)

cases). Radiotherapy offers no benefit, and the effects of chemotherapy are unknown.

For the benign form, the prognosis for life is excellent. With malignant tumors, the overall mortality rate is more than 40%.

## RHABDOMYOSARCOMA

### Key Points

Rhabdomyosarcoma is the most common soft tissue mesenchymal tumor in children, accounting for 3.4% of all childhood malignancies.<sup>36–38</sup> The tumors arise from pluripotential mesenchymal precursors that normally differentiate into striated muscle cells. About 70% occur during the first decade of life (mean age, 7–8 years; range, 0–78 years), and boys are affected more commonly than girls at a ratio of 5:3. In the orbit, the most common histological variant is the embryonal type, followed by the alveolar type.

Symptoms may be acute to subacute, with rapidly progressive proptosis, eyelid edema, and ptosis. This rapidity may cause diagnostic confusion with an infectious process. The tumor is located in the retrobulbar muscle cone in 50% of cases, and in the superior orbit in 25% of cases.

### Orbital Imaging

Typically, the tumor presents as an irregular but well-defined soft tissue mass (Fig. 12.10.6). Bony erosion may be seen but is uncommon. On MRI the T1 signal is isointense to hyperintense, and the T2 signal is hyperintense with respect to muscle.

### Pathology

Cross-striations may be seen in 50%–60% of embryonal-type tumors and in 30% of the alveolar type (Fig. 12.10.7). Myoglobulin is a specific



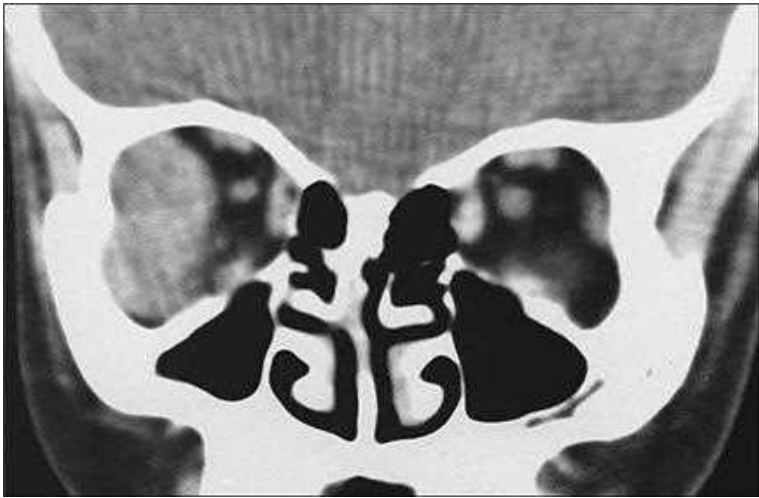


Fig. 12.10.6 Rhabdomyosarcoma of the Lateral Orbital Wall in a 7-Year-Old Girl.

TABLE 12.10.6 Frequency of the Most Common Neurogenic Orbital Lesions

Lesion	Frequency (%)
Sphenoid wing meningioma	30
Optic nerve glioma	22
Neurofibroma	19
Schwannoma	14
Optic sheath meningioma	11
Other	4

Data from Rootman JL. Diseases of the orbit. A multidisciplinary approach. Philadelphia, PA: JB Lippincott; 1988. p. 119–39; Shields JA, editor. Diagnosis and management of orbital tumors. Philadelphia, PA: WB Saunders; 1989. p. 291–315; and the author’s personal data.

immunohistochemical marker. Electron microscopy shows actin myofilaments and myosin filaments.

Staging

There are four stages:

- Localized tumor, completely resected.
- Regional spread, ± positive nodes, grossly resected.
- Gross residual tumor remaining after incomplete resection.
- Distant metastases.

Treatment and Prognosis

An immediate biopsy is required to confirm the diagnosis. Surgical excision is carried out only if the lesion is well circumscribed and the excision can be performed easily without excessive tissue damage. Local radiotherapy doses are 4000 cGy for stage II and 5000 cGy for stages III and IV. Adjuvant chemotherapy is given using vincristine, actinomycin D, and cyclophosphamide. Some centers prefer only surgery and chemotherapy to avoid the potential for radiation-induced orbital malignancies in children.<sup>39</sup>

The 5-year survival rate is 90%–95%. A more favorable prognosis exists for orbital tumors because of the near absence of orbital lymphatics. For local treatment failures, orbital exenteration may be necessary.

NEUROGENIC TUMORS

INTRODUCTION

Peripheral nerves in the orbit are subject to tumors that arise from various cellular components, such as Schwann cells, axons, endoneural fibroblasts, and nerve sheaths (Table 12.10.6). In contrast, the optic nerve, which represents a white-matter tract of the central nervous system (CNS), may give rise to CNS tumors such as astrocytomas and meningiomas.

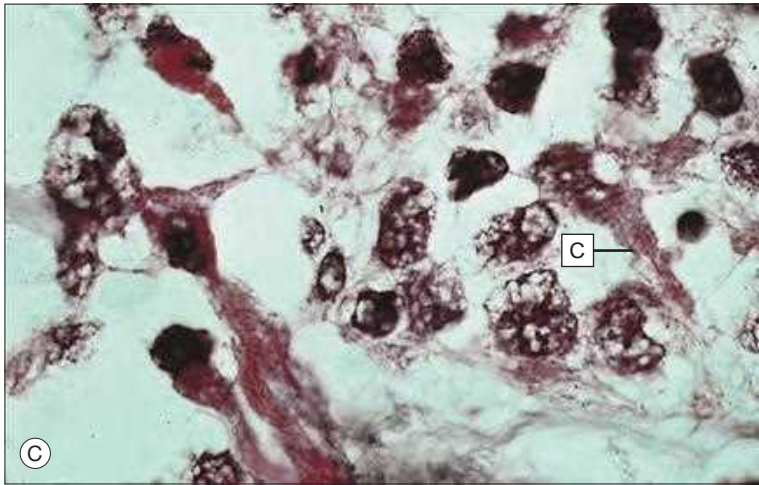
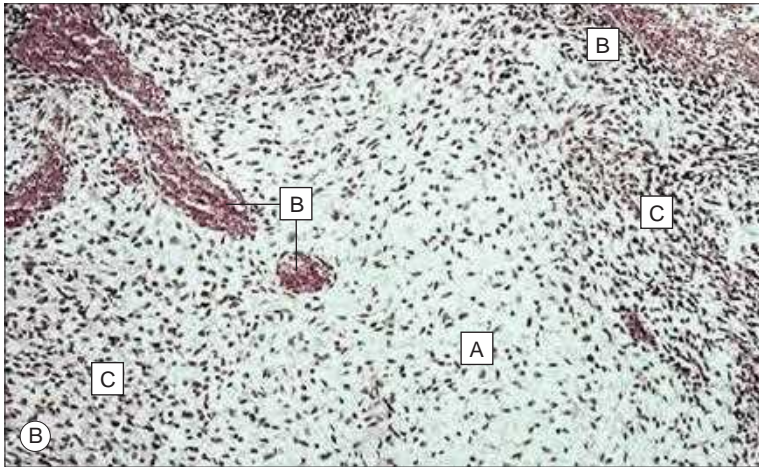


Fig. 12.10.7 Embryonal Rhabdomyosarcoma. (A) The patient has a unilateral right ocular proptosis of very recent onset. Often, rhabdomyosarcoma presents rapidly, causes lid redness, and is mistaken for orbital inflammation. (B) A marked embryonic cellular pattern is shown, hence the term embryonal rhabdomyosarcoma (A, relatively acellular area; B, blood vessels; C, relatively cellular area). (C) A trichrome stain shows characteristic cross-striations in the cytoplasm of some of the rhabdomyoblasts. Cross-striations (C), although not abundant in embryonal rhabdomyosarcoma, can be seen in sections stained with hematoxylin and eosin but are easier to see with special stains. (Reproduced with permission from Yanoff M, Fine BS. Ocular pathology. 5th ed. St Louis, MO: Mosby; 2002.)

PLEXIFORM NEUROFIBROMA

Key Points

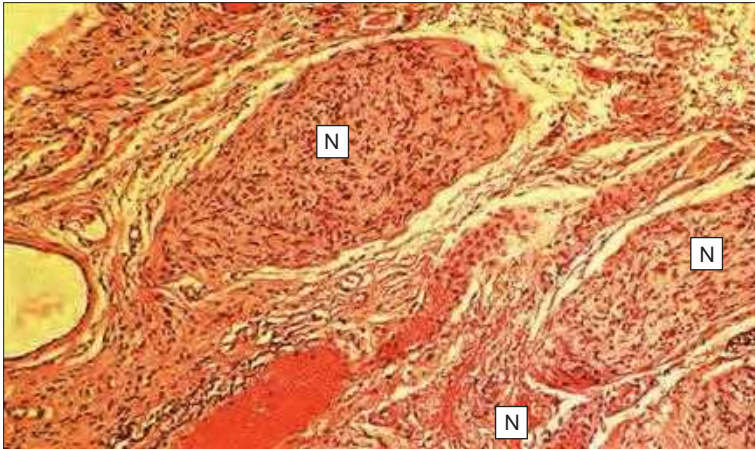
Plexiform neurofibroma is the most common benign peripheral nerve tumor in the eyelid and orbit and is considered characteristic of neurofibromatosis.<sup>40–43</sup> The tumor grows along the nerve, is invasive, and is not encapsulated. Key features are:

- A propensity for sensory nerves, but may also involve motor, parasympathetic, and sympathetic nerves.
- Children in the first decade of life are affected most commonly.
- 31% of plexiform neurofibromas occur in the eyelids.





**Fig. 12.10.8 Plexiform Neurofibroma of the Right Eyelid in a Child With Neurofibromatosis.**



**Fig. 12.10.9 Plexiform Neurofibroma.** Diffuse proliferation of Schwann cells within the nerve sheath enlarges the nerve. *N*, Thickened abnormal nerves.

Clinically, this tumor has been described as a palpable “bag of worms,” with thickened overlying skin and an S-shaped eyelid (Fig. 12.10.8).

It may be associated with uveal neurofibromas (50%), iris (Lisch) nodules (77%), prominent corneal nerves (25%), optic nerve gliomas (15%), and pulsatile proptosis from an absence of the greater sphenoid wing.

## Orbital Imaging

A diffuse, irregular mass is seen with variable contrast enhancement. It may involve extraocular muscles, orbital fat, and the cavernous sinus. On MRI the T1 is hypointense and the T2 hyperintense to muscle.

## Pathology

Interwoven bundles of axons, Schwann cells, and endoneurial fibroblasts are seen in a mucoid matrix (Fig. 12.10.9). A characteristic cellular perineural sheath defines the tumor cords. Immunohistochemistry is positive for S100.

## Treatment and Prognosis

Surgical excision is generally difficult and frustrating, with excessive bleeding and a poor cosmetic result. Repeated debulking may be necessary for severe symptoms, and orbital exenteration for extensive cases. Radiotherapy offers no benefit.

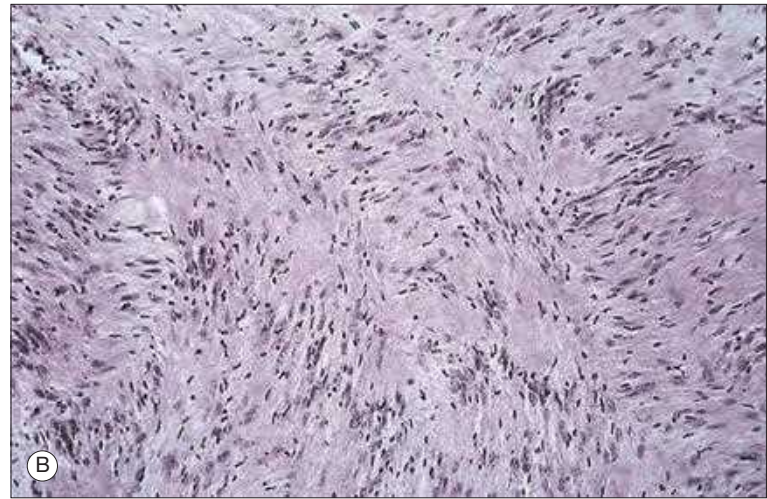
There is a small risk of malignant transformation. These tumors may occasionally erode into the anterior cranial fossa, which results in death.

## SCHWANNOMA (NEURILEMMOMA)

### Key Points

Schwannoma is a Schwann cell tumor of neural-crest origin that arises as an outpouching from peripheral or cranial nerves (e.g., acoustic neuroma).<sup>44</sup> Schwannomas represent 1% of all orbital tumors and 35% of peripheral nerve tumors. They are mostly benign but rarely may undergo malignant transformation in patients with neurofibromatosis.

Schwannoma is seen most commonly in young adults to middle-aged individuals (20–50 years). It presents as a slow-growing, painless,



**Fig. 12.10.10 Neurilemmoma.** (A) Proptosis of the patient's left eye had been present for many months and was increasing in size. An orbital tumor was removed. (B) Ribbons of spindle Schwann cell nuclei can be seen. This shows a tendency toward palisading. Areas of relative acellularity, mimicking tactile corpuscles, are called Verocay bodies. This pattern is called the Antoni type A pattern. (Reproduced with permission from Yanoff M, Fine BS. Ocular pathology. 5th ed. St Louis, MO: Mosby; 2002.)

well-defined solitary mass, usually in the superior orbit, and is frequently cystic. Orbital symptoms may include exophthalmos, diplopia, and visual loss from optic nerve compression.

## Orbital Imaging

The tumor is typically an extraconal, fusiform, well-defined, sometimes cystic mass that is aligned anteroposteriorly along the involved nerve. On MRI the signal is homogeneous to heterogeneous; T1 is hypointense and T2 isointense to muscle.

## Pathology

The encapsulated mass has yellow areas and patterns of cells described as Antoni A (whorls) or Antoni B (no palisading) patterns (Fig. 12.10.10). Spindle cells are seen with vesiculated nuclei in a palisading configuration. The cells are negative for alcian blue and positive for S100.

## Treatment and Prognosis

Surgical excision is required. The prognosis for life is good, except following intracranial spread. Late orbital recurrences may be seen after partial excision.

## MALIGNANT PERIPHERAL NERVE SHEATH TUMOR (MALIGNANT SCHWANNOMA)

### Key Points

Malignant peripheral nerve sheath tumors are rare malignant tumors of Schwann cells and perineural cells that arise de novo or in association with neurofibromatosis.<sup>45,46</sup> When associated with neurofibromatosis, the onset is slow and characterized by proptosis, globe displacement, and occasionally pain, ptosis, visual loss, diplopia, and chemosis. The tumors generally occur in patients 20–50 years of age, or earlier in neurofibromatosis.

The clinical course is characterized by relentless invasion along tissue planes to the middle cranial fossa. Metastases to the lungs are common.

## Orbital Imaging

A poorly defined, irregular mass is seen. Bone destruction may occur when the lesion is large.

## Pathology

The tumor has plexiform, swollen nerve bundles and spindle-shaped cells in whorls of interlacing fascicles.

## Treatment and Prognosis

Wide surgical resection is required. Ancillary chemotherapy and radiotherapy may be palliative only. Prognosis is very poor, with death from metastases or intracranial spread.

## NEUROBLASTOMA

### Key Points

Neuroblastoma is an undifferentiated malignant tumor of primitive neuroblasts, which may be metastatic to the orbit.<sup>47</sup> It represents the second most common malignant orbital tumor in children after rhabdomyosarcoma. It arises from the sympathetic system and ganglia and represents the peripheral nervous system counterpart of retinoblastoma. Rarely, neuroblastomas may be primary lesions in the orbit, where they may arise from the ciliary ganglion. Key features are:

- 60% of the primary tumors occur in the abdomen.
- 10%–40% of systemic neuroblastomas result in orbital metastases, on average 3 months after diagnosis of the primary.
- 90% of orbital lesions originate from the abdomen.
- Only 8% of cases first present with an orbital lesion; in 92% of cases the presence of an extraorbital primary tumor is already known.
- 40% of orbital lesions are bilateral.
- The mean age at presentation is 2 years old.
- 75% of cases occur before the age of 4 years.

Symptoms include rapid progression of proptosis over several weeks, lid ecchymosis from necrosis and hemorrhage, eyelid edema, ptosis, Horner's syndrome (from mediastinal tumors), papilledema, retinal striae, and decreased vision. Systemic symptoms may involve fever, weakness, and an abdominal or thoracic mass.

## Orbital Imaging

An irregular, poorly circumscribed mass is seen, frequently associated with bone destruction and separation of sutures, especially at the zygoma. Metastases to the skull bones occur in 74% of cases.

## Pathology

The lesion is a soft, friable, bluish mass; small round cells that resemble lymphocytes with specks of calcium and areas of necrosis are seen. Electron microscopy reveals neurosecretory tubules.

## Treatment and Prognosis

If no systemic primary disease exists, the orbital tumor can be excised. With systemic primary disease, chemotherapy yields resolution in 60%–70% of cases in 4–6 months. Radiotherapy (1500 cGy in children and 4000 cGy in patients older than 10 years) may be used for local orbital disease.

Recurrences may be seen in 90% of cases over 1–2 years, and a 50%–60% mortality rate occurs after 2 years. Bony and orbital metastases are associated with a poorer prognosis.

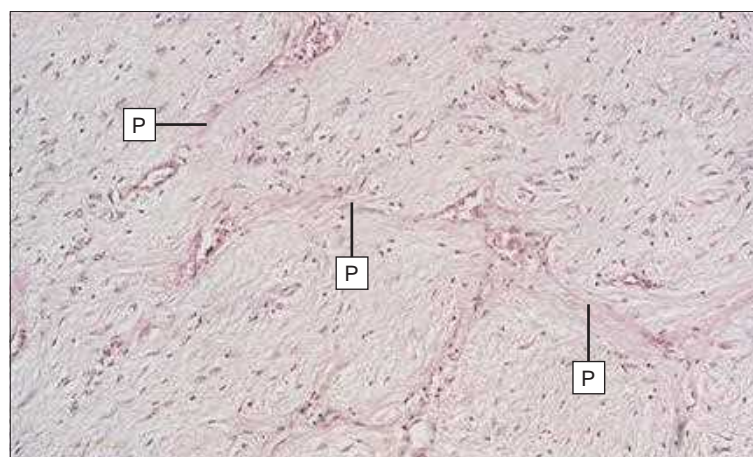
## OPTIC NERVE GLIOMA (PILOCYTIC ASTROCYTOMA OF CHILDHOOD)

### Key Points

Optic nerve glioma is a neoplasm of astrocytes<sup>48</sup> that affects primarily children (mean age, 8 years). No sex predilection exists. The optic nerve alone is affected in 28% of cases; 72% involve the optic chiasm, and of these, 43% involve the chiasm and midbrain. In 29% there is an association



**Fig. 12.10.11** Optic Nerve Glioma in a Child With Neurofibromatosis Type 1.



**Fig. 12.10.12** Optic Nerve “Glioma.” Well-differentiated astrocytes spread out the pial septa (P). (Reproduced with permission from Yanoff M, Fine BS. Ocular pathology. 5th ed. St Louis, MO: Mosby; 2002.)

with type 1 neurofibromatosis. In neurofibromatosis, the lesion may be bilateral.

Symptoms include slow loss of vision, optic atrophy or edema, and proptosis. After an initial decrease, vision remains stable in 80% of patients. Hypothalamic signs may be seen in 22% of cases. Rapid enlargement of the lesion occurs from mucoid degeneration and arachnoid hyperplasia.

## Orbital Imaging

Typically the lesion appears as an intraconal, fusiform enlargement of the optic nerve with or without a chiasmal mass. The nerve may appear kinked with cystic spaces. On MRI the T1 signal is hypotense to isointense, and the T2 signal shows variable intensity compared with muscle (Fig. 12.10.11). Enhancement with gadolinium is variable.

## Pathology

Optic nerve gliomas demonstrate cystic spaces that contain a mucoid material and pial septae that are separated by well-differentiated astrocytes (Fig. 12.10.12). Eosinophilic Rosenthal fibers may represent degenerated astrocytic processes. Immunohistochemistry is positive for neuron-specific enolase.

## Treatment and Prognosis

Treatment consists of observation if the vision is good. The patient should be followed with serial MRI scans. Surgical excision is offered if a tumor approaches the chiasm. Surgery also is indicated for pain or disfiguring proptosis. The role of radiotherapy remains controversial; it may be associated with CNS complications. More recently, chemotherapy has shown promising results.<sup>49</sup>

Prognosis for vision is poor. For lesions confined initially to the optic nerve, prognosis for life is good. For those lesions that involve the chiasm, mortality approaches 20%. Once the midbrain and hypothalamus are involved, the overall prognosis is poor, with mortality exceeding 55%.



BOX 12.10.2 Calcified Orbital Lesions

- Phlebolith
- Orbital varix
- Lymphangioma
- Thrombosed atrioventricular shunt
- Chronic inflammation
- Malignant lacrimal gland tumors
- Optic nerve sheath meningioma
- Dermoid cyst
- Mucocele walls
- Fibro-osseous tumors

OPTIC NERVE SHEATH MENINGIOMA

Key Points

Optic nerve sheath meningioma is a benign neoplasm of meningothe-lial cells of arachnoid tissue<sup>50</sup> that affects primarily middle-aged adults (20–60 years). Women are involved slightly more commonly than men, at a ratio of 3:2. In 4%–9% of cases there is an association with type 1 neuro-fibromatosis, and in 6% of cases the lesion may be bilateral; 5% of menin-giomas are confined to the optic canal, which makes diagnosis difficult.

Symptoms and signs include slowly progressive proptosis over several years, visual loss, optic disc edema, optic atrophy, development of optico-ciliary shunt vessels, and ocular motility restriction.

Orbital Imaging

The lesion is usually seen as a tubular enlargement of the optic nerve with a characteristic “tram-track” pattern of an enhancing nerve sheath with a lucent central nerve. Small areas of calcification may be seen. Marked contrast enhancement on CT is characteristic. On MRI the T1 signal is hypointense, and the T2 signal is hyperintense. Heterogeneity results from low signal areas that represent calcium. Areas of subarachnoid fluid dis-tention are hyperintense.

Pathology

There are several histological types. The meningothe-lial type of lesion shows syncytial lobules of meningothe-lial cells. The psammomatous type demonstrates calcified concretions or psammoma bodies (Box 12.10.2). A rare angioblastic type contains vascular elements that resemble a hemangiopericytoma.

Treatment and Prognosis

Treatment consists of observation if the vision remains good. Surgical exci-sion is indicated in patients with blindness and significant proptosis or when the optic canal is threatened.<sup>51</sup> Radiotherapy may slow progression.<sup>52,53</sup> Prognosis for life is excellent, but visual outcome typically is poor.

LYMPHOPROLIFERATIVE DISEASES

INTRODUCTION

Lymphoid lesions are uncommon in the orbit and account for 6% of all orbital mass lesions (Table 12.10.7). This group includes lymphocytic, plas-macytic, and leukemic lesions. Among the lymphoid infiltrates, lesions are divided into three categories: idiopathic inflammations (pseudotumors), lymphoproliferative reactive and atypical diseases, and lymphomas. The relationships between the last two groups and their relationship to sys-temic disease are not always clear, and some confusion still surrounds the diagnosis and prognosis of each.

BENIGN REACTIVE LYMPHOID HYPERPLASIA

Key Points

This disease constitutes a benign proliferation of lymphoid follicles that contain polymorphic lymphocytes that are immunohistochemically poly-clonal.<sup>54,55</sup> Benign reactive lymphoid hyperplasia (BRLH) occurs most

TABLE 12.10.7 Frequency of Lymphoproliferative Diseases of the Orbit

Disease	Frequency (%)
Lymphoma	51
Reactive and atypical lymphoid hyperplasia	36
Plasma cell dyscrasias	7
Leukemia	2
Histiocytoses	4

Modified from Dutton JJ, Frazier Byrne S, Proia A. Diagnostic atlas of orbital diseases. Philadelphia, PA: WB Saunders; 2000. p. 1–5.

commonly in the anterior superior orbit, with a predilection for the lac-rimal gland (15%). The clinical course is indolent, with painless exoph-thalmos, globe displacement, and typically normal vision. A firm, rubbery mass is often palpable beneath the orbital rim, and there may be a pink subconjunctival “salmon-patch” infiltrate.

Orbital Imaging

An infiltrative mass is seen in the eyelids or anterior orbit. It typically molds to the globe and other adjacent structures and may extend along the rectus muscles. On MRI the T1 signal is hypointense and the T2 signal hyperintense to muscle.

Pathology

Typically, the tumor is a polymorphous array of small lymphocytes and plasma cells with mitotically active germinal centers (Fig. 12.10.13). Immu-nohistochemistry is positive for polyclonal T- and B-cell markers.

Treatment and Prognosis

Treatment involves systemic corticosteroids or local radiotherapy at 1500–2000 cGy. Some lesions may require cytotoxic agents (chlorambucil) for control. There is a 15%–25% chance of developing systemic lymphoma within 5 years.

ATYPICAL LYMPHOID HYPERPLASIA

Key Points

Atypical lymphoid hyperplasia (ALH) represents an intermediate between BRLH and malignant lymphoma and may be unilateral or bilateral. Pre-sentation is as for BRLH, but ALH may involve other systemic organs and more frequently does not respond to corticosteroids. There is a 15% inci-dence of extraorbital involvement. Systemic lymphoma may develop.

Orbital Imaging and Echography

CT and MRI scans are similar to those for BRLH.

Pathology

Monomorphous sheets of lymphocytes that have larger nuclei than those of BRLH are seen. Some abortive follicles may be present.

Treatment and Prognosis

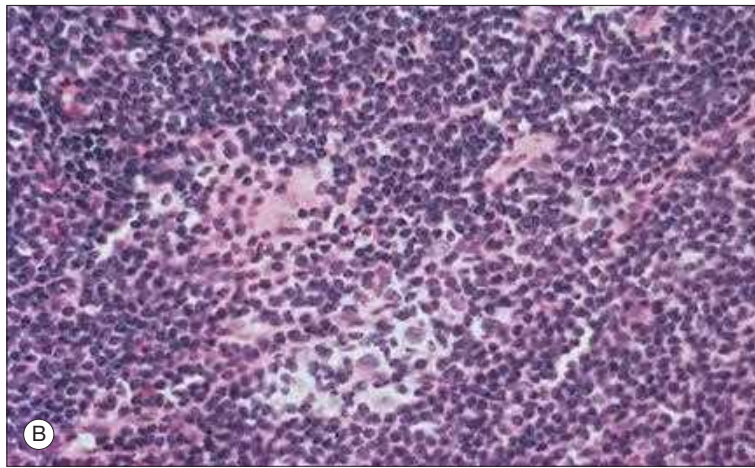
If no systemic involvement exists, radiotherapy at 2500–3000 cGy is appro-priate. There is a 40% chance of systemic lymphoma developing within 5 years.

MALIGNANT ORBITAL LYMPHOMA (LYMPHOSARCOMA)

Key Points

Malignant orbital lymphoma is a low-grade malignancy characterized by a proliferation of monoclonal B cells (non-Hodgkin’s) that arise in lymph nodes or in an extranodal site such as the orbit.<sup>56–59</sup> Most commonly affected is the older age group (50–70 years). Clinically, a palpable mass





**Fig. 12.10.13 Reactive Lymphoid Hyperplasia.** (A) The patient noted a fullness of the lower right lid. Large, thickened, redundant folds of conjunctiva in the inferior cul-de-sac are seen. The characteristic “fish flesh” appearance of the lesion suggests the clinical differential diagnosis of a lymphoid or leukemic infiltrate or amyloidosis. (B) Lymphocytes are mature, quite small, and uniform; occasional plasma cells and large monocytoid lymphocytes. The uniformity of the lymphocytes makes it difficult to differentiate this benign lesion from a well-differentiated lymphosarcoma. The very mature appearance of the cells and the absence of atypical cells, along with the presence of plasma cells, suggests the diagnosis of a benign lesion. In such cases, testing using monoclonal antibodies may be quite helpful. If the population is of mixed B and T cells, the chances are that the tumor is benign. If it is predominantly of one cell type or the other, usually B cells, it is probably malignant and may represent mucosal-associated lymphoid tissue of the conjunctiva. (Reproduced with permission from Yanoff M, Fine BS. *Ocular pathology*. 5th ed. St Louis, MO: Mosby; 2002.)

may be present in the anterior orbit. Symptoms include exophthalmos, occasional diplopia, lid edema, and ptosis (Fig. 12.10.14).

In 75% of cases the process is unilateral, and in 25% it is bilateral; 40% of cases are associated with systemic disease at the time of diagnosis.

### Orbital Imaging

A well-defined mass is seen that molds to encompass adjacent structures. Most lesions are located in the anterior, superior, and lateral orbit and frequently involve the lacrimal gland (Fig. 12.10.15).

### Pathology

Infiltrative, anaplastic lymphocytes with large cleaved nuclei and frequent nucleoli are seen. Follicles are absent. Immunohistochemistry reveals a monoclonal proliferation of B cells.

### Treatment and Prognosis

If no systemic involvement occurs, observation is warranted for low-grade differentiated lesions. For less well-differentiated types, chemotherapy or radiotherapy at 2500–4000 cGy is recommended, with local control rates of 60%–100%.<sup>60</sup>



**Fig. 12.10.14 Subconjunctival Anterior Orbital Lymphoma.**



**Fig. 12.10.15 Lymphoma Infiltrating Along the Lateral Orbital Wall.**

When the disease is confined to the orbit, the visual prognosis is excellent, but the overall prognosis for life is variable. A 60% chance exists of developing systemic lymphoma within 5 years.

## HISTIOCYTIC TUMORS

### INTRODUCTION

Histiocytic tumors are rare proliferative disorders of histiocytes that range from solitary benign lesions to those that exhibit a more malignant course. A typical feature of all these lesions is the presence of Langerhans' cells, a type of histiocyte normally found in the epidermis.

### EOSINOPHILIC GRANULOMA (HISTIOCYTOSIS X)

#### Key Points

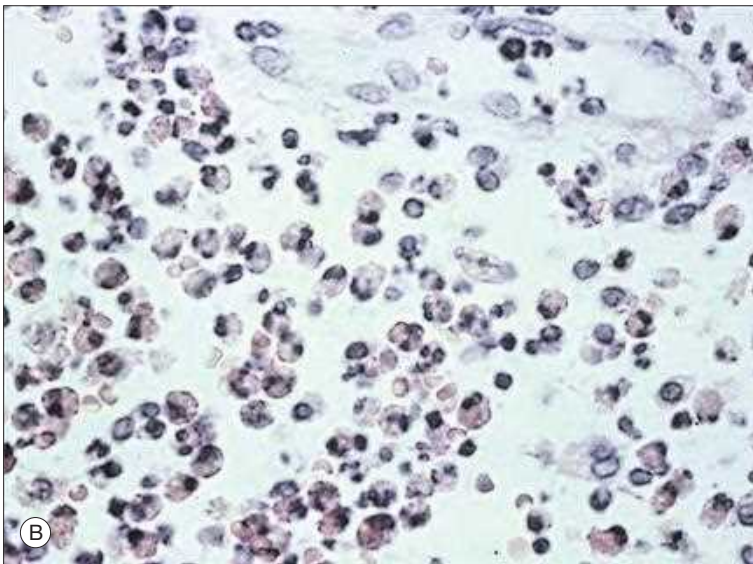
Eosinophilic granuloma is the most common and benign form of the histiocytosis X group. The disease affects primarily children and teenagers (from birth to 20 years of age). It consists of a unifocal, granulomatous proliferation in bone. Orbital involvement occurs in up to 20% of cases, most commonly in the superotemporal orbit.

Clinically, a rapid onset of axial displacement of the globe and painful superolateral swelling occur. Erythema and inflammatory signs are seen in the overlying skin.

### Orbital Imaging

Typically, an osteolytic lesion is seen near the superotemporal bony rim. Usually an irregular contour is noted, with marginal hyperostosis. Occasionally, the lesion may extend into the cranial fossa.





**Fig. 12.10.16 Eosinophilic Granuloma.** (A) A 4-year-old boy presented clinically with rapid onset of erythema and swelling over the lateral edge of the left orbit. Osteomyelitis versus rhabdomyosarcoma was diagnosed clinically; the area was explored surgically. (B) Histological section shows large histiocytes (abnormal Langerhans' cells) and numerous eosinophils characteristic of a solitary eosinophilic granuloma. ([A], Courtesy Dr D.B. Schaffer. [B] Courtesy Schaffer DB. In: Yanoff M, Fine BS. Ocular pathology. 5th ed. St Louis, MO: Mosby; 2002.)

## Pathology

This is a soft, friable, tan-yellow tumor with sheets of binuclear, atypical histiocytes, eosinophils, and giant cells (Fig. 12.10.16). Characteristic Langerhans' granules are seen in the cytoplasm.

## Treatment and Prognosis

Surgical curettage generally is curative, but radiotherapy at 900–1500 cGy also may be used. The prognosis is very good.

## INFLAMMATIONS AND INFECTIONS

Inflammatory diseases are common orbital lesions that may simulate neoplasms. They include a variety of acute and subacute idiopathic processes, chronic inflammations, and specific inflammations of uncertain etiology. Most notable among these lesions is thyroid eye disease, which accounts for more than half of all such cases. See Chapter 12.15 for a discussion of inflammatory and infectious disorders of the orbit.



**Fig. 12.10.17 Right Superomedial Superficial Orbital Dermoid Cyst in a Young Child.**

### BOX 12.10.3 Common Cystic Lesions of the Orbit

- Dermoid cysts
- Conjunctival cysts
- Sweat gland cysts
- Microphthalmos with cyst
- Lacrimal gland cysts
- Lymphangioma
- Schwannoma
- Infectious abscesses

## THYROID EYE DISEASE

Thyroid eye disease is an autoimmune disorder that affects the orbital muscles and fat.<sup>61,62</sup> This accounts for nearly half of all orbital diseases seen clinically. See Chapter 12.14 for a complete discussion of this disorder.

## CYSTIC LESIONS

### INTRODUCTION

Structural lesions of the orbit include choristomatous lesions such as dermoid cysts, which arise from errors in embryogenesis, and anatomical abnormalities such as mucocoeles, which result from local disease processes (Box 12.10.3).

## DERMOID CYST

### Key Points

A dermoid cyst is a developmental choristoma (tumor of tissue not normally found in area), lined with epithelium and filled with keratinized material.<sup>63,64</sup> The majority of such cysts are located in the eyelids and orbit (Fig. 12.10.17). These cysts represent 24% of all orbital and lid masses, 6%–8% of deep orbital masses, and 80% of cystic orbital lesions. Dermoid cysts may lie latent for many years before growth and may be located superficially in the eyelid and anterior orbit or deep in the orbit. If ruptured, sudden growth may occur because of a secondary granulomatous inflammatory reaction.

### Superficial Lesions

Superficial lesions arise from a sequestration of epithelium during embryogenesis along bony suture lines. They are present in early infancy, typically in the superotemporal or superonasal quadrants. Clinically, they present as a slowly enlarging, unilateral, painless, firm mass. They may be mobile or fixed to underlying structures and are free from overlying skin.

### Orbital Imaging

The round, well-defined lesions have an enhancing rim that may contain calcium and a lucent center. They may be associated with a well-corticated bone defect.

### Pathology

The cyst usually has a thin, fibrous capsule and a central lumen lined with keratinized stratified squamous epithelium. If derived from conjunctiva, the lining may be cuboidal with goblet cells. The cyst wall contains hair follicles and sweat and sebaceous glands. The cyst contains keratin debris, hair shafts, and oily material. About 38% of cysts are associated with chronic granulomatous inflammation.

### Treatment and Prognosis

Complete surgical excision in one piece is required. The prognosis is excellent, but recurrences with infiltration may follow incomplete excision or rupture of the capsule.

### Deep Lesions

Deep lesions are seen in both children and adults. They are associated with any bony suture in the orbit and may extend across bones into the frontal sinus, temporal fossa, or cranium.

Symptoms from the slow-growing mass include proptosis, occasionally motility restriction, and decreased vision. Spontaneous rupture produces marked orbital inflammation.

### Orbital Imaging

The well-defined lesion has an enhancing rim that may contain areas of calcification. The central lumen is nonenhancing and of variable density, depending on its contents; it may show a fluid-fat interface. A bone defect may be seen.

### Pathology

A smooth, thin rim of keratinized squamous epithelium, which may have goblet cells if derived from conjunctiva, lines the cyst. The cyst wall contains hair shafts, and sweat and sebaceous glands are characteristic.

### Treatment and Prognosis

Treatment consists of total excision without rupture of the capsule. The prognosis is excellent.

## MUCOCELE

### Key Points

Mucoceleles arise from a primary obstruction of a paranasal sinus following trauma, sinusitis, or, rarely, a tumor.<sup>65</sup> Frequently, they expand into the orbit by expansion of a bony wall. Mucoceleles consist of a cystic mass filled with mucus and may be bounded by an eggshell layer of bone (when they become infected, mucoceleles are referred to as pyoceles). The majority of mucoceleles (70%) occur in adults (aged 40–70 years), and the frontal and ethmoid sinuses are most commonly involved—rarely the sphenoid sinus.

Symptoms include headache, exophthalmos, and a palpable fluctuant mass in the medial or superomedial orbit.

### Orbital Imaging

An opacified frontal or ethmoid sinus, loss of ethmoid septae, and a bony dehiscence (Fig. 12.10.18) are observed. The cystic content shows variable density and is nonenhancing.



Fig. 12.10.18 Anterior Ethmoid Sinus Mucocele Eroding Into the Orbit.

### Pathology

The lining is composed of pseudostratified, ciliated columnar epithelium with goblet cells. The cyst content is mucoid with chronic inflammatory debris.

### Treatment and Prognosis

Treatment consists of surgical excision with restoration of sinus drainage. Obliteration of the sinus with fat or muscle may be necessary to treat recurrences.

The prognosis is very good, but there is a significant rate of recurrence.

## MICROPHTHALMOS WITH CYST

### Key Points

Microphthalmos is a severe malformation of the globe that may be associated with cyst formation.<sup>66</sup> The microphthalmic eye may be associated with colobomas of the globe where the overlying sclera is thinned and bulging. Less commonly, a cyst may originate from the optic nerve, where it usually communicates with the subarachnoid space. The disorder presents at birth with a variably small eye and reduced visual acuity and the cyst is typically located in the inferior orbit.

### Orbital Imaging

On CT scan the globe is small or severely deformed. The cyst appears as a dark, low-attenuating density, similar to cerebrospinal fluid (CSF). A thin rim of higher density tissue similar to sclera surrounds it. The bony orbit is often enlarged from remodeling. Following contrast administration there is no enhancement of the cyst or its enclosing wall. On MRI T1-weighted images the cyst produces a homogeneous low signal that varies from iso-intense to hypointense similar to vitreous or CSF. On the T2-weighted image the cyst contents are hyperintense, and there is no enhancement with gadolinium.

### Pathology

This entity has a small malformed eye with a cyst composed of connective tissue continuous with the sclera. The cyst is lined by disorganized retinal and/or glial tissue and may contain choroidal remnants. Retinal tissue may not be recognizable in all cases.

### Treatment and Prognosis

When cysts are small with minimal symptoms, specific therapy is not necessary. If the globe is disfigured and there is no proptosis, a scleral shell may be applied for cosmetic improvement. With significant proptosis or orbital pain, the cyst can be deflated with repeated needle aspiration. In some cases, better cosmesis will be obtained with enucleation. The prognosis for vision is poor, but with appropriate and timely management the prognosis for cosmesis can be quite good.

## VASCULAR NEOPLASTIC AND STRUCTURAL LESIONS

### INTRODUCTION

Neoplastic lesions that arise from the vascular system include both benign and malignant tumors (Table 12.10.8). Unlike nonneoplastic vascular lesions, which usually reflect the hemodynamic functions of the underlying vascular structures, neoplastic lesions typically manifest only a mass effect, occasionally modified by some hemodynamic characteristics. They may be well circumscribed or infiltrative.

### CAPILLARY HEMANGIOMA (HEMANGIOENDOTHELIOMA)

### Key Points

Capillary hemangioma is a congenital hamartoma of tightly packed capillaries that typically presents during the first 6 months of life.<sup>6,56,67</sup>





**Fig. 12.10.19** Capillary Hemangioma of the Lower Eyelid in a Young Child.

**TABLE 12.10.8** Frequency of the Most Common Vascular Orbital Lesions

Lesion	Frequency (%)
Cavernous hemangioma	50
Capillary hemangioma	18
Hemangiopericytoma	13
Lymphangioma	10
Orbital varices	5
Other	5

Modified from Shields JA, editor. Diagnosis and management of orbital tumors. Philadelphia, PA: WB Saunders; 1989. p. 291–315.

It is generally unilateral and usually visible on the surface, but it may lie deep in the orbit (**Fig. 12.10.19**). More common in the superonasal quadrant of the upper lid, capillary hemangioma appears as a fluctuant mass that may involve the overlying skin as a reddish lesion. Capillary hemangiomas show rapid growth over weeks to months, followed by slow spontaneous involution over months to years.

## Superficial Lesions

Also known as the “strawberry nevus,” capillary hemangioma is confined to the dermis. It may be single or multiple and is generally elevated. Symptoms include ptosis, sometimes associated with astigmatism and amblyopia.

### Treatment and Prognosis

Observation is warranted in most cases because involution usually occurs. Recently systemic propranolol for 8–12 months has been shown to achieve dramatic resolution for superficial lesions.<sup>68</sup> Intralesional corticosteroids, radiotherapy, and, more recently, topical corticosteroids also have been advocated.<sup>69</sup> Surgery is useful for small, circumscribed lesions, but for larger ones, this may result in cosmetic compromise.

The prognosis is good; 30% of cases involute by 3 years of age, 60% by 4 years of age, and 75% by 7 years of age. Large lesions may not completely disappear.

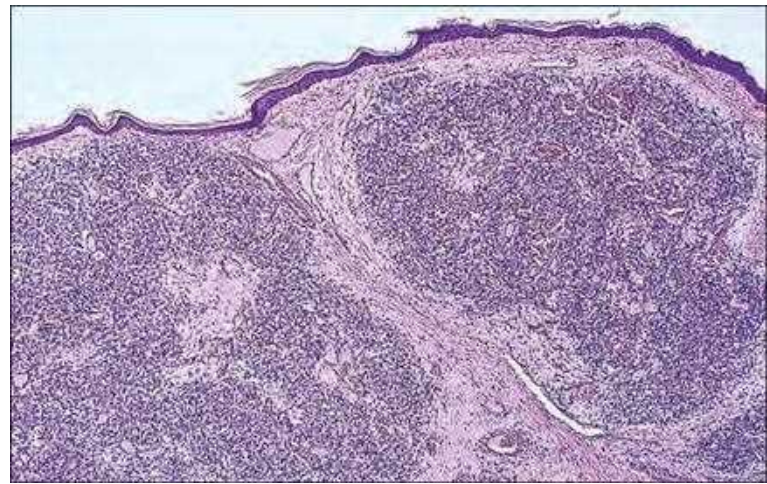
## Deep Lesions

Deep lesions occur most frequently in the lids or posterior to orbital septum and are more common in the superonasal quadrant.

Symptoms are proptosis, displacement of the globe, subtle pulsations as a result of high vascular flow, and increasing size with the Valsalva maneuver or crying. Secondary amblyopia may result from distortion of the globe. Large lesions may sequester platelets.

### Orbital Imaging

A well-defined to infiltrating intraconal or extraconal lesion is observed with moderate to intense enhancement. On MRI the signals are homogeneous



**Fig. 12.10.20** Capillary Hemangioma. The tumor is composed of blood vessels of predominantly capillary size. (From a presentation by Dr W.C. Frayer to the meeting of the Verhoeff Society, 1989.)

to heterogeneous, being hypointense on T1 and hyperintense on T2 images. Flow voids appear as hypointense regions. Moderate enhancement is seen with gadolinium.

### Pathology

A florid proliferation of capillary endothelial cells and small capillaries is seen, with few spaces (**Fig. 12.10.20**). Mitoses are common, but this is not a malignant tumor.

### Treatment and Prognosis

Treatment consists of observation because many lesions will involute, although few orbital lesions completely disappear. If the lesion is large or amblyopia is present, local radiotherapy (500 cGy) or corticosteroids (systemic or local) may be indicated. If the lesion is small and well defined, surgery may be attempted. Recently propranolol has been shown to cause significant involution for tumors in the proliferative phase.<sup>70</sup>

The prognosis is excellent for vision and for life.

## CAVERNOUS HEMANGIOMA

### Key Points

Cavernous hemangioma is a benign, noninfiltrative, slowly progressive tumor of large endothelial-lined channels.<sup>5,6</sup> Although it is congenital, it typically becomes symptomatic in adults (aged 20–40 years). Cavernous hemangioma is usually found in an intraconal location, more commonly in the temporal quadrant. Rarely, it may be intraosseous.

Symptoms relate to its mass effect, which produces proptosis and late motility restriction. When cavernous hemangiomas are very large, choroidal folds and decreased vision may result. The lesions may enlarge during pregnancy.

### Orbital Imaging

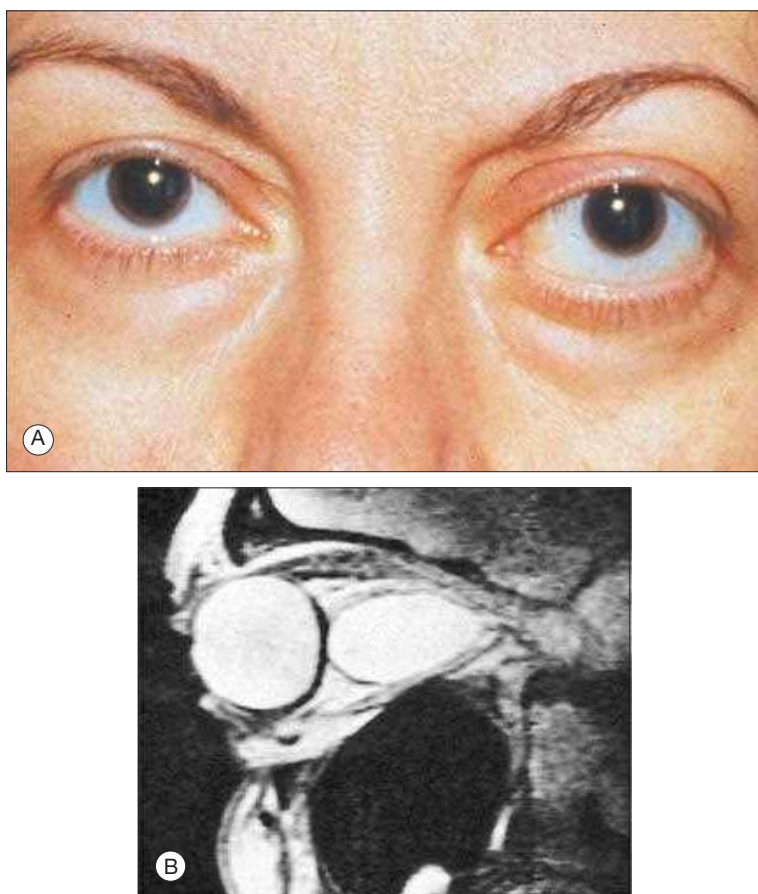
A well-defined, oval to round, typically intraconal mass is seen with minimal enhancement. With large, long-standing lesions, molding of bone and internal calcification may occur. On MRI the lesion is isointense on T1 and hyperintense on T2 with respect to muscle. Signal voids represent calcific phleboliths. Enhancement with gadolinium is moderate.

### Pathology

The encapsulated nodular mass consists of dilated, vascular spaces lined by flattened endothelial cells (**Fig. 12.10.21**). Septae may contain lymphocytes and smooth muscle cells.

### Treatment and Prognosis

Surgical excision is required if the lesion is symptomatic—typically, there is little or no bleeding. There is no role for radiotherapy. The prognosis is excellent for vision and life.



**Fig. 12.10.21 Cavernous Hemangioma.** (A) Clinical appearance of left exophthalmos. (B) MRI shows optic nerve stretched over tumor that “lights up” in the T2-weighted image, characteristic of a hemangioma. ([A] From a presentation by Dr W.C. Frayer to the meeting of the Verhoeff Society, 1989. [B] Reproduced with permission from Yanoff M, Fine BS. *Ocular pathology*. 5th ed. St Louis, MO: Mosby; 2002.)

## LYMPHANGIOMA

### Key Points

Lymphangioma is a rare vascular hamartoma of lymphatic channels that is hemodynamically isolated from the vascular system.<sup>71</sup> It occurs in children and teenagers but most frequently in the first decade of life. The size of the lesion fluctuates with posture and the Valsalva maneuver and with upper respiratory infections.

### Superficial Lesions

Superficial lesions occur in the conjunctiva or lid and are visible as cystic spaces with clear fluid; they may be partially filled with blood.

### Deep Lesions

Symptoms with deep lesions are proptosis and diplopia. Spontaneous hemorrhage may lead to sudden enlargement and orbital pain and possible visual loss with the formation of “chocolate cysts.”

### Orbital Imaging

The orbital lesion is seen as a low-density cystic, intra- and extraconal mass with variable enhancement. No vascular component is seen on angiography. On MRI the lesion is hypointense on T1; on T2 the signal is hyperintense but may be variable depending on the state of hemoglobin degeneration.

### Pathology

Lymphangiomas show infiltrative endothelium-lined channels with a sparse cellular framework and lymphocytes. Lymphatic follicles often are seen in the walls of the tumor. Red blood cells are not present unless a secondary hemorrhage has occurred.

## Treatment and Prognosis

Observation is justified in most cases. Surgery may be hazardous and lead to poor cosmetic results. If acute hemorrhage causes severe symptoms, the lymphangioma may be evacuated and partial resection or ligation attempted. Recurrences are common. The lesion shows limited radiosensitivity. The prognosis is variable. Amblyopia is common from globe compression and recurrent hemorrhage.

## ARTERIOVENOUS FISTULA

### Key Points

Arteriovenous fistulas can be traumatic (more common in males than females, age range 15–30 years) or spontaneous (more common in females than males, age range 30–60 years).<sup>5,6</sup> Symptoms depend on blood flow rate—most fistulas are associated with venous dilation, fluid transudation, sludging, and thrombosis.

### Low-Flow Type

Low-flow fistulas usually result from dural artery-to-cavernous sinus shunts. Symptoms are chemosis, increased episcleral venous pressure, and venous dilatation.

### High-Flow Type

High-flow fistulas usually result from carotid artery-to-cavernous sinus shunts. Symptoms are chemosis, orbital edema, proptosis, pulsatile exophthalmos, audible bruit, secondary glaucoma, retinal vascular dilation, papilledema, afferent pupillary defect, decreased vision, and cranial nerve palsies (third and sixth nerves most common).

### Primary Shunts

Primary shunts (mainly congenital malformations) are rare in the orbit and are usually associated with syndromes (e.g., Wyburn–Mason and Osler–Weber–Rendu).

### Secondary Shunts

Secondary shunts are located outside the orbit, usually in the cavernous sinus. Retrograde blood flow is directed forward into the orbital veins. Secondary shunts may be spontaneous (from venous thrombosis or hypertension) or secondary (from trauma). The latter are usually of the high-flow type, with 40%–50% causing visual loss.

### Orbital Imaging

A dilated superior ophthalmic vein with enlargement of the superior orbital fissure is seen; erosion of the anterior clinoid processes occurs.

## Treatment and Prognosis

Resolution of small, spontaneous low-flow shunts frequently occurs from thrombosis and is seen in up to 40% of cases. Embolization is not indicated unless visual loss, glaucoma, or severe pain is present. With traumatic, high-flow shunts, spontaneous resolution is less common. The rate of visual loss is 40%–50%, and intervention is therefore required. Balloon or other embolization is the treatment of choice.

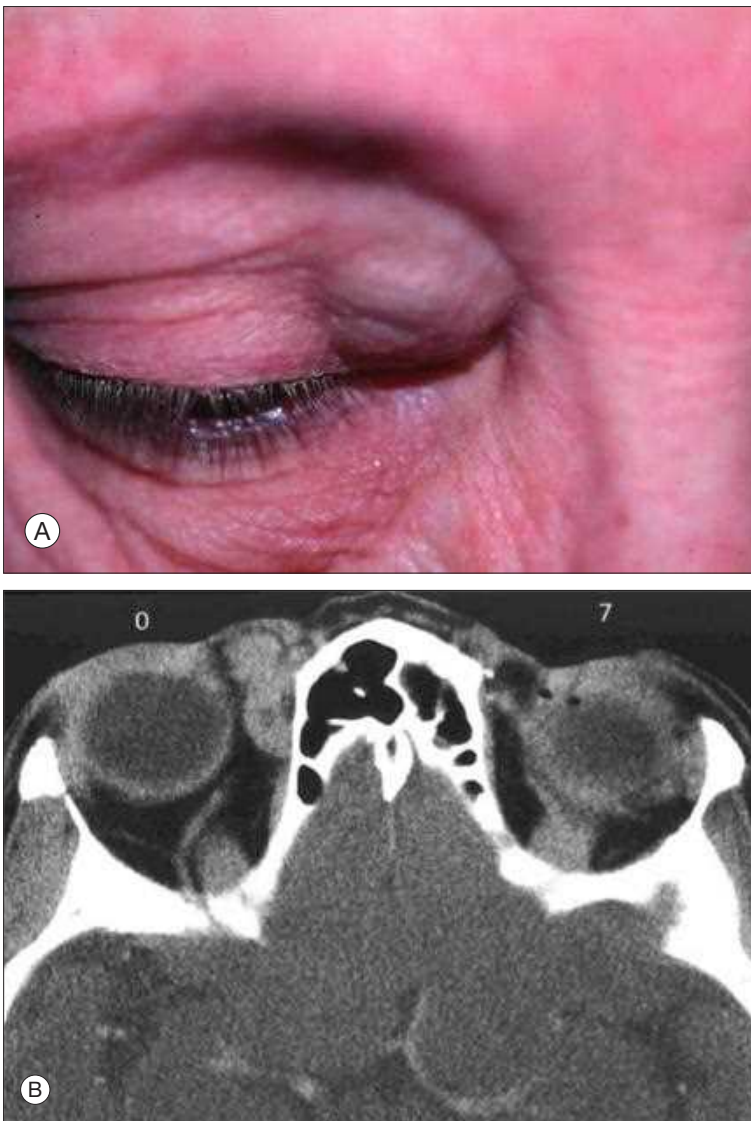
With treatment, the prognosis is generally good for vision.

## VARICES

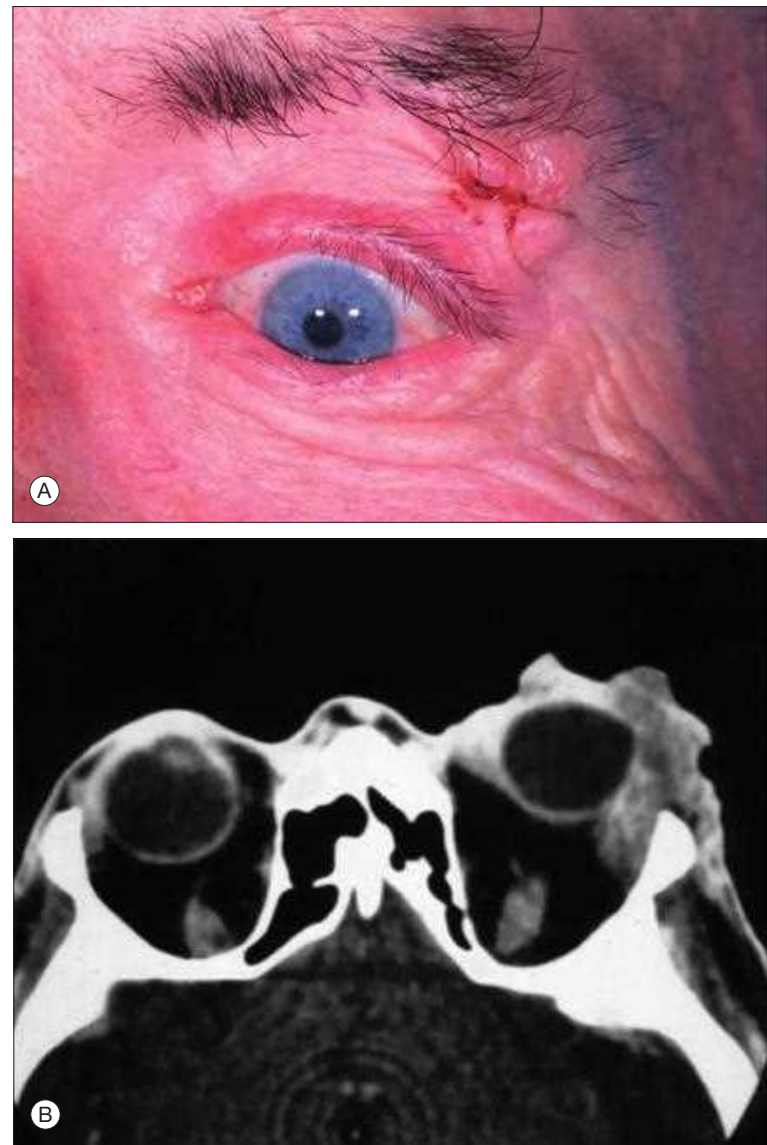
### Key Points

Orbital varices are dilated venous channels that represent one end of the spectrum of developmental venous anomalies that also includes lymphangiomas.<sup>72</sup> They are prone to spontaneous hemorrhage and thrombosis formation. Varices typically present with slowly progressive intermittent proptosis. Ophthalmoplegia and pain are variable depending on the size and location. Symptoms frequently are exacerbated by changes in head position, bending forward, or by Valsalva maneuver (Fig. 12.10.22).





**Fig. 12.10.22 Orbital Varix.** (A) Clinical appearance of a dilated anterior superomedial orbital varix during Valsalva. (B) Orbital computed tomography of a different patient showing a heterogeneous dilated venous channel in the posterior orbit with areas of enhancement and low-density regions representing thrombus.



**Fig. 12.10.23 Basal Cell Carcinoma.** (A) Patient with a basal cell carcinoma of the left upper eyelid and brow. (B) Computed tomography scan showing an irregular multilobulated medium density mass in the superolateral eyelid extending into to orbit.

## Orbital Imaging

On CT, dilated varices appear as serpiginous structures of increased density. The vascular channels can be seen to enlarge with Valsalva maneuver, even in patients without orbital symptoms. With contrast administration there is marked enhancement where the vascular channels are patent to blood flow. On MRI T1 images the varix produces a low isointense signal that typically shows marked enlargement in size with Valsalva. On T2 images flowing blood produces a dark signal void. With gadolinium, enhancement is marked, except in areas of thrombus formation where there is little or no enhancement.

## Pathology

A single large vessel may dominate an orbital varix or there may be multiple ectatic veins. The vessel walls may be fibrotic, and the lumens may be thrombosed or contain phleboliths resulting from calcification of old thrombus.

## Treatment and Prognosis

No treatment is required if symptoms are mild. For more severe orbital symptoms, surgical evacuation of clots and partial excision of ectatic venous channels may be necessary. Embolization with coils may limit traumatic dissection. The prognosis for vision is generally good. With very large lesions, visual loss can result from prolonged optic nerve compression.

## SECONDARY TUMORS

### INTRODUCTION

Secondary tumors of the orbit invade from adjacent structures and areas. They may spread from the globe by extending through the sclera or expand backward through the orbital septum from the conjunctiva or through the orbital walls from the paranasal sinuses or intracranial compartment.

### BASAL CELL CARCINOMA

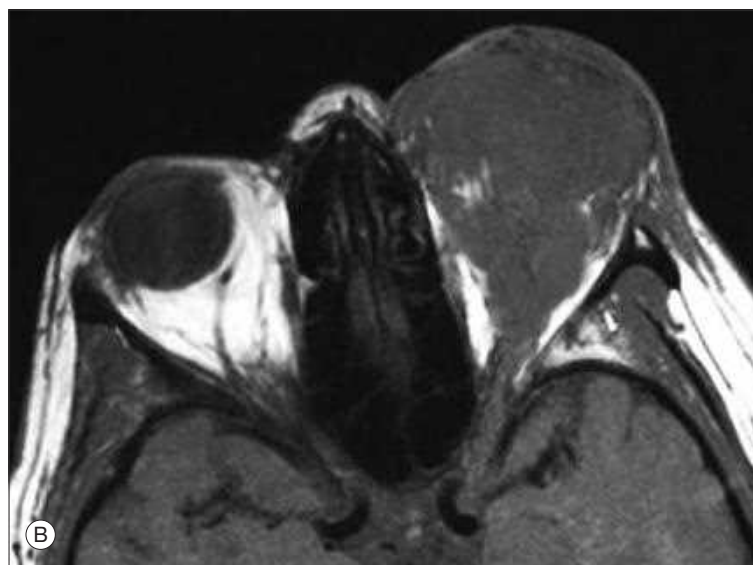
#### Key Points

Basal cell carcinoma is the most common secondary tumor involving the orbit. It typically spreads backward from the eyelids or brow (Fig. 12.10.23). Lesions originating in the medial canthus are more likely to invade the orbit because of anatomical discontinuities in the orbital septal complex.<sup>73</sup> Most patients are 50–80 years of age and have a history of a previous skin tumor. The patient may present with proptosis, diplopia, ptosis, and orbital pain.

#### Orbital Imaging

On CT scan, orbital basal cell carcinoma appears as an irregular, often lobulated, well-defined density extending into the retroseptal space. Less dense cystic spaces can be present and enhancement is moderate. On MRI





**Fig. 12.10.24 Malignant Melanoma.** (A) Recurrent secondary orbital malignant melanoma in an enucleated socket from extrascleral extension of a uveal tumor. (B) Computed tomography scan showing a homogeneous medium density mass filling the orbit.

T1 images, basal cell carcinoma appears as a homogeneous isointense mass. On the T2 images, the tumor produces a somewhat brighter image. Marked enhancement occurs with gadolinium.

## Pathology

Strands of basaloid cells in a dense fibrous stroma extend into the orbit. Basophilic tumor cells are arranged radially with their long axes parallel to each other, creating so-called “peripheral palisading.” Sometimes the tumor lobules have central necrosis or a prominent adenoid pattern.

## Treatment and Prognosis

Localized lesions in the anterior orbit are excised when possible. Heroic attempts to retain visual function frequently result in scarring with a fixed globe. Deep orbital tumors that invest the globe require limited or radical orbital exenteration. With appropriate surgery, prognosis for life is good but recurrences may be seen after many years.

## MALIGNANT MELANOMA

### Key Points

Most malignant melanomas in the orbit are secondary tumors spreading from an intraocular choroidal primary site or from the conjunctiva.<sup>74,75</sup> Primary melanomas are extremely rare but can arise from a cellular blue nevus or in the setting of oculodermal melanocytosis. Occasionally malignant melanoma may metastasize to orbital structures from distant sites. In advanced cases proptosis, ptosis, chemosis, ophthalmoplegia, and orbital pain may be seen (Fig. 12.10.24).

### Orbital Imaging

CT demonstrates a homogeneous orbital mass of moderate density. When extension is from the choroid the mass is typically intraconal and may be infiltrative around orbital structures. A similar and contiguous mass may be seen as a dome or collar-button density within the globe. In cases of prior enucleation for intraocular melanoma, the orbital implant may be displaced forward by the tumor. On MRI images an infiltrative mass is seen that produces a high intensity signal on both T1 and T2 weighted sequences. With gadolinium there is diffuse enhancement.

## Pathology

Choroidal melanoma extending into the orbit through a scleral canal will have the appearance of the primary intraocular tumor, which is usually pigmented. In contrast, melanoma recurrent in the orbit may be composed solely of amelanotic, polygonal or spindle-shaped tumor cells. Paraffin sections can be immunostained for S100 protein and/or HMB-45 (a marker for cutaneous and uveal melanoma) to confirm the diagnosis.

## Treatment and Prognosis

The best treatment is not yet firmly established. Although local resection has been advocated for some well-defined low-grade tumors arising from blue nevi, in most cases a more radical procedure will be needed for cure. This implies a limited anterior exenteration for lesions arising in conjunctiva or a radical exenteration for tumors originating from the choroid with deep orbital invasion. Overall, the prognosis is guarded with a high mortality rate from metastatic spread.

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# Enucleation, Evisceration, and Exenteration

12.11

Myron Tanenbaum

## Definitions:

- Enucleation: surgical removal of the entire globe.
- Evisceration: surgical removal of the entire contents of the globe, leaving a scleral shell.
- Exenteration: removal of the entire orbit including the globe, eyelid, and orbital contents—usually performed for malignant tumors.

## Key Features

- Indications for enucleation, evisceration, or exenteration surgery.
- Careful preoperative patient evaluation and counseling.
- Detailed presentation of specific surgical techniques for enucleation, evisceration, and exenteration.
- Postoperative management, and possible surgical complications.

## INTRODUCTION

Enucleation, evisceration, and exenteration surgery all involve the permanent removal of the patient's eye. In this chapter the important aspects of each procedure are emphasized, including:

- Indications for surgery.
- Preoperative patient counseling.
- Surgical techniques.
- Postoperative management.
- Complications of surgery.

## PREOPERATIVE EVALUATION AND DIAGNOSTIC APPROACH

### Indications for Surgery

Enucleation or evisceration surgery may be indicated for a blind painful eye, endophthalmitis, or cosmetic improvement of a deformed eye. In cases of intraocular neoplasms or the treatment of severe ocular trauma with a ruptured globe, where sympathetic ophthalmia is a concern, enucleation is appropriate and evisceration is contraindicated. Other indications for enucleation may include progressive phthisis bulbi, severe microphthalmia, and biopsy in a bilateral process where one eye is blind and the other eye is not as involved.

In the vast majority of situations, the indication for exenteration surgery is to eradicate life-threatening malignancy or life-threatening orbital infection. The extent of the procedure should be explained to the patient, especially which tissues are to be removed (this includes the eyeball, orbital soft tissues, and part or all of the eyelid structures). A summary of the indications for surgery is given in [Box 12.11.1](#).

### Preoperative Counseling

Faced with the permanent loss of an eye, a patient requires the physician's reassurance, caring explanations, and psychological support. The patient (and family) should understand that evisceration and enucleation surgery involve the complete, permanent removal of the diseased or deformed eye. The indication for surgery should be clearly explained. The patient should be informed of the choices between enucleation and evisceration surgery

and of the availability of a variety of orbital implants, including common alloplastic implants,<sup>1,2</sup> newer implants designed to maximize ultimate ocular prosthesis motility,<sup>3,4,5</sup> or autologous tissue orbital implants such as dermis fat.<sup>6</sup>

The patient should understand the risks and benefits of wrapping orbital implants with either autologous tissues or preserved donor tissue and that donor tissues may carry the risks of communicable diseases, such as syphilis, hepatitis, and human immunodeficiency virus. A thorough explanation allows the patient and family to make a well-informed decision regarding surgery.

## ANESTHESIA

Enucleation surgery may be performed using local anesthesia. For psychological reasons, and occasionally for medical reasons, however, general anesthesia is usually employed. Under any circumstance, agents should be used that maximize intraoperative hemostasis, suppress the oculocardiac reflex,<sup>7</sup> and minimize postoperative pain. The author's choice is to instill 10% phenylephrine eyedrops into the conjunctival cul-de-sac to achieve intense vasoconstriction and to infiltrate extensive retrobulbar and peribulbar bupivacaine 0.5% with epinephrine (adrenaline) 1:100 000 and hyaluronidase. After adequate time, an excellent anesthetic and vasoconstrictive effect is achieved.

Most evisceration surgeries are performed under local anesthesia with intravenous sedation. A mixture of lidocaine (lignocaine) 2% with epinephrine 1:100 000, bupivacaine 0.5% with 1:100 000 epinephrine, and hyaluronidase is injected in retrobulbar fashion into the muscle cone. The use of intravenous anesthetic sedatives prevents either the local anesthetic injection or the surgical procedure itself from being unpleasant or producing anxiety.

Exenteration surgery is usually performed under general anesthesia, which may be combined with bupivacaine and epinephrine infiltration to aid hemostasis and provide postoperative analgesia.

### BOX 12.11.1 Indications for Surgery

#### Enucleation

- Blind painful eye
- Intraocular tumor
- Severe trauma with risk of sympathetic ophthalmia
- Phthisis bulbi
- Microphthalmia
- Endophthalmitis/panophthalmitis
- Cosmetic deformity

#### Evisceration

- As for enucleation, except for intraocular tumors or risk of sympathetic ophthalmia

#### Exenteration

- Cutaneous tumors with orbital invasion
- Lacrimal gland malignancies
- Extensive conjunctival malignancies
- Other orbital malignancies
- Mucormycosis
- Chronic orbital pain
- Orbital deformities



## SPECIFIC TECHNIQUES

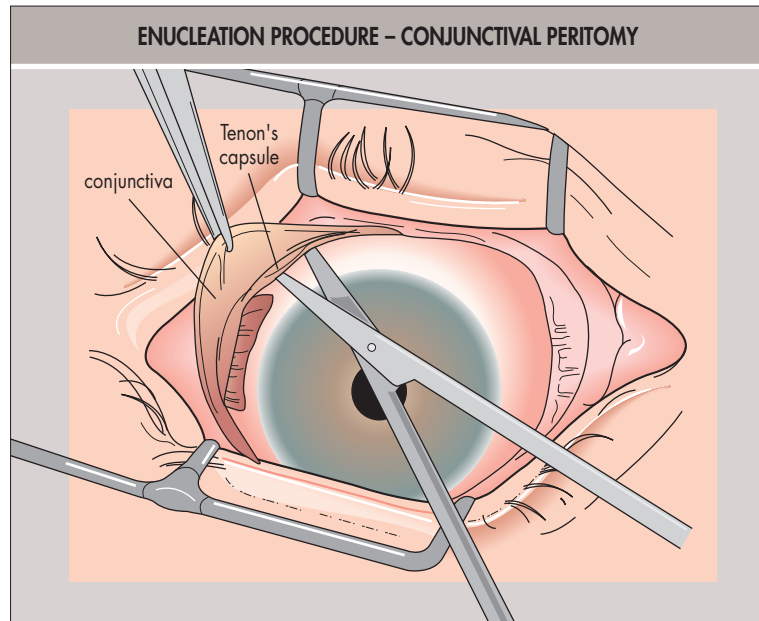
### Enucleation

The indications for enucleation surgery and important aspects of preoperative counseling have already been discussed. Here, two surgical techniques are described:

- Enucleation with placement of a simple sphere implant.
- Enucleation with placement of a sclera-wrapped porous implant for improved motility.

#### Enucleation With Simple Sphere Implant

A self-retaining lid speculum is placed to expose the entire epibulbar surface. A 360° conjunctival peritomy is performed (Fig. 12.11.1). Tenon's fascia is bluntly dissected away from the sclera in all four quadrants. Each of the four rectus muscles is sequentially gathered on a muscle hook, secured with a double-armed 6-0 Vicryl suture, and detached from the globe. The superior oblique tendon is severed and detached from the globe. The inferior oblique muscle should be hooked and secured with a 6-0 Vicryl suture, detached, and saved for later attachment to the inferior



**Fig. 12.11.1 Enucleation Procedure.** Following a 360° conjunctival peritomy, a small pair of tenotomy scissors is used to dissect bluntly Tenon's fascia in all four quadrants.

border of the lateral rectus muscle. This use of the inferior oblique muscle is perhaps more important as an eventual “hammock” for the orbital implant than to enhance meaningfully anophthalmic socket motility.

After the extraocular muscles are detached, the surgeon is ready to sever the optic nerve. Anterior traction on the globe is useful when cutting the optic nerve and can be achieved with a curved hemostat applied to the medial rectus tendon. It is the author's preference to clamp the optic nerve with a curved hemostat inserted behind the globe in the superonasal direction (Fig. 12.11.2). With the hemostat in place, a slender, curved pair of Metzenbaum scissors is used to transect the optic nerve, and the entire eyeball is removed. The surgeon should inspect the entire globe for intactness and/or unusual findings before submitting the specimen for histopathological examination. Malleable retractors are placed so the still clamped cut edge of the optic nerve can be visualized directly. The central retinal vessels are cauterized to obtain meticulous hemostasis before removal of the clamp (Fig. 12.11.3). If the optic nerve is not clamped, such as for intraocular tumors, orbital packing with direct pressure for 5–10 minutes can be applied to achieve adequate hemostasis. In select enucleations, as with tumors in contact with the optic disc or with retinoblastoma-containing eyes, it may be necessary to obtain a long segment of optic nerve.<sup>8</sup>

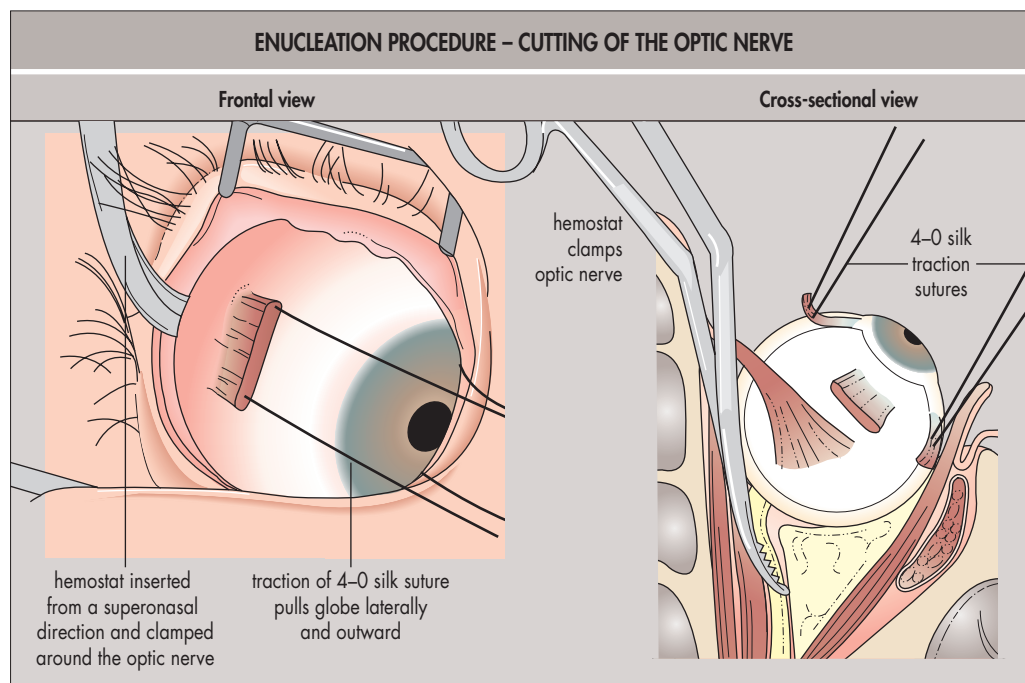
For the average-sized adult orbit, a 20 mm polymethyl methacrylate orbital implant is usually adequate. The implant type and size can, of course, vary, and it may also be wrapped in either autologous fascia or donor sclera. The orbital implant is inserted behind posterior Tenon's fascia through the central rent left by cutting the optic nerve. Multiple interrupted 6-0 Vicryl sutures securely close posterior Tenon's fascia that overlies the orbital implant.

Each of the four rectus muscles is sutured to the adjacent fornix by passing the previously placed double-armed 6-0 Vicryl sutures full thickness through Tenon's fascia and conjunctiva (Fig. 12.11.4). This will provide motility to the ocular prosthesis. Care should be taken to avoid advancing the superior rectus suture too close to the midline to avoid inadvertent tension or traction on the superior rectus muscle, which could induce an upper lid ptosis. After anterior Tenon's fascia is closed in the midline with 6-0 Vicryl sutures (Fig. 12.11.5),<sup>9</sup> the conjunctival edges are loosely reapproximated with a 6-0 plain gut running suture.

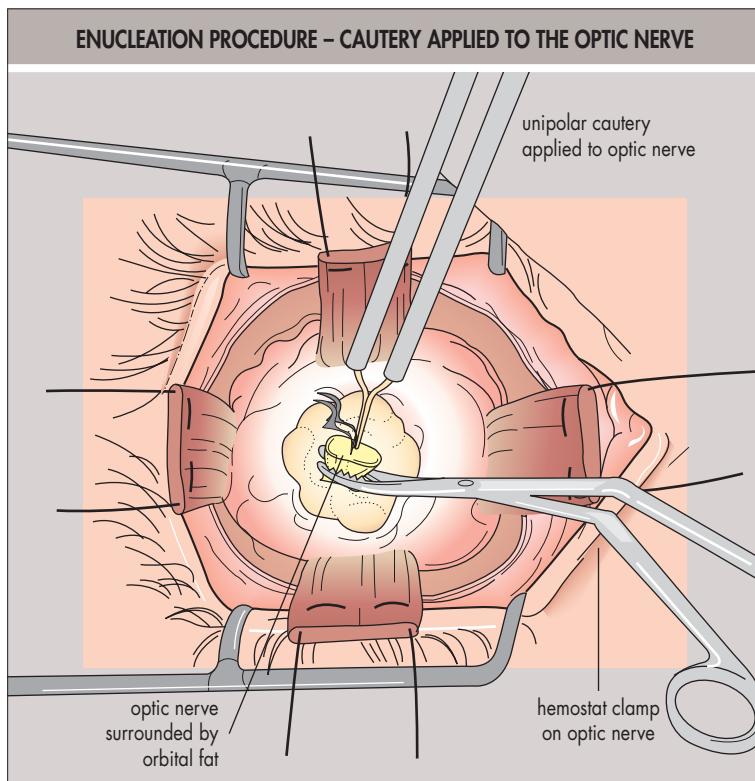
A broad-spectrum ophthalmic antibiotic ointment is applied to the conjunctiva. A medium-sized clear, acrylic lid conformer is placed and a firm pressure bandage applied over the socket. The pressure bandage remains intact for 3–4 days postoperatively, and, upon its removal, the patient uses topical cool compresses with crushed ice. Pain medication is prescribed as appropriate. This perioperative and postoperative management regimen allows the large majority of enucleation procedures to be performed as outpatient procedures, with adequate control of postoperative pain.

#### Enucleation With Porous Implant

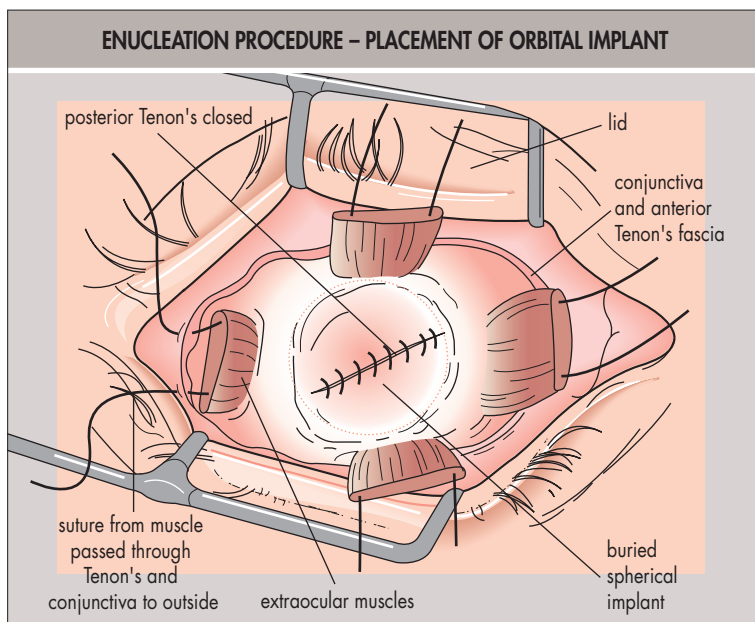
The purpose of the porous implant, such as the hydroxyapatite, porous polyethylene, or aluminum oxide implant, is to allow the potential for



**Fig. 12.11.2 Each of the Four Rectus Muscles Is Tagged With a Double-Armed 6-0 Vicryl Suture and Detached From the Globe.** Some 4-0 silk sutures may be placed through the medial and lateral recti muscle stumps to provide anterior traction on the globe, as a slender, curved hemostat is used to clamp the optic nerve.



**Fig. 12.11.3** The Globe Has Been Removed and Cautery Is Applied to the Optic Nerve Stump to Maintain Meticulous Hemostasis.

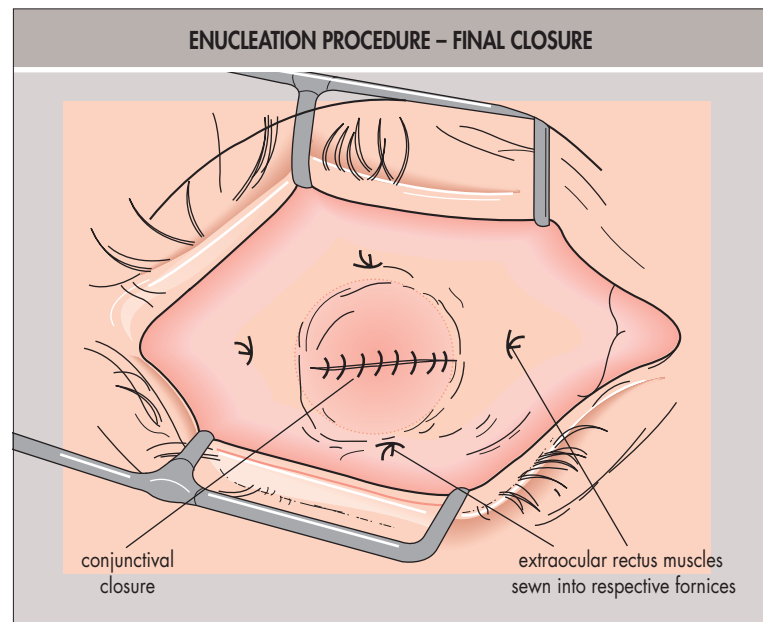


**Fig. 12.11.4** An Orbital Implant Has Been Placed Behind Posterior Tenon's Fascia. This layer is then closed with multiple interrupted 6-0 Vicryl sutures. The four rectus muscle stumps remain free with the 6-0 Vicryl sutures attached.

maximum motility of the ocular prosthesis.<sup>10,11</sup> The microstructure of these implants allows fibrovascular ingrowth of the host tissues into the implant.<sup>3,12</sup> Once the implant is well vascularized, it can be secondarily fitted with a motility peg. This motility peg is then coupled to the ocular prosthesis to *maximally enhance* prosthesis motility.

A standard enucleation technique is performed, as already described. The socket may be "sized" using sterile trial spheres, but in most cases an 18- or 20-mm implant is appropriate. Keep in mind that wrapping the implant with sclera or fascia adds approximately 1–1.5 mm to the overall diameter of the implant.

If a wrapping material such as sclera is used, the scleral shell should be cut to the appropriate size and shape to enclose the implant securely. Multiple interrupted 6-0 Vicryl sutures are suitable for securely closing the sclera. The round opening where the cornea was removed from the wrapping scleral shell should be positioned posteriorly. Rectangular windows, approximately 2–4 mm, are cut through the sclera located within 8–10 mm



**Fig. 12.11.5** Enucleation Surgery—Final Closure. The 6-0 Vicryl rectus sutures are sewn onto their respective fornices by passing the sutures through Tenon's fascia and conjunctiva. The anterior Tenon's is closed with 6-0 Vicryl and the conjunctiva with a running 6-0 plain suture.

from the anteriormost apex of the implant for attachment of the extraocular muscles. To promote further fibrovascular ingrowth into a hydroxyapatite implant, a handheld 20-gauge needle is used to create drill holes at the site of each window and at the site of the posterior round corneal window.<sup>13</sup>

The wrapped or unwrapped implant is placed into the anophthalmic orbit and the four rectus muscles are secured to the anterior lip of the corresponding rectangular scleral window. Anterior Tenon's fascia is sutured over the implant with multiple interrupted 6-0 Vicryl sutures. The conjunctiva can be closed with a loosely running 6-0 plain suture, which is tied and cut on each end. Implant exposure is a significant problem with porous implants<sup>14</sup> compared with alloplastic sphere implants,<sup>15</sup> thus emphasizing the need for meticulous closure of Tenon's. As is the case with any enucleation procedure, a polymethyl methacrylate lid conformer is placed in the conjunctival cul-de-sac with broad-spectrum antibiotic ointment and a pressure bandage applied.

The unique properties of porous implants allow fibrovascular ingrowth and integration of the implant with the ocular prosthesis. Without placement of the motility peg, no demonstrable motility difference exists between a porous implant and a polymethyl methacrylate implant.<sup>2,16</sup> Thus porous implants are most appropriate for patients who express a strong interest in eventual second-stage procedure to maximize prosthesis motility. These titanium motility pegs are surgically inserted after adequate fibrovascular ingrowth into the hydroxyapatite implant has occurred.<sup>17–19</sup>

Surveys of oculoplastic surgeons in the United States and United Kingdom show that less than 10% of porous implants are currently pegged because of excessive peg complications. If a peg is not placed, a simple and inexpensive silicone implant with muscles directly attached can provide equal motility with fewer potential complications.<sup>20</sup>

## Evisceration

### Overview

Evisceration is the surgical technique that removes the entire intraocular contents of the eye while leaving the scleral shell and extraocular muscle attachments intact. Evisceration surgery is a simpler procedure than enucleation surgery and offers better preservation of the orbital anatomy<sup>21</sup> and natural motility of the anophthalmic socket tissues. A combined enucleation and evisceration technique<sup>22</sup> and modified evisceration techniques<sup>23</sup> have been described as an alternative, particularly in patients with a phthisical eye.

Evisceration is contraindicated in cases of documented or suspected intraocular malignant tumors. A preoperative ocular ultrasound is mandatory to rule out occult malignancy. Evisceration surgery may be more difficult in an eye with severe phthisis or scleral contracture or that is severely deformed. Finally, the issue of potential sympathetic ophthalmia should be considered.<sup>24–26</sup> Evisceration surgery in a recently injured eye carries a definite small risk of sympathetic ophthalmia in the opposing eye

because some uveal tissue is always left behind in scleral canals.<sup>24</sup> Except in these situations, evisceration can be considered as an alternative to enucleation.<sup>27,28</sup>

### Surgical Technique

The procedure begins with a 360° conjunctival peritomy (Fig. 12.11.6). Tenon's fascia is bluntly separated from the underlying sclera in all four quadrants. A full-thickness incision around the corneal limbus is made with a sharp scalpel blade and the entire corneal button removed. The sclera is grasped with a forceps, and a cyclodialysis spatula is used to separate the iris root and ciliary body from the sclera. The remainder of the uveal tissue is dissected away from the scleral wall back to the attachment around the optic nerve with an evisceration spoon (Fig. 12.11.7). The intraocular contents are lifted from the scleral shell and submitted for histopathological examination. All remaining uveal tissue is carefully removed from the scleral shell with a small curette or the sharp end of a caudal periosteal elevator. Cotton-tip applicators saturated with 70% ethanol may be used to cleanse the interior of the scleral shell and denature any remaining uveal pigmented tissue. Cautery is applied if needed to control the oozing of blood.

A polymethyl methacrylate spherical implant is placed in the evisceration scleral shell (Fig. 12.11.8). When the cornea is removed, it is unusual to place an implant larger than 14–16 mm. The scleral edges are closed with multiple interrupted 6-0 Vicryl sutures, with the medial and lateral scleral edges cut to reduce any dog ears (Fig. 12.11.9). The conjunctiva is gently closed with a running 6-0 plain gut suture. If a larger implant is desired, it is necessary to perform radial relaxing sclerotomy incisions posteriorly<sup>29</sup> between the rectus muscles (Fig. 12.11.10). If a porous implant is used, such sclerotomy openings are necessary to enhance vascular ingrowth.<sup>30</sup>

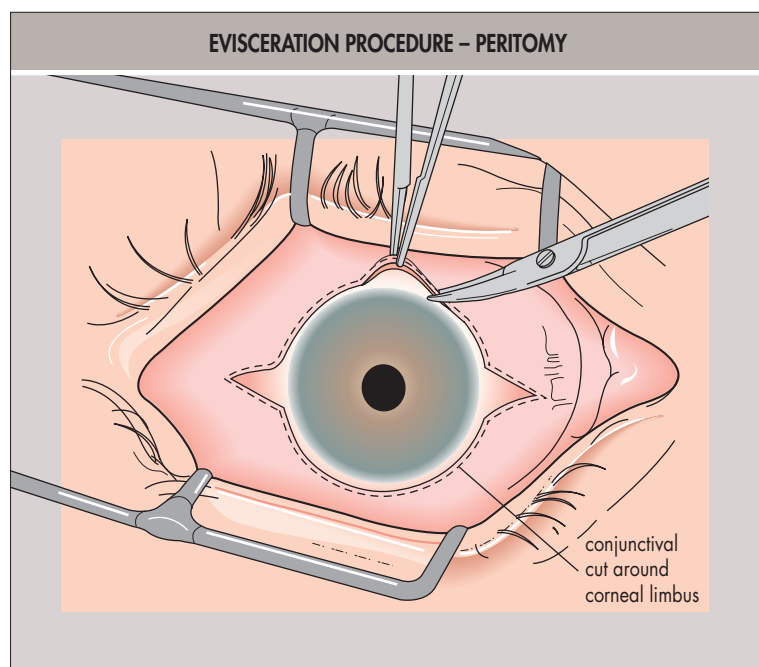
Multiscleral flap evisceration techniques safely allow placement of 18–20 mm spherical implants in most cases.<sup>31,32</sup>

Dressing and postoperative care are as for enucleation.

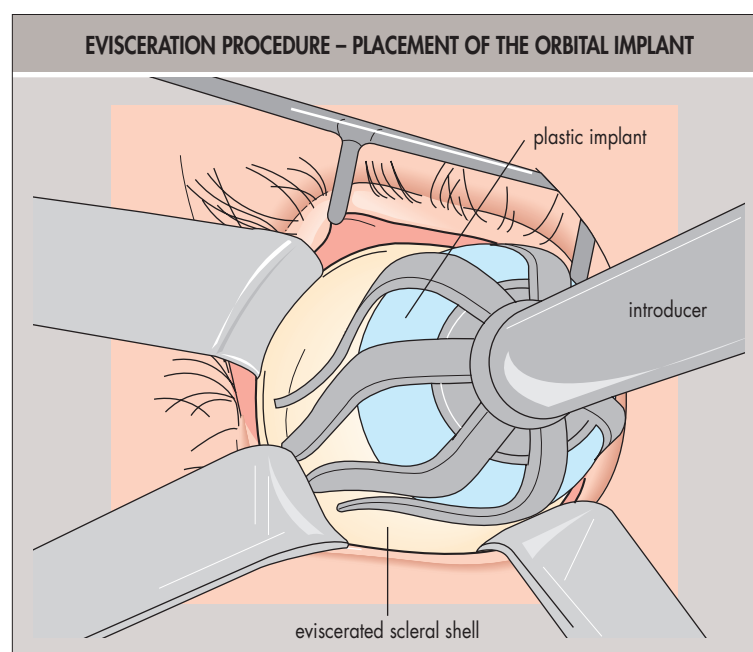
### Exenteration

#### Overview

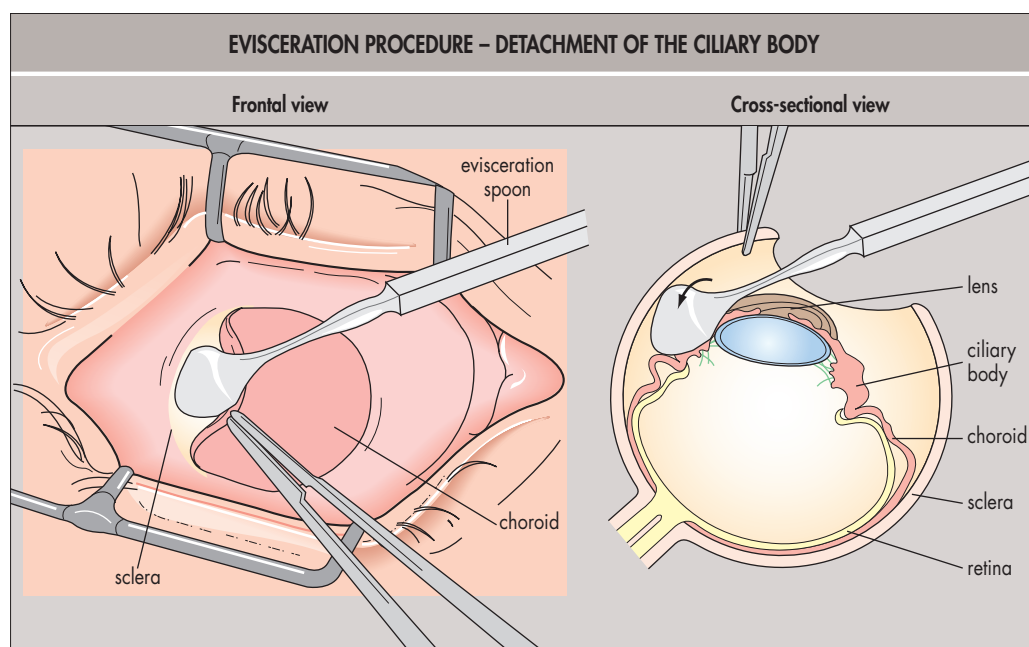
Exenteration surgery involves complete removal of the eyeball and a total or subtotal removal of the retrobulbar orbital soft tissues and most or all of the eyelids.<sup>33,34</sup> The most common indication for exenteration surgery is for the treatment of epithelial malignancy with orbital invasion.<sup>35,36</sup> Because



**Fig. 12.11.6 Evisceration Procedure.** A 360° conjunctival peritomy is made, followed by complete excision of the corneal button.



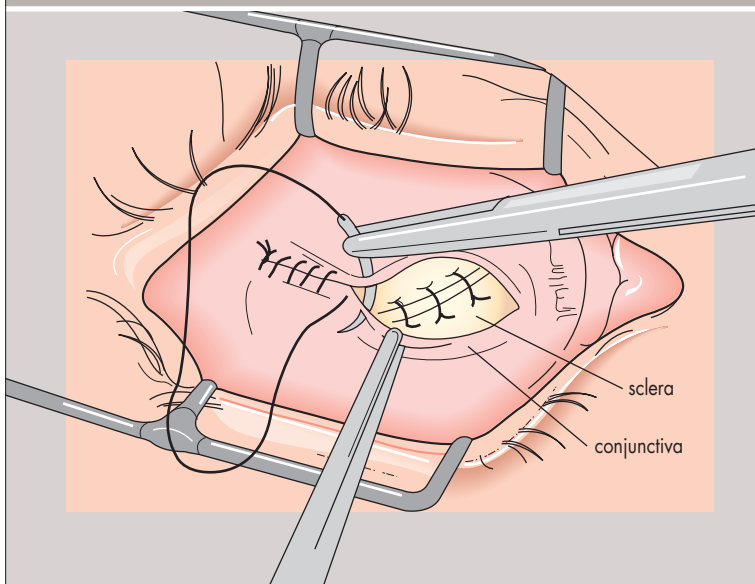
**Fig. 12.11.8 A Sphere Introducer Is Used to Place the Orbital Implant Into the Evisceration Scleral Shelf.**



**Fig. 12.11.7 An Evisceration Spoon Is Used to Detach the Ciliary Body and Bluntly Elevate the Choroid From the Scleral Wall.**

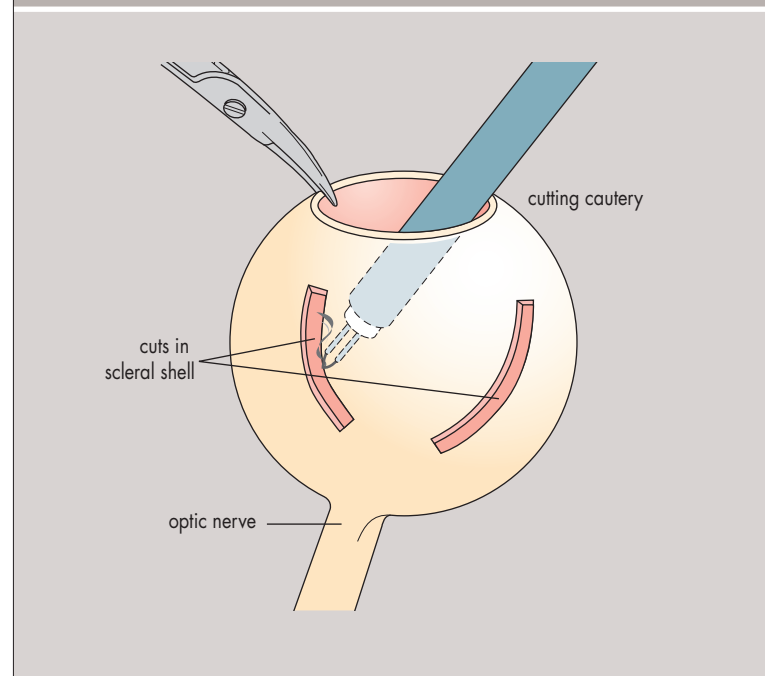


## EVISCERATION PROCEDURE – CLOSURE OF THE SCLERAL SHELL



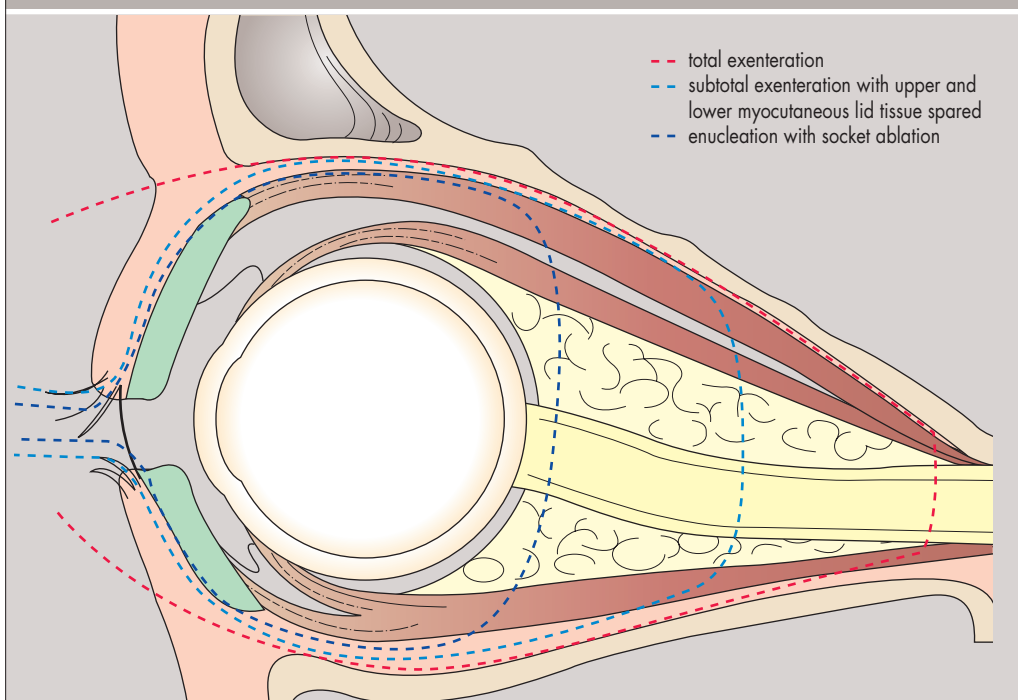
**Fig. 12.11.9** The Scleral Opening Is Closed With Multiple Interrupted 6-0 Vicryl Sutures. Conjunctiva is subsequently closed over the scleral wound using running 6-0 plain gut sutures.

## EVISCERATION PROCEDURE – RELAXING SCLEROTOMY



**Fig. 12.11.10** A Unipolar Cautery Is Used to Incise Relaxing Sclerotomy Slits to Expand the Scleral Shell. This sclerotomy technique to enlarge the scleral shell volume is “optional” with polymethyl methacrylate sphere implants. Sclerotomy slits are “mandatory” when hydroxyapatite spheres are used to facilitate vascular ingrowth.

## EXENTERATION – SURGICAL PLANES OF DISSECTION



**Fig. 12.11.11** Cross-Sectional View of Surgical Planes of Dissection for Exenteration Surgical Techniques. Total exenteration, subtotal exenteration with sparing of myocutaneous eyelid tissue, and enucleation with partial socket ablation.

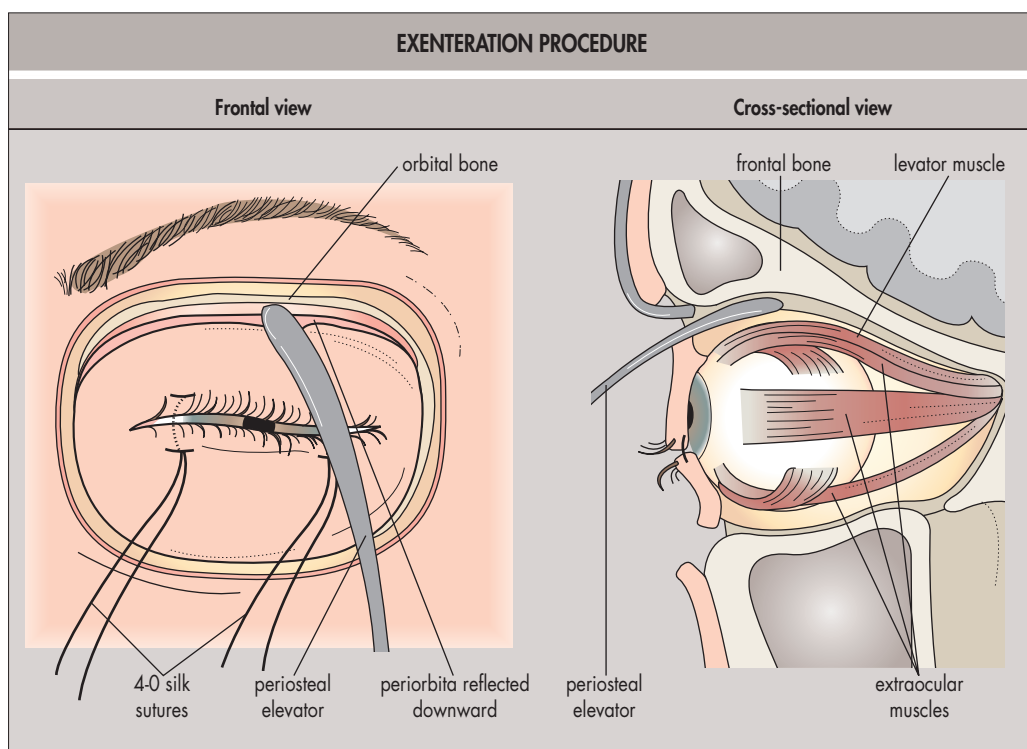
in many cases this procedure is done for recurrent tumor, the need for exenteration can be minimized by aggressive primary management of the initial lesion.<sup>37</sup>

When exenteration is performed for orbital malignancies, periorbital is usually excised to remove completely all potentially involved tissues. The bare orbital bone can slowly heal by second intention, but in most situations the exenterated orbit is covered with a split-thickness skin graft at the time of the procedure. As there is potential for recurrent tumor, reconstruction with thick, bulky tissue grafts or flaps, which could obscure recurrence, is avoided. In very select situations, however, a variety of ancillary reconstructive techniques may be of use, such as those involving

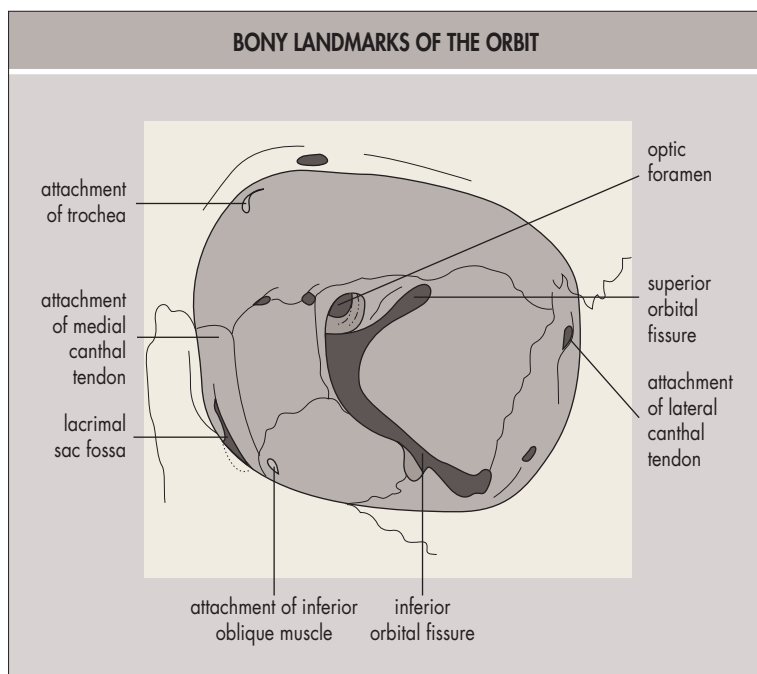
ipsilateral temporalis muscle flaps,<sup>38</sup> free dermis-fat grafts,<sup>39</sup> latissimus dorsi myocutaneous free flaps,<sup>40</sup> osteofasciocutaneous fibula flap<sup>41</sup>, osseointegrated implant techniques,<sup>42</sup> and other procedures.<sup>43–48</sup>

### Surgical Technique

The area of the proposed exenteration incision is marked with adequate wide margins where necessary for tumors, yet with preservation of as much normal periocular soft tissue as possible (Fig. 12.11.11). If necessary, adjacent areas of the medial canthus, temple, or forehead are included in the excision site. When surgery is necessary for a conjunctival or deep orbital tumor, a subciliary incision around the eyelid margins and wrapping



**Fig. 12.11.12 Exenteration Procedure.** A 360° skin incision is made down to the periosteum of the orbital rim. A periosteal elevator is used to begin reflecting the superior periorbital tissue downward.



**Fig. 12.11.13 Bony Orbit Demonstrating the Normal Sites of Increased Resistance to Dissection During Orbital Exenteration.**

around the inner canthus preserve the eyelid skin and orbicularis muscle, which can be used for reconstruction.<sup>46</sup>

The skin is incised along the mark, and any orbicularis muscle to be spared is dissected in a suborbicular plane. The dissection is carried down through periorbital to expose the orbital rim. A periosteal elevator is used to elevate periosteum over the orbital rim and periorbital from the orbital walls (Fig. 12.11.12). Firm attachments to bone are encountered at the lateral orbital tubercle, the superior oblique trochlea, the medial canthal tendon, the distal lacrimal sac as it enters the bony nasolacrimal canal, the inferior oblique origin near the posterior lacrimal crest, and the superior and inferior orbital fissure attachments (Fig. 12.11.13; see Chapter 12.2). Except for these sites of resistance, the periorbital can be elevated quite easily. Medially, the surgeon should use particular care when elevating periorbital so as to avoid inadvertent penetration of the lamina papyracea into the ethmoid sinus air cells, which could result in a chronic sino-orbital fistula.

Superiorly, the superior orbital bone may be quite attenuated in elderly patients, and atrophic bony defects may be present. Monopolar cautery to

the orbital roof should be avoided, as this may cause inadvertent cerebrospinal fluid leakage.<sup>49</sup> It is generally safe to use bipolar cautery along the orbital roof and deep orbital tissues without the risk of cerebrospinal fluid leakage.

The periorbital lining is mobilized along all orbital walls toward the orbital apex. The dissection and mobilization of soft tissues must extend posteriorly beyond the extent of tumor invasion. A thin, curved hemostat can be used to clamp the apical tissues while a slender pair of Metzenbaum scissors is used to excise the exenteration specimen anterior to the clamp (Fig. 12.11.14). An enucleation snare may be used to incise the apical stump to complete the severing of the exenteration specimen.<sup>50</sup> When necessary, frozen section pathology analysis of the apical stump tissues should be used to verify that the margins of resection are free and clear of neoplasm. The orbital bone should be carefully inspected for subtle bone pitting or other signs of bone erosion or destruction.

In patients who have very bulky or massive orbital neoplasms, exenteration may be difficult, with little space in which to separate periorbital from orbital bone. It may be helpful here first to enucleate the eyeball to make enough room for access to the deeper apical soft tissues under good visualization.

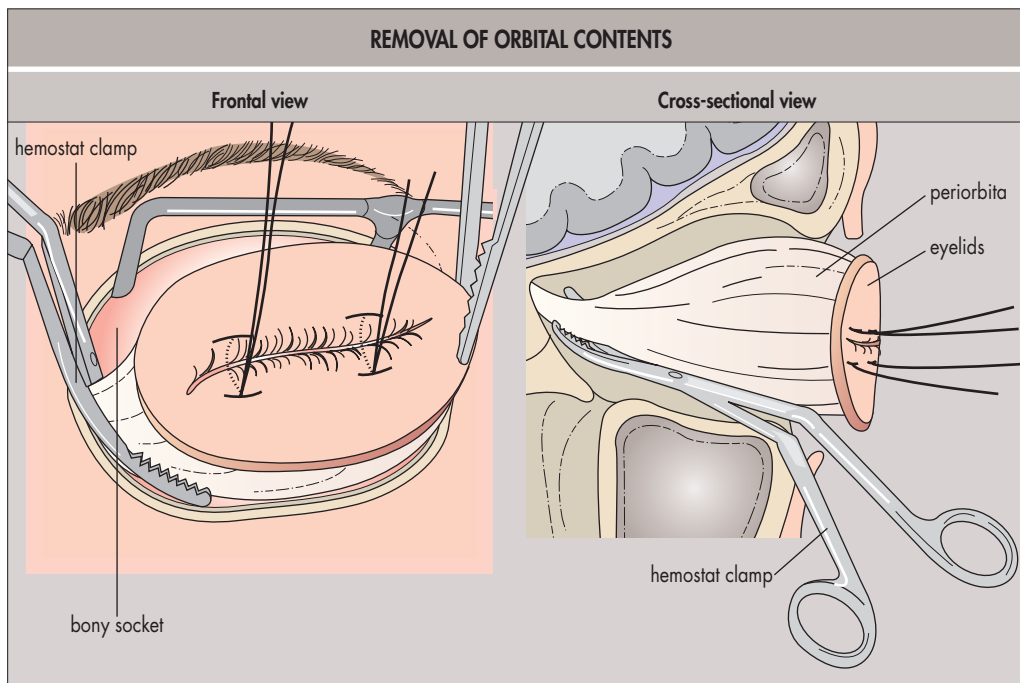
In most patients, the orbit will be lined with a split-thickness skin graft harvested from the anterior surface of the thigh. It is usually preferable to expand the skin graft in a mesh. Multiple interrupted 6–0 Vicryl sutures secure all residual host skin edges to the meshed skin graft. The graft is tamponaded within the orbit with a Telfa dressing and Xeroform gauze packing under pressure.

If the upper lid and lower eyelid skin and muscle are preserved, it may be possible in elderly patients with a lot of loose eyelid skin simply to suture the skin edges together and then place a pressure dressing to tamponade the myocutaneous edges against the bare bone. In selected cases, the socket can be allowed to heal by granulation.<sup>51</sup>

### Postoperative Management

The orbital pack and pressure dressing should remain in place for approximately 5–7 days. Following removal of the dressing, the patient can use gentle hydrogen peroxide rinses to cleanse the socket. Generally, these orbits heal best when left open to the air, so the patients should wear a patch only when going out in public. The surgeon should remain vigilant to the possibility of infection of the skin graft, especially by *Pseudomonas*, *Staphylococcus*, or *Streptococcus*. Systemic antibiotics may be necessary if these infections arise. In some patients, the exenterated orbit retains chronic, moist, ulcerated areas intermixed with areas of healthy keratinizing epidermis. The use of a gentle handheld hair dryer can help “cure” these slower-healing areas.

A combined eyelid–ocular prosthesis can be made by an anaplastologist. Many exenteration patients prefer simply to wear a black patch.



**Fig. 12.11.14 Periorbital Has Been Elevated for 360°.** Forward traction is applied to the orbital contents as a hemostat is used to clamp the apical orbital tissues.

## COMPLICATIONS

### Evisceration

Postoperative infection is always of concern when evisceration surgery is performed in the setting of endophthalmitis or panophthalmitis. The use of broad-spectrum systemic antibiotics usually minimizes this risk, and the surgeon can generally use a primary orbital implant. Postoperative extrusion of the orbital implant is a complication of evisceration surgery that may be related to postoperative scleral shell shrinkage, to poor wound healing of the scleral edges, or to improper selection of the orbital implant size. Postoperative pain is more common when the cornea is retained.

### Enucleation

Orbital implant exposure<sup>52</sup> or extrusion is another complication of enucleation surgery.<sup>14,53</sup> Meticulous attention to careful Tenon's fascia wound closure and the proper selection of implant size are important principles in avoiding this outcome. Risk of implant extrusion is increased with prior irradiation treatment of the eye and orbit, severe traumatic injuries to the eye and orbit, and severe eye and orbital infections. Careful surgical technique is very important in cases involving secondary orbital sphere implantation following enucleation (or evisceration) surgery.<sup>54</sup> Secondary orbital implants carry a much higher complication rate (e.g., implant extrusion or migration) than primary orbital implants.<sup>55</sup> Long-term complications of the anophthalmic socket are numerous, including generalized volume deficiency of the anophthalmic socket, lower eyelid laxity with poor prosthesis support, orbital implant migration, upper eyelid ptosis, chronic conjunctivitis, and mucoid discharge. Integrated orbital implants (e.g., hydroxyapatite) with motility pegs have high complication rates, including pyogenic granuloma formation around the peg and chronic anophthalmic socket secretions.

### Exenteration

Exenteration surgery carries the risk of severe blood loss. It is important preoperatively to discontinue aspirin and all other medicines that could

adversely affect blood clotting. Other complications unique to exenteration surgery include cerebrospinal fluid leakage via orbital roof transgression of the dura and chronic sino-orbital fistulas through the region of the lamina papyracea and ethmoid sinus air cells.<sup>32</sup> Free skin grafts are susceptible to infection during the first few weeks of healing. Patients may require treatment with broad-spectrum systemic antibiotics for coverage of *Staphylococcus*, *Streptococcus*, *Pseudomonas*, and other bacteria. The administration of systemic antibiotics is combined with maintenance of vigorous topical hygiene of the split-thickness skin graft using hydrogen peroxide rinses. Long term, the surgeon should always remain vigilant for the possible recurrence of tumor.

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# The Lacrimal Drainage System

Jeffrey J. Hurwitz, Jane M. Olver

12.12

**Definition:** The tear disposal system of the eye that consists of the punctum, canaliculi, lacrimal sac, and nasolacrimal duct. The eyelids also form a physiological lacrimal pump.

Key Features

- The orbicularis muscle and eyelids act as a lacrimal pump for tear drainage.
- The drainage system is composed of the punctum, canaliculi, lacrimal sac, and lacrimal duct.
- Eyelid malposition or malfunction results in epiphora.
- Stenosis or occlusion results in epiphora.
- Clinical testing localizes the site of obstruction.

Associated Features

- Congenital obstruction is usually caused by an imperforate membrane at the nasal end of the lacrimal duct (valve of Hasner).
- Acquired obstruction may result from chronic fibrosis of the duct, trauma, or previous nasal or sinus surgery.
- Correction of congenital obstruction is typically achieved with a simple probing procedure.
- For acquired obstructions, a dacryocystorhinostomy (DCR) is usually required for permanent resolution.
- Eyelid position, laxity, and malfunction must be assessed.

INTRODUCTION

Under normal circumstances, the tears secreted should equal those eliminated so that neither a dry eye nor symptoms of a watery eye occur. Tearing (a watery eye) may be caused by hypersecretion of tears or decreased elimination, called epiphora (Table 12.12.1). Hypersecretion may result from an increased production of tears from stimulation of the neurophysiological pathway either centrally or as a local reflex. Decreased elimination is caused by reduced passage of tears into or through the lacrimal drainage system, as a result of eyelid malfunction or malposition, or outflow stenosis/obstruction. The cause of the tearing can be estimated by the clinical symptoms and confirmed by clinical signs and tests.

ANATOMY AND PHYSIOLOGY

Tears are secreted by the lacrimal gland, with a 24-hour secretory volume of approximately 10 mL.<sup>1</sup> With blinking, the palpebral aperture closes from

lateral to medial, and tears are pumped along the marginal tear strips of the upper and lower lids toward the lacrimal lake at the inner canthus. In the normal resting state, most tears are lost by evaporation, and only a small volume passes down through the nasolacrimal passageways.

Tears pass from the lacrimal lake into the canaliculi through the puncta mainly by capillarity. It is important that the puncta of each lid contact the opposite lid on closure and thereby become physiologically occluded. When the lids separate, capillarity draws the tears into the empty canaliculi. Tears then flow to the common canaliculus and lacrimal sac due to a combination of factors<sup>2-5</sup>:

- A change in the caliber of these passages.
- A change in pressure within the canalicular passages.
- A pumping function (lacrimal pump) of the orbicularis muscle that surrounds these passages.

Tears flow into the inferior meatus of the nose through the effect of the lacrimal pump, gravity, and to a lesser extent pressure changes within the nose due to respiration. Valves within the drainage system permit only one-way flow of tears.

EVALUATION OF EPIPHORA

Clinical History

The history of symptoms associated with tearing is important. Outflow obstruction is typically worse in the morning, when outside, or in the cold. The tears usually drain down medially along the tear trough.

Pain at the side of the nose suggests dacryocystitis, but pain in the eye may be due to foreign bodies, keratitis, recurrent corneal erosion, iritis, or glaucoma. Itchiness suggests an allergic problem rather than lacrimal obstruction. Grittiness and burning of the eyes associated with tearing suggest a lid margin and tear film problem, such as occurs in blepharitis and meibomian gland dysfunction, keratitis sicca, or dysthyroid eye disease.

A history of topical medication such as echothiophate iodide (Phospholine Iodide), epinephrine (adrenaline), or pilocarpine drops is important, because they may produce lacrimal obstruction. Chemotherapy such as 5 fluorouracil (5-FU) and radiotherapy can cause obstruction in the canaliculi. Photodynamic therapy also has been associated with canalicular stenosis.

Physical Examination

Eyelids

Poor orbicularis muscle tone and reduced lacrimal pump dysfunction may be presumed if the lid can be pulled more than 8 mm away from the globe, if there is decreased snap-back, or if there is frank ectropion or floppy eyelid syndrome. The puncta should normally be directed backward into the lacrimal lake to catch the tears. Lesions of the caruncle such as megacaruncle may interfere with tear drainage. Blepharitis and meibomian gland dysfunction with dry eyes may cause secondary oversecretion of tears. It is important to detect and correct any eyelid malposition or laxity and treat eyelid margin disease well to reduce watering before embarking on lacrimal surgery.

Lacrimal Passages

Facial asymmetry suggests congenital or traumatic anatomical blockage of the nasolacrimal canal. Any mass at the inner canthus should be palpated to determine whether it is soft (indicating mucus) or firm (suggesting a possible tumor) and whether it is compressible or noncompressible. Orbital signs such as proptosis, displacement of the globe, diplopia,

TABLE 12.12.1 Causes of Tearing

Lacrimation (Hypersecretion)	Epiphora (Decreased Tear Elimination)	
	Anatomical factors	Physiological dysfunction
Anterior blepharitis and meibomian gland dysfunction Corneal foreign bodies Corneal irritation with dry spots Ocular surface inflammation Refractive errors Thyroid dysfunction	Punctal, canalicular or nasolacrimal duct strictures or obstructions Foreign bodies (e.g., lacrimal stones) Extrinsic or intrinsic tumors	Orbicularis muscle weakness Punctal or eyelid malpositions Nasal obstruction with normal lacrimal pathway

and ptosis could indicate that the lacrimal lesion involves the orbit or vice versa.

### Nose

The endoscopic nasal examination is an essential part of every lacrimal evaluation. Nasal and sinus conditions, which range from infections and inflammations to tumors, may result in epiphora. Coexistent sinus disease often causes chronic inflammation and narrowing of the nasolacrimal duct. Symptoms include anosmia (loss of smell), epistaxis, anesthesia around the roof of the nose, and nasal obstruction, which may occur with intranasal tumor.

## Clinical Diagnostic Tests

### Tear Tests

#### Dye Tests

The tear meniscus can be seen elevated with fluorescein 2% instilled into the conjunctival fornix when there is delayed outflow.

The fluorescein dye retention test is a physiological test where more fluorescein-stained tears are visible on the white of the eye after 3 to 5 minutes when there is outflow narrowing or obstruction. Often the tears overflow medially down the tear trough in outflow obstruction and laterally over the outer cheek when there is an eyelid cause such as wick syndrome caused by excess upper eyelid overhanging skin

### Excretory Tests

#### Lacrimal Syringing

In syringing, a 27-gauge lacrimal irrigation cannula is passed into the punctum and advanced through the canaliculus to the medial wall of the lacrimal sac fossa (see Chapter 12.2). During its passage the examiner can feel if there is a small pop at the entry of the common canaliculus into the sac that is consistent with a membranous obstruction. If there is a complete block affecting the common canaliculus, a soft stop is felt as the cannula does not reach bone. If the cannula hits bone, called hard stop, the obstruction is probably in the sac or the duct. Be gentle, as the medial wall of the sac can be tender especially when there is some inflammation of the sac. If there is an obvious dacryocystitis or nonexpressable mucocele, avoid syringing beyond the canaliculus as it will be very tender for the patient.

Clear water or saline is gently irrigated through the cannula. If fluid passes into the nose without reflux, the system is totally patent. If fluid passes into the nose with resistance and reflux occurs, the system is anatomically patent but physiologically stenotic (partially occluded). If no fluid passes into the nose but it all comes back through either punctum, complete nasolacrimal duct obstruction is present.

### Jones Fluorescein Dye Test

The original Jones I and II<sup>5</sup> dye tests are now rarely used. Instead the endoscopic Jones test is performed.<sup>6</sup>

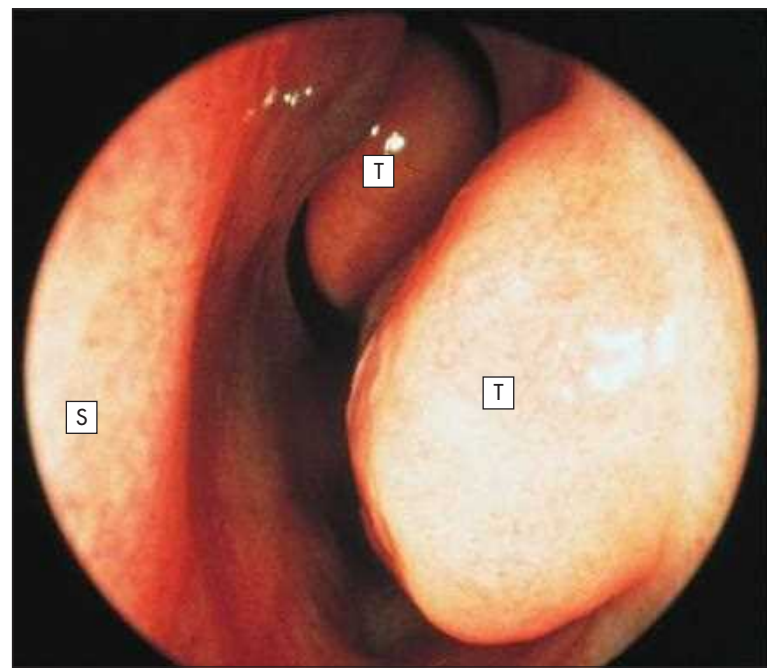
A drop of fluorescein is placed into the conjunctival cul-de-sac. The nose is examined using the Hopkins rigid nasal endoscope (4 mm) after 3 minutes to determine whether the dye has passed through the lacrimal system spontaneously, which indicates that it is functionally patent. The endoscope is directed at the inferior meatus after nasal decongestion to shrink the inferior meatus mucosa.

In the second part of the test, the cannula is placed in the sac and the system is irrigated. Any fluid that passes into the nose during irrigation will be subsequently seen with the nasal endoscope. If no fluorescein is visualized, this suggests that it did not pass into the sac during the initial fluorescein test, so the problem is likely in the upper (canalicular) system. If fluorescein is present, this indicates that it reached the sac during the initial test and that the upper system is probably normal, meaning that the problem is in the lower (sac, duct) system. Although the endoscopic Jones test is useful, it is interpreted along with the tear meniscus, the fluorescein dye retention test, and other tests and radiological investigations such as lacrimal scintigraphy (nuclear imaging) and dacryocystography.

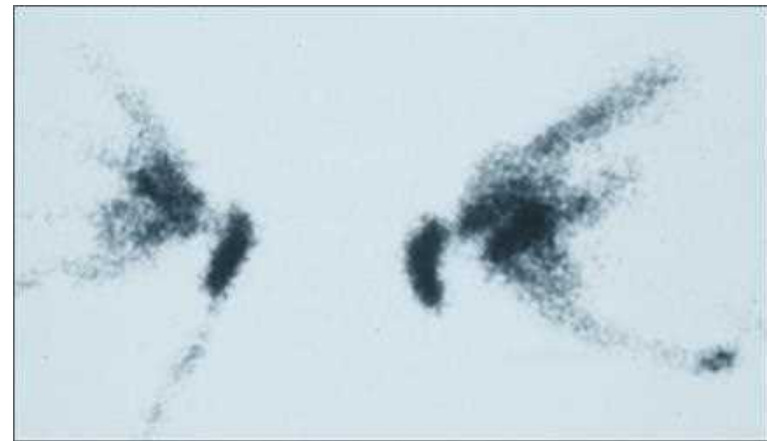
The tests help point to the diagnosis and location of the narrowing or obstruction and hence help surgical planning.

### Endoscopy

Nasal endoscopy using a rigid telescope is useful to observe the anatomy of the opening of the nasal lacrimal duct in the inferior meatus and to diagnose any disease within the nose itself (Fig. 12.12.1). If a lacrimal drainage operation is contemplated, the endoscope is the best method to assess the future surgical site. Should tearing persist following lacrimal surgery, it is useful to view the size and location of the previous dacryocystorhinostomy



**Fig. 12.12.1 Endoscopy.** Endoscopic view of the nose demonstrates the nasal septum (S), lateral wall, and turbinates (T).



**Fig. 12.12.2 Lacrimal Scan.** Complete obstruction on the left side and stenosis on the right side.

(DCR) opening using an endoscope to determine whether the opening is obstructed by fibrous tissue, polyps, granuloma, or foreign bodies.

## Diagnostic Imaging

### Nuclear Lacrimal Scan

Also called nuclear lacrimal scintigraphy, this is a physiological test of lacrimal function. It does not demonstrate anatomical structures but can help localize whether eyelid, punctual, presaccal, or postsaccal obstruction is present. A drop of technetium-99m pertechnetate is placed into the palpebral aperture and a pinhole collimator of a gamma camera is used to record its transit to the nose. The lacrimal scan can help determine the extent of delay from a physiological or functional point of view (Fig. 12.12.2).

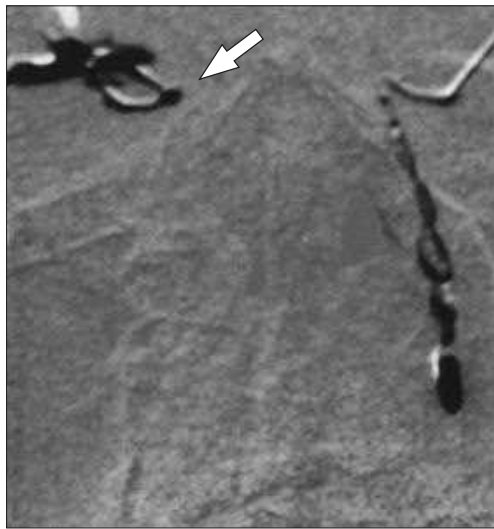
### Dacryocystography

Dacryocystography (DCG) is extremely useful to determine the exact anatomical site of obstruction or stenosis within the system (Figs. 12.12.3 and 12.12.4) and to visualize any deflection of the passages by diseases of the surrounding structures (Fig. 12.12.5; Box 12.12.1). Injection of a water-soluble contrast material (digital subtraction dacryocystography)<sup>7</sup> through a catheter demonstrates the lacrimal drainage pathways and outlines any anatomical abnormalities. This test does not evaluate physiological function.

### Computed Tomography

High-resolution computed tomography (CT) in the axial and coronal planes is a useful anatomical study to assess those patients who have





**Fig. 12.12.3 Dacryocystogram.** Complete obstruction of the lacrimal drainage pathways at the medial common canalicular level on the right side.



**Fig. 12.12.4 Dacryocystogram.** Stenosis at the sac-duct junction is greater on the left side than on the right.



**Fig. 12.12.5 Dacryocystogram.** Medial deflection of contrast material within the right sac indicates sac stones.

#### BOX 12.12.1 Uses of Dacryocystography

- Complete obstruction where the site of block (canalicular vs sac) cannot be determined clinically
- Incomplete obstruction where the area of stenosis cannot be localized on clinical testing
- In cases of suspected lacrimal sac tumors, to visualize a filling defect
- In adnexal disease, to image compression or deflection of the sac or duct

diseases in the structures adjacent to the nasolacrimal drainage pathways (Fig. 12.12.6).<sup>8</sup> Injection of the canaliculi with contrast provides simultaneous visualization of the lacrimal drainage system (CT-DCG).<sup>9</sup>

## OBSTRUCTIONS OF THE LACRIMAL SAC AND DUCT

### Congenital Obstruction

Congenital nasolacrimal obstruction is due to an imperforate membrane at the valve of Hasner into the inferior meatus, which usually opens spontaneously at the time of birth. Sometimes this may persist into adult life. If spontaneous resolution does not occur by age 1 year, the patient may be treated by probing through the membrane. Probing and syringing is often monitored endonasally using the rigid endoscope because there may be an intranasal cyst in the inferior meatus that requires opening and draining. With increasing age and after previous failed probings, the likelihood of having to treat the obstruction with a DCR increases.

### Acquired Obstruction

Acquired obstructions of the sac and duct may be classified as nonspecific (idiopathic) obstructions and specific obstructions.

#### Nonspecific Acquired Obstruction

The evolution of nonspecific lacrimal sac and nasolacrimal duct inflammation from an early inflammatory stage through an intermediate phase to a late fibrotic stage has been proposed by Linberg and McCormick.<sup>10</sup> The early phase is characterized by vascular congestion, lymphocytic infiltration, and edema. These changes tend to occur at the superior aspect of the nasolacrimal canal just beneath the point where the sac passes into the nasolacrimal intraosseous duct. This occurs more commonly in older patients. It is more common in women than in men. It has also been suggested that it is more common in people from lower socioeconomic levels.<sup>11</sup> Inflammatory conditions that affect the mucosa in the inferior meatus of the nose also may involve the respiratory-like mucosa of the inferior aspect of the nasolacrimal canal, thereby leading to obstruction.



**Fig. 12.12.6 Tearing Secondary to Neoplasm.** (A) Patient with right-sided tearing and a mass at the inner canthus. The system was fully patent to syringing. (B) Computed tomography scan in this patient demonstrates an ethmoidal orbital plasmocytoma with compression of the lacrimal sac.

### Specific Acquired Obstruction

Specific causes of nasolacrimal drainage system obstruction include inflammatory diseases such as sarcoidosis and Wegener's granulomatosis affecting the mucosal lining of the nose, duct, and sac.<sup>12</sup> Sarcoidosis is often treated with systemic corticosteroids before a DCR becomes necessary, and the Wegener's is treated either with dacryocystectomy and removal of all involved mucosa or with a full DCR, as they often have a chronic discharge from mucocele or dacryocystitis.

Infection, trauma, surgical injury, and foreign bodies, such as retained silicone or eyelashes, also may cause obstruction.<sup>12</sup> Lacrimal stones or tumor are to be suspected in younger persons aged 30 to 45 years with unilateral tearing. However, primary neoplasms of the lacrimal sac and duct or secondary tumors arising in the adjacent sinuses are rare causes of obstruction (Box 12.12.2).

### Dacryocystitis

Dacryocystitis is acute, subacute, or chronic. It may be localized in the sac, extend to include a pericystitis, or progress to anterior orbital cellulitis. It very rarely causes posterior orbital cellulitis with proptosis and muscle limitation. When dacryocystitis is localized to the sac, a palpable painful swelling occurs at the inner canthus (Fig. 12.12.7) and obstruction is present at the junction of the nasolacrimal sac and duct. When the infection develops, the lateral expansion of the nasolacrimal sac tends to push on the common canaliculus and produce a kink within it, with the result that the sac is no longer reducible, called nonexpressible. Approximately 40% of initial attacks do not recur, but in the other 60% of patients, repeated attacks occur. Chronic dacryocystitis may be the end stage of acute or subacute dacryocystitis, but it may present initially as a subclinically infectious cause of nasolacrimal duct obstruction. A common organism involved is *Staphylococcus aureus*. In some cases, especially in young women, stones may develop that lead to intermittent attacks of dacryocystitis, termed acute dacryocystic retention syndrome.

In dacryocystitis with pericystitis, percolation of infected debris occurs through the mucosal lining of the wall of the sac, and infection around the

#### BOX 12.12.2 Specific Causes of Acquired Nasolacrimal Pathway Obstruction

##### Inflammatory Diseases

Sarcoidosis  
Wegener's granulomatosis

##### Infections

- *Staphylococcus*
- *Actinomyces*
- *Streptococcus*
- *Pseudomonas*
- Infectious mononucleosis
- Human papillomavirus
- *Ascaris*
- Leprosy
- Tuberculosis

##### Trauma and Postsurgical

- Nasoethmoid fractures
- Nasal and endoscopic sinus surgery
- Rhinoplasty
- Orbital decompression

##### Neoplasms

- Primary lacrimal sac tumors
- Benign papillomas
- Squamous and basal cell carcinoma
- Transitional cell carcinoma
- Fibrous histiocytoma
- Midline granuloma
- Lymphoma

sac is present. The infection may spread to the anterior orbit and produce a tremendous amount of eyelid swelling (Fig. 12.12.8). If the infection proceeds posterior to the orbital septum, a true orbital cellulitis may occur, resulting in globe proptosis or displacement, afferent pupillary defect, motility disturbance, optic neuropathy, and even blindness.

The treatment is both medical (systemic antibiotics) and surgical. Temporary surgical relief is obtained by draining the dacryocystitis via the skin and packing the cavity. Increasingly, surgeons are performing early endoscopic, endonasal internal drainage.

## TREATMENT OF LACRIMAL SAC AND DUCT OBSTRUCTION

### Congenital Nasolacrimal Obstruction

More than 90% of patients with congenital nasolacrimal obstruction undergo spontaneous resolution by age 1 year.<sup>13</sup> Therefore, except under extreme circumstances, initial probing should be postponed until this age. Congenital amniocoeles usually resolve on their own and rarely require probing. Persistent swelling at the medial canthus may represent a widened nasolacrimal duct and dilated inferior meatus cyst that requires endoscopic marsupialization.

Probing is performed more easily with the infant under general anesthesia. The probe is passed into the lower canaliculus with the lid stretched laterally. The probe is advanced to the lacrimal bone. It is turned past the 90° angulation and advanced inferiorly until it perforates the membrane at the lower end of the nasolacrimal duct. Fluorescein-tinted irrigation saline is introduced to see whether it passes into the inferior meatus, or metal-to-metal contact may be obtained by inserting a probe in the nose. The success rate of probing is greater than 90%. If this fails, however, one should wait 3 months before doing another procedure, during which time most cases of seemingly failed probing resolve spontaneously. Endoscopic monitoring of syringe and probing is recommended for second procedures because the probe may have remained in the lateral wall or the inferior meatus or merely perforated a small hole in the membrane or cyst originally. Direct view of the inferior meatus enables thorough drainage.

If the repeat probing does not proceed easily, Silastic tubes should be placed and left for at least 3 months (preferably 6 months). If these tubes fail and the child is still tearing, a DCR is performed at a later date.

### Acquired Nasolacrimal Obstruction

Quiet, progressive nasolacrimal-duct stenosis and obstruction is treated by DCR.

After an attack of dacryocystitis, symptoms may resolve spontaneously. If not and syringing demonstrates a persistent block, DCR is indicated.

In the presence of acute or chronic dacryocystitis, first treat the infection with an antistaphylococcal agent such as oral cloxacillin. If post-septal orbital cellulitis is present, a CT scan is obtained to rule out an orbital abscess and intravenous antibiotics are used. If the infection does not resolve and perforation is impending, a dacryocystotomy (external



Fig. 12.12.7 A Patient Who Has Dacryocystitis Localized to the Lacrimal Sac.



Fig. 12.12.8 A Patient Who Has Dacryocystitis and Orbital Cellulitis. Ocular mobility is limited, indicating infection posterior to the orbital septum.



drainage) or early endoscopic, endonasal DCR is performed. For dacryocystotomy, after lidocaine (lignocaine) is injected, a cruciate incision is made directly over the lacrimal sac and the debris within the sac is aspirated and curetted. Transcutaneous aspiration of sac contents for culture may be done with a No. 22 needle or the end of a 1 mL syringe.

Definitive treatment of complete obstruction with dacryocystitis is DCR.<sup>14,15</sup>

## Dacryocystorhinostomy

DCR is an operation whereby the lacrimal sac is drained into the nose via a bypass conduit called the ostium or rhinostomy as an opening is made in the lacrimal fossa and ascending process of the maxilla, which is lined with lacrimal sac and nasal mucosa.<sup>16</sup> The classic transcutaneous procedure of Toti<sup>17</sup> has undergone many minor modifications, but the basic operation has withstood the test of time and has a high success rate of 93% to 95%.<sup>18</sup> It may be performed with the patient under general or local anesthesia.<sup>19</sup> In either case, the nose is anesthetized and decongested before surgery.

The procedure is well described elsewhere.<sup>20,21</sup> An incision as small as 8 mm is made on the side of the nose below the medial canthal tendon or within the tear trough, and the dissection is carried down to bone. The periosteum is reflected from the anterior lacrimal crest to reveal the lacrimal sac fossa. The sac is then reflected laterally.

The nasal space is entered by pushing a blunt instrument such as a Traquair periosteal elevator through the suture line between the lacrimal bone and the frontal process of the maxilla. Kerrison punches are used to remove bone between the sac fossa and the nose to create an opening large enough to anastomose the sac and nasal mucosa. Flaps are created in the medial sac wall and in the adjacent nasal mucosa. The posterior flaps and then the anterior flaps of the sac and nasal mucosa are sutured together to form a mucosa-lined opening across the ostium (Fig. 12.12.9). Intervening anterior ethmoid air cell (Agger nasi) may have to be removed for access and partial anterior turbinectomy done adjunctively. Silicone tubes usually are not necessary, but if desired, they can be placed at this time and left in for 2 to 4 weeks. However, recent studies have shown that silicone stents offer no significant increase in success rate.<sup>22</sup>

Indeed, complications of silicone include cheese-wiring, with destruction of the punctum and proximal canaliculus, and dislocation of the tubes laterally over the cornea. In this latter situation, it is better to reposition the tubes than to remove them. If a canalicular DCR is being done or there is marked distal common canalicular stenosis with membranous block, tubes are beneficial.

Nasal packing is usually not necessary unless there is a bleeding point at the end of the operation.

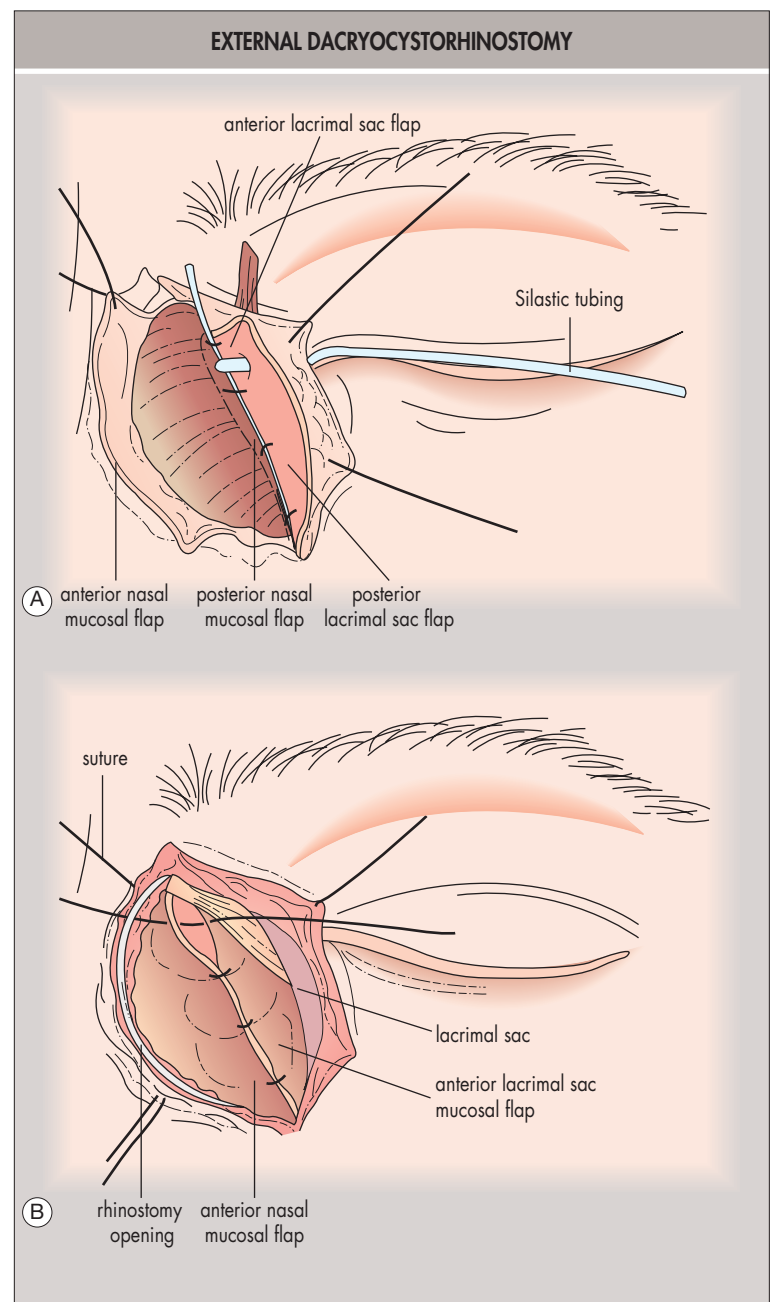
Complications of hemorrhage within the first 24 hours should be controlled by sitting the patient up, pushing fluids and lowering the blood pressure to normal values, and nasal packing. Delayed hemorrhage 4 to 7 days after surgery is due to clot retraction, hence patients are instructed not to blow their nose for 5 to 7 days in case it dislodges that clot.

A hypertrophic cutaneous scar is unusual, but if present, it usually settles quite well with massage. Triamcinolone also may be injected into the scar.<sup>23</sup>

Surgical failure may result from closure of the DCR anastomosis,<sup>24</sup> or an obstruction may occur at the common canaliculus, either undiagnosed preoperatively or developing postoperatively. Mucosal inflammation and subsequent scar tissue is the main cause of DCR failure, hence antimetabolites such as mitomycin-C (MMC) have been recommended, but studies show no conclusive advantage. Careful delicate surgery with correct placement of the ostium, respect for the mucosa, and avoiding any residual tissue or bony fragments facing the ostium is probably more important than adding antimetabolite.

Endoscopic revision of a simple inflammatory membrane can be done using a probe and fine blade, which often produces a permanent cure. In some situations, more extensive probing with placement of bicanalicular Silastic tubes may be useful to prevent granulation tissue from closing over the newly formed DCR opening.<sup>25</sup> If these smaller measures fail, a redo of external approach DCR with revision of flaps may be performed, and a bicanalicular Silastic stent tube is left in place for a minimum of 3 months. Using the endoscope simultaneously helps provide internal illumination and helps to confirm full new anastomosis. The success rate of this last procedure is greater than 80%.

If the obstruction is at the common canalicular level, a canaliculodacryocystorhinostomy (CDCR) may be useful. The scar tissue at the common canaliculus is excised; then the individual canaliculi or residual common canaliculus can be sutured into the nose.<sup>26</sup>



**Fig. 12.12.9 External Dacryocystorhinostomy.** (A) Posterior flaps of the sac and nasal mucosa being sutured. (B) Anterior flaps of the sac and nasal mucosa being anastomosed. (Adapted with permission from Hurwitz JJ. *Diseases of the sac and duct*. In: Hurwitz JJ, editor. *The lacrimal system*. Philadelphia, PA: Lippincott-Raven; 1996. Artwork courtesy Terry Tarrant, London.)

Even without suturing, a good result can often be obtained if a wide bony opening is made and silicone tubes placed for 4 to 6 weeks.

## Endonasal Dacryocystorhinostomy

When the obstruction is in the lower drainage system (below the lacrimal sac) and the canaliculi are anatomically normal, an endonasal approach is a good alternative to an external DCR; this will avoid cutaneous incisions and risk of scar.<sup>27-29</sup>

Endonasal endoscopy has a success rate reported to be equal to or slightly lower than the external approach.<sup>29,30</sup> However, the success rate can be improved by combining the external and endoscopic approach. After the nasal mucosa is decongested, a light pipe is passed through the canaliculus to the lacrimal bone and visualized in the nose. Many surgeons have abandoned using the light pipe as they become more experienced in endonasal lacrimal surgery, arguing that the light pipe risks damaging the canaliculi.

The nasal mucosa is incised, elevated, and reflected away from the opening with the use of a scalpel or fine blade.<sup>31</sup> The thin bone of the



lacrimal bone is removed and enlarged with Kerrison punches or a mechanical diamond bur.<sup>32</sup> The ostium should not extend behind the posterior lacrimal crest or above the lacrimal sac. The sac mucosa is opened with Vannas scissors or fine blade, and a portion of the medial wall of the sac is excised if it is a large sac. Silicone stents are placed through the system and left for 3 to 4 weeks. The endonasal approach also allows the surgeon to deal with nasal adhesions, granulation tissue, and hypertrophic turbinates at the same time. Endonasally the options are to use a nasal endoscope or a microscope for visualisation.

## TUMORS OF THE LACRIMAL SAC

Primary lacrimal sac tumors are rare and present as masses at the medial canthus. Depending on the age of the patient, there may or may not be symptoms of tearing. These patients often exhibit patency to syringing because the tumor usually arises in the epithelium and only later grows toward the lumen. Bloody tears may be present. Lacrimal sac tumors may be benign or malignant, epithelial or nonepithelial.<sup>33</sup> DCG and CT are useful to demonstrate the location of the mass and its extent and associated involvement of the lacrimal drainage pathways. Bony erosion is often present in these cases.

## DISEASES OF THE CANALICULI

Canalicular obstruction may have inflammatory, traumatic, idiopathic (topical or systemic drug related), or suppurative (canaliculitis—usually actinomycotic) causes. Whereas some diseases certainly involve both the punctum and the canaliculus (such as chronic staphylococcal lid margin disease), many involve either one or the other and so should be considered separately.<sup>34</sup>

## PUNCTAL STENOSIS

Punctal stenosis can be congenital or acquired.<sup>35</sup> Congenital obstruction may be caused by a membrane overlying the punctal papilla. In such situations, the rest of the punctum and the canaliculus are patent, so merely perforating the membrane with a No. 25 needle may be sufficient to achieve permanent patency. If the papilla of the punctum is absent, the distal canaliculus often has not developed either, so affected patients usually require the placement of a Jones tube. Marsupialization of the remaining canaliculus into the lacrimal lake does not offer a good solution. A Jones tube is done as part of—or secondarily after—a conjunctivo-DCR.

Acquired punctal obstructions may result from antiviral or antiglaucoma medications, cicatrizing diseases of the conjunctiva, various infections, radiation, and chemotherapeutic agents, which may also obstruct the canaliculi.<sup>36</sup> Intrinsic tumors, such as papillomas and skin malignancies (e.g., basal cell and squamous carcinoma), also may obstruct the puncta. Most acquired punctal obstructions, however, are secondary to punctal eversion, which may be related to eyelid laxity or to cicatrizing diseases of the skin.

## USEFUL LACRIMAL TIPS

- Take a good history of the watering eye/sticky eye/inflamed swelling at the corner of the nose.
- Watering eyes can be caused by eyelid or tear duct disease. Therefore examine both clinically, with dye tests, syringing, nasal endoscopy, and/or radiological imaging, to determine the cause and plan the treatment or surgery.
- Both external and endoscopic approach DCR give comparable good surgical results. Silicone intubation is being used less, for a shorter period, or not at all.
- A Jones tube is placed if there is a complete blockage of the canaliculi or their loss, for instance following a medial canthal tumour excision.

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# Thyroid Eye Disease

Peter J. Dolman

# 12.13

**Definition:** Thyroid eye disease (TED) is an inflammatory orbital disease associated with autoimmune thyroid disorders that causes expansion and fibrosis of orbital fat and striated muscle, resulting in cosmetic and functional morbidity.

## Key Features

- Graves' disease is the most common autoimmune disorder.
- Approximately 50% of patients with Graves' disease may develop orbitopathy.
- The orbital target of the immune response is likely the pluripotential orbital fibrocyte.
- The most important clinical features of the orbitopathy are eyelid retraction, proptosis, restrictive strabismus, and dysthyroid optic neuropathy.
- Management is medical during the active inflammatory phase and surgical during the chronic fibrotic phase.

## INTRODUCTION

Thyroid eye disease (TED) is an orbital inflammatory disorder that is associated with thyroid autoimmune diseases and causes expansion and scarring of orbital fat and striated muscle.<sup>1,2</sup>

Although it is self-limited, TED may significantly disrupt cosmesis, vision, and quality of life.<sup>3</sup>

## EPIDEMIOLOGY, RISK FACTORS, AND ASSOCIATED CONDITIONS

TED is the most common orbital disease globally, with a prevalence estimated between 0.5%–2%, and with females outnumbering males by 4:1. It is most common between the second and sixth decade and occurs in all races.<sup>4,5</sup>

Risk factors for developing TED include a positive family history, smoking, life stressors, and poorly controlled hypothyroidism following radioactive iodine.<sup>6</sup> Predictors for more serious involvement by TED

include male gender, increasing age, smoking, and a rapid onset of orbitopathy.<sup>7</sup>

Cigarette smoking is strongly correlated with both the development of TED and with its severity.<sup>8</sup>

Patients with TED have an increased probability of developing associated immune diseases, including superior limbic keratitis (SLK), myasthenia gravis, diabetes mellitus, alopecia, and vitiligo.<sup>9</sup>

## PATHOGENESIS

TED often occurs in conjunction with autoimmune thyroid diseases such as Graves' disease (90%) or Hashimoto thyroiditis (3%); 90% of patients with orbitopathy have a current or past history of abnormal systemic thyroid hormone levels, whereas others may develop abnormal levels in the future.

In Graves' disease, an aberrant population of lymphocytes produce thyrotropin-receptor antibodies (TRAB), also known as thyroid-stimulating hormone receptor (TSH-R) antibodies.<sup>1</sup> Differing subtypes may cause more, less, or unchanged levels of serum thyroxine.

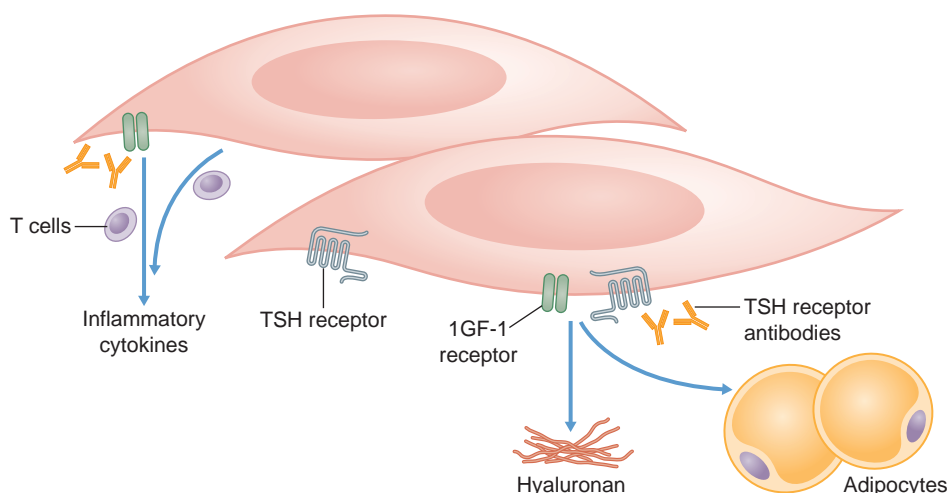
Similar receptor sites on skin and orbital fat and muscle fibrocytes also may be targeted by these autoantibodies in Graves' disease, resulting in orbitopathy in 50% and dermopathy (pretibial myxedema or acropachy) in 5%–10%.<sup>10</sup>

The target cell in TED is the pluripotential orbital fibrocyte, present both in orbital fat and striated muscle.<sup>11</sup> Binding of circulating TRAB to fibrocyte receptors induces adipogenesis and hyaluronic acid production, resulting in expansion and remodeling of orbital tissues. The process is enhanced by the release of cytokines by T-helper cells, potentiated by binding of adjacent insulin-growth factor receptors (IGF-1) (Fig. 12.13.1).<sup>1,12,13</sup>

## CLINICAL PRESENTATION: DISEASE SEVERITY AND ACTIVITY

TED presents with a spectrum of clinical features determined by which orbital tissues are involved. The pattern and extent of involvement are graded as "disease severity."

Approximately two-thirds of TED patients develop primarily fat expansion, often in association with focal levator muscle inflammation, resulting



**Fig. 12.13.1 Binding of Autoantibodies to TSH Receptors on Fibroblasts Leads to Activation of T-Helper Cells, Secretion of Inflammatory Cytokines, and Production of Hyaluronan.** Some of the pluripotential fibrocytes differentiate into adipocytes following binding to TSH receptor antibodies. Binding of IGF-1 to nearby IGF-1 receptors may synergistically enhance TSH receptor signaling, hyaluronan production, and adipogenesis. The resulting connective tissue remodeling produces the varying degrees of extraocular muscle enlargement and orbital fat expansion characteristic of TED. (Reprinted from Bahn RS and Kazim M. Thyroid. In: Fay A, Dolman PJ, editors. Diseases and disorders of the orbit and ocular adnexa. Elsevier; 2016. p. 223.)





**Fig. 12.13.2** (A) Young female demonstrates proptosis and bilateral upper lid retraction with lateral flare. (B) Axial computerized tomography (CT) scan of same patient shows marked proptosis from fat expansion but minimal muscle enlargement. (Courtesy Fay A, Dolman PJ, editors. *Diseases and disorders of the orbit and ocular adnexa*. Elsevier; 2016. p. 220.)

in eyelid retraction, proptosis, and ocular exposure. This pattern typically evolves very slowly in a younger, predominantly female population (Fig. 12.13.2).<sup>2</sup>

The remaining third have significant enlargement of one or more extraocular muscles and present with more severe features, including congestion and edema of the conjunctiva and eyelids, restricted ocular ductions with diplopia, and dysthyroid optic neuropathy (DON), resulting from apical compression of the optic nerve by the swollen muscles. Muscle-centric disease usually develops more rapidly in an older population with a more balanced gender distribution and is more likely to be associated with smoking and a positive family history of TED (Fig. 12.13.3).<sup>7,14</sup>

TED has a biphasic course, with a progressive (“active”) phase lasting 6–18 months, followed by a stable (“inactive”) phase.<sup>15</sup> These disease phases are graded as “clinical activity.” “Rundle’s curve” is a graph of orbital disease severity against time (Fig. 12.13.4), with a steeper slope in the progressive phase reflecting more aggressive disease.<sup>7</sup> Immunomodulators and radiotherapy administered during the early active phase may limit the destructive consequences of the immune cascade. Surgery is usually performed in the postinflammatory phase for orbital cosmesis, comfort, and function but may be needed during the progressive phase to prevent vision loss from DON or corneal breakdown.<sup>16</sup>

Recurrence of TED occurs in less than 10% of cases.<sup>17</sup>

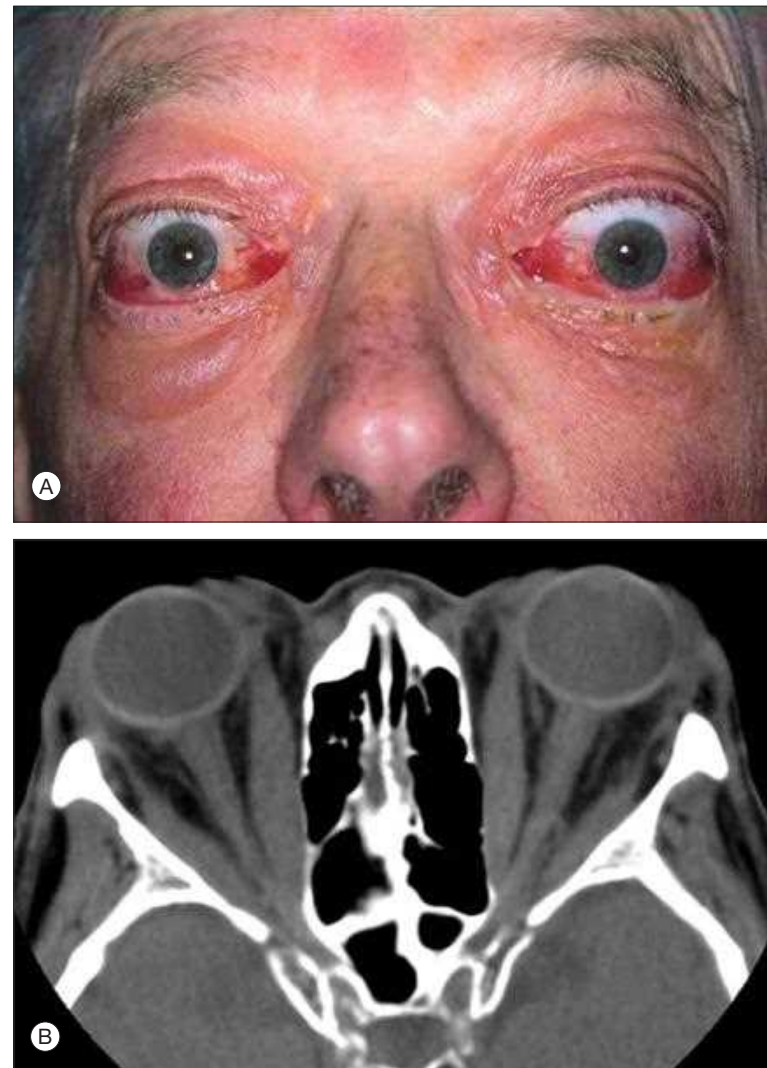
## DIAGNOSIS

Diagnosis of TED is based on three aspects of the disease:

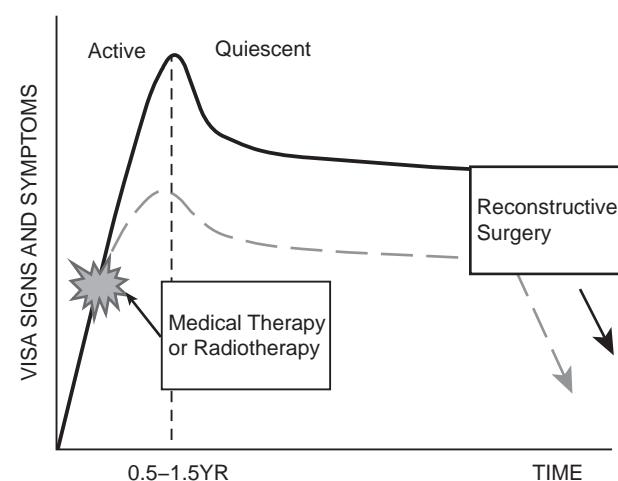
(i) **Clinical Features:** Characteristic findings such as lid retraction combined with proptosis and limited motility are highly suggestive of TED, particularly when bilateral.

(ii) **Thyroid Function and Antibody Tests:** Abnormal thyroid function tests (thyroxine and TSH levels) or a history of thyroid dysfunction help confirm the diagnosis, although 10% of TED patients may be euthyroid at onset. The presence of TSH-R antibodies has high sensitivity for active Graves’ disease.<sup>18</sup>

(iii) **Orbital Imaging:** Computerized tomography (CT), magnetic resonance imaging (MRI), or ultrasound may help confirm the diagnosis, particularly



**Fig. 12.13.3** (A) Older male shows periorbital soft tissue congestion associated with restricted ocular movements and dysthyroid optic neuropathy (DON). (B) Axial CT scan of same patient shows enlargement of muscles with proptosis and apical crowding. (Courtesy Dolman PJ. *Assessment and management plan for Graves’ orbitopathy*. In: Bahn RS, editor. *Graves’ disease: a comprehensive guide for clinicians*. New York: Springer; 2015.)



**Fig. 12.13.4** Rundle Curve Plots Disease Severity (y-axis) vs Time (x-axis), With an Active, Progressive Phase Followed by an Inactive, Stable Phase. Medical or radiotherapy are offered during the progressive phase to reduce the severity of the orbital changes. Surgical reconstruction is typically performed once the disease is quiescent.

for atypical or uncertain clinical situations. The CT scan documents fat or muscle enlargement and apical crowding and allows assessment of bony walls and sinuses for possible surgical decompression. Contrast CT scans may show enhancement of the extraocular muscle sheaths or stranding of surrounding orbital fat in the active inflammatory phase<sup>2</sup> or reduced

TABLE 12.13.1 Werner's NOSPECS Classification

Class	Grade	
0		No signs or symptoms
1		Only signs
2		<b>Soft tissue involvement, with symptoms and sign</b>
	0	Absent
	A	Minimal
	B	Moderate
	C	Marked
3		<b>Proptosis</b>
	0	<23 mm
	A	23-24 mm
	B	25-27 mm
	C	≥28 mm
4		<b>Extraocular muscle involvement</b>
	0	Absent
	A	Limitation of motion in extremes of gaze
	B	Evident restriction of movement
	C	Fixed eyeball
5		<b>Corneal involvement</b>
	0	Absent
	A	Stippling of cornea
	B	Ulceration
	C	Clouding
6		<b>Sight loss</b>
	0	Absent
	A	20/20 – 20/60
	B	20/70 – 20/200
	C	<20/200

(Modified from Werner SC. Classification of the eye changes of Graves' disease. J Clin Endocrinol Metab 1969;29:982–4).

enhancement and lucent spaces in the extraocular muscles in the inactive phase. MRI identifies edema within the extraocular muscles on T2 or STIR sequence in active disease.<sup>19,20</sup>

EVALUATION OF DISEASE SEVERITY AND ACTIVITY

Early diagnosis permits an accurate evaluation of TED, including assessment of disease severity and activity and identification of those individuals at high risk of developing more serious complications.

(i) **Disease Severity:** Werner's NO SPECS Classification grades specific clinical features of TED and assigns a global severity score (Table 12.13.1).<sup>21</sup> This highlights the different manifestations of the disease in order of frequency of presentation, but the descriptors for each grade focus on only one aspect while summary scores hide details about how the patient is specifically affected. Werner's scale does not assess clinical activity nor provide a means for defining management.<sup>2</sup>

The European Group on Graves' Orbitopathy (EUGOGO) TED severity scale is based on three management categories.<sup>22</sup> "Mild disease" includes lid retraction, mild proptosis, and minimal muscle involvement and is usually treated conservatively. "Moderate to severe disease" incorporates individuals with greater proptosis, inflammation, or motility restriction interfering with ability to function and is often treated medically. "Very serious disease" refers to sight-threatening conditions such as DON or corneal ulceration and may necessitate urgent surgical intervention. In this system, the distinction between mild and moderate disease is imprecise, and the moderate class is a broad, heterogeneous category, including individuals with soft tissue congestion, motility disturbances, and severe proptosis.<sup>2</sup>

(ii) **Disease Activity:** Determination of activity in cases with primarily fat expansion and an indolent course may be challenging, but these cases often are referred in a stable phase when surgery can be offered on a nonurgent basis. Cases with significant muscle involvement have a more obvious progression through the active and postinflammatory inactive phases, with congestive and inflammatory periocular changes usually developing from expanding ocular muscles, alerting the clinician that the disease is progressive and may lead to significant visual impairment from diplopia or DON.

BOX 12.13.1 Clinical Activity Score (CAS)

For initial CAS, only score items 1–7

1. Spontaneous orbital pain.
  2. Gaze evoked orbital pain.
  3. Eyelid swelling that is considered to be due to active (inflammatory phase) Graves' orbitopathy (GO).
  4. Eyelid erythema.
  5. Conjunctival redness that is considered to be due to active (inflammatory phase) GO.
  6. Chemosis.
  7. Inflammation of caruncle or plica.
- Patients assessed after follow-up between 1 and 3 months can be scored out of 10 by including items 8–10.
8. Increase of >2 mm in proptosis.
  9. Decrease in uniocular excursion in any field of gaze >8°.
  10. Decrease in visual acuity of >1 line on Snellen chart.

The affected patient may report the date and rate of disease onset as well as the recent disease course, even on the first visit.<sup>2</sup>

The *Clinical Activity Score (CAS)* is a global scale of soft tissue inflammation designed to identify active TED patients who might benefit from immunosuppressive therapy<sup>23</sup> (Box 12.13.1). It uses a binary scale to assess seven periocular soft tissue inflammatory/congestive features as surrogate markers of disease activity. On follow-up visits, additional points are given for increased proptosis (2 mm or more), decreased ocular motility (8° or more), or decreased visual acuity over the previous 3 months. A CAS score of 4 or higher has an 80% positive predictive value and a 64% negative predictive value for response to corticosteroid therapy. However, it has not been proven to correlate with risk of developing significant complications such as diplopia or DON. It is limited by significant false-positive and -negative cases. DON may develop in the context of low CAS values, patients with fat-centered disease may develop dramatic proptosis and lid retraction without any soft-tissue inflammatory changes, and some individuals with high CAS may have long-standing congestive changes that are unresponsive to any immunotherapy but respond best to mechanical surgical decompression.<sup>2</sup>

Lastly, both laboratory studies (urine and serum glycosaminoglycans and TSH-R antibodies) and imaging techniques (contrast-enhanced CT, T2/STIR sequence MRI, octreotide scans, and facial thermography) have been used to quantify activity, but none have proven more reliable than clinical assessment of disease progression.<sup>24</sup>

(iii) **VISA Classification:** This recording form grades both disease severity and activity using subjective and objective inputs.<sup>25</sup> It clusters the clinical features of TED into four discrete parameters: V (vision, DON); I (inflammation, congestion); S (strabismus, motility restriction); A (appearance, exposure).

The standard visit form (Fig. 12.13.5) is divided into four sections recording specific symptoms on the left and validated signs for each eye on the right. After each section is a progress row (better, same, worse) documenting the impression of both patient and clinician of the change in that parameter since the previous visit. Progress is documented on the basis of defined interval changes (i.e., 2 mm change in proptosis, 12° change in ocular ductions) rather than on global scores.

The layout follows the usual sequence of the eye examination and facilitates comparison of measurements between visits as well as data collation for research.

Summary grades for the severity and progress for each of the four disease parameters are documented at the bottom of the form. Unlike the EUGOGO scale that rates severity based on the presence of specific TED measurements, the VISA classification grades the severity and activity of each parameter independently.

Activity is determined by a defined interval deterioration in any one of the four parameters. The VISA I-score (for inflammation/congestion) assesses periocular soft tissue congestive features in a similar manner to CAS but uses a more sensitive 0–2 score for chemosis and eyelid edema. However, the CAS defines active disease on the basis of an absolute score >4, whereas VISA defines activity on the basis of a deterioration in I-scores (>2) or a specified progression in any of the other VISA parameters.

On the first visit, the date and rate of onset and historic progress of both the systemic and orbital symptoms are recorded, defining characteristics of the disease course. Additional questions also determine risk

**ITEDS - VISA FOLLOW-UP FORM**

Date:

Visit #:

Patient Label:

Date of birth:

Age:

Gender:

**ORBITOPATHY**

Symptoms:

**THYROID**

Symptoms:

**GENERAL**

Smoking:

Meds:

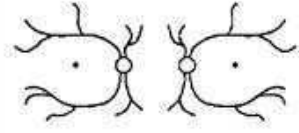


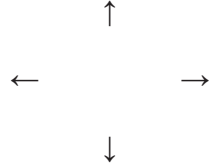

Progress:

Status:

Therapy:

Therapy:

QOL: ☹️ ----- 😊

SUBJECTIVE	OBJECTIVE	OD	OS	
<b>VISION</b>				<b>Refractions</b>
Vision: n / abn	Central vision: sc / cc / ph	20/___	20/___	Wearing _____ + _____ X _____
	with manifest	20/___	20/___	_____ + _____ X _____
Color vis: n / abn	Color vision plates (HRR) / 14			Manifest _____ + _____ X _____
	Pupils (afferent defect)	y / n	y / n	_____ + _____ X _____
	Optic nerve: Edema	y / n	y / n	
	Pallor	y / n	y / n	
<b>Progress: s / b / w</b>	Macular/ lens pathology	y / n	y / n	
<b>INFLAMM<sup>N</sup>/ CONGESTION</b>				<b>Inflammatory Index (worst eye/eyelid)</b>
Retrobulbar ache	Caruncular edema (0-1)			Caruncular edema (0-1):
At rest (0-1)	Chemosis (0-2)			Chemosis (0-2):
With gaze (0-1)	Conjunctival redness (0-1)			Conj redness (0-1):
Lid swelling: y / n	Lid redness (0-1)			Lid redness (0-1):
Diurnal variation: (0-1)	Lid edema Upper (0-2)			Lid edema (0-2):
	Lower (0-2)			Retrobulbar ache (0-2):
<b>Progress: s / b / w</b>				Diurnal Variation (0-1):
				<b>Total: (10):</b>
<b>STRABISMUS/ MOTILITY</b>				Prism Measure:
Diplopia:	Ductions (degrees):			
None (0)	Restriction > 45°	0	0	
With gaze (1)	30-45°	1	1	
Intermittent (2)	15-30°	2	2	
Constant (3)	< 15°	3	3	
Head turn/ tilt: y / n				
<b>Progress: s / b / w</b>				
<b>APPEARANCE/EXPOSURE</b>				Fat prolapse and eyelid position:
Lid stare y / n	Upper lid position: MRD	mm	mm	
	Scleral show (upper)	mm	mm	
	(lower)	mm	mm	
	Levator function	mm	mm	
Light sensitivity y / n	Lagophthalmos	mm	mm	
Bulging eyes y / n	Exophthalmometry (Base: mm)	mm	mm	
Tearing y / n	Corneal erosions	y / n	y / n	
Ocular irritation y / n	Corneal ulcers	y / n	y / n	
<b>Progress: s / b / w</b>	IOP -straight	mm Hg	mm Hg	
	-up	mm Hg	mm Hg	
<b>DISEASE GRADE</b>		<b>Grade</b>	<b>Progress / Response</b>	<b>DISEASE ACTIVITY</b>
V (optic neuropathy) y / n		/ 1	s / b / w	
I (inflammation/congestion) 0-10		/ 10	s / b / w	Active
S (diplopia) 0-3		/ 3	s / b / w	
(restriction) 0-3		/ 3	s / b / w	Quiescent
A (appearance/exposure): normal - severe		/ 3	s / b / w	

**MANAGEMENT****FOLLOW-UP INTERVAL:**

**Fig. 12.13.5 VISA Classification Follow-up Form, Documenting and Grading Severity Based on Four Clinical Parameters With Activity Based on Progression in Any of These Four Parameters.** (Courtesy International Thyroid Eye Disease Society: <http://thyroideyedisease.org/>.)



factors for more serious TED outcomes associated with extraocular muscle involvement, including smoking, family history, and diabetes. A first-visit form (2 pages) and follow-up form (1 page) may be downloaded from the International Thyroid Eye Disease Society (ITEDS) website: <http://thyroideyedisease.org/>.

## QUALITY OF LIFE

Although objective measurements document disease severity, and interval changes document disease activity, subjective measurements of quality of life are also important to gauge the disease. The European Graves' Ophthalmopathy Quality of Life questionnaire (GO-QOL) consists of 16 questions, half pertaining to visual functioning and half to appearance.<sup>26</sup> The Graves' Ophthalmopathy Quality of Life Scale (GO-QLS) consists of a single question about overall well-being, a single question about appearance, and seven questions about visual function. The Thyroid Eye Disease Quality of Life scale (TED-QOL) is a simple three-item questionnaire with a 10-point Likert scale relating to satisfaction with overall quality of life, ability to function, and appearance. The latter is simple to administer and score and is designed to function both as a research tool and a simple office questionnaire.<sup>27,28</sup>

## BASIC MANAGEMENT

Management of TED is ideally performed using a multidisciplinary team, each with an area of expertise. The endocrinologist manages the thyroid status, the ophthalmologist the orbital disease, a rheumatologist prescribes immunomodulators, the radiation oncologist plans radiotherapy, and a surgeon may perform thyroidectomies.

The patient and their family should be taught the natural history of the disease, the role of the immune system, and how management varies depending on the disease phase. Young patients with fat-targeted indolent disease can be reassured they are unlikely to develop serious complications, whereas high-risk individuals with rapid onset of more muscle-targeted disease should be advised about potential complications and that it may take up to 2 years until the disease is quiescent and restorative surgery performed.

Supportive measures, such as cool compresses and head elevation for periorbital congestion and lubricants for exposure, should be offered to all patients.

## MEDICAL THERAPY

**(i) Gluco-corticosteroids (CS):** These remain the first choice for active TED with significant inflammatory signs. They may reverse DON, although this may be incomplete or temporary so that adjunctive radiotherapy or surgical decompression may be necessary. They also are recommended preventively to avoid exacerbation of active TED at time of radioactive iodine thyroid ablation.<sup>29</sup>

Standard oral therapy is daily prednisone 0.5–1.0 mg/kg daily for 6 weeks, but this route has side effects in 50% of cases, including Cushing's syndrome, diabetes mellitus, insomnia, mood disturbances, gastric ulcers, osteopenia, necrosis of the femoral head, and susceptibility to infections.<sup>30</sup>

Intravenous CS therapy reduces the incidence of side effects and allows a longer duration of therapy.<sup>31</sup> A popular protocol is IV methylprednisolone 500 mg weekly for 6 weeks, reducing to 250 mg weekly for 6 weeks. The author prefers to titrate the dose or prolong the intervals depending on clinical response. Liver failure and rare cases of death have been reported in cumulative doses over 8 g of methylprednisolone.<sup>32</sup>

Depot CS injection into the inferolateral orbital fat pocket is beneficial for focal orbital congestion<sup>33</sup> but carries a small risk of intravascular emboli with visual loss.

Retrospective studies find efficacy of 60% overall for oral CS and 85% for IV CS in reducing inflammatory features in active TED.<sup>34</sup> The effect occurs within 24 hours but is short lived, so prolonged therapy is required (Fig. 12.13.6). A recent large series from Vancouver found that although appropriate doses of CS effectively reduced inflammatory scores, 17% of patients in the high-risk muscle-targeted group developed DON and 35% had worsening of diplopia or ocular restriction. In a comparable group in which combined CS and radiotherapy was provided, none developed DON, and improved diplopia and motility scores were observed.<sup>35</sup>

**(ii) Nonsteroidal Immunotherapy:** Cyclosporine combined with CS enhances its benefit against inflammatory soft tissue changes.<sup>36</sup>



**Fig. 12.13.6** (A) 47-year-old female with recent onset of inflammatory changes (CAS score 7/10, VISA inflammatory score 9/10). The history of progression indicates active disease, and the congestive changes indicate extraocular muscle enlargement (and the risk for serious sequelae) based on the VISA classification criteria. (B) She was treated with corticosteroid for control of the inflammatory changes and later with radiotherapy to prevent onset of motility disruption and optic neuropathy. The inflammatory soft tissue changes resolve in response to corticosteroids and radiotherapy, but the upper lids remain retracted, suggesting levator scarring has already occurred. (Courtesy Dolman PJ. Assessment and management plan for Graves' orbitopathy. In: Bahn RS, editor. Graves' disease: a comprehensive guide for clinicians. New York: Springer; 2015.)

Intravenous immunoglobulin (IVIg) therapy is reported to be as effective as oral GC with a low rate of adverse effects but is prohibitively expensive.<sup>37</sup>

**(iii) Rituximab (RTX):** This anti-CD20 chimeric monoclonal antibody induces transient B-cell depletion and blocks early B-cell and T-cell activation.<sup>38</sup> Small case series have found benefit in reducing CAS scores in cases refractory to CS. Two recent randomized controlled trials have studied the use of rituximab for moderately severe, active TED. The Mayo Clinic study randomized 25 participants into infusions of either RTX or saline.<sup>38</sup> Both groups improved over a year follow-up with no significant difference noted between CAS or QOL scores. A study by Salvi et al. ( $n = 32$ ) found RTX given either as two biweekly 1000-mg infusions or as a single 500-mg infusion was better at reducing CAS scores compared with IVCS (methylprednisolone 7.5 g total).<sup>39</sup> The inactivation rate (defined as a reduction of CAS to 3) at 24 weeks was 100% in the RTX group and 69% in the IVCS group ( $P < 0.04$ ).

**(iv) Tocilizumab:** A prospective study on a series of 18 active TED patients resistant to IVCS found significant benefit in terms of proptosis, CAS, and strabismus reduction using tocilizumab, a humanized monoclonal antibody against the interleukin-6 receptor.<sup>40</sup> A randomized double-blind

prospective trial is now being conducted to confirm these promising findings. This drug is administered intravenously monthly until disease control with significant side effects including gastrointestinal ulcers and respiratory infections in up to 10% of individuals. A subcutaneous delivery system may have fewer complications.

(v) **Selenium** is an oral antioxidant mineral found in Brazil nuts, tuna, and dark green leafy vegetables. A EUGOGO randomized controlled study in patients with mild TED found greater improvement in lid retraction, CAS, and QOL scores in those supplemented with selenium 100 µg twice daily compared with a placebo group after 6 months of therapy and 6 months after cessation of the drug. No adverse effects were identified.<sup>41</sup> This study was conducted in countries with selenium-deficient diets, so a follow-up study is planned by ITEDS for North America, where selenium dietary levels are adequate.

## ORBITAL RADIOTHERAPY

(i) **Mechanism:** External beam radiotherapy (RT) has been used for TED for more than 60 years and is thought to work by inhibiting or depleting lymphocytes and fibroblasts in the involved orbital tissue. Typically 20 Gy (2000 Rads) divided over 10 days are delivered to the retrobulbar orbit through a lateral port, avoiding ocular or intracranial exposure.<sup>42</sup>

### (ii) Indications:

V: DON: The addition of RT to CS was shown to reduce the incidence of developing DON in high-risk progressive TED from 17% (CS alone) to 0% (CS and RT).<sup>35</sup> In patients with established DON, the addition of RT to CS was shown to reduce the need for decompression surgery compared with CS treatment alone.<sup>43</sup> RT may also be useful in preventing progressive expansion of muscles and recurrence of vision loss following successful orbital decompression.<sup>42</sup>

I: Inflammation/congestion: RT reduces periocular inflammation in 60% of patients with active TED, similar to the success rate for oral CS.<sup>44</sup> The benefit of prednisone tends to be more rapid, whereas for RT it is longer lasting. Prednisone combined with RT has greater benefit than treatment with prednisone alone.<sup>45</sup>

S: Strabismus/motility: Two randomized controlled studies from the Netherlands found that patients with TED treated with RT ultimately had better ocular excursions than patients treated with sham (no) RT.<sup>46,47</sup>

A: Appearance/exposure: Radiotherapy has little benefit in reducing ultimate proptosis or lid retraction.

RT is most effective for active (progressive) disease and is unlikely to reverse orbital changes in stable, postinflammatory thyroid eye disease.<sup>48</sup>

(iii) **Safety and Complications:** Modern linear accelerator radiotherapy units have an excellent safety record with retrospective series in TED showing no increased risk of cataract and no reports of radiation induced tumors.<sup>49</sup> Because of a small theoretical lifetime risk of developing tumors, its use for TED is contraindicated in people younger than 35 years.<sup>37</sup>

RT may increase the incidence of retinal vascular disease in patients with diabetes mellitus (DM) or hypertension, and its use is often avoided in patients with DM.

Radiotherapy may cause some temporary redness and hair loss in the temple area near where the beam is focused. Orbital inflammation may increase during RT, but this can be controlled with concurrent oral CS.

## SURGICAL THERAPY

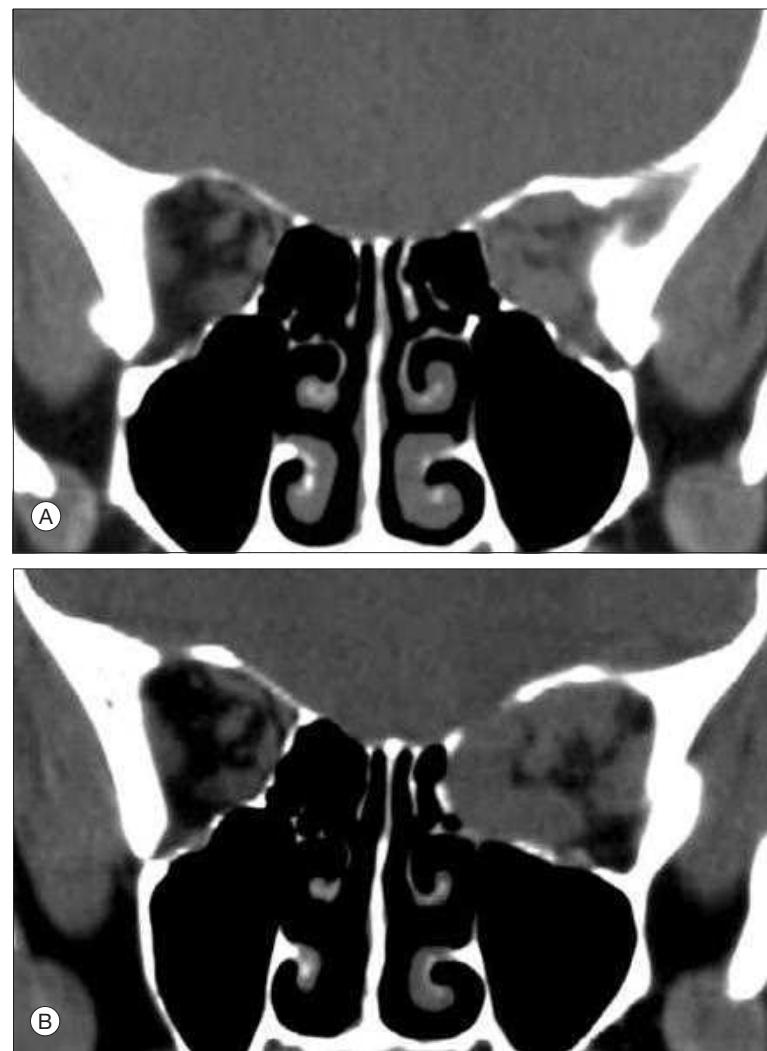
(i) **Timing of surgery:** Surgical rehabilitation for TED is considered during the inactive phase following several months of stable measurements and controlled thyroid status (see Fig. 12.13.4). Surgery may be necessary during the active phase when vision is threatened and may include orbital decompression for refractory DON or tarsorrhaphy and lid-narrowing procedures for corneal breakdown from prominence of the eyes or severe lid retraction.

Surgery for TED is staged sequentially: 1. Orbital decompression; 2. Strabismus repair; and 3. Eyelid retraction surgery and blepharoplasties.

(ii) **Orbital Decompression:** This is used for dysthyroid optic neuropathy, proptosis, and chronic orbital congestion. The surgery involves a combination of bone wall removal and resection of orbital fat.

Decompression involves bone wall and/or fat removal, depending on the indication, the targeted tissue, and the desired amount of proptosis reduction.

Optic nerve apical compression by expanded extraocular muscle is relieved by out-fracture of the medial orbital wall into the posterior ethmoid sinus and the medial floor into the maxillary sinus (Fig. 12.13.7). Even significant or longstanding vision loss may be reversed by an effective decompression. Adjunctive CS or RT may be offered to avoid postoperative



**Fig. 12.13.7** (A) Coronal CT scan showing left orbital apex optic nerve crowding from enlarged extraocular muscles. Little perineural fat is visible, and Snellen visual acuity was reduced to 6/60 in the left eye. (B) Postoperative coronal CT scan demonstrates medial wall decompression relieving pressure on optic nerve. Vision was restored to 6/6. Notice that the medial rectus muscle continued to expand following the decompression, and this may be reduced with concomitant radiotherapy. (Courtesy Dolman PJ. Evaluating graves orbitopathy. *Best Pract Res Clin Endocrinol Metab* 2012;26:229–48. p. 240.)

deterioration in vision, because the disease is typically in an active stage with progressive muscle expansion.<sup>42</sup>

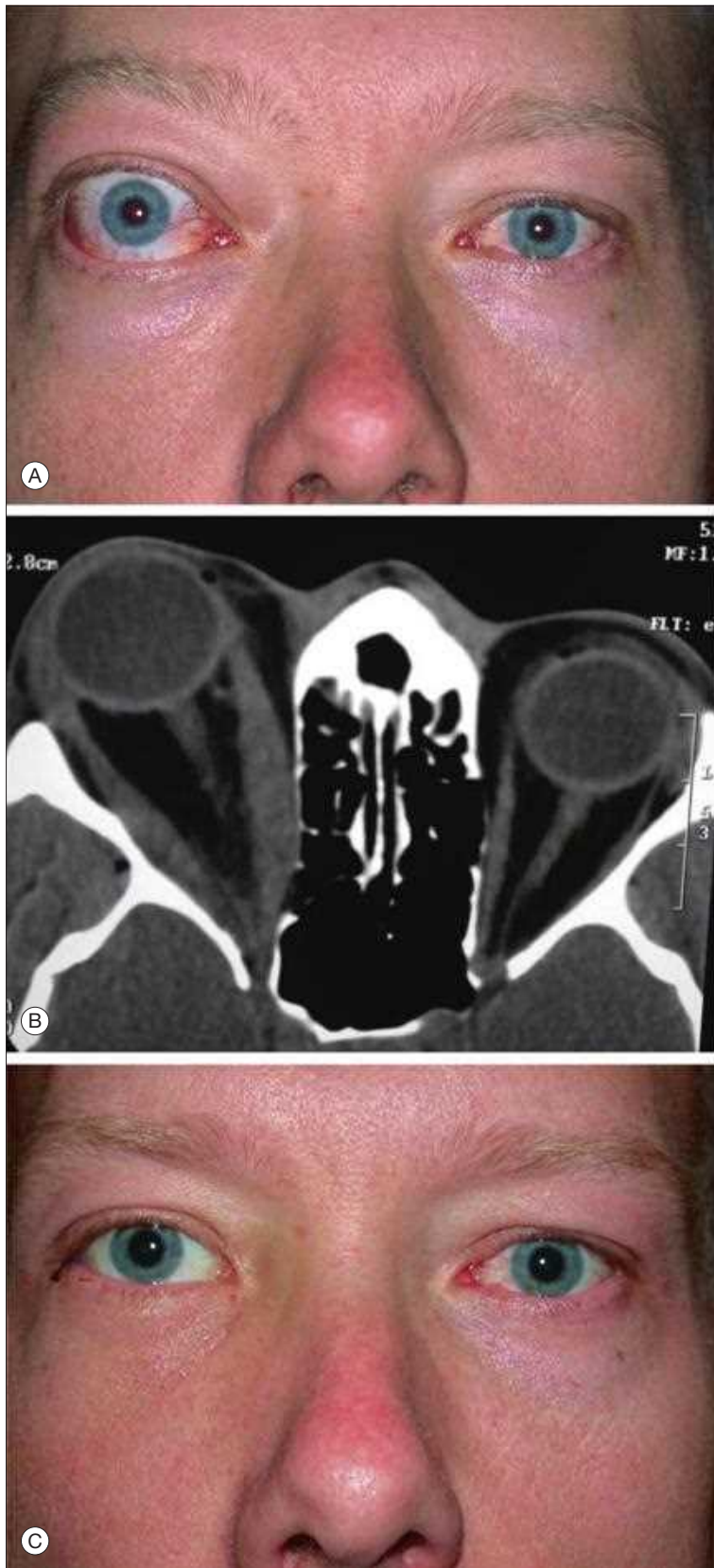
The most common indication for decompression is proptosis reduction during the inactive phase to improve comfort and appearance (Fig. 12.13.8). A swinging eyelid approach allows access to the lateral wall, floor, and medial wall, and any combination of bone wall removal and fat removal may be chosen, depending on the relative contribution of fat versus muscle tissue expansion. Specific complications are associated with each of the walls removed. Cheek numbness and globe inferior displacement may occur with floor decompression, oscillopsia may occur with lateral rectus/temporalis muscle apposition following lateral wall decompression,<sup>50</sup> and sinusitis and ethmoidal nerve anesthesia may arise following medial wall decompression.

A rare indication for decompression is relief of long-standing soft tissue congestion. These individuals may have high CAS/VISA inflammatory scores, but the disease is inactive with no change in VISA grades and no response to CS. Improved venous drainage following expansion of the orbital compartment often results in a gratifying and immediate improvement in congestion and inflammatory scores (Fig. 12.13.9).

Strabismus is a troublesome consequence of decompression surgery. This is particularly common in cases with enlarged extraocular muscles and pre-existing strabismus, often seen in cases of optic neuropathy or chronic congestion. It occurs in less than 10% of cases of fat-targeted disease, regardless of the approach or technique.

(iii) **Strabismus Surgery:** Individuals with muscle-targeted progressive TED have a significant risk of developing muscle scarring, restriction, and strabismus with significant impact on QOL.





**Fig. 12.13.8** (A) Asymmetrical right proptosis with upper and lower eyelid retraction. (B) Orbital CT scan demonstrating right axial proptosis with muscle and fat enlargement. (C) Same patient following right orbital decompression, right upper lid lowering and lower lid elevation. (Courtesy Dolman PJ. *Evaluating Graves' orbitopathy*. *Best Pract Res Clin Endocrinol Metab* 2012;26:229–48. p. 235.)

At the first symptoms of diplopia, combined radiotherapy and corticosteroid therapy might limit progression and preserve the greatest field of single binocular vision.

Strabismus and ductions can be assessed both in the office and by an orthoptist so that a temporary prism can be fitted and measurements repeated until stable for at least 6 months, when surgery may be offered. The orthoptist also measures fusional amplitudes and torsion to assist in surgical planning.



**Fig. 12.13.9** (A) 62-year-old female with a high VISA inflammatory score based on her soft tissue changes. However, she had been referred on combination oral corticosteroids and cyclosporine for over a year with no history of progression, and was *inactive* following the VISA classification guideline (although her CAS score would have been interpreted as active). (B) One month following bilateral orbital decompression and upper lid lowering, her congestive features had resolved and her medications were tapered off. Both the VISA inflammatory score and CAS scores were reduced to zero. (Courtesy Dolman PJ. *Assessment and management plan for Graves' orbitopathy*. In: Bahn RS, editor. *Graves' disease: a comprehensive guide for clinicians*. New York: Springer; 2015.)

Most strabismus surgery for TED consists of recessions, often on adjustable sutures (Fig. 12.13.10). Inferior rectus recessions are prone to slippage, which might be mitigated by use of nonabsorbable sutures and undercorrecting slightly.<sup>51</sup>

Inferior rectus recessions may induce a secondary lower lid retraction, necessitating subsequent lower lid spacer grafts.

**(iv) Eyelid Surgery:** Upper eyelid retraction is associated with enlargement and scarring of the levator complex and is treated with recession of the scarred complex (Fig. 12.13.11).<sup>52</sup> Lower eyelid retraction is mostly associated with proptosis, although secondary retraction from inferior rectus recession is well recognized. Orbital decompression with floor removal may actually accentuate upper lid retraction (as the upper lid remains tethered while the globe is relatively lowered), whereas lower lid retraction may be reduced.

In progressive disease, retraction is usually managed conservatively with topical lubricants unless the cornea is threatened, in which case a temporary tarsorrhaphy or levator release may be performed.

## MANAGEMENT PLAN USING THE VISA CLASSIFICATION

The VISA classification organizes the four disease parameters in order of descending priority for management.





**Fig. 12.13.10** (A) 45-year-old female with progressive disease with bilateral upgaze restriction, constant diplopia, and upper lid retraction. (B) Quiescent disease following combined IV corticosteroids and radiotherapy and subsequent ocular alignment surgery and upper lid lowering surgery. (Courtesy Dolman PJ. Assessment and management plan for Graves' orbitopathy. In: Bahn RS, editor. Graves' disease: a comprehensive guide for clinicians. New York: Springer; 2015.)

(i) **V: Vision:** DON is recognized by progressive color and central vision loss with inferior paracentral visual field defects and apical nerve crowding on coronal CT scans. Initial treatment includes systemic corticosteroids, administered either orally (1.5 mg/kg prednisone daily) or intravenously (1 g IV methylprednisolone on alternate days for a week). Incomplete restoration of vision or relapse on tapering of CS may necessitate orbital decompression, usually with excellent response.

Adjunctive external beam radiotherapy may reduce the need for surgical decompression and has been used following decompression to prevent continued postoperative expansion of muscle and recurrence of visual impairment.<sup>42</sup>

Rituximab may be useful in some cases of DON refractory to corticosteroids.<sup>53</sup>

(ii) **I: Inflammatory and congestive soft tissue changes:** These are scored using the VISA inflammatory score or CAS.

Cases with mild soft tissue inflammatory changes (low scores) are managed conservatively with cold compresses and head elevation. Cases with moderate scores can be given a trial of oral prednisone and assessed for improvement. Patients with high scores are typically treated with intravenous corticosteroids with good response on a short-term basis and radiotherapy for long-term effect. Because high inflammatory scores may reflect disease activity, close attention to signs of progress in the other VISA parameters is vital. Refractory cases may respond to combination therapy



**Fig. 12.13.11** (A) Right upper eyelid retraction with 3 mm scleral show and lateral flare. (B) Coronal CT scan of same patient showing corresponding enlargement of right levator palpebrae superioris muscle (asterisk). (Courtesy Dolman PJ. Assessment and management plan for Graves' orbitopathy. In: Bahn RS, editor. Graves' disease: a comprehensive guide for clinicians. New York: Springer; 2015.)

(including cyclosporine or newer monoclonal antibody biologic agents). In chronic nonprogressive cases refractory to medical therapy, surgical decompression often is beneficial.

(iii) **S: Strabismus and restricted motility:** Diplopia is treated with prisms or patching during the active phase, and systemic corticosteroids combined with orbital radiotherapy may limit restriction in ocular motility. Once a stable phase is documented, alignment surgery or permanent prisms are beneficial.

(iv) **A: Appearance and exposure changes:** These are treated with lubricant drops and patching during the active phase. Rarely, a tarsorrhaphy or an orbital decompression may be required for corneal breakdown or ulceration. Once the disease becomes inactive, surgery may reduce proptosis, eyelid retraction, and orbital fat prolapse.<sup>42</sup>

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Orbital Infection and Inflammation

Alan A. McNab

12.14

**Definition:** Inflammation or infection of the orbital contents.

Key Features

- Clinical signs of orbital inflammation or infection include redness (eyelids and/or conjunctiva), swelling (proptosis, eyelid swelling and conjunctival chemosis), pain (not always present), and loss of function (reduced ocular motility, loss of vision).
- Every effort should be made to differentiate infection from noninfective inflammation and to establish the nature of any noninfectious inflammation (by appropriate investigation often with tissue biopsy).

INTRODUCTION

Infections or noninfectious inflammations are probably the most common orbital conditions encountered in clinical practice. The most common inflammatory orbital condition, Graves’ orbitopathy, is covered in a separate chapter (see Chapter 12.13).

The cardinal features of acute inflammation (redness, heat, pain, swelling, and loss of function) are seen in many of the conditions covered in this chapter but not all. Noninfectious orbital inflammations are often sub-acute or chronic and may have few signs of inflammation.

GENERAL ASSESSMENT

When assessing a patient with possible orbital infection or inflammation, the first and most important step is to obtain an accurate and thorough clinical history. This will include time and rapidity of onset of symptoms, a systematic review of ocular and orbital symptoms, and a full general medical history, as orbital inflammations are often associated with systemic diseases.

A complete examination of the eyes and orbits, the nasal cavity, and regional lymph nodes and salivary glands should be performed.

First-line imaging is usually a computed tomography (CT) scan. This will be adequate in most circumstances. An orbital magnetic resonance imaging (MRI) scan may provide additional information in some patients.

Material for microbiological examination should be sought for suspected bacterial orbital cellulitis. Conjunctival swabs are rarely helpful. Pus obtained from the ostia of infected sinuses or abscess cavities is most useful. Blood cultures are rarely positive<sup>1</sup> but may be helpful in an acutely ill, febrile patient.

In practice, it is often unclear whether a patient has an infectious or noninfectious orbital inflammation, and a trial of antibiotics is reasonable. If there is no response, investigations should be directed toward establishing a specific cause for the inflammation. Blind treatment with corticosteroids or other anti-inflammatory medications should be avoided, as this will often cloud or delay the diagnosis.

For patients with suspected noninfectious orbital inflammation, blood tests may help establish a diagnosis.<sup>2,3</sup> The usual panel of blood tests and imaging are listed in Table 12.14.1.

For patients with noninfectious orbital inflammation, tissue for histopathological examination should be obtained if possible. Many specific forms of inflammation cannot be diagnosed without a biopsy. Exceptions might include a patient with a typical presentation of orbital myositis or orbital apical inflammation.

Orbital Infection

Orbital infection is most commonly bacterial (orbital cellulitis), but viral, fungal, and parasitical infections may occur (Table 12.14.2).

Orbital Cellulitis

Bacterial infection of the orbital tissues (orbital cellulitis) is the most common orbital infection, and untreated it can lead to blindness and spread of infection to the cranial cavity. It is important to distinguish between preseptal (eyelid) cellulitis and the more dangerous orbital cellulitis. Orbital cellulitis, in addition to signs of eyelid inflammation (redness and swelling), will have signs of orbital inflammation—conjunctival redness and swelling (chemosis), proptosis, and potentially loss of function (visual loss and reduced eye motility) (Fig. 12.14.1).

The most common source of infection in orbital cellulitis is paranasal sinusitis complicating upper respiratory tract infection.<sup>1</sup> Bacterial overgrowth in the sinuses spreads to the adjacent orbit. Other much less common sources are spread from the globe (panophthalmitis), the eyelids, the lacrimal sac, infected teeth, and orbital foreign bodies.

Abscesses may form, either in the subperiosteal space or within the orbital tissues. The most common site is the medial subperiosteal space adjacent to the ethmoid sinuses. (Fig. 12.14.2A) In children, these medial subperiosteal collections may be sterile.<sup>4,5</sup>

All patients with orbital cellulitis should be admitted to the hospital for careful observation and documentation of clinical signs, including visual

TABLE 12.14.1 Blood Tests and Imaging for Patients With Noninfectious Orbital Inflammation

FBC, ESR, CRP
Thyroid function tests
Thyroid autoantibodies
Antinuclear antibodies
Angiotensin converting enzyme
Antineutrophil cytoplasmic antibodies
Sjögren’s syndrome antibodies
Serum IgG and IgG4 levels
Orbital CT scan (first line) and/or MRI
Chest x-ray or CT scan of chest (sarcoidosis)

CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; FBC, full blood count.

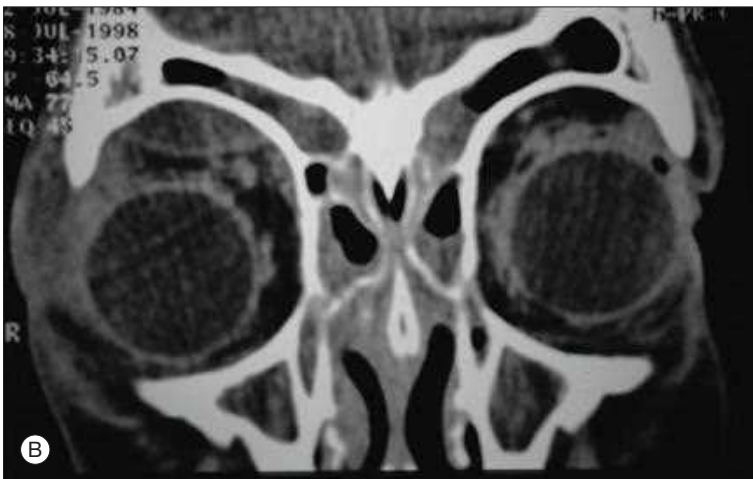
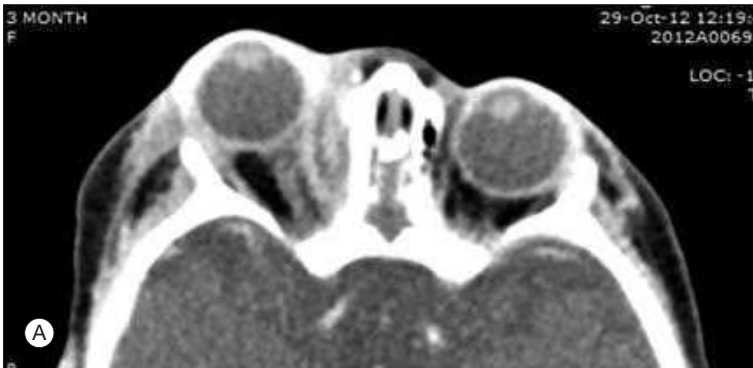
TABLE 12.14.2 Causes of Orbital Infection

1. Bacterial
  - orbital cellulitis
    - spread from adjacent structures
      - paranasal sinuses
      - eyelids
      - dental infections
      - panophthalmitis
    - orbital foreign bodies
    - hematogenous
    - tuberculosis
2. Viral
  - herpes zoster ophthalmicus
3. Fungal
  - mucormycosis
  - aspergillus
4. Parasitical
  - cysticercosis
  - echinococcosis (hydatids)





**Fig. 12.14.1** A Young Man With Severe Right Orbital Cellulitis. There is proptosis, chemosis, reduced ocular motility, and reduced vision.



**Fig. 12.14.2** (A) An axial orbital CT scan of an infant with a medial subperiosteal collection adjacent to opacified and underdeveloped ethmoid paranasal sinuses. (B) A coronal CT scan of a 14-year-old male with right orbital cellulitis and a superior subperiosteal abscess. There is pansinusitis, including frontal sinusitis. The location of the abscess and presence of frontal sinusitis are both indications for drainage of the abscess. (Harris GJ. Subperiosteal abscess of the orbit. Age as a factor in the bacteriology and response to treatment. *Ophthalmology* 1994;101:585–95. Garcia GH, Harris GJ. Criteria for non-surgical management of subperiosteal abscess of the orbit. *Ophthalmology* 2000;107:1454–8.)

function, and immediate intravenous antibiotics. The choice of antibiotic should be in consultation with local infectious diseases experts, but a common combination is ceftriaxone and flucloxacillin. Anaerobic cover may be required in older patients.

All patients should have a CT scan of the orbits and paranasal sinuses. If there is evidence of an orbital abscess, consideration should be given to urgent surgical drainage, especially with visual compromise or progression of clinical signs. In children 9 years of age or younger, most medial subperiosteal abscesses (SPAs) are sterile and often small. Provided vision is not compromised, they may be observed and most resolve without surgical intervention. Surgery should be performed if the abscess is elsewhere (see Fig. 12.14.2B), visual compromise exists, the SPA is large, frontal sinusitis is present (see Fig. 12.14.2B), or the collection has recurred after previous



**Fig. 12.14.3** (A) An adult male with redness, swelling, and pain over the left lacrimal gland due to bacterial dacryoadenitis. Note the S-shaped deformity of the upper eyelid. (B) There is redness and conjunctival chemosis laterally with purulent material visible in the palpebral lobe of the lacrimal gland.

drainage.<sup>4,5</sup> If an organism is found in this age group, it is usually a single aerobic bacterium.

For children over 15 years of age and adults, more complex infections are more common, with multiple organisms and often anaerobes as well. These patients should have any SPA or other abscess drained. Between ages 9 and 15, there is a transition, and a more active surgical role is often—but not always—required.

In recent years, antibiotic-resistant bacteria have become a more common cause of orbital infection. The most common is methicillin-resistant *Staphylococcus aureus* (MRSA). Orbital infection with MRSA usually occurs without antecedent upper respiratory tract infection or adjacent paranasal infection, abscess formation is commonly multiple, and the lacrimal gland is often involved.<sup>6</sup> Despite the emergence of these more aggressive and atypical infections, the guidelines established for management of subperiosteal collections remains valid.<sup>7</sup>

### Bacterial Dacryoadenitis

Suppurative dacryoadenitis, bacterial infection of the lacrimal gland, is an uncommon infection and a rare cause of lacrimal gland inflammation. Signs of inflammation are maximal over the lacrimal gland (Fig. 12.14.3A). Pus may be seen coming from lacrimal ductules (Fig. 12.14.3B), and should be sent for microbiological examination. Infection may spill over into the adjacent orbit. Abscesses may occasionally form and require drainage.<sup>8</sup>

### Orbital Tuberculosis

Orbital tuberculosis is rare, especially in the West. It occurs usually by hematogenous spread and can occur in several forms: periostitis, soft tissue tuberculoma (cold abscess) with or without bony involvement, or dacryoadenitis. It may also spread from adjacent paranasal sinuses.<sup>9</sup> Diagnosis depends on biopsy confirmation of caseating or necrotizing granulomatous inflammation with acid-fast bacilli seen, preferably with a positive tissue culture.

### Orbital Viral Infection

The only significant orbital viral infection is that due to herpes zoster ophthalmicus (HZO). In rare instances, an orbital apex syndrome can occur with multiple cranial nerve palsies and loss of vision. The orbit may also be more generally inflamed with proptosis.<sup>10,11</sup>



### Orbital Fungal Infection

Fungal infections of the orbit fall generally into two groups: acute, fulminant infection with fungi of the Mucorales family (rhino-orbital-cerebral mucormycosis), and invasive aspergillus infection, a more indolent infection.

#### Rhino-Orbital-Cerebral Mucormycosis

Mucormycosis usually occurs in the setting of one of the following: diabetes, usually with ketoacidosis, hematological malignancies with poor white cell function, and solid organ and bone marrow transplantation with immunosuppression. Altered iron metabolism is a risk factor that may also occur in diabetics.<sup>12,13</sup>

The fungus is saprophytic and invades the orbit from adjacent affected paranasal sinuses. The organism is angiotropic (invades blood vessels) and leads to tissue necrosis. Clinical signs progress rapidly, usually with ophthalmoplegia, proptosis, ptosis, and often a central retinal artery occlusion with optic neuropathy (Fig. 12.14A and B). Necrosis of tissues (eyelids, scalp, palate) can occur as a late sign. Changes on CT or MRI are often deceptively mild (Fig. 12.14C).

The prognosis for patients with mucormycosis is poor, and many die of cerebral involvement. Survival depends on a high index of suspicion, prompt diagnosis by obtaining tissue for histopathological examination (urgent) and culture, reversal of any factors such as ketoacidosis, antifungal agents, and soft tissue debridement, often in the form of orbital exenteration.

#### Orbital Aspergillus Infection

Aspergillus is a widespread, usually harmless saprophyte. Widespread infection in immune-compromised patients will usually present with endophthalmitis. In the orbit, infection with aspergillus may occur in immunocompetent<sup>14</sup> or immunocompromised patients<sup>15</sup> and usually invades from the adjacent sinuses but also may occur as an isolated orbital lesion with indolent onset.<sup>16</sup> Diagnosis requires identification of septate hyphae in tissue specimens. Treatment may require debridement (if possible) and long-term antifungals. Cavernous sinus and cranial involvement may be fatal.

#### Orbital Parasitical Infection

Parasitical orbital infections are rare in the West, but may be common in developing nations. The two principal types are cysticercosis and echinococcosis.

Cysticercosis is a parasitical infection caused by *Cysticercus cellulosae*, the larval form of the pork tapeworm *Taenia solium*. It occurs commonly in areas with poor hygiene. Cerebral cysticercosis is most common, but orbital involvement is not rare. It usually involves extraocular muscle.<sup>17</sup> Successful treatment with albendazole and prednisolone precludes surgery in almost all cases.<sup>17</sup>

Echinococcosis, or hydatid disease, is due to infection with the worm *Echinococcus granulosus*. The infection is widespread in certain parts of the world and primarily affects the liver. The orbit is rarely affected (0.3% of 3736 cases in one report from China).<sup>18</sup> Cysts develop gradually in the orbit in patients, usually with evidence of cysts elsewhere. The main treatment is surgical excision.

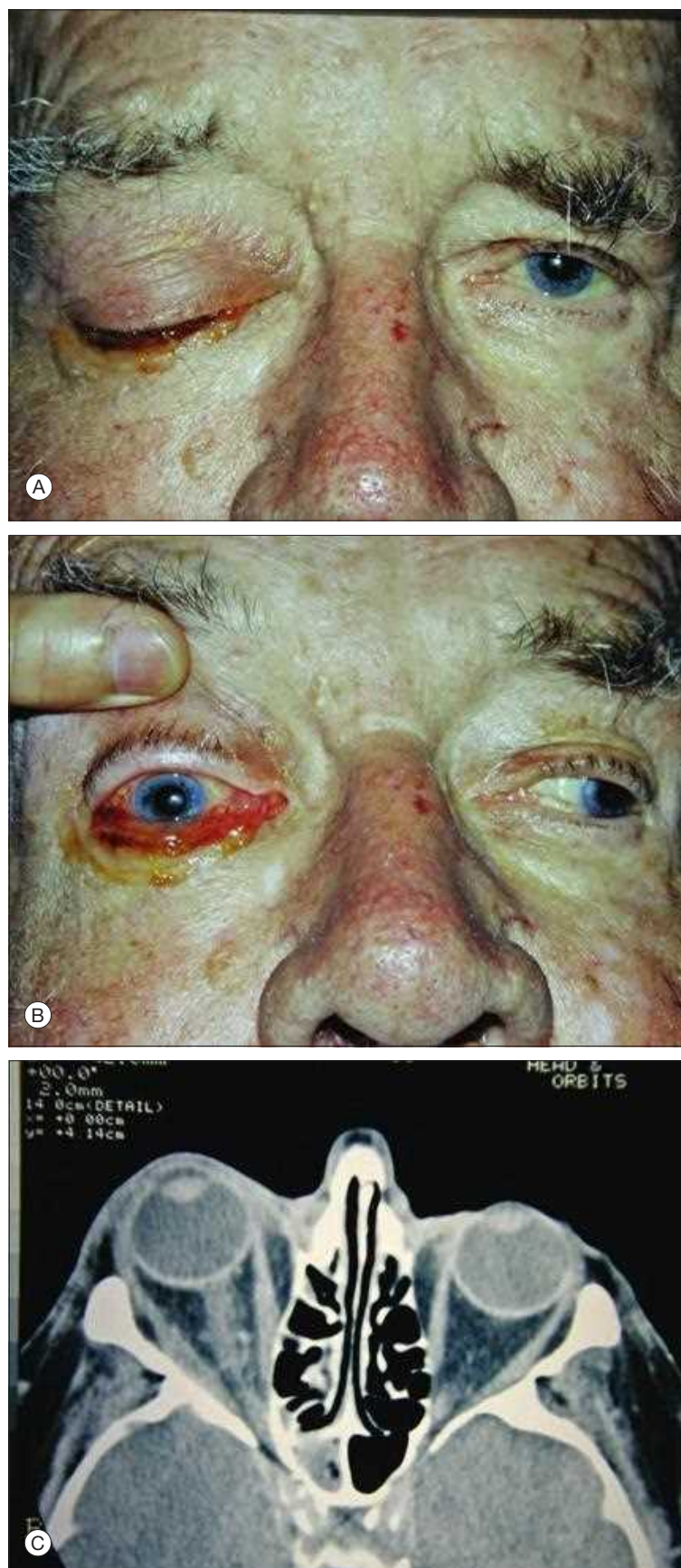
### Noninfectious Orbital Inflammation

Noninfectious orbital inflammation is common. The more common causes are listed in Table 12.14.3. By far the most common, Graves' orbitopathy, is discussed elsewhere (see Chapter 12.13). For many decades the term orbital pseudotumor was used to describe orbital inflammation where no cause could be identified, but the term has been largely supplanted by idiopathic (or nonspecific) orbital inflammation (IOI). This should be reserved for cases where no "specific" cause can be identified. Many "specific" forms of inflammation are just as "idiopathic" as IOI, but there are important pathological and clinical features of specific inflammatory disorders, including involvement of other organs.

Over time, the proportion of patients with orbital inflammation that can be labeled IOI has diminished. The largest recent cause of this reduction has been the recognition of IgG4-related disease.

#### Granulomatous Orbital Inflammation

Granulomatous inflammation is a specific form of inflammation characterized by the formation of granulomas with macrophages or histiocytes. Sarcoidosis is the most common cause of granulomatous inflammation in the orbit. Other causes of granulomatous inflammation such as



**Fig. 12.14.4** (A) and (B). An older man with diabetes presenting with 48 hours of rapidly progressive right proptosis, complete ptosis, and ophthalmoplegia and no perception of light and evidence of a central retinal artery occlusion due to mucormycosis. (C) An axial CT scan shows right proptosis, patchy change within the orbit, and relatively mild changes in the ethmoid and sphenoid sinuses.

**TABLE 12.14.3 Causes of Orbital Inflammation (Noninfectious)**

1. Specific
  - Graves' orbitopathy (not discussed in this chapter)
  - granulomatous
    - sarcoidosis
    - xanthogranulomatous
    - foreign body reaction
  - IgG4-related disease
  - vasculitic
    - granulomatosis with polyangiitis (Wegener's disease)
    - Churg–Strauss syndrome
    - others (giant cell arteritis, polyarteritis nodosa)
  - Sjögren's
  - others (Castleman's disease, Kimura's disease, Rosai–Dorfman disease)
2. Idiopathic orbital inflammation
  - by acuity or pathological process
    - acute
    - subacute
    - chronic
    - sclerosing
  - by anatomical site
    - orbital myositis
    - dacryoadenitis
    - anterior
    - diffuse
    - apical
3. Masquerade syndromes
  - rapid tumor growth (mimicking inflammation)
  - tumor necrosis (causing acute inflammation)

mycobacterial infection (tuberculosis), fungal infection, or foreign bodies must be excluded.

### Sarcoidosis

Uveitis due to sarcoidosis is far more common than orbital sarcoidosis, and strangely, the two are often not seen together. The most common orbital or ocular adnexal site of involvement is the lacrimal gland (42%–63%), which may be unilateral or bilateral,<sup>19–21</sup> (Fig. 12.14.5A–C) followed by the anterior orbit, usually inferiorly (13%–38%), the eyelid (11%–17%), and less commonly the lacrimal sac or optic nerve and sheath.

Angiotensin-converting enzyme levels are not commonly elevated in ocular adnexal sarcoidosis (20% in one series).<sup>20</sup> Concurrent systemic disease is common at presentation (50%),<sup>20</sup> with the diagnosis already known (37%)<sup>21</sup> or found on testing (a further 27%).<sup>21</sup> It may never be found (30%) or develop after some years.<sup>21</sup>

Treatment, if required, is usually with oral or local injection of corticosteroids or corticosteroid sparing agents such as methotrexate. Response rates are good.

### Xanthogranulomatous Disease

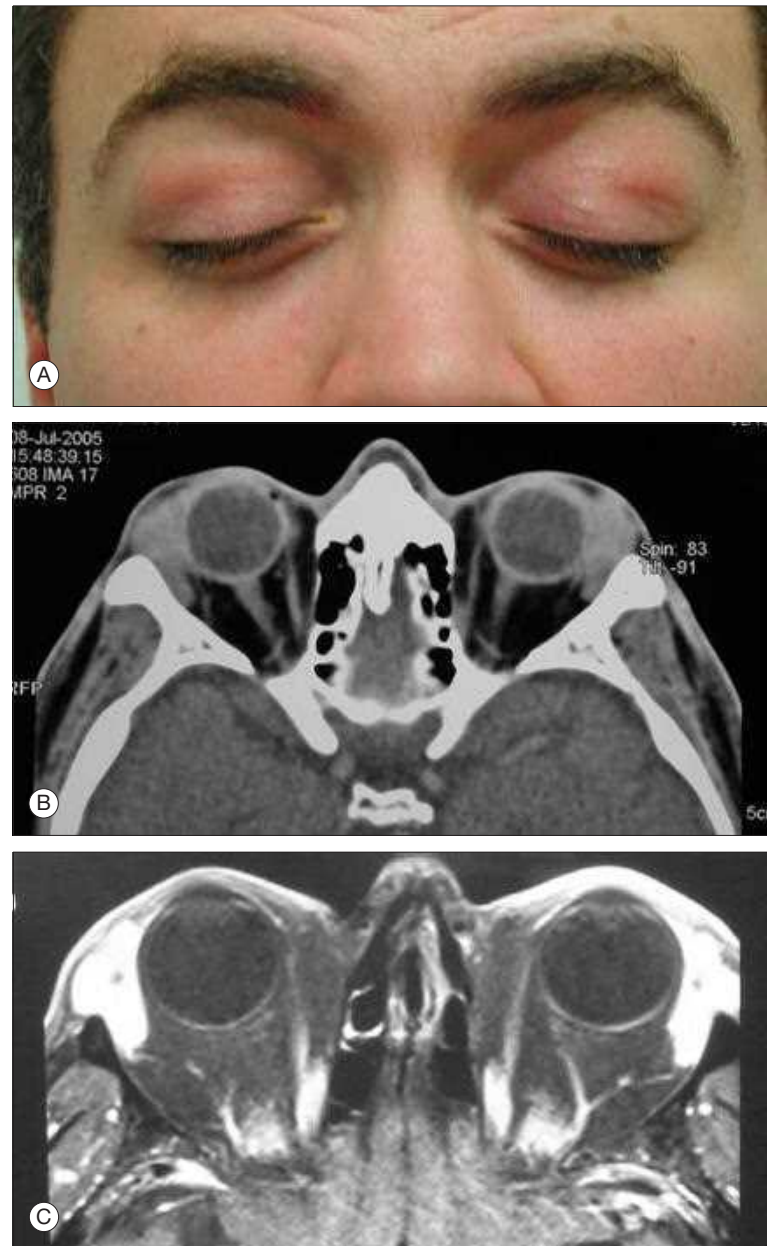
This group of diseases is rare and in adults comprises four entities: adult onset xanthogranuloma (AOX), adult onset asthma and periocular xanthogranuloma (AAPOX), necrobiotic xanthogranuloma (NBX), and Erdheim–Chester disease (ECD).<sup>22</sup> They are non-Langerhans' cell histiocytic disorders and have characteristic foamy macrophages and Touton giant cells present.

AOX, AAPOX, and NBX tend to involve the eyelids and anterior orbit, with swelling, erythema, and yellowish discoloration of tissues (Fig. 12.14.6A–C). AOX and AAPOX are usually bilateral and symmetrical. AOX and AAPOX respond well to rituximab.<sup>23</sup> NBX is often associated with hematological malignancies.

ECD usually involves both posterior orbits symmetrically and widely and is a systemic disease often affecting retroperitoneum, kidney, lung, long bones, pericardium, or meninges and is the only member of this group with an identified gene mutation (in the BRAF gene),<sup>24</sup> making it amenable to treatment with monoclonal antibodies.

### IgG4-Related Disease

IgG4-related disease (IgG4-RD) is a recently recognized entity characterized by tumefactive lesions with dense lymphoplasmacytic infiltration, rich in IgG4-positive plasma cells, fibrosis, usually of a storiform pattern, and in some organs, an obliterative phlebitis. Serum IgG4 levels may be elevated or normal. Large numbers of tissue eosinophils also may be seen.<sup>25</sup> It may affect one or more organs; the orbit and ocular adnexa are frequently involved (IgG4-related ophthalmic disease, IgG4-ROD). Almost any tissue



**Fig. 12.14.5** (A) A middle-aged man with several months of bilateral lacrimal gland enlargement due to sarcoidosis. On imaging, there is bilateral symmetrical enlargement of the lacrimal glands on both an axial CT scan (B) and an axial T1-weighted gadolinium-enhanced MRI (C).

may be affected, but the most common are pancreas, hepatobiliary tract, lymph nodes, and salivary glands.

The most commonly affected orbital tissues are lacrimal gland (Fig. 12.14.7A), orbital fat, extraocular muscle, and infraorbital nerve.<sup>26</sup> Enlargement of the infraorbital nerve by lymphoid hyperplasia is characteristic of this disorder (Fig. 12.14.7B).<sup>27</sup> Disease may be unilateral or bilateral. Bilateral disease is a strong indicator of likely systemic disease.<sup>28</sup>

Patients usually present with a subacute or chronic inflammatory process. Diagnosis requires biopsy and appropriate tissue immunohistochemistry.<sup>25</sup> The presence of IgG4+ plasma cells alone is insufficient for the diagnosis, and these may be seen in a variety of other conditions, especially xanthogranulomatous disease<sup>24</sup> and granulomatosis with polyangiitis.<sup>25</sup> A ratio of IgG4+ to IgG+ plasma cells over 40% may be more important than the actual number.

Treatment is usually with oral corticosteroids, but relapse is common on withdrawal. A variety of corticosteroid-sparing agents have been used, but rituximab is very effective.<sup>29</sup> An increased risk of the development of lymphoma exists with IgG4-RD.<sup>26</sup>

### Orbital Vasculitic Disease

The most common vasculitic disease to affect the orbit is granulomatosis with polyangiitis (GPA, formerly known as Wegener's granulomatosis). Churg–Strauss disease and polyarteritis nodosa rarely affect the orbit.





**Fig. 12.14.6** (A) An older man with unilateral left proptosis and eyelid swelling, lateral conjunctival chemosis, and yellowish discoloration of the eyelids due to adult onset xanthogranulomatous disease. This is usually bilateral. (B) A coronal CT scan from another patient with adult onset asthma and periocular xanthogranuloma (AAPOX) shows bilateral lacrimal gland infiltration with patchy extension into the adjacent soft tissues associated with paranasal sinus disease. (C) An axial CT of the patient in (A). (B) shows extension of the disease process along the lateral wall of the left orbit and extensive sinus disease.

Giant cell (or temporal) arteritis commonly affects the optic nerve but very rarely other orbital tissues.

### Granulomatosis With Polyangiitis

GPA is a granulomatous and sometimes necrotizing vasculitic disease that commonly affects the kidneys and lungs (generalized GPA). Untreated, it is fatal. Up to 60% of patients with generalized GPA will have orbital or adnexal disease.<sup>30</sup> Conversely, many patients present with a more localized form of the disease without systemic involvement.<sup>31,32</sup> In this group of



**Fig. 12.14.7** (A) An axial CT scan of a patient with IgG4-related ophthalmic disease (IgG4-ROD) manifesting as bilateral lacrimal gland enlargement. (B) A coronal CT scan of another patient with IgG4-ROD shows bilateral enlargement of several extraocular muscles, patchy infiltration along the left orbital roof, and enlargement of both infraorbital nerves (the left is larger and indicated by the arrow).

patients, the diagnosis may be difficult because of atypical biopsy findings and a negative c-ANCA.<sup>31,32</sup>

Patients present with orbital mass lesions, often adjacent to the sinuses (Fig. 12.14.8A,B), lacrimal gland disease, and sometimes ocular features such as scleritis, sclerokeratitis, or retinal vasculitis. The presence of nasal and paranasal sinus disease, usually with bone destruction (see Fig. 12.14.8B), is very suggestive of GPA.<sup>33,34</sup> A proportion of patients previously diagnosed with idiopathic orbital inflammation may have limited GPA on the basis of gene expression profiling of biopsies.<sup>35</sup>

Treatment is usually with corticosteroids and cyclophosphamide; more recently, rituximab has been shown to be very effective.

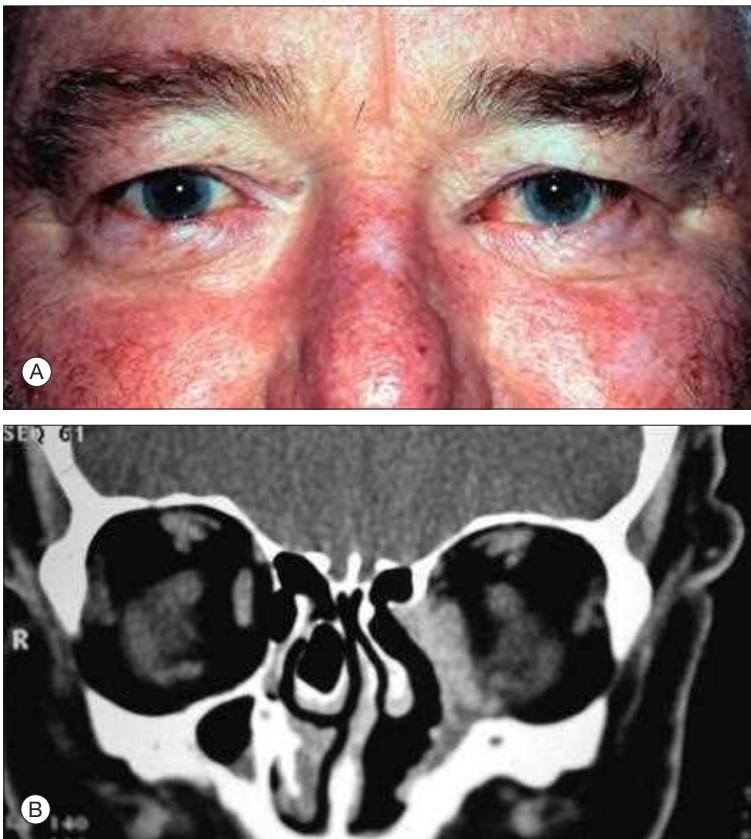
### Sjögren's Syndrome

Primary Sjögren's syndrome (pSS) is a common systemic autoimmune rheumatic disease causing sicca syndrome (dry mouth, nose, and eyes), swollen salivary glands (and sometimes lacrimal glands), and in some patients, joint, skin, lung, and other disease.<sup>36</sup> Depending on the duration of the disease, the lacrimal glands may be swollen,<sup>37</sup> normal in size, or atrophic. Diagnosis can be difficult and relies on serology (anti Ro and La autoantibodies) and labial salivary gland biopsies. Dry eye is usual but non-specific. Many cases previously diagnosed as "atypical Sjögren's syndrome" (negative serology) were probably IgG4-RD.

Sjögren's syndrome carries an increased risk of the development of non-Hodgkin's lymphoma,<sup>38</sup> and enlarged lacrimal glands in these patients should be biopsied to exclude lymphoma.

### Idiopathic Orbital Inflammation

IOI is a diagnosis of exclusion. More specific forms of inflammation (as described earlier) should be excluded, and tissue biopsy is the best way of doing this. However, where the presentation is sufficiently typical, or the risk of biopsy is high, a diagnosis of IOI may be made on the basis



**Fig. 12.14.8** (A) A 65-year-old man with several years of progressive diplopia, left epiphora, and a sunken appearance at the left medial canthus with a hard medial palpable mass. (B) A coronal CT scan shows a mass in the medial orbit involving the medial rectus muscle and the lacrimal drainage apparatus. There is loss of bone in the medial orbital wall and adjacent turbinates and ethmoid sinuses. He has a limited form of granulomatosis with polyangiitis, and is ANCA negative.

of clinical presentation and imaging without biopsy. Examples are typical orbital myositis and orbital apex IOI (Tolosa–Hunt syndrome).

Pain and periorbital swelling are the most common features.<sup>39</sup> The majority will respond to a slow tapering course of oral corticosteroids, but relapses or incomplete responses are common.<sup>39</sup> IOI may be acute, sub-acute, chronic, or sclerosing, the latter being a distinct clinicopathological entity,<sup>40,41</sup> although IgG4-ROD and GPA need to be excluded in this group. IOI can affect any orbital tissue, but there are several recognized anatomical patterns (see Table 12.14.3).

### Idiopathic Orbital Myositis

Idiopathic orbital myositis typically presents acutely with painful diplopia, a single extraocular muscle (EOM) involved, and rapid response to oral corticosteroids, usually in 1 mg/kg doses tapering over several weeks.<sup>42–44</sup> The involved muscle usually shows fusiform enlargement and involvement of the tendon. Other forms of inflammation of the EOMs should be excluded (IgG4-RD and other autoimmune conditions such as Crohn's disease), usually on the basis of a history of other disease and other organ or orbital tissue involvement.

Relapse after withdrawal of corticosteroids is common (56% in one series).<sup>42</sup> Repeat treatment with corticosteroids or corticosteroid-sparing agents may be required, but if the course is atypical, a biopsy should be obtained.

### Idiopathic Dacryoadenitis

Idiopathic dacryoadenitis is a diagnosis of exclusion and should be diagnosed only with a biopsy and appropriate investigations to exclude other conditions such as sarcoidosis, Sjögren's syndrome, IgG4-ROD, GPA, or lymphoma.

Idiopathic dacryoadenitis is more commonly unilateral, and inflammation may extend to adjacent fat and EOM. Incomplete response to treatment is associated with male gender and EOM involvement, and recurrence is more common in bilateral disease.<sup>45</sup>

### Tolosa–Hunt Syndrome (Orbital Apex IOI)

IOI of the orbital apex and superior orbital fissure is rare. It presents with pain, double vision, and sometimes sensory loss of the face and optic neuropathy.<sup>46</sup> Again, it is a diagnosis of exclusion.

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## Cosmetic Blepharoplasty and Browplasty

12.15

François Codère, Nancy Tucker, Jonathan J. Dutton

**Definition:** Surgeries to correct changes in the eyelids and forehead area that are secondary to aging and manifest by redundancy and displacement of tissues.

## Key Features

- Facial aging results in bone remodeling with changes in soft tissue draping and midface fat atrophy.
- Any aesthetic eyelid or brow surgery must evaluate the patient's complaints and goals.
- Detailed examination is mandatory to uncover specific anatomical abnormalities that need to be addressed.
- When brow and eyelid surgery are planned, the brow should be elevated first to avoid removing too much upper eyelid skin.

## INTRODUCTION

Aging changes in the face involve progressive remodeling of the facial skeleton with bone projection in the forehead and brows and facial regression in the mid and lower face. Loss of collagen and elastin in the various layers of the skin and subcutaneous tissues is seen in the eyelids and midface. Changes that occur in the upper eyelid skin are compounded due to passive stretching, loss of support, or redundancy of skin secondary to lowering of the brows.

Most patients do not appreciate the extent to which brow malposition contributes to the overall appearance of the aging periorbital area. This needs to be pointed out specifically to help them understand why a blepharoplasty alone often will not fully correct the problem. If a manual lift of the brow to the desired position significantly improves the patient's appearance, a browplasty—either alone or combined with blepharoplasty—should be considered. If a blepharoplasty is performed without recognizing any associated brow ptosis, the lateral eyebrow can appear pulled down, which produces an undesirable sad appearance.

## ANATOMICAL CONSIDERATIONS

## Eyelids

Key anatomical features that cause excess upper eyelid skin include brow ptosis from the loss of forehead deep tissue support, loss of the deep invagination of the eyelid skin in the principal lid crease as a result of anterior displacement of the suborbicularis fat pads, and stretching of attachments between the levator aponeurosis and the skin. For the sake of understanding the anatomy, the lid may be divided arbitrarily into two distinct portions (Fig. 12.15.1).

## Upper Eyelid

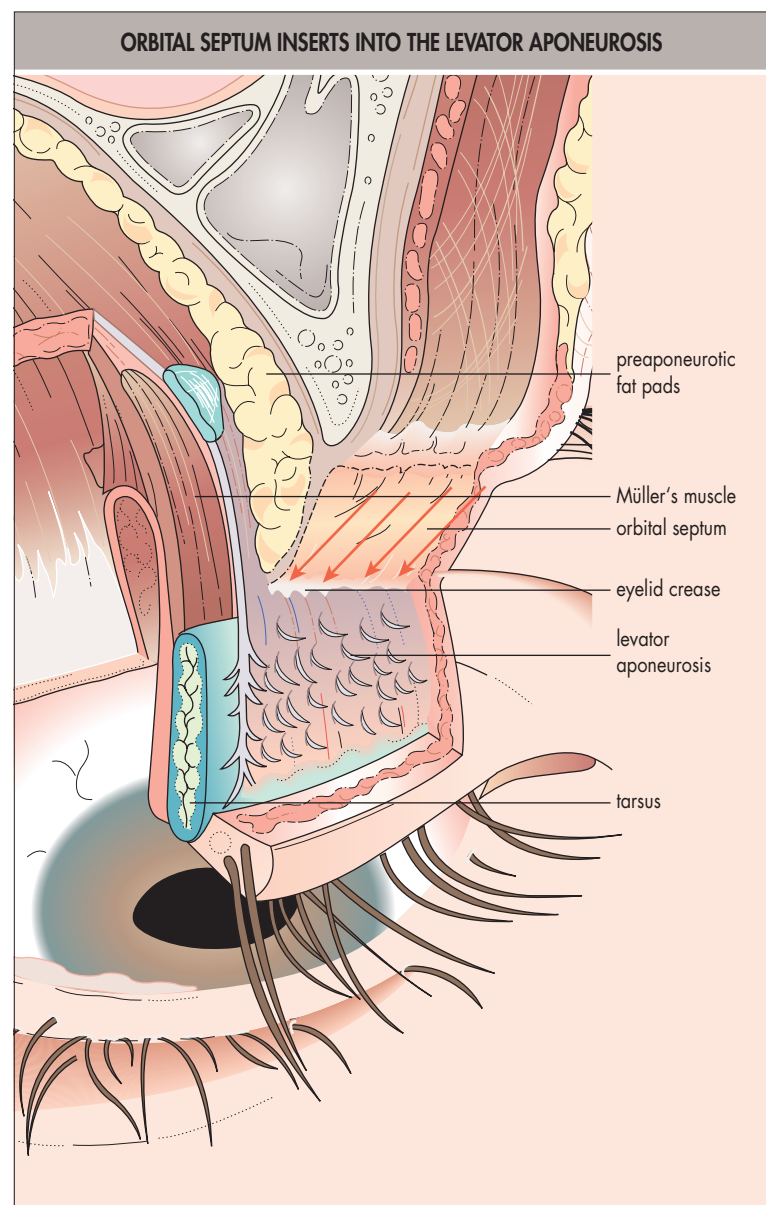
Anatomy of the upper eyelid is discussed in Chapter 12.1. The eyelid crease is an important anatomical and aesthetic landmark. The skin and muscle between the crease and the brow form the eyelid skin fold. If upper lid fat recedes or the levator aponeurosis becomes stretched or disinserted, the crease assumes a higher position. In the Asian eyelid, the crease (if present) is lower because of the low insertion of the orbital septum into the aponeurosis with consequent descent of the preaponeurotic fat pockets.<sup>1</sup>

When the eyelid opens, the lid crease skin is pulled upward and backward by the aponeurosis as it retracts under the fat pad (Fig. 12.15.2).<sup>2</sup> The

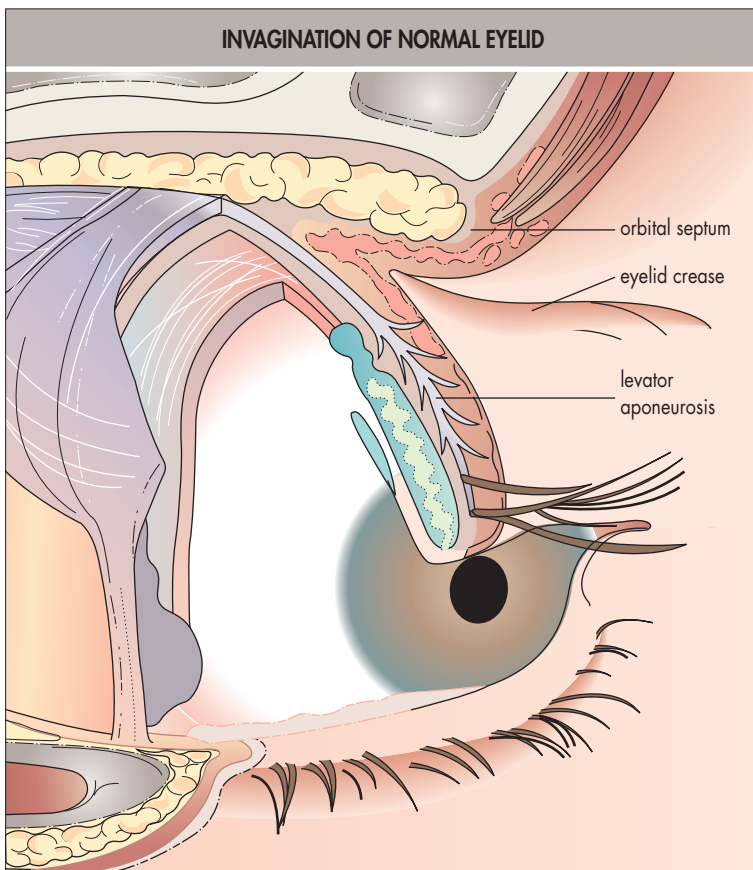
eyelid fold then bulges slightly as this fat pushes the skin forward. During downgaze, tension in the aponeurosis becomes lax, resulting in a weakened or absent lid crease.

## Lower Eyelid

The lower eyelid has a similar but simpler anatomy and is reviewed in Chapter 12.1. Integrity of the medial and lateral canthal tendons is very important to maintain a proper lid position, especially in the aging face.<sup>3</sup> However, the bony configuration of the midface also plays a key role. Because the lower eyelid is less mobile than the upper, less redundancy



**Fig. 12.15.1 The Orbital Septum Inserts Into the Levator Aponeurosis (Arrows).** The preaponeurotic fat pads are located posterior to the septum. In downgaze the lid crease becomes attenuated (weakened), and in a normal young eyelid the fold is absent. (Adapted with permission from Zide BW, Jelks BW. Surgical anatomy of the orbit. New York: Raven Press; 1985 [chapter 4]. p. 23.)



**Fig. 12.15.2** The Invagination of the Normal Eyelid Crease Is Created by the Posterior Pull on the Septal Insertion by the Elevating Levator Aponeurosis. The preaponeurotic fat is also retracted by the septum. The flat portion of the lid under the crease slips inside the upper preseptal portion. (Adapted with permission from Zide BW, Jellus BW. *Surgical anatomy of the orbit*. New York: Raven Press; 1985 [chapter 4]. p. 23.)

of the skin and muscle occurs. The major aging changes include sagging of skin, deepening of wrinkles, descent of the lateral canthus from loss of bony support, and atrophy of subcutaneous fat.

## Brows

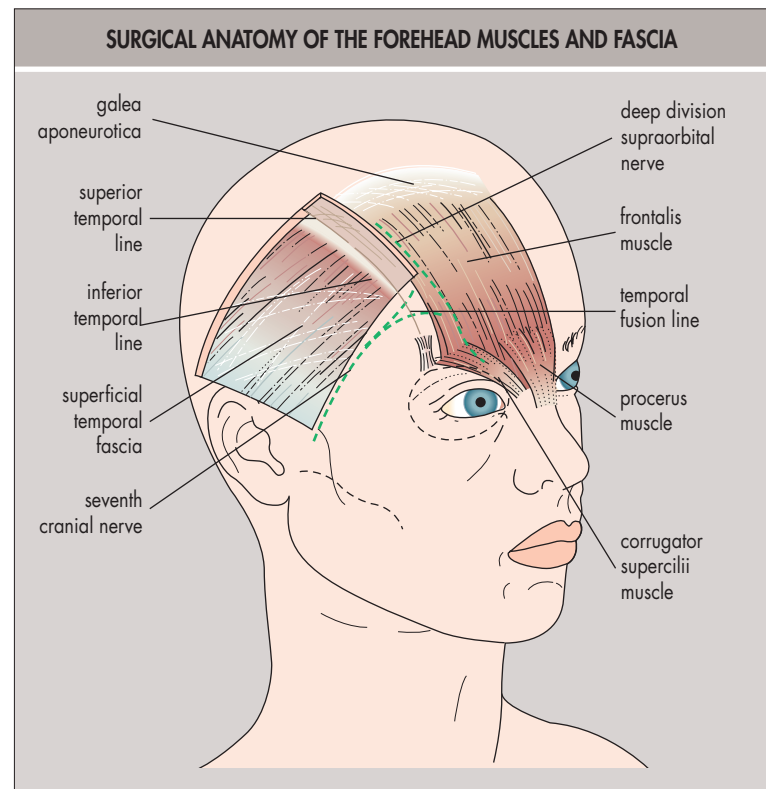
A thorough understanding of the forehead anatomy is essential to evaluate brow ptosis (Fig. 12.15.3).<sup>4</sup> The layers in the midforehead are skin, dermis, superficial galea, frontalis muscle, deep galea, and periosteum. The forehead skin is much thicker than the eyelid skin. The dermis and subcutaneous fat are connected to the underlying frontalis muscle by multiple fibrous septa. The paired frontalis muscles originate just anterior to the coronal suture line. A smooth fibrous sheath, the galea aponeurotica, envelops the frontalis to form both superficial and deep galeal layers.

Laterally, the frontalis muscle ends and does not extend beneath the lateral third of the brow. Here the superficial galea, the superficial temporal fascia, and the periosteum of the frontal bone fuse. The confluence of these tissue planes is called the “zone of fixation.” The eyebrow fat pad (subgaleal fat pad) is a transverse band of fibroadipose tissue 2–2.5 cm above the orbital rim. It allows movement of the frontalis muscle in the lower forehead.

Medially, the procerus muscle is continuous with the medial portion of the frontalis muscle and inserts into the nasal bone and glabellar subcutaneous tissue. It causes horizontal wrinkles of the glabella.<sup>5</sup> The corrugator supercilii muscle is obliquely oriented, passing from the subcutaneous brow to the frontal bone medially. It causes vertical glabellar furrows.<sup>6,7</sup>

Several important neurovascular structures occur in the forehead. The frontal branch of the facial nerve lies within the superficial temporal fascia before entering the deep surface of the frontalis muscle. Several nerves are found along the superior orbital rim: the lacrimal nerve laterally, the supraorbital nerve with its deep and superficial divisions centrally, and the supratrochlear nerve more nasally.

Several factors contribute to the appearance of the aging forehead and brow. These include changes in the quality of the skin, loss of tissue support, and horizontal forehead and glabellar furrows related to action



**Fig. 12.15.3** Surgical Anatomy of the Forehead Muscles and Fascia.

of the underlying facial muscles.<sup>8,9</sup> The lateral eyebrow segment is more prone to becoming ptotic because of less structural support in this area. The final brow position depends on the dynamics between the frontalis muscle pulling the brow up and the descending temporal soft tissue and lateral orbicularis muscle dragging it down.<sup>7</sup>

## BLEPHAROPLASTY

### Preoperative Evaluation and Diagnostic Approach

#### History and Psychological Evaluation

When evaluating patients who seek cosmetic improvement of the periorbital area, the surgeon should understand the patients' motives for undergoing surgery and the decision-making process they have undertaken. Asking patients what they expect the surgery will change for them can sometimes reveal unexpected motives or unrealistic expectations. The psychological screening should include a medical and surgical history with specific questions about previous cosmetic surgery. Outcomes of previous surgeries might give a clue to unrealistic expectations, especially if the objective results of these previous surgeries are not in harmony with the patient's perception. Previous mental illness should alert the surgeon—a psychiatric consultation is sometimes useful.

In assessing expectations, the surgeon can help by carefully discussing the surgery and explaining the improvements to be expected. It is important to detail the cosmetic defects that cannot be changed by surgery and establish a realistic plan for facial rejuvenation.<sup>10</sup>

The patient is asked to consider carefully the decision to undergo surgery and, if one is sought, should be encouraged to obtain a second opinion. Establishing a relationship of trust is of paramount importance. If in any doubt, even for unclear objective reasons, a conservative attitude is recommended.

#### Physical Examination

The position and shape of the different periorbital structures are evaluated along with the quality of the skin.<sup>5,11</sup> In the forehead area, the level and shape of the hairline, the quality of skin of the forehead, and the position and shape of the brows are evaluated with specific attention to detecting brow asymmetry. The muscular layer is judged by looking at the frown lines in the forehead and glabellar area and by asking the patient to relax the forehead. The bony orbit is then evaluated, especially laterally at the orbital rim, where some prominence can mimic lacrimal gland prolapse. This is a good time to evaluate the position of the globe in relation to the

## WORKSHEET TO DOCUMENT PHYSICAL FINDINGS AND SURGICAL PLAN

**Physical Findings:**

- Brow ptosis:
- Corrugator?: ☐
- Procerus?: ☐
- Exophthalmos?: ☐
- Lid retraction?: ☐
- Type lift -
- Skin resection:
- Upper- (right)
- Aperture deformities?: ☐
- Tone:
- Fat:
- Festoons or Malar bags:
- Tear troughs:
- Thickness:  mm
- Epicanthal folds?:
- Malar complex:
- Hollow?: ☐
- Transpose fat?: ☐
- Retraction?: ☐
- Ptosis?: ☐
- Skin (Left)
- Type
- Canthopexy resection: ☐
- Skin
- Muscle
- Type flap skin, skin and muscle, tarsus conjunctiva:
- Orbital rims?: ☐
- Encroaching: ☐
- Anterolateral: ☐
- Corrugator insertion: ☐
- Hemioxophthalmos?: ☐

**Surgical plan:**

- Coronal.....
- Corrugator.....
- Procerus.....
- Incision location.....
- Orbital rims.....
- Forehead excision.....
- Upper blepharoplasty.....
- Medial epicanthoplasties.....
- Transconjunctival fat.....
- Low skin excision.....
- Canthopexy.....
- Tear trough implants.....
- Malar implants.....

**Fig. 12.15.4 A Sample Worksheet to Document the Physical Findings and Surgical Plan.** (Adapted with permission from Flowers RS, Flowers SS. Precision planning in blepharoplasty. Clin Plast Surg 1993;20:303-10.)

bony orbit, as this is an important determinant of the type of lid fold to aim for. A fuller orbit with a large eye leads to a convex upper eyelid above the crease, whereas a large orbit with a small eye results in a more concave upper lid above the crease. A prominent globe with recessed zygoma often leads to lower lid malposition.

For the eyelids, precise measurements of the eyelid vertical and horizontal apertures should be recorded, noting the high point of the upper lid both from the lower lid and from the mid pupil. The general shape of the palpebral fissure is noted. The position of the lid crease and upper eyelid skin fold should be documented. The amount of fat to be removed in all fat pad areas is estimated, and any prolapse of the lacrimal glands is noted. In the lower lids the fat pads are carefully assessed, with any areas of prolapse noted. The inferior periorbital area over the upper cheek is evaluated in a similar fashion. The quality of the skin is important, and cicatricial changes from dermatological conditions or chronic sun exposure can make the lid more susceptible to malposition after surgery. The cheek is examined for the presence of festoons, noting whether they consist of only skin and orbicularis muscle or also of suborbicularis fascia and/or orbital fat.<sup>12</sup> The lower lid is assessed with the distraction test by pulling the central lower lid margin away from the eye. A distance of more than 6 mm is considered abnormal and may require a lift tightening. The position of the lateral canthus is noted and normally is 1-2 mm higher than the medial canthus. As an aging phenomenon, the lateral canthus is often lower. Laxity of the canthal tendons is noted and if present is manually tightened with the finger before estimating the amount of skin to be removed. The nasojugal area should be examined to detect tear trough deformities, which may need correction instead of fat pad removal.<sup>13</sup>

The use of a flow sheet to outline systematically the physical findings is an excellent way to plan present and future surgery. Surgical planning must take into account the patient's desires, what he or she is willing to undergo, and what the surgeon thinks is reasonable and safe. Fig. 12.15.4 gives an overview of the patient consultation evaluation for blepharoplasty and correction of any brow malposition. A good set of photographs should carefully document the changes noted and must be kept as part of the patient's medical record.

## Anesthesia

Local infiltrative anesthesia containing epinephrine for hemostasis is adequate for all blepharoplasty procedures. Some surgeons prefer a supraorbital and supratrochlear nerve block.

## General Techniques

Draping should be done carefully to avoid distortion of the brow and lateral canthi and to allow the patient to sit up, if necessary, during the operation. The amount of skin to be removed is marked before infiltration of anesthetic, which will distort the tissues. In the upper eyelid, excessive removal of thin lid skin may result in a dragging down of thick brow skin and should not be substituted for first repositioning the brows. In the lower lids the same principle applies: The lid should be repositioned and the scleral show corrected with appropriate lateral canthal surgery before any skin is removed.

## Specific Techniques

### Upper Lid Blepharoplasty

Before upper eyelid blepharoplasty is begun, the brow should be repositioned as needed, especially lateral brow droop. A proposed skin incision is marked in the existing eyelid crease, or if there is no visible crease, the line is marked about 8-10 mm above the lash line, taking into account the racial background of the patient. The crease marking usually goes from a point above the superior punctum to—but not beyond—the lateral orbital rim. Skin excess is evaluated by placing one arm of a forceps on the crease incision line and pinching the redundant skin within the opposite arm so that in downgaze the skin is tight without lagophthalmos. In general, 20-24 mm of skin should be left between the brow and the lid margin to prevent postoperative lagophthalmos.<sup>14</sup> The long-taught rule that the eyes should not close on the operating table has certainly become obsolete. Excessive skin removal medially may result in hood formation. If disproportionate tissue is still present in this region after surgery, a glabellar lift can be considered. An optional small triangular flap of skin can be added to the usual skin pattern medially to minimize folding of the skin at the time of closure in patients with excess of skin medially (Fig. 12.15.5).

The lid is placed under downward traction, and a Bard-Parker No. 15 blade is used to incise the skin. The skin flap is removed with a blade or scissors, leaving the orbicularis muscle intact at this stage.

Gentle pressure on the globe will prolapse the orbital fat pockets that bulge behind the orbicularis muscle and orbital septum. The fat is exposed by a small buttonhole that is made centrally through the orbicularis and the septum above its insertion on the aponeurosis. The septum is opened laterally and medially from this buttonhole (Fig. 12.15.6). Each fat pad



capsule is opened. The fat is gently prolapsed and transected. The section line is cauterized with a bipolar cautery (see Fig. 12.15.6).

The orbicularis muscle is thinned, but some surgeons prefer to remove it completely along with the overlying skin. The aponeurosis is exposed above the tarsal border. Invagination of the skin by fixing the skin edge to the aponeurosis at the time of closure ensures a good position of the crease in fuller lids but is not always necessary. The orbicularis can be tacked down to the aponeurosis immediately under the upper skin edge using two or three 6-0 plain sutures. This defines the position of the eyelid crease and controls the position of the fat pad in the lid (Fig. 12.15.7). The skin is closed with a running 6-0 nylon or 6-0 plain gut suture. The area beyond the lateral canthal angle is closed with interrupted sutures to obtain an edge-to-edge closure without folds (Fig. 12.15.8).

### Lower Lid Blepharoplasty

Two specific techniques are popular for lower lid blepharoplasty.<sup>15</sup> The skin approach allows modification of the interaction between the muscle and the skin planes and makes lid tightening or canthal repositioning easier. When only fat prolapse is present, the transconjunctival approach allows surgical access without a visible scar and avoids the risk of lid malposition.

### Skin Approach

In the skin approach, the skin is marked 3 mm below the lash line from the inferior punctum to the lateral canthal angle. If excess skin is to be

removed or if the orbicularis muscle is to be tightened, the incision is extended laterally and downward toward the earlobe for a short distance.

The skin and orbicularis muscle are incised with a No. 15 blade. Scissor dissection exposes the suborbicularis plane and the anterior surface of the orbital septum. The septum is easily identified with a gentle push on the globe to prolapse the fat and is opened with scissors. The temporal and central fat pads are one continuous pad separated by a vertical band of fascial connections between the capsulopalpebral fascia and the orbital septum.<sup>3</sup> The capsule of each fat pad is opened. Care is taken to tease the fat out of the respective pockets without undue traction in order to avoid deep bleeding in the orbit. In the medial lid the fat capsule is opened separately; care must be taken to protect the inferior oblique muscle, which lies between the medial and central fat pockets. The fat is carefully examined for bleeders before it is allowed to retract into the orbit. In some cases, repositioning of the lower eyelid orbital fat into the suborbicularis oculi fat (SOOF) plane is another useful procedure to fill in a tear trough deformity.<sup>16</sup>

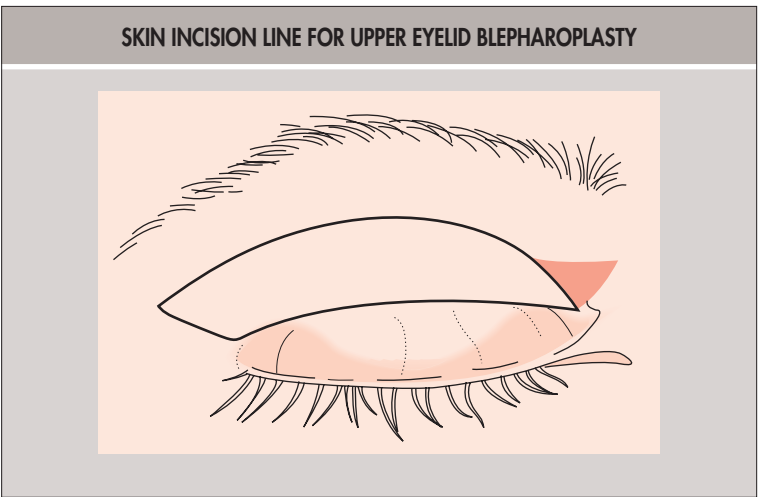
A canthopexy can be used to lift a sagging lateral canthal angle through placement of a suture through the lateral canthal tendon that is attached to periosteum.<sup>17</sup> If horizontal lid laxity is present, a tarsal strip procedure can be performed (see Chapter 12.6).<sup>18</sup> A small triangle of skin and orbicularis muscle may be excised laterally to prevent a dog-ear. Closure of the orbicularis as a sliding flap often helps to rejuvenate an older lid. Hemostasis is attained carefully before the skin is closed with a continuous suture of 6-0 nylon or 6-0 plain gut.

### Transconjunctival Approach

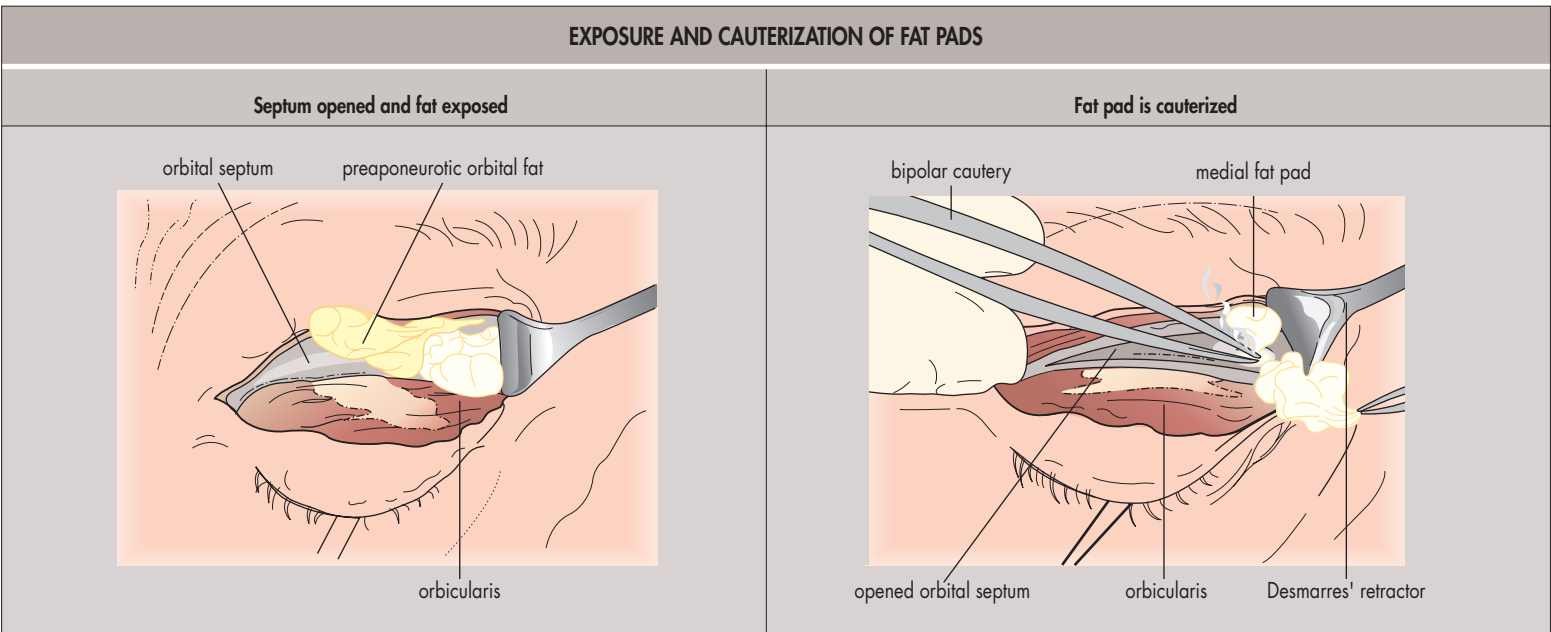
With the transconjunctival approach, the lid is everted over a Desmarres retractor. The retractor is used to pull the lid toward the cheek to expose the conjunctiva and fat pads. The lateral fat pad is often the most difficult to expose—a buttonhole through the conjunctiva laterally about 4 mm from the inferior tarsal border can be helpful. The fat is prolapsed through the defect, cauterized at the base, and carefully cut with fine scissors. This approach allows early identification of the lateral fat pad before any bleeding occurs. The conjunctival incision then can be extended medially to expose the central and medial pads, which are removed in the same way. Closure of the conjunctiva is completed with a few 6-0 plain catgut sutures.

### Other Surgical Techniques

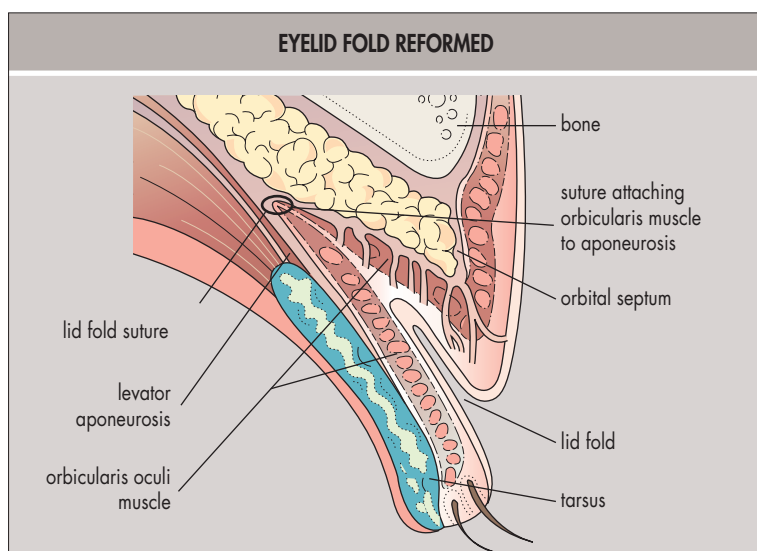
Specific techniques should be used when operating on Asian eyelids—the goals determine the technique to be used.<sup>19</sup> In general, the skin incision is made lower toward the lid margin, depending on the desired position of the resulting crease.<sup>20</sup> Some preaponeurotic fat should be left to act as a barrier between the levator and the skin if the Asian-type lid is to be preserved. Other minimally invasive adjuncts can be added to upper lid



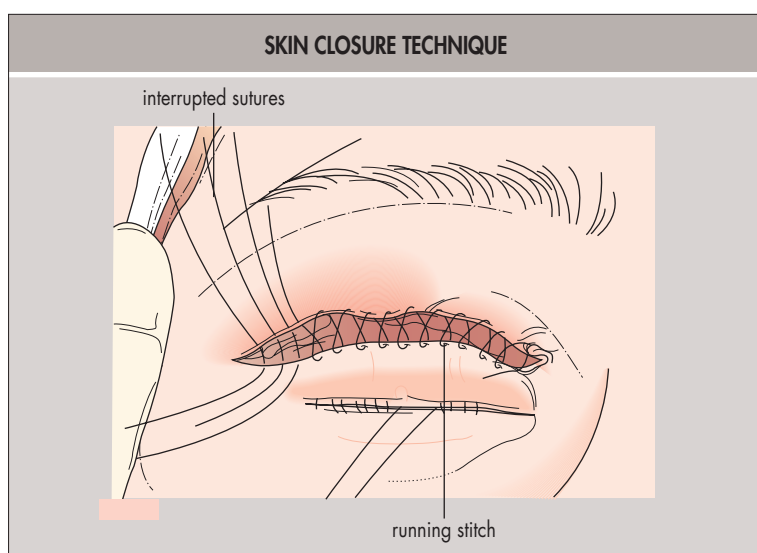
**Fig. 12.15.5 Typical Skin Incision Line Used for Upper Eyelid Blepharoplasty.** A small additional medial flap is added (shaded area) if a dog-ear or fold develops because of excessive skin nasally.



**Fig. 12.15.6 Exposure and Cauterization of Fat Pads.** Preaponeurotic fat pads are a key landmark just anterior to the aponeurosis. The orbital septum is opened to expose the fat, and each pad is carefully cauterized along its base before being cut with scissors.



**Fig. 12.15.7** The Eyelid Fold or Crease Is Reformed by Passing Several Sutures From the Orbicularis Muscle to the Aponeurosis at the Appropriate Height.



**Fig. 12.15.8** The Skin Is Closed With Two to Three Interrupted Sutures Laterally, Where the Skin Is Thicker, and With a Running Suture Along the Remainder of the Wound.

blepharoplasty to enhance the surgical results and patient satisfaction. These include internal browpexy, fat redistribution, and lacrimal gland repositioning.<sup>21</sup>

## Postoperative Care

A medium-pressure bandage is applied to the lids with an appropriate antibiotic ointment. The patient can remove the patches soon after surgery and start applying cold packs to the surgical site for 20 minutes each hour during the first evening and then four or five times the next day. Light analgesia for blepharoplasty is usually sufficient. Severe pain is not expected and warrants immediate examination to rule out orbital hemorrhage, infection, or corneal abrasion. The sutures on the skin can be removed 5–7 days postoperatively if 6–0 nylon is used.

## Complications

Blepharoplasty is one of most common operations performed and the least invasive cosmetic procedure. Nevertheless, devastating complications can occur, including blindness. Most complications result from unrecognized anatomical abnormalities or from errors in measurement or excessive removal of tissue.<sup>22</sup>

Complications of blepharoplasty are of two orders. One group of complications can occur from events unrelated to the technique used; a second group can occur following improper surgery for particular deformities. For

example, despite the best surgical technique, infection will occur in a small number of patients; the same is true of milia formation along a scar line. Lower lid ectropion or canthal angle rounding in the lower eyelid is usually the result of improper surgical planning or techniques.

## Orbital Hemorrhage and Blindness

Orbital hemorrhage following blepharoplasty is an emergency. It has been associated with permanent loss of vision in some cases, especially if the lower eyelid is involved.<sup>14,23,24</sup> Prevention involves careful preoperative screening for the use of anticoagulants, including aspirin. Meticulous hemostasis, gentle manipulation of fat during surgery, and good control of blood pressure postoperatively are important. Early removal of patches and application of cold packs will minimize swelling. Strenuous activities should be avoided for the first 3–4 days. Anticoagulants should not be restarted for at least 5–6 days after surgery. The surgeon and medical staff should be alerted by unusual pain, swelling under tension, or double or blurred vision. If in doubt, the patient must be seen immediately for an assessment of visual acuity and pupillary response. In the presence of a deep hematoma the patient should be admitted for close monitoring of optic nerve function. If optic nerve dysfunction appears, the wounds are opened and the blood is evacuated. A lateral cantholysis helps decompress the soft tissues of the orbit, but with a deep hemorrhage, an orbital exploration may be required.

## Infections

Fortunately, the eyelids are well vascularized so that infections after blepharoplasty are rare. Patients should be aware that an increase in swelling with redness and pain might be the first sign of infection. If it is confirmed by examination, appropriate cultures and sensitivities should be obtained and the patient started immediately on wide-spectrum systemic antibiotics. Close follow-up to rule out abscess formation in the orbit is necessary in severe cases, and proper orbital imaging should be obtained. Blindness is a rare complication of infection, but it has occurred following blepharoplasty.<sup>25</sup>

## Ptosis

Ptosis may be present but unrecognized on initial preoperative examination in patients with severe skin excess. Palpebral fissures should be evaluated along with the levator action as if all patients were consulting for ptosis (see Chapter 12.4). If present, ptosis should be corrected by advancing the levator aponeurosis on the tarsal surface. Otherwise, at the time of blepharoplasty, care should be taken not to damage the aponeurosis. If impending ptosis is present and the lid crease is reconstructed by supratarsal fixation, a slight tightening of the aponeurosis may be wise. When ptosis appears after surgery, conservative observation for 6 months is recommended. If it persists, surgical correction may be necessary.

## Lagophthalmos, Lower Lid Retraction, Ectropion, and Lateral Canthal Deformities

If excessive skin has been removed in the upper lid, resulting in lagophthalmos, time is often of help; the brows continue their downward drift and the lagophthalmos often progressively decreases. Massage and ocular lubricants in the first few months after surgery may bring the patient out of this difficult phase. But if keratitis ensues and threatens the integrity of the eye, surgical correction should be done. In the lower lid, gravity works against spontaneous improvement. Frank ectropion might resolve with massage but almost invariably leaves lower scleral show. Using the transconjunctival approach when minimal or no skin excess is present, tightening the lateral canthal tendon if necessary, and avoiding excessive skin removal are the best ways to prevent this complication.<sup>26</sup> Revision using a lateral tarsal strip procedure combined with a disinsertion of the lower eyelid retractors can give satisfactory results in mild cases. A midfacial lift or a skin graft may become necessary with more severe deformities.<sup>27–31</sup>

## Other Complications

Tearing after blepharoplasty can be a complex problem, especially if lagophthalmos is present. Investigation of this complication should include a full lacrimal workup with assessment of the reflex component if keratitis is present. The integrity of the canaliculi and the position of the lid margin and puncta are all evaluated before correction is planned (see Chapter 12.13). Injury to the extraocular muscles can occur, especially in the lower lid where the inferior oblique and inferior rectus are prone to damage with

exploration of the medial fat pad.<sup>32</sup> The superior oblique tendon can also be damaged in upper lid surgery.<sup>33</sup> In these instances, a follow-up of at least 6 months is necessary before surgical interventions are considered, as spontaneous resolution is fortunately the rule.

## Outcome

Most patients who seek cosmetic eyelid or brow surgery expect some improvement in their appearance and in their self-image and are usually happy with the result. Some, in whom the anatomical deformity interferes with visual function (as in severe overhanging dermatochalasis), can also notice improvement in their visual field. Patients who enter into surgery with unrealistic goals, either physical or social, are more at risk of not being satisfied with the results.

## BROW MALPOSITION

### Preoperative Evaluation and Diagnostic Approach

The ideal brow position and shape are subjective, but in general the brow is straighter and at the superior orbital rim in a man and more curved and slightly above the rim in a woman. An evaluation of the most cosmetically pleasing brows in women suggests that the medial eyebrow should be positioned at or below the supraorbital rim, with the eyebrow shape having an apex lateral slant.<sup>34</sup>

The clinical evaluation should include brow position (estimated by the difference between the actual resting brow position and the desired position), the amount of excess forehead skin and degree of furrowing, the hairline position, and the length of the forehead. The length of the forehead can be determined by passing imaginary horizontal lines through the hairline, the upper border of the eyebrows, and directly below the nose. These lines divide the balanced face into three equal portions. An increase or reduction of the upper segment is an important factor when selecting the incision site using the coronal approach.<sup>35</sup> The extent to which the procerus and corrugator muscles contribute to furrowing of the forehead should be determined. A family history of male pattern baldness should be sought. It is important to determine how extensive a surgery the patient is willing to undergo to achieve the best results. Often the final surgical choice is a compromise between the most effective technique and the least invasive procedure.<sup>36</sup>

## Anesthesia

Anesthesia is provided by supraorbital and supratrochlear regional blocks along with direct local infiltration, depending on the extent of anesthesia desired for each of the various techniques. In selected patients, general anesthesia may be considered. Gentle but constant pressure minimizes the formation of hematomas that can distort anatomy.

## General Techniques

Surgical approaches to the correction of brow ptosis include the direct, midfrontal, and endoscopic brow lift; transblepharoplasty fixation; and the bicoronal brow lift (Fig. 12.15.9). The choice of technique depends on the amount of correction required and on the patient's expectations.<sup>37</sup>

## Specific Techniques

### The Bicoronal Forehead Lift

The bicoronal forehead lift allows the maximal effect of brow elevation with a well-camouflaged incision site.<sup>38</sup> It is ideally suited for patients with significant brow ptosis, without frontal baldness, and with a normal to low hairline.

The incision is hidden posterior to the hairline (posttrichion). Alternatively, in patients who have a high forehead, the incision can be placed at the hairline (pretrichion) to avoid further elevating the hairline. There are two major choices for the surgical dissection plane: subcutaneous and subgaleal.<sup>35</sup> Factors that influence the choice of dissection plane include the quality and elasticity of the skin, the amount of skin wrinkling, and the depth of the furrows, but surgeon preference is likely to be the most significant factor.<sup>8,35</sup> A combined coronal brow lift and blepharoplasty can be used in patients with excessive eyelid fat and brow ptosis but little or no dermatochalasis.<sup>39</sup> The major disadvantages of the bicoronal technique include its invasive surgical approach, which can be intimidating to the patient, and the increased risk of hematoma and nerve injury.

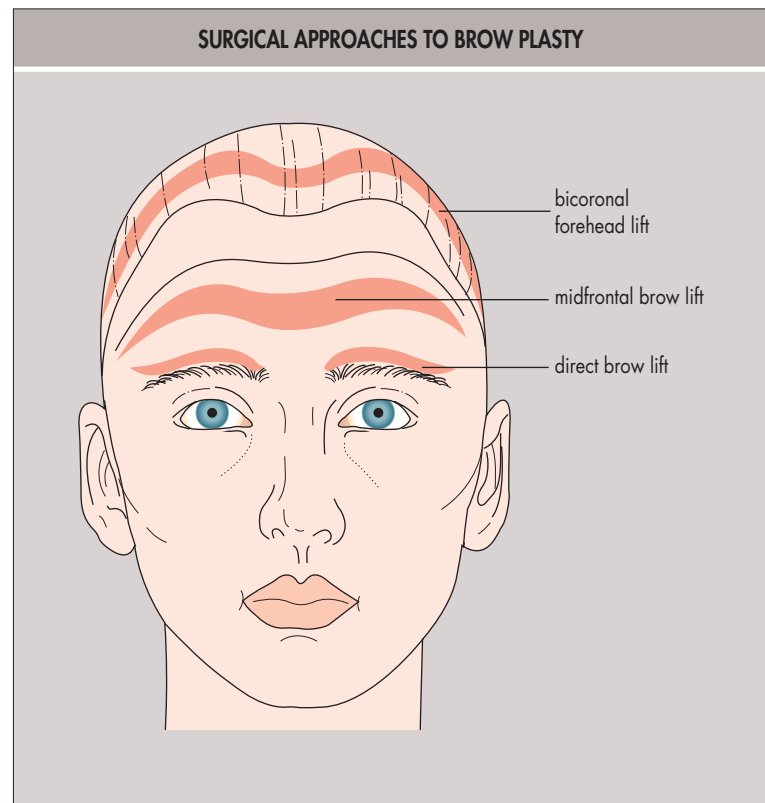


Fig. 12.15.9 Surgical Incision Sites for Correction of Brow Ptosis.

### The Midfrontal Brow Lift

The midfrontal approach provides less brow lift effect than does the bicoronal but more than the direct brow lift approach. Advantages include less risk of hematoma (because only moderate undermining is required and it is performed above the frontalis muscle) and less risk of nerve damage. The corrugator supercilii and procerus may be resected directly through this approach. It is ideally suited for patients who have deep horizontal furrows in the forehead (usually men), especially when frontal baldness prevents the use of a bicoronal incision. There are various types of incisions that can be used:

- Along a furrow line the entire length of the forehead.
- Along a furrow line staggered centrally.
- Two separate fusiform excisions, each extending from the medial to lateral end of the brow.

The major disadvantage of this technique is the resultant scar line.

### The Direct Brow Lift

The direct brow lift is the oldest and simplest surgical approach. Its advantages include a less invasive surgical dissection with less risk of damage to the facial nerve and minimal risk of hematoma. It is ideally suited for patients with bushy brows and mild brow ptosis. It also can be used in patients who have unilateral brow ptosis, which most commonly occurs following peripheral facial nerve palsy. It does not fully correct the medial brow ptosis, and it results in a visible scar even when placed directly above the eyebrow with often an unnaturally sharp border due to loss of the fine upper brow hairs. In patients who have large bushy brows, the incision tends to be less apparent. Modifications include a more temporal skin excision to correct isolated temporal brow ptosis.

### Endoscopic Brow Lift

Recently less invasive techniques have emerged in an attempt to reduce complications and achieve faster recovery. These techniques include endoscopic procedures, which involve small incisions placed temporally and/or centrally on the scalp posterior to the hairline.<sup>40</sup> A subperiosteal or subgaleal dissection is carried down to the level of the brow. The procerus and corrugator muscles are usually cut and excised, and the periosteum is transected at the superior orbital rim. The forehead is pulled upward and the periosteum fixed into position.



### **Transblepharoplasty Brow Fixation**

For minimal brow ptosis, especially laterally, the brow can be elevated through a blepharoplasty incision through suturing of the subbrow dermis higher on to the frontalis muscle or periosteum. This approach can help correct mild brow ptosis or small asymmetries.<sup>36,41</sup> An absorbable Endotine fixation device has been advocated to fix the deep frontalis galea to the brow rim periosteum with significant brow elevation.<sup>42,43</sup>

### **Complications**

Complications of browplasty depend on the technique used. There are two major groups of complications: those related to the incision site and those related to the extent of dissection.

#### ***Excessive Cutaneous Scar and Alopecia***

The forehead skin is thicker and less vascular than the eyelid skin, so incisions in the forehead often heal with a visible scar. Meticulous closure with adequate subdermal tension-bearing sutures and careful approximation of the wound edges is important. However, placement of the incision is the main determinant of scar visibility. It is generally preferable to locate the incision site at or above the hairline. Alopecia can be secondary to tension of wound, ischemia, or superficial dissection.

#### ***Paresthesia and Hematoma***

Related to the extent of dissection are the potential associated nerve injuries, which can result in frontal paresis, numbness, and an increased risk of hematoma formation. Temporary paresthesia following browplasty is common but usually resolves within 6 months. Hematomas can occur after bicoronal brow lift. They can be prevented at the end of surgery by placement of suction drains under the flaps. Small hematomas often resolve spontaneously, but larger ones should be evacuated to avoid flap necrosis, especially with a subcutaneous dissection where necrosis is more likely.

#### ***Overcorrection and Undercorrection***

Overcorrection of brow position or loss of movement of the brow can result in a “look of perpetual surprise,” particularly if the brow has been

fixed to the underlying periosteum in an overzealous direct brow lift. Undercorrection occurs when insufficient elevation is achieved; it is more common with the endoscopic technique and with posterior fixation of the brow through a blepharoplasty incision.

### **Outcome**

Following brow elevation procedures, the patient should experience an improvement in appearance and a restoration of superior visual field. In order to achieve these results, the brow repair may have to be combined with a blepharoplasty.

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# Aesthetic Fillers and Botulinum Toxin for Wrinkle Reduction

12.16

Jean Carruthers, Alastair Carruthers

**Definition:** The use of neuromodulators to adjust the power of muscles of facial expression has become the most popular aesthetic treatment worldwide. Changing the contours of the aging face with the use of three-dimensional fillers is a powerful adjunctive treatment.

## Key Features

- The functional and aesthetic importance of the periorbital region.
- Mechanisms of action of neuromodulators.
- Soft tissue augmentation mechanisms.
- As in surgery, a knowledge of anatomy of the facial regions is crucial both for superior results and for patient safety.

## INTRODUCTION

A focal point of attraction,<sup>1</sup> the periorbital region is one of the first areas of the face to manifest early signs of aging.<sup>2</sup> In youth, the forehead is high and gently rounded, the brow well defined and of appropriate height and shape, the upper orbit full, with a crisp upper eyelid crease and a lower lid that transitions smoothly to the cheek. Over time, these smooth contours are lost. Bony changes and atrophy of subcutaneous soft tissues lead to a loss of cutaneous support. It is this loss of skeletal and soft-tissue support that has the greatest impact on the appearance of the aging face.<sup>2-5</sup> As the skin repositions itself over the changing landscape of the face, the brow sinks toward the orbital rim, wrinkles bloom between and around the eyes, and the eye itself takes on a hollow, skeletonized appearance.

The multifactorial nature of aging provides the rationale for a combined, panfacial approach that simultaneously targets loss of support and volume and the appearance of wrinkles as indicated.<sup>6,7</sup> Rejuvenation of the periorbital region using soft-tissue fillers and botulinum neurotoxin type A (BoNTA) restores harmony and balance that has been lost during the aging process. However, the highly innervated and vascularized upper face requires a cautious approach and a deft touch. A thorough knowledge of anatomy and the interaction between musculature and the surrounding soft tissue is the key to consistent, favorable outcomes.

## APPROACH TO PERIORBITAL REJUVENATION

The periorbital region is prone to early manifestations of aging. The brow lowers progressively because of loss of structural forehead support (bone and fat), a decrease in neocollagenesis in the skin and facial planes, and the repetitive activity of the depressor muscles pulling on the inelastic skin of the forehead.<sup>8</sup> Mimetic musculature leads to the formation of glabellar rhytides and horizontal lines in the forehead that become more pronounced over time and produces lateral canthal and infraorbital rhytides, while the forehead and temples lose soft-tissue fullness.<sup>9</sup> Bony resorption widens the orbital cavity, giving the eye a sunken or shadowed appearance. The upper eyelid—the thinnest skin on the body with little to no subcutaneous fat—is prone to further thinning and stretching, whereas the lower lid is subject to fat redistribution, laxity, and weakening of the connective tissue.

The recognition of volume loss as a cardinal feature of aging has had a significant and lasting impact on the approach to facial rejuvenation with

injectable agents. The original treatment paradigm—using fillers or BoNTA separately in clearly delineated areas—has shifted toward more equal use of toxin and fillers in all facial zones with the objective of restoring youthful contours and creating facial proportions that more closely approximate the ideals of beauty. When used in combination throughout the face, neuromodulators and fillers work in synergy to produce optimal and durable aesthetic outcomes. It is an ideal marriage: Fillers correct volume loss in the periorbital complex and fill deeper folds and static wrinkles that cannot be alleviated by BoNTA alone.<sup>7</sup>

## Botulinum Toxin

Derived from the bacterium *Clostridium botulinum*, BoNTA blocks the release of acetylcholine from motor neurons at the neuromuscular junction, producing temporary chemodenervation of muscles lasting upward of 3 months.<sup>10</sup> Of the seven serotypes, type A is the most widely used across the world in multiple formulations for cosmetic and therapeutic indications. BoNTA has a long history of use in the periorcular region and was first used as an alternative to surgery in patients with strabismus.<sup>11</sup> Since its introduction for the treatment of glabellar rhytides over two decades ago,<sup>12</sup> BoNTA has become the most frequently performed cosmetic procedure in the world and is considered the gold standard treatment for dynamic facial wrinkles.<sup>13</sup> Moreover, progressive reduction in wrinkle severity and improvements in skin quality and biomechanical properties have been observed after repeated treatments over a long period of time,<sup>14-18</sup> suggesting that the effects of BoNTA go beyond muscle paralysis.

Of the available formulations, onabotulinumtoxinA (Botox Cosmetic, Allergan Inc., Irvine, CA) has the most approved clinical indications and has been the most widely studied for cosmetic and therapeutic purposes.<sup>6</sup> Subsequently, all doses discussed herein refer to onabotulinumtoxinA.

## Fillers

Although there is a wide variety of fillers on the market today, hyaluronic acid (HA) is most suitable for the delicate skin of the periorbital area. HA occurs naturally in the skin, making up a significant portion of the extracellular matrix involved in tissue repair, structural support, and cell proliferation and migration.<sup>19</sup> Injectable cross-linked HA derivatives, cultivated from the synthetic fermentation of the *Streptococcus equus* bacterium, attract and bind to water in the skin for immediate volume enhancement and appear to induce neocollagenesis via mechanical stretching for more persistent aesthetic effects.<sup>20</sup> HA fillers are available in multiple formulations. Highly viscous fillers provide greater lift and are ideal for deeper implantation, whereas products with low viscoelasticity are lighter and better suited for more superficial injection.<sup>21</sup> Importantly, HA is the only filler on the market that is considered “reversible,” in that unwanted or misplaced HA may be dissolved with the injection of hyaluronidase.<sup>22,23</sup>

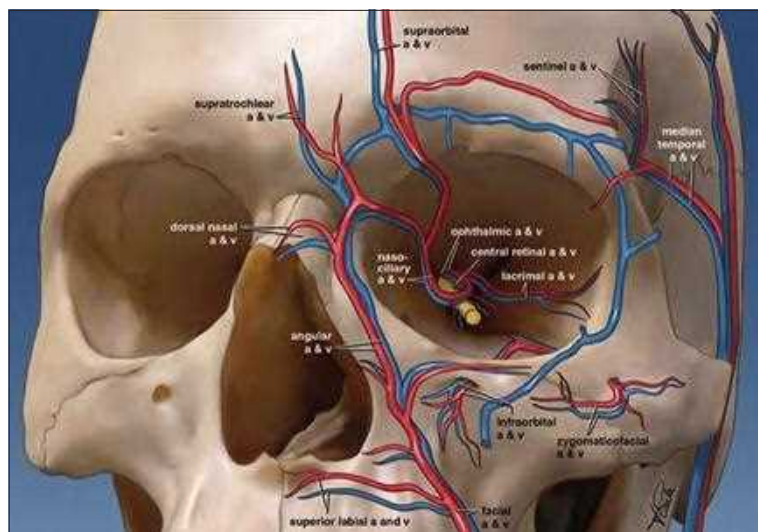
## ANATOMICAL CONSIDERATIONS

The upper face is an area of substantial physical variability and anatomically unforgiving with respect to safety and aesthetic considerations. A thorough knowledge of periorbital musculature, vasculature (Fig. 12.16.1), and innervation is critical in achieving optimal outcomes and avoiding potentially catastrophic adverse events (see “Precautions” section).

Four muscles—the corrugator supercilii, procerus, depressor supercilii, and orbicularis oris—work together to cause the head of the brow to rotate medially and descend in the frown.<sup>24</sup> The frontalis, the sole elevator



muscle, raises the forehead and eyebrows medially and can elevate the eyelid as high as 5 mm at maximal action.<sup>25</sup> Contraction of the frontalis produces horizontal forehead rhytides. The depressor muscles—the procerus and corrugator supercilii—move the eyebrow medially and downward and contribute to the formation of glabellar rhytides. The orbicularis oculi—the sphincter muscle of the eyelids—is a wide, concentric band of muscle responsible for blinking, eyelid closure, and the production of lateral canthal and lower eyelid rhytides. The orbicularis oculi also contributes to glabellar frown lines and helps lower the brow as part of a protective mechanism of the eye.



**Fig. 12.16.1** Vascular Structures of the Upper Face.

## THE BROW AND TEMPLE

The forehead, glabella, and temples are often assessed as one aesthetic unit and treated simultaneously with a combined approach using BoNTA for muscle control and soft-tissue fillers to improve temporal hollowing and the contours of the forehead.<sup>26</sup>

### Rhytides in the Upper Face

Hyperkinetic musculature contributes to the emergence of rhytides in the forehead, glabellar region, lateral canthal area (“crow’s feet”), and infra-orbital region. Targeting overactive muscles with appropriate doses of BoNTA reduces mimetic musculature and softens the appearance of lines and wrinkles (Figs. 12.16.2 and 12.16.3). Some evidence exists that regular, repeated treatments over many years not only prevent the formation of new wrinkles but may reduce the appearance of established rhytides.<sup>14–16,18</sup> Current consensus guidelines recommend a panfacial approach to the treatment of facial rhytides using lower minimum doses and number of injection points than previously recommended (Fig. 12.16.4, Table 12.16.1).<sup>6</sup> Growing evidence supports simultaneous treatment of multiple areas for significant improvements in clinical outcomes and patient satisfaction. One study of 917 subjects revealed greater benefit when lateral canthal and glabellar lines were treated simultaneously than when crow’s feet were treated alone.<sup>27</sup>

### Shaping the Brow

Adept use of neuromodulators can lift and shape the brow as required, particularly for women, who often desire a higher, more arched eyebrow.<sup>28</sup> Indeed, the position of the eyebrows is critical for emotional expression. Changes to the angle, height, and curve of the eyebrow, alone or in combination with other facial movements, can produce a broad range of signals



**Fig. 12.16.2** Full frown before (A) and after (B) BoNTA in the glabella of a patient from the first published report of the efficacy of botulinum neurotoxin for the treatment of glabellar rhytides.



**Fig. 12.16.3** Crow’s feet at maximum smile (A) before and (B) after injections of BoNTA.





**Fig. 12.16.4** Injection points for treatment of glabellar rhytides with BoNTA in (A) men and (B) women.

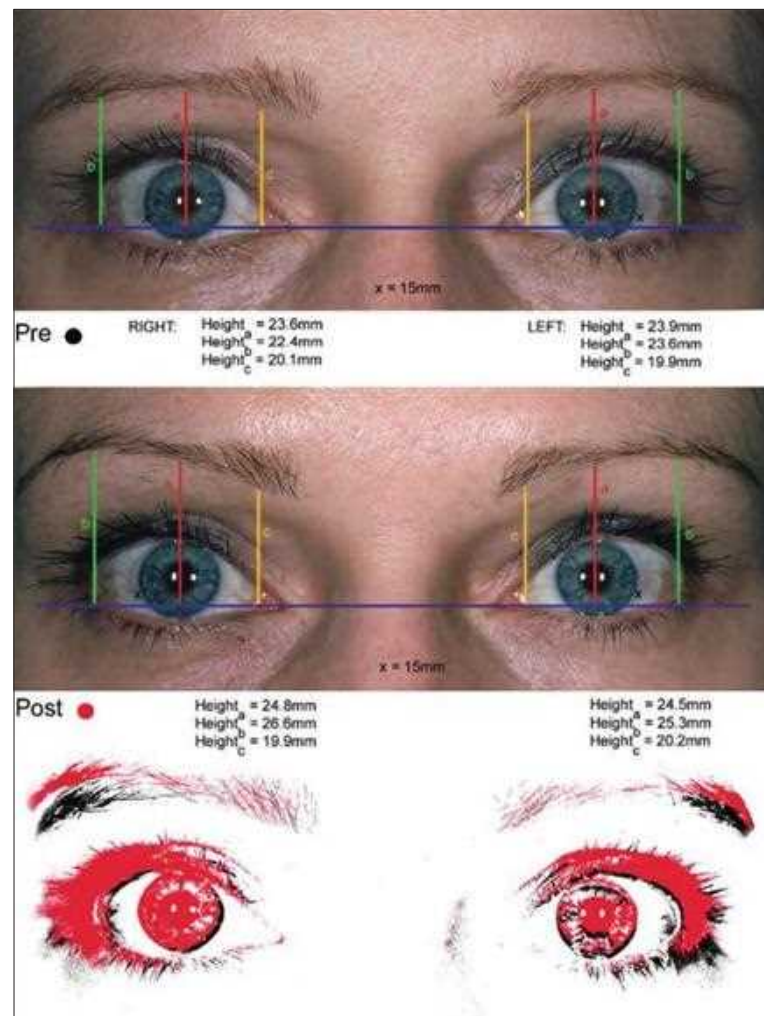
**TABLE 12.16.1** Recommendations for Periorbital Treatment With OnabotulinumtoxinA

Indication	Number of Injection Points	Total Dose
Glabellar rhytides	3–7	12–40 U
Horizontal forehead lines	4–8	8–25 U
Lateral canthal rhytides	1–5 per side	6–15 U per side
Infraorbital rhytides	1–3 per side	0.5–2 U per side

Adapted from Sundaram H, Signorini M, Liew S, et al. Global Aesthetics Consensus: botulinum toxin type A—evidence-based review, emerging concepts, and consensus recommendations for aesthetic use, including updates on complications. *Plast Reconstr Surg* 2016;137:518e–529e.

across the spectrum of human emotion that radically alter the expression of the face and serve as nonverbal forms of communication to convey emotion.<sup>29</sup>

Following the first published report of glabellar frown lines treated with BoNTA in 1992, clinicians began to observe subtle brow elevation after treatment of the brow depressors.<sup>30</sup> Central injections of 20–40 U of onabotulinumtoxinA into the glabella alone (with the most lateral injection at the midpupillary line) produced a dramatic lateral eyebrow elevation, followed by an entire chemical brow lift, due to diffusion of the toxin into the inferomedial frontalis, causing a compensatory increase in the resting tone of the lateral remainder of this muscle (Fig. 12.16.5).<sup>31</sup> Understanding that the shape and height of the eyebrow are determined by the opposing activity of the frontalis muscle and the brow depressors allows the clinician to manipulate eyebrow position at will to improve aesthetic appearance and correct asymmetry.



**Fig. 12.16.5** Eyebrow Lift After Bonta.

## Temple and Forehead Contouring

Facial recontouring aims to restore facial proportion that may or may not have been present naturally. The forehead and temple area are particularly amenable to contouring with fillers. Over time, skin laxity and relative muscle atrophy create temporal wasting and the development of concavity between the frontal eminence of the forehead and the supraciliary arches.

When injecting in the temple, there are three main anatomical structures to avoid: the superficial temporal artery and frontal branch of the facial nerve, which are located in the subcutaneous fat, and the median temporal vein, which lies 1.5–2 cm above the superficial border of the zygoma and deep in the temporalis muscle.<sup>32</sup> Subsequent massage of the area will evenly distribute the filler material.

To augment the forehead, deep injections are placed laterally at least 1 cm from the supraorbital foramen and directed posterior to the frontalis muscle in the preperiosteal plane using a low to medium viscosity filler with some lift capability, taking care to avoid the danger zones with the adjacent neurovascular bundles. The use of small aliquots of no more than 0.4 mL each rather than bolus and restricting tissue molding to the immediate postinjection period are recommended to reduce or eliminate the risk of migration.<sup>33</sup>

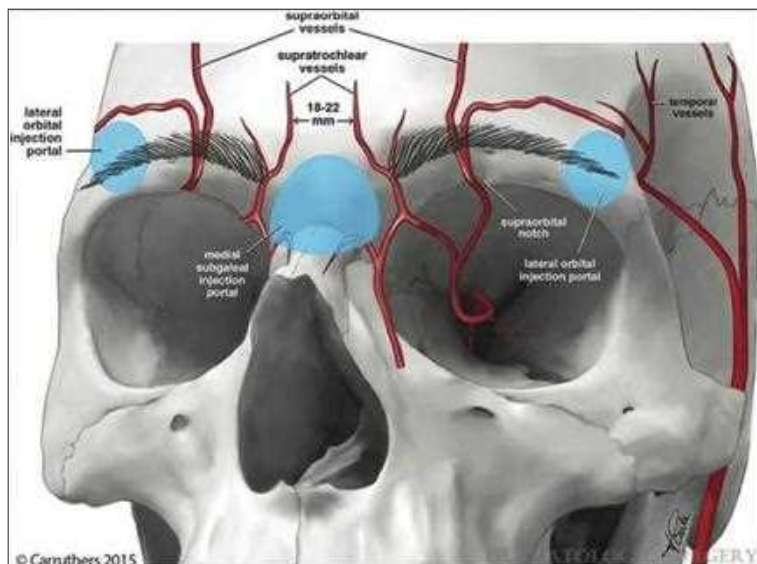
Alternately, a subgaleal injection technique has been developed for three-dimensional forehead augmentation in which 0.5 cc HA is diluted with 2% lidocaine with 1/200 000 epinephrine and preserved bacteriostatic saline to reduce viscosity and injected at three injection points in the forehead: centrally above the nasal bridge between the supratrochlear vessels and at the tail of each eyebrow between the temporal and supraorbital vessels (Fig. 12.16.6).<sup>34</sup> The needle or cannula is inserted into the subgaleal space as the skin is lifted away from the periosteum in the glabella and lateral brow before injection (Fig. 12.16.7). This technique results in a soft, rounded forehead, a reduction in etched forehead rhytides, and mild brow elevation without loss of expressivity (Figs. 12.16.8 and 12.16.9).

Superficial injections (high subcutaneous or intradermal) may be used for glabellar rhytides and horizontal forehead lines.<sup>33,35</sup> However, the forehead is an unforgiving area, with too much or inappropriate placement

of product leading to contour irregularities or the Tyndall effect, in which superficial implantation of certain formulations of HA imparts a bluish discoloration. Low-viscosity formulations are recommended for intradermal injection and subgaleal volumizing.<sup>34</sup>

## THE EYE

The eye speaks volumes about health, youth, and sense of attractiveness. Orbits that are large, round, and hollow are associated with age.<sup>36</sup>



**Fig. 12.16.6** Three Injection Portals Used for Three-Dimensional Forehead Reflation. (Reprinted with permission from Carruthers J, Carruthers A. Three-dimensional forehead reflation. *Dermatol Surg* 2015;41[Suppl 1]:S321–4.)

Manipulating the shape and appearance of the eye with injectables—BoNTA or soft-tissue fillers—is an evolving art, with techniques that are sometimes difficult to describe and results that cannot always be predicted.

## Widening the Palpebral Aperture

The palpebral aperture can be widened by subcutaneous injections of BoNTA into the lower lid with concomitant treatment of crow's feet.<sup>37</sup> Small doses (2–4 U onabotulinumtoxinA) placed subdermally in the lower eyelid in the midpupillary line, 3 mm below the ciliary margin, will simultaneously increase the vertical palpebral aperture by 2–3 mm at rest and full smile, respectively, lending to a more rounded appearance to the lower eyelid (Fig. 12.16.10).

## Lid Ptosis, Malposition, and Asymmetry

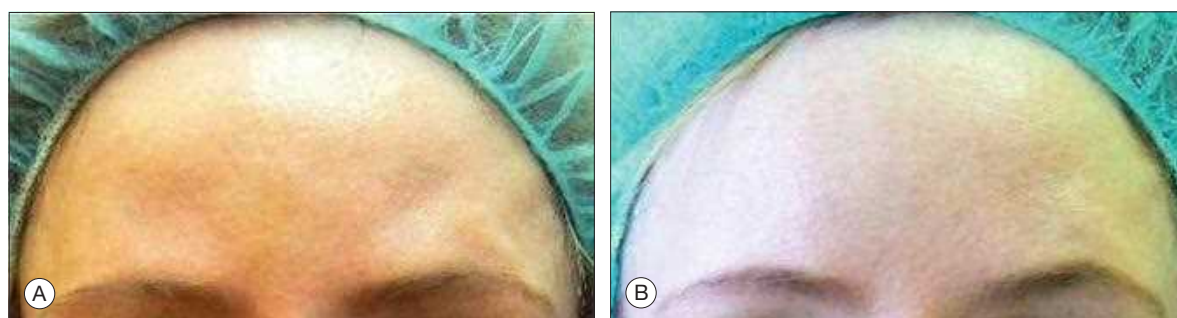
BoNTA is an effective treatment for the temporary management of mild-to-moderate upper lid ptosis, malposition, and eyelid-fissure asymmetry.<sup>38</sup> In the upper lid, low doses injected subdermally into the extreme medial and lateral aspects of the pretarsal region of the orbicularis just above the lash line allow unopposed activity of the levator palpebrae and Müller's muscle and a return to symmetry. Likewise, malposition and asymmetry in the lower eyelid (such as retraction, ectropion, and entropion) can be restored by weakening the lower lid elevators on the side opposite the lower lid retractions by two injections of BoNTA: one placed at the extreme lateral aspect of the lower eyelid and the other at the mid aspect of the lower eyelid pretarsal region, located approximately midpupil, inducing a similar retracted effect. Doses range from 0.5–1.5 U of onabotulinumtoxinA per injection site, with higher doses reserved for cases of lower eyelid hypertrophy and severe ptosis or when changing the position of the lower eye.

## Orbital Augmentation

Using fillers around the orbit is more complicated. The periorbital region is not an area for novice injectors. There are no hard and fast rules; only experience can predict individual aesthetic outcomes. The goal of treatment is not necessarily to make the orbit fuller or fill a hollow but



**Fig. 12.16.7** (A) Pinching up the lateral brow and (B) glabellar skin to enter the subgaleal plane. (C) Massaging the subgaleal HA to smoothness. (Reprinted with permission from Carruthers J, Carruthers A. Three-dimensional forehead reflation. *Dermatol Surg* 2015;41[Suppl 1]:S321–4.)



**Fig. 12.16.8** (A) Before and (B) after three-dimensional forehead reflation with HA. (Reprinted with permission from Carruthers J, Carruthers A. Three-dimensional forehead reflation. *Dermatol Surg* 2015;41[Suppl 1]:S321–4.)





**Fig. 12.16.9** (A) Before and (B) after three-dimensional forehead reflation with HA and 30 U onabotulinumtoxinA. (Reprinted with permission from Carruthers J, Carruthers A. Three-dimensional forehead reflation. *Dermatol Surg* 2015;41[Suppl 1]:S321–4.)



**Fig. 12.16.10** (A) Before and (B) after BoNTA to increase the width of the palpebral aperture.

to improve the appearance of the periorbital region as a whole. Not all eyes will respond favorably to the addition of volume, but a tiny amount of filler placed in appropriately selected patients can make a noticeable difference.

Injections placed deep to the orbicularis muscle but superficial to the bone keeps the needle or cannula away from the globe and the large immobile periosteal arteries. Trial injection of local anesthetic across the upper lid is a near-accurate demonstration of the intended effect of the subsequent reflation of the brow and upper lid and can be followed by actual injection of HA if the result is aesthetically pleasing.<sup>36</sup> Some injectors prefer to begin laterally and place three fanning fills—high, middle, and low—across the brow using tiny amounts of filler (typically 0.5 mL per side); avoiding overfill is difficult to do well and easily but is critical to success. Lateral and central injections typically do not drop below the border of the orbital bone.

### Infraorbital Hollow

The infraorbital hollow (IOH), or “tear trough,” refers to the U-shaped or curvilinear depression under the eyes that may be accentuated as part of the aging process. With thin skin overlying bone and little to no subcutaneous fat or muscle in this region, the IOH can be an unforgiving region and challenging to treat with injectable agents. The orbicularis oculi muscle has direct bony attachment for approximately one-third of the orbital rim length, from the nasal bone to the medial limbus. Injections seem to work best in patients with thick and smooth skin and a well-defined tear trough,

without excessively protruding eyelid fat or excess eyelid skin, and HA is the agent of choice for many injectors. Some patients have genetically determined pigmentation that may look like a tear trough but without an indentation that can be filled. Pigmented dark lower eyelid circles cannot be improved by fillers and can, in fact, be worsened by treatment.

Optimal revolumization recognizes that other areas of the face may influence the appearance of the lower eye.<sup>39</sup> A deflated medial cheek, for example, will look unnatural without concurrent augmentation, particularly on animation. Ideally, periorbital volume augmentation should be performed in conjunction with rejuvenation of the midface and sometimes to the entire face to preserve harmony and restore aesthetic proportion.

Anatomical areas of concern include the prominent infratrochlear vessels and the infraorbital nerve. Small amounts of filler—no more than 1 mL in total for both sides—are placed along the orbital rim deep in the suborbicularis plane at the suprapariosteal level except in the medial aspect of the orbicularis oculi, which attaches to bone and requires direct injection. A variety of injection techniques have been described in the literature, although linear threading and serial puncture are the most commonly used techniques.<sup>39</sup>

### ADJUNCTIVE THERAPIES

Other therapies used frequently in the periocular region include monopolar radiofrequency (MRF) to tighten the skin and reduce the appearance of fine lines,<sup>40</sup> and bimatoprost, a prostaglandin analog that was discovered serendipitously to lengthen and darken the eyelashes.<sup>41</sup>

MRF is noninvasive technology widely used in cosmetic dermatology to treat the clinical signs of photodamage—skin laxity, fine lines, and rhytides—without significant recovery time or complications.<sup>42</sup> RF devices use an electrical current rather than a light source to deliver uniform heat to the deep dermis and underlying tissue at a controlled depth with concomitant surface skin cooling. RF generates heat based on the tissue's natural resistance to the movement of electrons in the deeper dermis and underlying tissue, leading to immediate collagen contraction and a delayed wound healing response, with new collagen formation 2–6 months post treatment.<sup>42</sup> In the periorbital region, RF produces objective and subjective reductions in wrinkles and fine lines and measurable changes in brow position.<sup>43</sup>

In December 2008, bimatoprost ophthalmic solution 0.03% was approved for the treatment of hypotrichosis of the eyelashes in the United States.<sup>41</sup> Originally used in glaucoma to reduce high intraocular pressure, bimatoprost increases the length, fullness, and darkness of the eyelashes. Current evidence suggests topical application of bimatoprost to the upper lid margin once daily is a safe and effective method of enhancing the appearance of the eyelashes with a significant level of patient satisfaction.<sup>41,44,45</sup>

## PRECAUTIONS

Most side effects and complications associated with BoNTA and fillers are minor and transient. Some precautions must be taken with respect to injections in the upper face to avoid serious and potentially devastating complications.

### Chlorhexidine

A cornerstone of modern aesthetic practice is effective antiseptic before any minimally invasive procedure to reduce infection. Chlorhexidine gluconate-based antiseptics are among the most effective and widely used products for surgical and dermatological procedures. However, a recent investigative review of chlorhexidine in the face and neck unearthed abundant case reports clearly demonstrating the potential for permanent visual damage in the form of corneal injury when chlorhexidine inadvertently comes in contact with the eye.<sup>46</sup> Although povidone–iodine has been suggested as a suitable alternative, more evidence on chloroxenol-based skin antiseptics and other convenient, effective formulations is needed to make informed decisions about the choice of antiseptic for use on the face and neck.

### Vascular Compromise

The most feared complications in aesthetic ophthalmology and dermatology fall under the umbrella of vascular compromise, which is believed to be caused by compression of a vessel or direct injection of filler material into the vasculature.<sup>47</sup>

Vessel obstruction or compression causes impending tissue necrosis and possible scarring and typically occurs immediately after injection, although delayed presentation has been reported.<sup>48</sup> Vascular compromise is evident by painless blanching that may be subtle and initially unrecognized; untreated, this progresses to a painful, violaceous reticulated patch, ulceration, and subsequent scar formation. Proper technique—using caution in high-risk areas, choosing low volumes of reversible HA fillers over multiple treatment sessions, using small-gauge needles or blunt canulas, and injecting slowly, with low pressure—may reduce the risk.

Inadvertent injection into the terminal or proximal branches of the ophthalmic artery results in often-irreversible blindness and possible

concomitant stroke. Blindness occurs abruptly and painfully.<sup>47</sup> Prevention is critical but not always possible due to anatomical variation; vascular compromise does occur despite extensive knowledge of vasculature and relevant injector experience. Extreme caution and the use of HA formulations are advised when injecting fillers into high-risk areas. Blindness is most often associated with injections in the glabella,<sup>49</sup> a watershed of small vessels, with minimal collateral circulation, requiring only small amounts of filler material to cause obstruction of blood flow. The central retinal artery is the final branch of the ophthalmic artery; proximal branches include the supratrochlear, supraorbital, and dorsal nasal artery, which partly supplies the dorsum of the nose. The angular artery—the terminal branch of the facial artery—ascends along the nasolabial fold and is particularly susceptible to vascular injury.<sup>47</sup> Treatment protocols advocate early recognition of retinal artery occlusion and timely retrobulbar injection of large amounts of hyaluronidase to decomplex intravascular HA for the best chance of preventing otherwise almost certain partial or complete loss of vision.<sup>47</sup>

## CONCLUSION

Modern rejuvenation of the periorbital region comprises a global, panfacial approach using a combination of neuromodulators and soft-tissue fillers to restore balance and youthful contours to the face. With its long history of use in ophthalmology, BoNTA reduces mimetic musculature contributing to dynamic and static rhytides and can be used to lift the eyebrows and widen the eyes. HA fills deeper lines and folds and targets the loss of subcutaneous support, shaping the orbit and recontouring the forehead and temples. However, certain areas of the upper face pose a greater risk for sometimes devastating complications. Proper injection technique and recognition of risk factors may reduce the incidence of vascular compromise and promote safe and successful outcomes.

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